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## (54) MULTIPLE SPECIFICITY BINDERS OF CXC CHEMOKINES AND USES THEREOF

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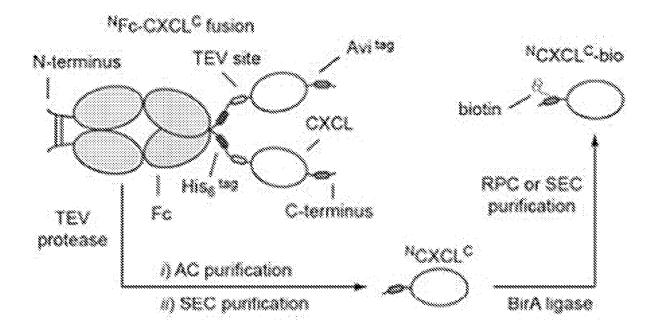
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#### ABSTRACT (57)

The present disclosure provides for fusion proteins comprising multispecific variable regions that bind more than one ELR+ CXC chemokine. The disclosure also provides methods of treating or preventing a condition associated with an abnormal immune response.

#### Specification includes a Sequence Listing.



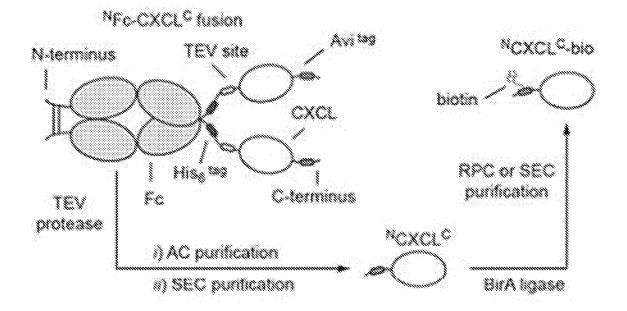


FIG. 1

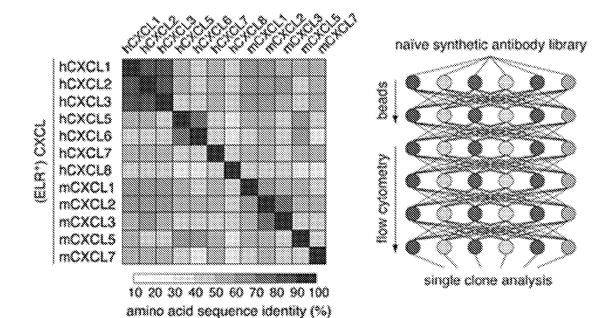
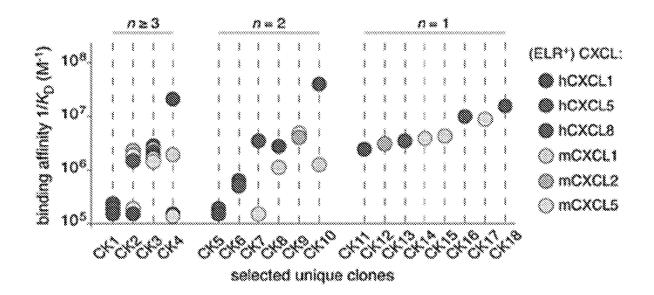
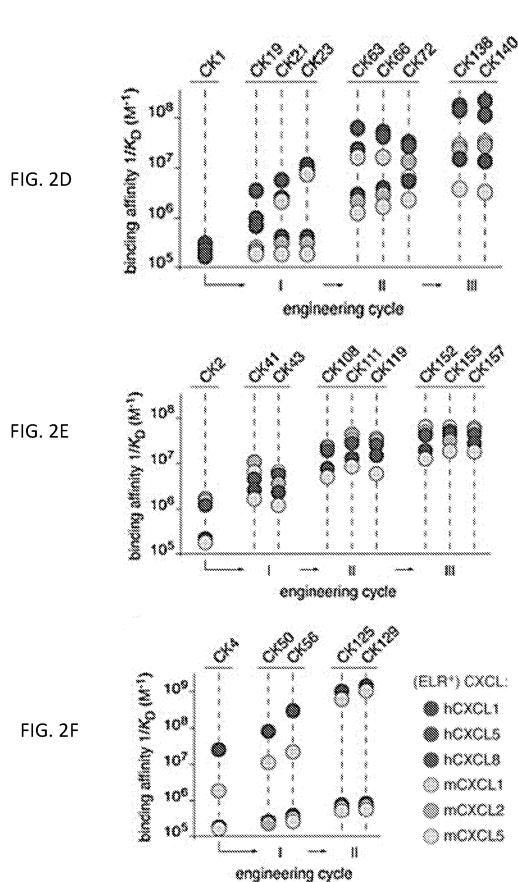


FIG. 2A









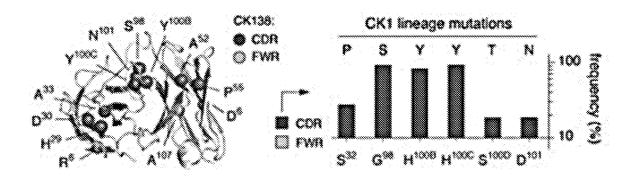


FIG. 2G

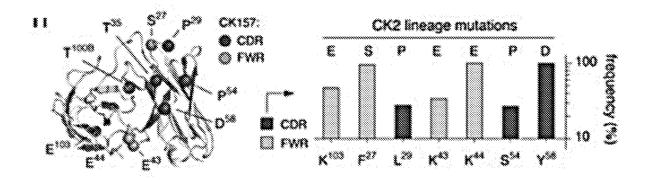


FIG. 2H

FIG. 3A

FIG. 3B

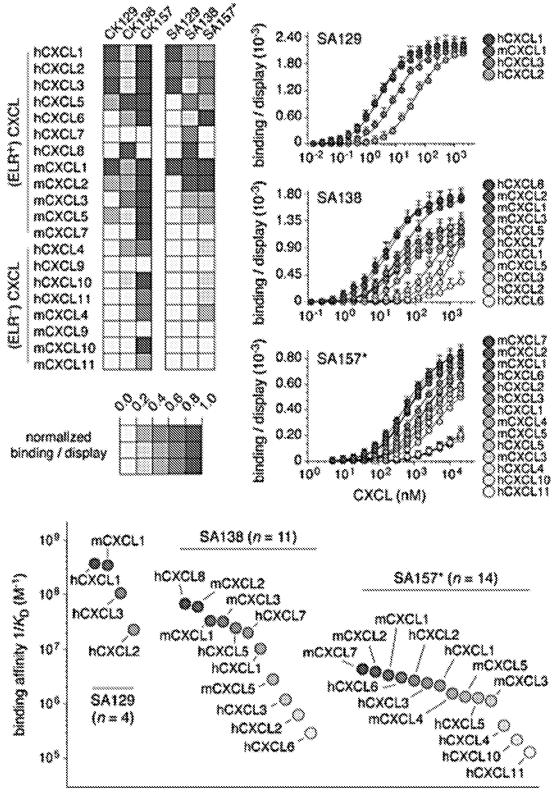
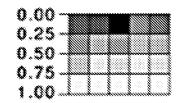


FIG. 3C

hCXCL1: 975

WT			
A4S			
T5A			
E6A			
L7A			
R8A			
Q10A			
L12A			
Q13A			
T14A			
L15A			
Q16A			
G17A			
118A			
H19A			
K21A	- North State	8 3	11111
N22A			
N22A Q24A			
Q24A			
Q24A S25A			
Q24A S25A N27A			
Q24A S25A N27A K29A			
Q24A S25A N27A K29A S30A			
Q24A S25A N27A K29A S30A G32A			

	Q,	9	g	Ŷ	× 4	×
Q37A						
T38A						
T43A						
K45A						
N46A						
G47A						
R48A						
K49A						
A50S						
N53A						
A55S						
S56A						
158A						
K60A						
K61A						
E64A						
K65A						
M66A						
L67A						
N68A						
S69A						
D70A						
K71A						
S72A						
N73A						



(binding / display) mutants

(binding / display) wild-type

FIG. 4A

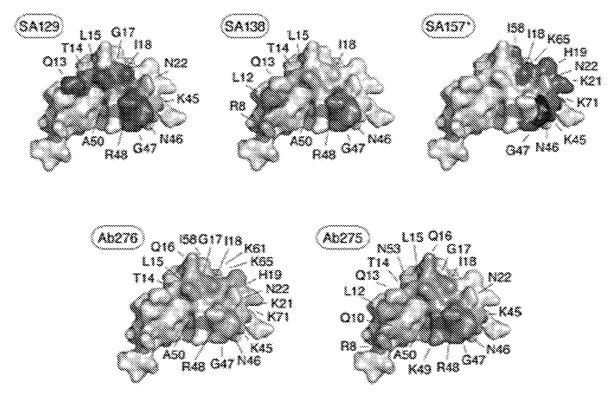


FIG. 4B

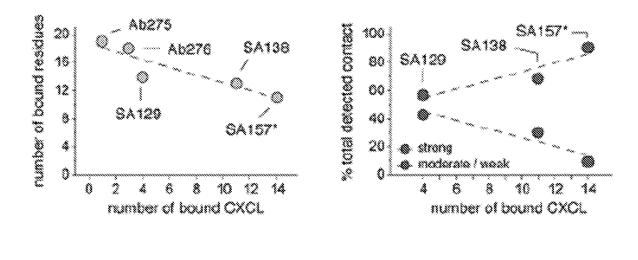
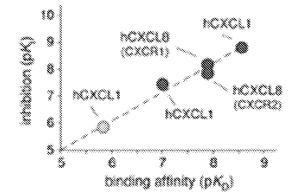


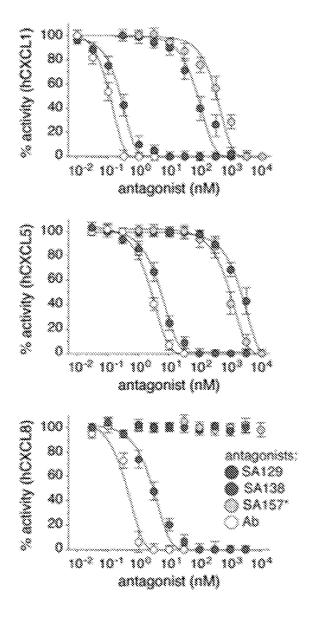
FIG. 4C

FIG. 4D









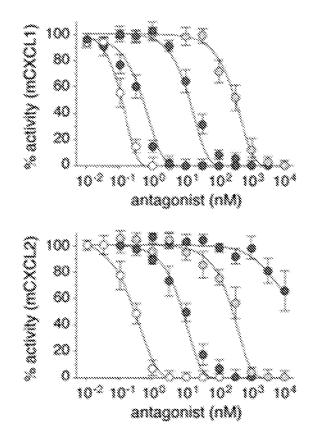


FIG. 5C

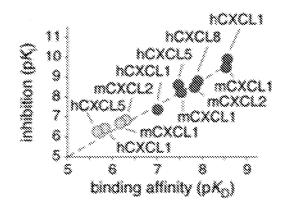
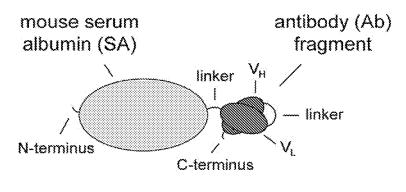


FIG. 5D



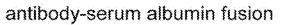


FIG. 6



FIG. 7C

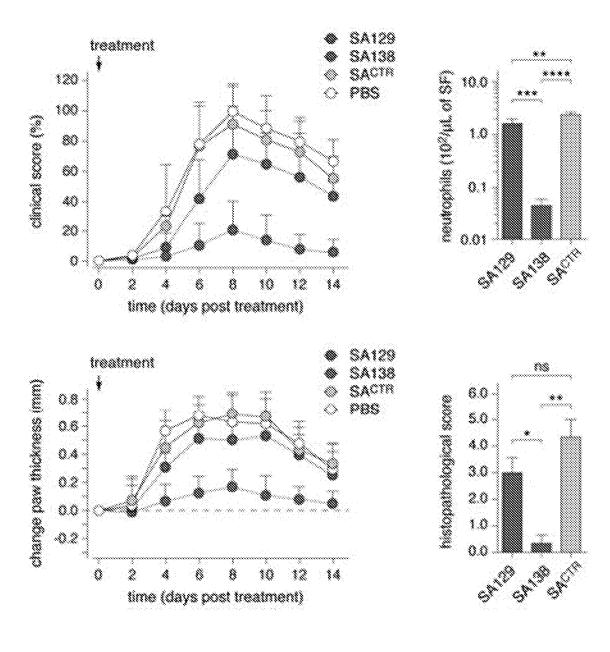




FIG. 7D



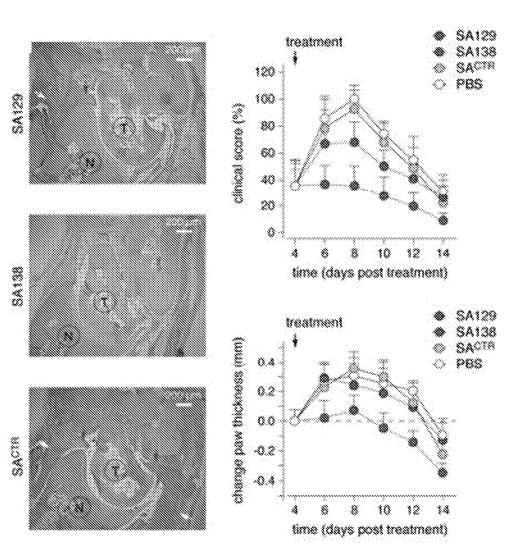


FIG. 7G

#### MULTIPLE SPECIFICITY BINDERS OF CXC CHEMOKINES AND USES THEREOF

#### RELATED INFORMATION PARAGRAPH

**[0001]** This application claims the benefit of the priority date of U.S. Provisional Application No. 62/546,814, filed on Aug. 17, 2017, the content of which is hereby incorporated by reference in its entirety.

#### BACKGROUND

**[0002]** Chronic inflammatory diseases usually involve multiple ligands that act synergistically through promiscuous and diverse receptors (Cho, J. H & Feldman, M., *Nat Med.* 21, 730-738 (2015)). This complexity is well exemplified by the ELR+ CXC chemokine system, a large family of secreted proteins that play a prominent role in the development and progression of numerous inflammatory diseases, including rheumatoid arthritis (RA) (Cho, J. H & Feldman, M., *Nat Med.* 21, 730-738 (2015); Charo, I. F. & Ransohoff, R. M. *N. Engl. J. Med.* 354, 610-621 (2006); Viola, A. & Luster, A. D. *Annu. Rev. Pharmacol. Toxicol.* 48, 171-197 (2008)).

[0003] Despite their clinical and commercial success, monoclonal antibodies often fail to reduce the level of small antigens in circulation. For example, while small chemokines (~8-10 kDa) are rapidly eliminated through renal filtration (t<sub>1/2</sub><10 min) (Van Zee, K. J. et al. J Immunol 148, 1746-1752 (1992)), strategies targeting single or multiple chemokines using large monoclonal antibodies (150 kDa) that are long-lived in circulation ( $t_{1/2}$ ~2 weeks) extends the systemic lifetimes of chemokines, thus increasing circulating chemokine levels. This buffering effect has been experimentally observed with numerous antibodies targeting small antigens (Mihara, M., Koishihara, Y., Fukui, H., Yasukawa, K. & Ohsugi, Y, Immunology 74, 55-59 (1991); Finkelman, F. D. et al. J Immunol 151, 1235-1244 (1993); May, L. T. et al. J Immunol 151, 3225-3236 (1993); Jayson, G. C. et al. Eur J Cancer 41, 555-563 (2005); Mostbock, S. Curr Pharm Des 15, 809-825 (2009); Letourneau, S. et al. Proceedings of the National Academy of Sciences of the United States of America 107, 2171-2176 (2010); O'Hear, C. & Foote, J. Eur J Haematol 84, 252-258 (2010)), including chemokines (Haringman, J. J. et al Arthritis and rheumatism 54, 2387-2392 (2006)), and is consistent with the affinity, binding kinetics and pharmacokinetic profiles of the circulating antibody-small antigen complexes in the absence of efficient clearance (O'Hear, C. E. & Foote, J. Proceedings of the National Academy of Sciences of the United States of America 102, 40-44 (2005)). Furthermore, functional full length antibodies that are able to recruit additional immune system cells via FcyR receptors are not ideal for the treatment of inflammatory diseases that exploit autoantibodies.

**[0004]** As chronic inflammatory diseases are complex and involve multiple ligands and receptors acting in concert, therapies targeting a single pathological molecule are often insufficient to achieve the desired clinical outcome. Accordingly, therapeutics that bind multiple targets are needed.

#### SUMMARY OF THE DISCLOSURE

**[0005]** The present disclosure is based on the discovery of engineered crossreactive therapeutic proteins that bind mul-

tiple homologus and orthologus targets, and are capable of preventing and reversing inflammation in an autoimmune model.

[0006] Accordingly, in some aspects the disclosure provides fusion proteins comprising a multispecific variable region operably coupled to a polymer, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines. In some aspects, the fusion protein comprises a multispecific variable region that binds human or murine ELR+ CXC chemokines. In other aspects, the fusion protein comprises a multispecific variable region that binds human and murine ELR+ CXC chemokines. In some aspects, the disclosure provides a fusion protein comprising a multispecific variable region that binds at least four ELR+ CXC chemokines selected from the group consisting of: human CXCL1 (Groα), human CXCL2 (Groβ), human CXCL3 (Groy), human CXCL5 (ENA-78), human CXCL6 (GCP-2), human CXCL7 (NAP-2), human CXCL8 (IL-8), murine CXCL1 (KC), murine CXCL2 (MIP-2), murine CXCL3 (DCIP-1), murine CXCL5 (LIX), and murine CXCL7 (NAP-2). In some aspects, the at least four ELR+ CXC chemokines are hCXCL1, hCXCL2, hCXCL3 and mCXCL1.

[0007] In some aspects, the disclosure provides a fusion protein comprising a multispecific variable region that binds at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or at least twelve ELR+ CXC chemokines selected from the group consisting of: human CXCL1 (Groa), human CXCL2 (Groß), human CXCL3 (Groy), human CXCL5 (ENA-78), human CXCL6 (GCP-2), human CXCL7 (NAP-2), human CXCL8 (IL-8), murine CXCL1 (KC), murine CXCL2 (MIP-2), murine CXCL3 (DCIP-1), murine CXCL5 (LIX), and murine CXCL7 (NAP-2). In some aspects, the at least six chemokines are human CXCL1, human CXCL5, human CXCL8, murine CXCL1, murine CXCL2 and murine CXCL5. In other aspects, the at least eleven chemokines are human CXCL8, murine CXCL2, murine CXCL1, murine CXCL3, human CXCL7, human CXCL5, human CXCL1, murine CXCL5, human CXCL3, human CXCL2, and human CXCL6

**[0008]** In any of the foregoing aspects, the multispecific variable region is operably coupled to a polymer via a linker. In some aspects, the linker is a Gly-Ser linker.

**[0009]** In some aspects, the disclosure provides a fusion comprising a multispecific variable region operably coupled to a polymer, wherein the multispecific variable region is a scFv. In some aspects, the scFv is operably coupled to the C-terminus of the polymer. In some aspects, the scFv is operably coupled to the N-terminus of the polymer. In some aspects, the scFv is a linker. In some aspects, the linker is a Gly-Ser linker.

**[0010]** In some aspects, the disclosure provides a fusion protein comprising a multispecific variable region described herein operably coupled to a polymer, wherein the polymer is a serum albumin moiety. In some aspects, the serum albumin moiety is mouse serum albumin. In other aspects, the serum albumin moiety is human serum albumin. In other aspects, the disclosure provides a fusion protein comprising a multispecific variable region operably coupled to a polymer, wherein the polymer is an Fc domain.

**[0011]** In any of the foregoing aspects, the disclosure provides a fusion protein wherein the multispecific variable region comprises a heavy chain variable region and a light

chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21.

**[0012]** In any of the foregoing aspects, the disclosure provides a fusion protein wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**[0013]** In any of the foregoing aspects, the disclosure provides a fusion protein wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21, and wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**[0014]** In other aspects, the disclosure provides a fusion protein comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in:

[0015] (a) SEQ ID NOs: 1 and 2, respectively;

[0016] (b) SEQ ID NOs: 11 and 12, respectively; or

[0017] (c) SEQ ID NOs: 21 and 22, respectively.

**[0018]** In another aspect, the disclosure provides a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises a heavy chain variable region and light chain variable region comprising amino acid sequences having 90% identity to the amino acid sequences set forth in:

[0019] (a) SEQ ID NOs: 1 and 2, respectively;

[0020] (b) SEQ ID NOs: 11 and 12, respectively; or

[0021] (c) SEQ ID NOs: 21 and 22, respectively.

**[0022]** In some aspects, the disclosure provides a fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises heavy and light chain CDRs selected from the group consisting of:

**[0023]** (a) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively;

**[0024]** (b) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 15, 16 and 17, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 18, 19 and 20, respectively; and **[0025]** (c) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**[0026]** In another aspect, the disclosure provides a fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises heavy and light chain variable regions, wherein

the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 11 and 21; and wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 12 and 22.

[0027] In another aspect, the disclosure provides a fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively. In another aspect, the disclosure provides a fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least human CXCL8, murine CXCL2, murine CXCL1, murine CXCL3, human CXCL7, human CXCL5, human CXCL1, murine CXCL5, human CXCL3, human CXCL2, and human CXCL6, and wherein the multispecific variable region comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively.

[0028] In yet another aspect, the disclosure provides a fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively. In yet another aspect, the disclosure provides a fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least murine CXCL1, human CXCL1, human CXCL3, and human CXCL2, and wherein the multispecific variable region comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**[0029]** In another aspect, the disclosure provides a fusion protein comprising an amino acid sequence selected from the group consisting of SEQ ID Nos: 95-105 and 160-170. **[0030]** In another aspect, the disclosure provides a fusion protein comprising an amino acid sequence having at least 90% identity to an amino acid sequence selected from the group consisting of SEQ ID Nos: 95-105 and 160-170.

**[0031]** In any of the foregoing aspects, the fusion protein inhibits binding of ELR+ CXC chemokines to their cognate CXCR1 and CXCR2.

**[0032]** In another aspect, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof, that binds to at least four ELR+ CXC chemokines. In some aspects, the isolated monoclonal antibody, or binding fragment thereof, binds human or murine ELR+ CXC chemokines. In some aspects, the isolated monoclonal antibody, or binding fragment thereof, binds human and murine ELR+ CXC chemokines. In some aspects, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof, that binds to at least four ELR+ CXC chemokines.

selected from the group consisting of: human CXCL1 (Gro $\alpha$ ), human CXCL2 (Gro $\beta$ ), human CXCL3 (Gro $\gamma$ ), human CXCL5 (ENA-78), human CXCL6 (GCP-2), human CXCL7 (NAP-2), human CXCL8 (IL-8), murine CXCL1 (KC), murine CXCL2 (MIP-2), murine CXCL3 (DCIP-1), murine CXCL5 (LIX), and murine CXCL7 (NAP-2). In some aspects, the at least four ELR+ CXC chemokines are hCXCL1, hCXCL2, hCXCL3 and mCXCL1

[0033] In some aspects, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof that binds at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or at least twelve ELR+ CXC chemokines selected from the group consisting of: human CXCL1 (Groa), human CXCL2 (Groß), human CXCL3 (Groy), human CXCL5 (ENA-78), human CXCL6 (GCP-2), human CXCL7 (NAP-2), human CXCL8 (IL-8), murine CXCL1 (KC), murine CXCL2 (MIP-2), murine CXCL3 (DCIP-1), murine CXCL5 (LIX), and murine CXCL7 (NAP-2). In some aspects, the at least six chemokines are human CXCL1, human CXCL5, human CXCL8, murine CXCL1, murine CXCL2 and murine CXCL5. In other aspects, the at least eleven chemokines are human CXCL8, murine CXCL2, murine CXCL1, murine CXCL3, human CXCL7, human CXCL5, human CXCL1, murine CXCL5, human CXCL3, human CXCL2, and human CXCL6.

**[0034]** In any of the foregoing aspects, the binding fragment thereof is a single chain variable fragment (scFv).

**[0035]** In any of the foregoing aspects, the antibody or binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21.

**[0036]** In any of the foregoing aspects, the antibody or binding fragment thereof, comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**[0037]** In any of the foregoing aspects, the antibody or binding fragment thereof, comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21, and wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**[0038]** In another aspect, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof, that binds to at least four ELR+ CXC chemokines, comprising a heavy chain variable region and light chain variable region comprising the amino acid sequences set forth in:

[0039] (a) SEQ ID NOs: 1 and 2, respectively;

[0040] (b) SEQ ID NOs: 11 and 12, respectively; or

[0041] (c) SEQ ID NOs: 21 and 22, respectively.

**[0042]** In other aspects, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof, that binds at least four ELR+ CXC chemokines, comprising a heavy chain variable region and light chain variable region comprising amino acid sequences having 90% identity to the amino acid sequences set forth in:

[0043] (a) SEQ ID NOs: 1 and 2, respectively;

[0044] (b) SEQ ID NOs: 11 and 12, respectively; or

[0045] (c) SEQ ID NOs: 21 and 22, respectively.

**[0046]** In another aspect, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof, that

binds at least four ELR+ CXC chemokines, comprising heavy and light chain CDRs selected from the group consisting of:

**[0047]** (a) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively;

**[0048]** (b) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 15, 16 and 17, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 18, 19 and 20, respectively; and **[0049]** (c) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**[0050]** In other aspects, the disclosure provides an isolated monoclonal antibody, or binding fragment thereof, that binds at least four ELR+ CXC chemokines, comprising heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 11 or 21; and wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 12 or 22.

**[0051]** In any of the foregoing aspects, the isolated monoclonal antibody, or binding fragment thereof, inhibits binding of ELR+ CXC chemokines to their cognate CXCR1 and CXCR2.

**[0052]** In another aspect, the disclosure provides methods of treating an autoimmune disorder in a subject in need thereof, the method comprising administering an effective amount of a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein. In some aspects, the autoimmune disorder is rheumatoid arthritis.

**[0053]** In another aspect, the disclosure provides methods of blocking neutrophil infiltration in a subject with an autoimmune disorder, the method comprising administering an effective amount of a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein. In some aspects, neutrophil infiltration of the synovial fluid of arthritic joints is blocked.

**[0054]** In another aspect, the disclosure provides methods of preventing establishment of an autoimmune disorder in a subject, the method comprising administering an effective amount of a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein. In some aspects, the autoimmune disorder is rheumatoid arthritis.

**[0055]** In another aspect, the disclosure provides methods of reversing inflammatory arthritis in a subject in need thereof, the method comprising administering an effective amount of a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein.

**[0056]** In another aspect, the disclosure provides a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein, for use in treating an autoimmune disorder in a subject in need thereof, the method comprising administering an effective amount of. In some aspects, the autoimmune disorder is rheumatoid arthritis.

**[0057]** In another aspect, the disclosure provides a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein, for use in blocking neutrophil infiltration in a subject with an autoimmune disorder. In some aspects, neutrophil infiltration of the synovial fluid of arthritic joints is blocked.

**[0058]** In another aspect, the disclosure provides a fusion protein or isolated monoclonal antibody, or binding fragment thereof, described herein, for use in preventing establishment of an autoimmune disorder in a subject. In some aspects, the autoimmune disorder is rheumatoid arthritis. **[0059]** In another aspect, the disclosure provides a fusion

protein or isolated monoclonal antibody, or binding fragment thereof, described herein, for use in reversing inflammatory arthritis in a subject in need thereof.

#### BRIEF DESCRIPTION OF THE FIGURES

**[0060]** The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

**[0061]** FIG. **1** is a schematic representation of the (i) Fc-ELR+ CXC chemokine fusion protein constructs (Fc-CXCL) and (ii) purification scheme applied to obtain pure, active, and biotinylated ELR+ CXC chemokines (CXCLbio).

**[0062]** FIG. **2**A is a heat map displaying the sequence identity among multiple human and murine ELR+ CXC chemokines. h=human, m=murine.

**[0063]** FIG. **2**B is a schematic representation of the iterative selection pathways applied to isolate promiscuous binders from a naïve library of synthetic antibodies displayed on the surface of yeast. Two cycles of magnetic bead screening followed by four cycles of flow cytometry sorting are shown.

**[0064]** FIG. 2C is a plot showing the binding affinities of eighteen unique yeast-displayed synthetic antibody protein binders (CK) selected from six diverse human and murine ELR+ CXC chemokines. Data are represented as inverted equilibrium binding constants  $(1/K_D; M^{-1})$  and indicate the means of at least three independent experiments. h=human, m=murine.

**[0065]** FIGS. 2D-2F provide plots of binding affinities of engineered clones derived from CK1 (FIG. 2D), CK2 (FIG. 2E), and CK4 (FIG. 2F) lineage after two independent processes of selection (I and II), each including the generation of random yeast-display antibody libraries and cycles of flow cytometry sorting, followed by a third round of site-directed mutagenesis (III). Data are represented as inverted equilibrium binding constants  $(1/K_D; M^{-1})$  and indicate the means of at least three independent experiments.

**[0066]** FIGS. **2**G and **2**H show homology models and frequencies of enriched mutations of engineered CK138 (FIG. **2**G) and CK157 (FIG. **2**H) antibodies. The  $V_L$  and  $V_H$  backbones are represented as ribbons (light gray). Mutations acquired during the selection process are depicted as spheres at the Ca positions. Mutated amino acids belonging to CDR loops of CK138 and CK157 are shown in dark circles. Diversified amino acids belonging to FWR regions of CK138 and CK157 are shown in light circles.

**[0067]** FIG. **3**A is a heat map indicating the normalized binding/display intensities of the engineered antibodies against twenty diverse human and murine CXC chemokines. Binding between soluble CXC chemokines and yeast-displayed CK129, CK138 and CK157 is shown on the left, and binding between soluble serum-albumin antibody fusions SA129, SA138 and SA157\* are shown on the right. The intensity of color correlates with the strength of the inter-

action with weak and strong interactions shown in light and dark colors, respectively. h=human, m=murine.

**[0068]** FIG. **3**B provides graphs showing the binding isotherms of yeast-displayed human and murine CXC chemokines to soluble SA129, SA138 and SA157\* protein fusions. Equilibrium binding affinity ( $K_D$ ) values were determined only for clones exhibiting signals at high concentration of soluble agents. h=human, m=murine.

**[0069]** FIG. **3**C is a plot of the binding affinities of yeast-displayed human and murine CXC chemokines to soluble SA129, SA138 and SA157\* protein fusions. The indicated values are displayed as filled circles and represent the means of at least three independent experiments presented as inverted of equilibrium binding constants ( $1/K_D$ ;  $M^{-1}$ ). h=human, m=murine.

**[0070]** FIG. **4**A shows the normalized binding/display intensities of crossreactive protein fusions SA129, SA138 and SA157\*, and commercially available antibodies Ab276 and Ab275, to a defined panel of hCXCL1 alanine-mutants, as assessed by flow cytometry. The intensity of color correlates with the strength of the interaction with weak and strong interactions shown in light and dark colors, respectively. h=human.

**[0071]** FIG. 4B provides schematics showing residues of hCXCL1 contacted by SA129 (top left), SA138 (top middle), SA157\* (top right), Ab276 (bottom left) and Ab275 (bottom right). The intensity of color correlates with the strength of the interaction with weak and strong interactions shown in light and dark colors, respectively.

**[0072]** FIG. **4**C is a graph showing the number of interacting residues plotted against the number of bound CXC chemokine ligands (CXCL).

**[0073]** FIG. 4D is a graph showing the percent of strong and combined weak and moderate interactions of each selected protein binders (SA129, SA138 and SA157) plotted against the number of bound CXC chemokines. Weak/ moderate and strong interactions are shown in blue and red, respectively.

**[0074]** FIG. **5**A is a plot showing the ability of serum albumin-antibody fusion SA129 (red), SA138 (blue) and SA157\* (gray) to block binding of hCXCL1 and hCXCL8 chemokines to CXCR1 and CXCR2 receptors, assessed by a flow cytometry based assay. The  $K_i$  values were determined, transformed to log  $K_i$  and plotted against  $pK_D$ . h=human.

**[0075]** FIGS. **5**B and **5**C provide plots showing the ability of serum albumin-antibody fusion SA129, SA138 and SA157\* to antagonize the ELR+ CXC chemokine-induced receptors activation on mouse and human neutrophils, assessed by flow cytometry intracellular Ca<sup>2+</sup> mobilization assay. The residual activity of human chemokines (hCXCL1, hCXCL5 and hCXCL8) (FIG. **5**B) and mouse chemokines (mCXCL1 and mCXCL2) (FIG. **5**C) incubated with varying concentrations of SA129 (red), SA138 (blue), SA157\* (gray) and commercial neutralizing antibody (Ab, white). The indicated values are means of three independent experiments. h=human, m=murine.

**[0076]** FIG. **5**D is a plot showing calculated  $pK_i$  correlated linearly with the calculated  $pK_D$  suggesting a strict correlation between binding affinity and inhibitory activity. h=human, m=murine.

[0077] FIG. 6 is a schematic representation of the antibody single-chain variable fragment fused to the C-terminus of mouse serum albumin to generate SA129, SA138 and control  $SA^{CTR}$  fusion proteins.

[0078] FIG. 7A is a plot showing the percent clinical score of mice treated with serum albumin-antibody fusion proteins on day 0 (preventative regimen). Arrows indicate day begin of treatment. All data are presented as mean (dots)  $\pm$ SE (bars).

**[0079]** FIG. 7B is a plot showing the change in ankle thickness (mm) of mice treated with serum albumin-antibody fusion proteins on day 0 (preventative regimen). Arrows indicate day begin of treatment. All data are presented as mean (dots)  $\pm$ SE (bars).

**[0080]** FIG. 7C is a graph showing quantification of purified infiltrating synovial fluid neutrophils (Ly6G+ cells) from the ankles of serum transfer arthritic mice measured at day 8 by flow cytometry (n=3 per condition). Statistical comparisons were made between each group using one-way analysis of variance (ANOVA). P values: \*P<0.05, \*\* P<0. 01, \*\*\* P<0.001; \*\*\*\* P<0.0001. ns: non-significant.

[0081] FIG. 7D is a graph showing histopathological scoring of ankle tissue sections of mice treated with SA129, SA138 and control  $SA^{CTR}$  on day 8.

**[0082]** FIG. 7E provides representative H&E staining of ankle tissue sections of mice treated with SA129 (top), SA138 (middle) and control SA<sup>CTR</sup> (bottom) on day 8. Scale bar represents 200 White arrow indicates the infiltrated inflammatory cell in the joints and red arrow indicates pannus formation. T, taulus; N, navicular.

**[0083]** FIGS. 7F and 7G are plots providing the percent clinical score (FIG. 7F) and change in ankle thickness (mm) (FIG. 7G) of K/B×N serum-induced arthritic mice treated beginning on day 4 with serum albumin-antibody fusion proteins (therapeutic regimen). Arrows indicate day treatment began. All data are presented as mean (dots) ±SE (bars).

#### DETAILED DESCRIPTION

#### Overview

**[0084]** Various diseases are characterized by the development of immunological dysregulation in a patient. The presence of an impaired immune response in patients with autoimmune and related disorders has been particularly well-documented. Augmenting immune functions in patients may have beneficial effects for the alleviation of autoimmune and related diseases.

**[0085]** Described herein are fusion proteins, and isolated monoclonal antibodies, or antigen binding fragments thereof, that were designed to target soluble pro-inflammatory factors (e.g., ELR+ CXC chemokines).

**[0086]** ELR+ CXC chemokines (so-called because members of the chemokine family all possess an E-L-R amino acid motif immediately adjacent to their CXC motif) play an important role in a variety of pathogenic mechanisms, including the migration of neutrophils to sites of inflammation and angiogenesis. Neutrophils contribute to the pathogenesis of several acute and chronic inflammatory/autoimmune diseases.

**[0087]** In general, chemokines are grouped into four subfamilies: CXC, CC, (X)C, and CX3C. In the CXC chemokines, one amino acid separates the first two cysteines ("the CXC motif"). ELR+ CXC chemokines are ligands for CXCR1 and/or CXCR2 chemokine receptors, which are G-protein coupled seven transmembrane domain-type receptors that specifically bind ELR+ CXC chemokines. The seven human ELR+ CXC chemokines are human Gro-alpha (also known as CXCL1), human Gro-beta (also known as CXCL2), human Gro-gamma (also known as CXCL3), human ENA-78 (also known as CXCL5), human GCP-2 (also known as CXCL6), human NAP-2 (also known as CXCL7), and human IL-8 (also known as CXCL8). All ELR+ CXC chemokines bind the CXCR2 receptor; moreover, some ELR+ CXC chemokines bind both CXCR1 and CXCR2 receptors (i.e., CXCL6 and CXCL8), all of which contributes to redundancy in the activation pathways. The five murine ELR+ CXC chemokines are keratinocyte chemoattractant (KC) (also known as CXCL1), Macrophage Inflammatory Protein-2 (MIP-2) (also known as CXCL2), dendritic cell inflammatory protein-1 (DCIP-1) (also known as CXCL3), lipopolysaccharide-induced CXC chemokine (LIX) (also known as CXCL5), and neutrophil activating peptide-2 (NAP-2) (also known as CXCL7).

[0088] Crossreactive protein binders are challenging to obtain using traditional methodologies involving animal immunization and hybridoma development. Immune systems tend to remove self-reactive antibodies, making it difficult to generate in vivo antibodies against sequence- and structurally-related antigens derived from different species. In contrast, in vitro protein libraries associated with display technologies are unaffected by immune tolerance (Bradbury, A. R., et al. Nature biotechnology 29, 245-254 (2011)). Described herein are selection strategies for the isolation of protein binders with unprecedented crossreactivity towards a panel of structurally related, yet diverse in sequence, protein targets. Moreover, a serum albumin antibody fusionbased strategy was used to enable high drug dosing and optimal pharmacokinetic profiles, thus overcoming continuous receptor occupancy and buffering effect phenomena that have limited previous interventions.

**[0089]** Accordingly, in some aspects, the present disclosure provides fusion proteins comprising a multispecific variable region operably coupled to a polymer, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines. In other aspects, the present disclosure provides methods for treating or preventing a disorder associated with an abnormal immune response (e.g., autoimmune disorder, e.g., rheumatoid arthritis), comprising administering a fusion protein described herein.

#### Definitions

**[0090]** Terms used in the claims and specification are defined as set forth below unless otherwise specified.

**[0091]** As used herein, "about" will be understood by persons of ordinary skill and will vary to some extent depending on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill given the context in which it is used, "about" will mean up to plus or minus 10% of the particular value.

**[0092]** The term "ameliorating" refers to any therapeutically beneficial result in the treatment of a disease state, e.g., autoimmune disorder, including prophylaxis, lessening in the severity or progression, remission, or cure thereof.

**[0093]** "Amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline,  $\gamma$ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups {e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that function in a manner similar to a naturally occurring amino acid.

**[0094]** Amino acids can be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, can be referred to by their commonly accepted single-letter codes.

**[0095]** An "amino acid substitution" refers to the replacement of at least one existing amino acid residue in a predetermined amino acid sequence (an amino acid sequence of a starting polypeptide) with a second, different "replacement" amino acid residue. An "amino acid insertion" refers to the incorporation of at least one additional amino acid into a predetermined amino acid sequence. While the insertion will usually consist of the insertion of one or two amino acid residues, larger "peptide insertions," can also be made, e.g. insertion of about three to about five or even up to about ten, fifteen, or twenty amino acid residues. The inserted residue(s) may be naturally occurring or non-naturally occurring as disclosed above. An "amino acid residue from a predetermined amino acid sequence.

[0096] A polypeptide or amino acid sequence "derived from" a designated polypeptide or protein refers to the origin of the polypeptide. Preferably, the polypeptide or amino acid sequence which is derived from a particular sequence has an amino acid sequence that is essentially identical to that sequence or a portion thereof, wherein the portion consists of at least 10-20 amino acids, preferably at least 20-30 amino acids, more preferably at least 30-50 amino acids, or which is otherwise identifiable to one of ordinary skill in the art as having its origin in the sequence. Polypeptides derived from another peptide may have one or more mutations relative to the starting polypeptide, e.g., one or more amino acid residues which have been substituted with another amino acid residue or which has one or more amino acid residue insertions or deletions. A polypeptide can comprise an amino acid sequence which is not naturally occurring. Such variants necessarily have less than 100% sequence identity or similarity with the starting molecule. In some embodiments, the variant will have an amino acid sequence from about 75% to less than 100% amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide. In some embodiments, the variant has an amino acid sequence from about 80% to less than 100% amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide. In some embodiments, the variant has an amino acid sequence from about 85% to less than 100%, amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide. In some embodiments, the variant has an amino acid sequence from about 90% to less than 100% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%) amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide. In some embodiments, the variant has an amino acid sequence from about 95% to less than 100%, e.g., over the length of the variant molecule, amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide.

[0097] In some embodiments, there is one amino acid difference between a starting polypeptide sequence and the sequence derived therefrom. Identity or similarity with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical (i.e., same residue) with the starting amino acid residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. In some embodiments, a polypeptide consists of, consists essentially of, or comprises an amino acid sequence selected from SEQ ID NOs: 1, 2, 5-12, 15-22, 25-30, 37-42, 63-82, 95-106, 127-146, 148, and 160-182. In some embodiments, a polypeptide includes an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence selected from SEO ID NOs: 1, 2, 5-12, 15-22, 25-30, 37-42, 63-82, 95-106, 127-146, 148, and 160-182. In some embodiments, a polypeptide includes a contiguous amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a contiguous amino acid sequence selected from SEQ ID NOs: 1, 2, 5-12, 15-22, 25-30, 37-42, 63-82, 95-106, 127-146, 148, and 160-182. In some embodiments, a polypeptide includes an amino acid sequence having at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, or 500 (or any integer within these numbers) contiguous amino acids of an amino acid sequence selected from SEQ ID NOs: 1, 2, 5-12, 15-22, 25-30, 37-42, 63-82, 95-106, 127-146, 148, and 160-182.

[0098] In some embodiments, the polypeptides are encoded by a nucleotide sequence. Nucleotide sequences of the invention can be useful for a number of applications, including: cloning, gene therapy, protein expression and purification, mutation introduction, DNA vaccination of a host in need thereof, antibody generation for, e.g., passive immunization, PCR, primer and probe generation, and the like. In some embodiments, the nucleotide sequence described herein comprises, consists of, or consists essentially of, a nucleotide sequence selected from SEQ ID NOs: 3, 4, 13, 14, 23, 24, 31-36, 43-62, 83-94, 107-126, 147, 149, and 150-159. In some embodiments, a nucleotide sequence includes a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleotide sequence set forth in SEQ ID NOs: 3, 4, 13, 14, 23, 24, 31-36, 43-62, 83-94, 107-126, 147, 149, and 150-159. In some embodiments, a nucleotide sequence includes a contiguous nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a contiguous nucleotide sequence set forth in SEQ ID NOs: 3, 4, 13, 14, 23, 24, 31-36, 43-62, 83-94, 107-126, 147, 149, and 150-159. In some embodiments, a nucleotide sequence includes a nucleotide sequence having at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, or 500 (or any integer within these numbers) contiguous nucleotides of a nucleotide sequence set forth in SEQ ID NOs: 3, 4, 13, 14, 23, 24, 31-36, 43-62, 83-94, 107-126, 147, 149, and 150-159.

**[0099]** It will also be understood by one of ordinary skill in the art that the polypeptides (e.g., fusion proteins) disclosed herein may be altered such that they vary in sequence from the naturally occurring or native sequences from which they were derived, while retaining the desirable activity of the native sequences. For example, nucleotide or amino acid substitutions leading to conservative substitutions or changes at "non-essential" amino acid residues may be made. Mutations may be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis.

[0100] The polypeptides disclosed herein may comprise conservative amino acid substitutions at one or more amino acid residues, e.g., at essential or non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in a binding polypeptide is preferably replaced with another amino acid residue from the same side chain family. In some embodiments, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members. Alternatively, in some embodiments, mutations may be introduced randomly along all or part of a coding sequence, such as by saturation mutagenesis, and the resultant mutants can be incorporated into binding polypeptides of the invention and screened for their ability to bind to the desired target.

**[0101]** As used herein, the term "antibody" refers to a whole antibody comprising two light chain polypeptides and two heavy chain polypeptides. Whole antibodies include different antibody isotypes including IgM, IgG, IgA, IgD, and IgE antibodies. The term "antibody" includes a polyclonal antibody, a monoclonal antibody, a chimerized or chimeric antibody, a humanized antibody, a primatized antibody, a deimmunized antibody, and a fully human antibody. The antibody can be made in or derived from any of a variety of species, e.g., mammals such as humans, nonhuman primates (e.g., orangutan, baboons, or chimpanzees), horses, cattle, pigs, sheep, goats, dogs, cats, rabbits, guinea pigs, gerbils, hamsters, rats, and mice. The antibody can be a purified or a recombinant antibody.

**[0102]** As used herein, the term "antibody fragment," "antigen-binding fragment," or similar terms refer to a fragment of an antibody that retains the ability to bind to a target antigen(s) (e.g., ELR+ CXC chemokine(s)) and promote, induce, and/or increase the activity of the target antigen. Such fragments include, e.g., a single chain antibody, a single chain Fv fragment (scFv), an Fd fragment, an Fab fragment, an Fab' fragment, or an F(ab')2 fragment. An scFv fragment is a single polypeptide chain that includes both the heavy and light chain variable regions of the antibody from which the scFv is derived. In addition, intrabodies, minibodies, triabodies, and diabodies are also included in the definition of antibody and are compatible for use in the methods described herein. See, e.g., Todorovska et al. (2001) *J Immunol Methods* 248(1):47-66; Hudson and Kortt (1999) *J Immunol Methods* 231(1):177-189; Poljak (1994) *Structure* 2(12):1121-1123; Rondon and Marasco (1997) *Annual Review of Microbiology* 51:257-283, the disclosures of each of which are incorporated herein by reference in their entirety.

**[0103]** As used herein, the term "antibody fragment" also includes, e.g., single domain antibodies such as camelized single domain antibodies. See, e.g., Muyldermans et al. (2001) *Trends Biochem Sci* 26:230-235; Nuttall et al. (2000) *Curr Pharm Biotech* 1:253-263; Reichmann et al. (1999) *J Immunol Meth* 231:25-38; PCT application publication nos. WO 94/04678 and WO 94/25591; and U.S. Pat. No. 6,005, 079, all of which are incorporated herein by reference in their entireties. In some embodiments, the disclosure provides single domain antibodies comprising two VH domains with modifications such that single domain antibodies are formed.

**[0104]** In some embodiment, an antigen-binding fragment includes the variable region of a heavy chain polypeptide and the variable region of a light chain polypeptide. In some embodiments, an antigen-binding fragment described herein comprises the CDRs of the light chain and heavy chain polypeptide of an antibody.

[0105] As used herein, the term "autoimmune and/or related diseases" refers to diseases, disorders, conditions, and/or syndromes arising from and/or directed against a patient's own cells, tissues, and/or organs, or a co-segregate or manifestation thereof, or resulting condition therefrom. Examples of autoimmune and related diseases include graft rejection (e.g. graft vs. host disease), allergy, inflammatory diseases, and also include, but are not limited to, Acute Disseminated Encephalomyelitis (ADEM), Acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, Agammaglobulinemia, Allergic conjunctivitis, Allergic rhinitis, Allergic disorders of the gastrointestinal tract, Alopecia areata, Alzheimer's disease, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome (APS), Arteriosclerosis, Asthma, Autoimmune angioedema, Autoimmune aplastic anemia, Autoimmune-associated infertility, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hemophilia, Autoimmune hepatitis, Autoimmune hyperlipidemia, Autoimmune immunodeficiency, Autoimmune inner ear disease (AIED), Autoimmune lymphoproliferative syndrome, Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura (ATP), Autoimmune thyroid disease, Autoimmune urticaria, Autoimmune uveoretinitis, Axonal & neuronal neuropathies, Balo disease, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, Chronic fatigue syndrome, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal ostomyelitis (CRMO), Churg-Strauss syndrome, Cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST disease, Essential mixed cryoglobulinemia, Demyelinating neuropathies, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Eczema, Endometriosis, Eosinophilic esophagitis, Eosinophilic fasciitis, Erythema nodosum, Eustachian tube itching, Experimental allergic encephalomyelitis, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Giant papillary conjunctivitis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura, Herpes gestationis, Hypogammaglobulinemia, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related sclerosing disease, Immunoregulatory lipoproteins, Inclusion body myositis, Inflammatory Bowel Disease, Insulin resistance, Interstitial cystitis, Juvenile rheumatoid arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis, Kawasaki disease/syndrome, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lyme disease, chronic, Meniere's disease, Microscopic polyangiitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica (Devic's), Neutropenia, Osteoarthritis, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis (peripheral uveitis), Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Type I, II, & III autoimmune polyglandular syndromes, Polymyalgia rheumatic, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Progesterone dermatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Psoriasis, Psoriatic arthritis, Idiopathic pulmonary fibrosis, Pyoderma gangrenosum, Pure red cell aplasia, Raynauds phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Reiter's syndrome, Relapsing polychondritis, Restless legs syndrome, Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sinusitis, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia, Systemic lupus eythematosus (SLE), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, Transverse myelitis, Type 1 diabetes, Ulcerative colitis, Undifferentiated connective tissue disease (UCTD), Uveitis, Vernal conjunctivitis, Vernal keratoconjunctivitis, Vasculitis, Vesiculobullous dermatosis, Vitiligo, Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA). Any one or more of the aforementioned or unmentioned autoimmune and/or related diseases may be the target disease for a method of treatment as disclosed herein.

**[0106]** As used herein, the term "bispecific" or "bifunctional antibody" refers to an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny et al., *J. Immunol.* 148, 1547-1553 (1992).

[0107] Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chain/light-chain pairs have different specificities (Milstein and Cuello (1983) Nature 305:537-539). Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion of the heavy chain variable region is preferably with an immunoglobulin heavy-chain constant domain, including at least part of the hinge, CH2, and CH3 regions. For further details of illustrative currently known methods for generating bispecific antibodies see, e.g., Suresh et al. (1986) Methods in Enzymology 121:210; PCT Publication No. WO 96/27011; Brennan et al. (1985) Science 229:81; Shalaby et al., J Exp Med (1992) 175:217-225; Kostelny et al. (1992) J Immunol 148(5):1547-1553; Hollinger et al. (1993) Proc Natl Acad Sci USA 90:6444-6448; Gruber et al. (1994) J Immunol 152:5368; and Tutt et al. (1991) J Immunol 147:60. Bispecific antibodies also include cross-linked or heteroconjugate antibodies. Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of crosslinking techniques.

[0108] Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. See, e.g., Kostelny et al. (1992) J Immunol 148(5):1547-1553. The leucine zipper peptides from the Fos and Jun proteins may be linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers may be reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al. (1993) Proc Natl Acad Sci USA 90:6444-6448 has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VH and VL domains of one fragment are forced to pair with the complementary VL and VH domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (scFv) dimers has also been reported. See, e.g., Gruber et al. (1994) J Immunol 152:5368. Alternatively, the antibodies can be "linear antibodies" as described in, e.g., Zapata et al. (1995) Protein Eng. 8(10):1057-1062. Briefly, these antibodies comprise a pair of tandem Fd segments (VH-CH1-VH-CH1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific. Antibodies with more than two valencies (e.g., trispecific antibodies) are contemplated and described in, e.g., Tutt et al. (1991) J Immunol 147:60.

**[0109]** As used herein, the term "chemokine" refers to a member of the family of small cytokines, or signaling proteins, that induce directed chemotaxis. Chemokines are

grouped into four subfamilies: CXC, CC, (X)C, and CX3C. In some embodiments, the chemokine or chemokines of interest are CXC chemokines. In the CXC chemokines, one amino acid separates the first two cysteines ("the CXC motif").

[0110] As used herein, the term "cross-reacts" refers to the ability of an antibody or fusion protein of the disclosure to bind to chemokines from a different species. For example, an antibody or fusion protein of the present disclosure which binds human ELR+ CXC chemokines may also bind another species of ELR+ CXC chemokines. As used herein, crossreactivity is measured by detecting a specific reactivity with purified antigen in binding assays (e.g., SPR, ELISA). Methods for determining cross-reactivity include standard binding assays as described herein, for example, by Biacore<sup>TM</sup> surface plasmon resonance (SPR) analysis using a Biacore<sup>™</sup> 2000 SPR instrument (Biacore AB, Uppsala, Sweden), or flow cytometric techniques. In some embodiments, a fusion protein described herein comprises a multispecific variable region that binds human and murine ELR+ CXC chemokines.

[0111] As used herein, the term "ELR+ CXC chemokine" refers to a chemokine possessing an E-L-R amino acid motif immediately adjacent to a CXC motif. ELR+ CXC chemokines are ligands for CXCR1 and/or CXCR2 chemokine receptors, which are G-protein coupled seven transmembrane domain-type receptors that specifically binds ELR+ CXC chemokines. All ERL+ CXC chemokines bind the CXCR2 receptor, whereas some bind both CXCR1 and CXCR2 receptors. The ELR+ CXC chemokines are human Gro-alpha (also known as CXCL1), human Gro-beta (also known as CXCL2), human Gro-gamma (also known as CXCL3), human ENA-78 (also known as CXCL5), human GCP-2 (also known as CXCL6), human NAP-2 (also known as CXCL7), human IL-8 (also known as CXCL58). The five murine ELR+ CXC chemokines are keratinocyte chemoattractant (KC), Macrophage Inflammatory Protein-2 (MIP-2), dendritic cell inflammatory protein-1 (DCIP-1), neutrophil activating peptide-2 (NAP-2) and lipopolysaccharide-induced CXC chemokine (LIX). The table below provides the list of ELR+ CXC chemokines, their alternative names, including the murine equivalent, and what receptors they bind to.

Chemokine	Alternative Names	Receptor(s) Binding
CXCL1	GROα, MGSA, murine KC	CXCR2
CXCL2	GROβ, MIP-2a, murine MIP-2	CXCR2
CXCL3	GROγ, MIP-2b, murine DCIP-1	CXCR2
CXCL5 CXCL6	ENA-78, murine LIX GCP-2 (no murine equivalent)	CXCR2 CXCR2 CXCR1, CXCR2
CXCL7	NAP-2	CXCR2
CXCL8	IL-8 (no murine equivalent)	CXCR1, CXCR2

**[0112]** As used herein, the term "epitope" or "antigenic determinant" refers to a site on an antigen (e.g., ELR+ CXC chemokine) to which an immunoglobulin or antibody specifically binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial

conformation. Methods for determining what epitopes are bound by a given antibody (i.e., epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from a chemokine are tested for reactivity with the given antibody. Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, e.g., *Epitope Mapping Protocols in Methods in Molecular Biology*, Vol. 66, G. E. Morris, Ed. (1996)).

**[0113]** Also, encompassed by the present disclosure are antibodies that bind to epitopes on chemokines (e.g., ELR+CXC chemokines) which comprises all or a portion of an epitope recognized by the particular antibodies described herein (e.g., the same or an overlapping region or a region between or spanning the region).

[0114] Also encompassed by the present disclosure are antibodies that bind the same epitope and/or antibodies that compete for binding to chemokines (e.g., ELR+ CXC chemokines) with the antibodies described herein. Antibodies that recognize the same epitope or compete for binding can be identified using routine techniques. Such techniques include, for example, an immunoassay, which shows the ability of one antibody to block the binding of another antibody to a target antigen, i.e., a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli et al., Methods in Enzymology 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland et al., J. Immunol. 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel et al., Mol. Immunol. 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung et al., Virology 176:546 (1990)); and direct labeled RIA. (Moldenhauer et al., Scand. J. Immunol. 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more.

**[0115]** Other techniques include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen: antibody complexes which provides atomic resolution of the epitope. Other methods monitor the binding of the antibody to antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component. In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of interest to affinity isolate specific short

peptides from combinatorial phage display peptide libraries. The peptides are then regarded as leads for the definition of the epitope corresponding to the antibody used to screen the peptide library. For epitope mapping, computational algorithms have also been developed which have been shown to map conformational discontinuous epitopes.

[0116] As used herein, the term "Fc region" refers to the portion of a native immunoglobulin formed by the respective Fc domains (or Fc moieties) of its two heavy chains. As used herein, the term "Fc domain" refers to a portion of a single immunoglobulin (Ig) heavy chain wherein the Fc domain does not comprise an Fv domain. As such, an Fc domain can also be referred to as "Ig" or "IgG." In some embodiments, an Fc domain begins in the hinge region just upstream of the papain cleavage site and ends at the C-terminus of the antibody. Accordingly, a complete Fc domain comprises at least a hinge domain, a CH2 domain, and a CH3 domain. In some embodiments, an Fc domain comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, a CH4 domain, or a variant, portion, or fragment thereof. In some embodiments, an Fc domain comprises a complete Fc domain (i.e., a hinge domain, a CH2 domain, and a CH3 domain). In some embodiments, an Fc domain comprises a hinge domain (or portion thereof) fused to a CH3 domain (or portion thereof). In some embodiments, an Fc domain comprises a CH2 domain (or portion thereof) fused to a CH3 domain (or portion thereof). In some embodiments, an Fc domain consists of a CH3 domain or portion thereof. In some embodiments, an Fc domain consists of a hinge domain (or portion thereof) and a CH3 domain (or portion thereof). In some embodiments, an Fc domain consists of a CH2 domain (or portion thereof) and a CH3 domain. In some embodiments, an Fc domain consists of a hinge domain (or portion thereof) and a CH2 domain (or portion thereof). In some embodiments, an Fc domain lacks at least a portion of a CH2 domain (e.g., all or part of a CH2 domain). An Fc domain herein generally refers to a polypeptide comprising all or part of the Fc domain of an immunoglobulin heavy-chain. This includes, but is not limited to, polypeptides comprising the entire CH1, hinge, CH2, and/or CH3 domains as well as fragments of such peptides comprising only, e.g., the hinge, CH2, and CH3 domain. In some embodiments, the Fc domain is derived from an immunoglobulin of any species and/or any subtype, including, but not limited to, a human IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody. A human IgG1 constant region can be found at Uniprot P01857 and in Table 12 (i.e., SEQ ID NO: 172). The Fc domain of human IgG1 can be found in Table 12 (i.e., SEQ ID NO: 173). The Fc domain encompasses native Fc and Fc variant molecules. As with Fc variants and native Fc's, the term Fc domain includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means. The assignment of amino acid residue numbers to an Fc domain is in accordance with the definitions of Kabat. See, e.g., Sequences of Proteins of Immunological Interest (Table of Contents, Introduction and Constant Region Sequences sections), 5th edition, Bethesda, Md.:NIH vol. 1:647-723 (1991); Kabat et al., "Introduction" Sequences of Proteins of Immunological Interest, US Dept of Health and Human Services, NIH, 5th edition, Bethesda, Md. vol. 1:xiii-xcvi (1991); Chothia & Lesk, J. Mol. Biol. 196:901-917 (1987); Chothia et al., Nature 342:878-883 (1989), each of which is herein incorporated by reference for all purposes.

**[0117]** As set forth herein, it will be understood by one of ordinary skill in the art that any Fc domain may be modified such that it varies in amino acid sequence from the native Fc domain of a naturally occurring immunoglobulin molecule. In some embodiments, the Fc domain has reduced effector function (e.g., Fc $\gamma$ R binding).

**[0118]** In some embodiments, the Fc domains are derived from different immunoglobulin molecules. For example, an Fc domain may comprise a CH2 and/or CH3 domain derived from an IgG1 molecule and a hinge region derived from an IgG3 molecule. In another example, an Fc domain can comprise a chimeric hinge region derived, in part, from an IgG1 molecule and, in part, from an IgG3 molecule. In another example, an Fc domain can comprise a chimeric hinge derived, in part, from an IgG1 molecule and, in part, from an IgG4 molecule.

**[0119]** As used herein, the term "fusion protein" refers to a recombinant protein prepared by fusion of a multispecific variable region described herein, and a polymer (e.g., serum albumin).

[0120] As used herein, the term "gly-ser polypeptide linker" refers to a peptide that consists of glycine and serine residues. An exemplary gly-ser polypeptide linker comprises the amino acid sequence Ser(Gly<sub>4</sub>Ser)n. In some embodiments, n=1. In some embodiments, n=2. In some embodiments, n=3, i.e., Ser(Gly<sub>4</sub>Ser)3. In some embodiments, n=4, i.e., Ser(Gly<sub>4</sub>Ser)4. In some embodiments, n=5. In some embodiments, n=6. In some embodiments, n=7. In some embodiments, n=8. In some embodiments, n=9. In some embodiments, n=10. Another exemplary gly-ser polypeptide linker comprises the amino acid sequence (Gly<sub>4</sub>Ser)n. In some embodiments, n=1. In some embodiments, n=2. In some embodiments, n=3. In some embodiments, n=4. In some embodiments, n=5. In some embodiments, n=6. Another exemplary gly-ser polypeptide linker comprises the amino acid sequence (Gly<sub>3</sub>Ser)n. some embodiments, n=1. In some embodiments, n=2. In some embodiments, n=3. In some embodiments, n=4. In some embodiments, n=5. In some embodiments, n=6.

[0121] As used herein, "half-life" refers to the time taken for the serum or plasma concentration of a polypeptide to reduce by 50%, in vivo, for example due to degradation and/or clearance or sequestration by natural mechanisms. The fusion protein disclosed herein is stabilized in vivo and its half-life increased by, e.g., fusion to an Fc region, fusion to serum albumin (e.g., HSA or MSA), through PEGylation, or by binding to serum albumin molecules (e.g., human serum albumin) which resist degradation and/or clearance or sequestration. The half-life can be determined in any manner known per se, such as by pharmacokinetic analysis. Suitable techniques will be clear to the person skilled in the art, and may for example generally involve the steps of suitably administering a suitable dose of the amino acid sequence or compound to a subject; collecting blood samples or other samples from said subject at regular intervals; determining the level or concentration of the amino acid sequence or compound in said blood sample; and calculating, from (a plot of) the data thus obtained, the time until the level or concentration of the amino acid sequence or compound has been reduced by 50% compared to the initial level upon dosing. Further details are provided in, e.g., standard handbooks, such as Kenneth, A. et al., Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in Peters et al., Pharmacokinetic Analysis: A Practical Approach (1996). Reference is also made to Gibaldi, M. et al., Pharmacokinetics, 2nd Rev. Edition, Marcel Dekker (1982).

[0122] As used herein, the term "human antibody" includes antibodies having variable and constant regions (if present) of human germline immunoglobulin sequences. Human antibodies of the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or sitespecific mutagenesis in vitro or by somatic mutation in vivo) (see, Lonberg, N. et al. (1994) Nature 368(6474): 856-859); Lonberg, N. (1994) Handbook of Experimental Pharmacology 113:49-101; Lonberg, N. and Huszar, D. (1995) Intern. Rev. Immunol. Vol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) Ann. N.Y. Acad. Sci 764:536-546). However, the term "human antibody" does not include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences (i.e., humanized antibodies). [0123] As used herein, the term a "heterologous antibody"

**[0123]** As used herein, the term a "heterologous antibody" is defined in relation to the transgenic non-human organism producing such an antibody. This term refers to an antibody having an amino acid sequence or an encoding nucleic acid sequence corresponding to that found in an organism not consisting of the transgenic non-human animal, and generally from a species other than that of the transgenic non-human animal.

**[0124]** As used herein, "immune cell" is a cell of hematopoietic origin and that plays a role in the immune response. Immune cells include lymphocytes (e.g., B cells and T cells), natural killer cells, and myeloid cells (e.g., monocytes, macrophages, eosinophils, mast cells, basophils, and granulocytes).

**[0125]** As used herein, a subject "in need of prevention," "in need of treatment," or "in need thereof," refers to one, who by the judgment of an appropriate medical practitioner (e.g., a doctor, a nurse, or a nurse practitioner in the case of humans; a veterinarian in the case of non-human mammals), would reasonably benefit from a given treatment (such as treatment with a composition comprising a fusion protein described herein).

**[0126]** The term "in vivo" refers to processes that occur in a living organism.

**[0127]** As used herein, the term "isolated antibody" is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that binds to chemokines (e.g., ELR+ CXC chemokines) is substantially free of antibodies that specifically bind antigens other than chemokines (e.g., ELR+ CXC chemokines)). An isolated antibody that specifically binds to an epitope may, however, have cross-reactivity to other chemokines (e.g., ELR+ CXC chemokines) from different species. In addition, an isolated antibody is typically substantially free of other cellular material and/or chemicals.

**[0128]** As used herein, the term "isolated nucleic acid molecule" refers to nucleic acids encoding fusion proteins, antibodies or antibody portions (e.g.,  $V_H$ ,  $V_L$ , CDR3) that bind to chemokines (e.g., ELR+ CXC chemokines), is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the fusion protein, antibody or antibody portion are free of other nucleotide sequences encoding fusion proteins, antibodies or antibody portions

that bind antigens other than chemokines (e.g., ELR+ CXC chemokines), which other sequences may naturally flank the nucleic acid in human genomic DNA. For example, Table 12 shows nucleotide sequences comprising the heavy chain  $(V_H)$  and light chain  $(V_L)$  variable regions of multispecific monoclonal antibodies described herein.

**[0129]** As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by heavy chain constant region genes. In some embodiments, an antibody of the disclosure is of the IgG1 isotype. In some embodiments, an antibody of the disclosure is of the IgG2 isotype. In some embodiments, an antibody of the disclosure is of the IgG3 isotype. In some embodiments, an antibody of the disclosure is of the IgG3 isotype. In some embodiments, an antibody of the disclosure is of the IgG3 isotype. In some embodiments, an antibody of the disclosure is of the IgG4 isotype.

**[0130]** As used herein, the term "isotype switching" refers to the phenomenon by which the class, or isotype, of an antibody changes from one Ig class to one of the other Ig classes.

**[0131]** As used herein, the term "kd" is intended to refer to the off rate constant for the dissociation of an antibody from the antibody/antigen complex.

**[0132]** As used herein, the term "ka" is intended to refer to the on rate constant for the association of an antibody with the antigen.

**[0133]** As used herein, the terms "linked," "fused", or "fusion", are used interchangeably. These terms refer to the joining together of two more elements or components or domains, by whatever means including chemical conjugation or recombinant means. Methods of chemical conjugation (e.g., using heterobifunctional crosslinking agents) are known in the art.

**[0134]** As used herein, "local administration" or "local delivery," refers to delivery that does not rely upon transport of the composition or agent to its intended target tissue or site via the vascular system. For example, the composition may be delivered by injection or implantation of the composition or agent or by injection or implantation of a device containing the composition or agent. Following local administration in the vicinity of a target tissue or site, the composition or agent, or one or more components thereof, may diffuse to the intended target tissue or site.

**[0135]** The term "mammal" or "subject" or "patient" as used herein includes both humans and non-humans and includes, but is not limited to, humans, non-human primates, canines, felines, murines, bovines, equines, and porcines.

[0136] The term "multispecific" as used herein refers to a polypeptide (e.g., fusion protein and/or variable region) capable of binding more than one target of interest (e.g., ELR+ CXC chemokine). In some embodiments, the terms "multispecific" and "crossreactive" are interchangeable. In some embodiments, the polypeptide binds at least two targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least four targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least five targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least six targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least seven targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least eight targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least nine targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least ten targets

of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least eleven targets of interest (e.g., ELR+ CXC chemokines). In some embodiments, the polypeptide binds at least twelve targets of interest (e.g., ELR+ CXC chemokines).

[0137] "Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences and as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions can be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixedbase and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081, 1991; Ohtsuka et al., Biol. Chem. 260:2605-2608, 1985; and Cassol et al, 1992; Rossolini et al, Mol. Cell. Probes 8:91-98, 1994). For arginine and leucine, modifications at the second base can also be conservative. The term nucleic acid is used interchangeably with gene, cDNA, and mRNA encoded by a gene.

[0138] Polynucleotides used herein can be composed of any polyribonucleotide or polydeoxribonucleotide, which can be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of singleand double-stranded DNA, DNA that is a mixture of singleand double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and doublestranded regions, hybrid molecules comprising DNA and RNA that can be single-stranded or, more typically, doublestranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide can also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

**[0139]** As used herein, the term "operably linked" or "operably coupled" refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner.

**[0140]** As used herein, "parenteral administration," "administered parenterally," and other grammatically equivalent phrases, refer to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intranasal, intraocular, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, intracerebral, intracarnial, intracarotid and intrasternal injection and infusion.

**[0141]** As used herein, the term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

[0142] The term "percent identity," in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., BLASTP and BLASTN or other algorithms available to persons of skill) or by visual inspection. Depending on the application, the "percent identity" can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full length of the two sequences to be compared. For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

**[0143]** The percent identity between two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions×100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

**[0144]** Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al., infra).

**[0145]** One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., J. Mol. Biol. 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information website.

**[0146]** As generally used herein, "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

**[0147]** As used herein, a "pharmaceutically acceptable carrier" refers to, and includes, any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. The compositions can include a pharmaceutically acceptable salt, e.g., an acid addition salt or a base addition salt (see, e.g., Berge et al. (1977) *J Pharm Sci* 66:1-19).

[0148] As used herein, the term "PK" is an acronym for "pharmacokinetic" and encompasses properties of a compound including, by way of example, absorption, distribution, metabolism, and elimination by a subject. As used herein, an "extended-PK group" refers to a polymer, protein, peptide, or moiety that increases the circulation half-life of a biologically active molecule when fused to or administered together with the multispecific variable region. Examples of an extended-PK group include PEG, human serum albumin (HSA) binders (as disclosed in U.S. Publication Nos. 2005/ 0287153 and 2007/0003549, PCT Publication Nos. WO 2009/083804 and WO 2009/133208, and SABA molecules as described in US2012/094909), serum albumin (e.g., HSA), Fc or Fc fragments and variants thereof, transferrin and variants thereof, and sugars (e.g., sialic acid). Other exemplary extended-PK groups are disclosed in Kontermann et al., Current Opinion in Biotechnology 2011; 22:868-876, which is herein incorporated by reference in its entirety.

**[0149]** "Polypeptide," "peptide", and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

**[0150]** As used herein, the term "preventing" when used in relation to a condition, refers to administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition.

**[0151]** As used herein, the term "purified" or "isolated" as applied to any of the proteins (fusion proteins, antibodies or fragments) described herein refers to a polypeptide that has been separated or purified from components (e.g., proteins or other naturally-occurring biological or organic molecules) which naturally accompany it, e.g., other proteins, lipids, and nucleic acid in a prokaryote expressing the proteins. Typically, a polypeptide is purified when it constitutes at least 60 (e.g., at least 65, 70, 75, 80, 85, 90, 92, 95, 97, or 99) %, by weight, of the total protein in a sample.

**[0152]** As used herein, the term "recombinant host cell" (or simply "host cell") is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

**[0153]** As used herein, the term "recombinant human antibody" includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immuno-globulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and

constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (see, e.g., Lonberg (2005) Nature Biotech. 23(9):1117-1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (i.e., isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen may not have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (i.e., have at least 80% identity).

[0154] As used herein, the terms "specific binding," "selective binding," "selectively binds," and "specifically binds," refer to fusion protein or antibody binding to an epitope on a predetermined antigen. Typically, the fusion protein or antibody binds with an equilibrium dissociation constant (K<sub>d</sub>) of approximately less than  $10^{-6}$  M, such as approximately less than  $10^{-7}$  M,  $10^{-8}$  M,  $10^{-9}$  M or  $10^{-10}$  M or even lower when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument using an ELR+ CXC chemokine of interest as the analyte and the fusion protein or antibody as the ligand and binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "recognizing an antigen" and "specific for an antigen" are used interchangeably herein with the term "binds specifically to an antigen."

**[0155]** As used herein, the term "subject" includes any human or non-human animal. For example, the methods and compositions of the present disclosure can be used to treat a subject with an immune disorder. The term "non-human animal" includes all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

**[0156]** The term "sufficient amount" or "amount sufficient to" means an amount sufficient to produce a desired effect, e.g., an amount sufficient to reduce the size of a tumor.

**[0157]** The term "substantial homology" indicates that two nucleotide sequences or two amino acid sequences, when optimally aligned and compared, are identical, with appropriate insertions or deletions, in at least about 80% of the nucleotides or amino acids, usually at least about 90% to 95%, and more preferably at least about 98% to 99.5% of the nucleotides or amino acids. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

**[0158]** The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. See, F. Ausubel, et al., ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

**[0159]** The nucleic acid compositions of the present disclosure, while often in a native sequence (except for modified restriction sites and the like), from either cDNA, genomic or mixtures thereof may be mutated, in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, DNA sequences substantially homologous to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

[0160] The term "T cell" refers to a type of white blood cell that can be distinguised from other white blood cells by the presence of a T cell receptor on the cell surface. There are several subsets of T cells, including, but not limited to, T helper cells (a.k.a.  $T_H$  cells or CD4<sup>+</sup> T cells) and subtypes, including T<sub>H</sub>1, T<sub>H</sub>2, T<sub>H</sub>3, T<sub>H</sub>17, T<sub>H</sub>9, and T<sub>FH</sub> cells, cytotoxic T cells (a.k.a  $T_c$  cells, CD8<sup>+</sup> T cells, cytotoxic T lymphocytes, T-killer cells, killer T cells), memory T cells and subtypes, including central memory T cells ( $T_{CM}$  cells), effector memory T cells ( $T_{EM}$  and  $T_{EMRA}$  cells), and resident memory T cells ( $T_{RM}$  cells), regulatory T cells (a.k.a.  $T_{reg}$ cells or suppressor T cells) and subtypes, including CD4<sup>+</sup> FOXP3<sup>+</sup>  $T_{reg}$  cells, CD4<sup>+</sup> FOXP3<sup>-</sup>  $T_{reg}$  cells, Tr1 cells, Th3 cells, and  $T_{reg}$ 17 cells, natural killer T cells (a.k.a. NKT cells), mucosal associated invariant T cells (MAITs), and gamma delta T cells ( $\gamma\delta$  T cells), including V $\gamma9$ /V $\delta2$  T cells. Any one or more of the aforementioned or unmentioned T cells may be the target cell type for a method as disclosed herein.

**[0161]** The term "therapeutically effective amount" is an amount that is effective to ameliorate a symptom of a disease. A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy.

**[0162]** The terms "treat," "treating," and "treatment," as used herein, refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration to a subject, in need of such treatment, a fusion protein or antibody, or antigen binding fragment thereof, of the present disclosure, for example, a subject in need of a reduced immune response or a subject who ultimately may acquire such a disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

**[0163]** As used herein, the term "vector" is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell,

and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors") In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adenoassociated viruses), which serve equivalent functions.

**[0164]** It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

#### Multispecific Variable Regions and Antibodies

**[0165]** The present disclosure provides multispecific variable regions capable of binding more than one ELR+ CXC chemokine (e.g., at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve). In some embodiments, the multispecific variable region is a single chain variable fragment (scFv). In some embodiments, the present disclosure also provides isolated monoclonal antibodies, or antigen binding fragments thereof, capable of binding more than one ELR+ CXC chemokine (e.g., at least two, at least three, at least four, at least six, at least seven, at least seven, at least ten, at least eight, at least nine, at least six, at least seven, at least twelve).

[0166] The ELR+ CXC chemokine system consists of numerous small and structurally similar chemoattractant ligands capable of binding to and activating the related CXCR1 and CXCR2 G protein-coupled receptors (GCPRs) expressed abundantly on the surface of neutrophils (Griffith, J. W. et al. Annu Rev Immunol 32, 659-702(2014)). These ligands act either by autocrine or paracrine mechanisms to induce signaling networks that direct neutrophils to sites of inflammation. Studies in animals have demonstrated that genetic deletion of the most promiscuous ELR+ CXC chemokine receptor, CXCR2, can block the development of joint inflammation in anti-type II collagen antibody-induced arthritis (CAIA) (Min, S. H. et al Biochem Biophy Res Commun 391, 1080-1086 (2010)), adjuvant-induced arthritis (AIA) (Barsante, M. M. et al Br J Pharmacol 153, 992-2001 (2008); Coelho, F. M. et al Arthritis Rheum 58, 2329-2337 (2008); Grespan, R. et al Arthritis Rheum 58, 2030-2040 (2008)), and K/B×N serum transfer induced arthritis (Jacobs, J. P. et al Arthritis Rheum 62, 1921-1932 (2010); Chou, R. C. et al Immunity 33, 266-278 (2010)).

**[0167]** Inhibition of ELR+ CXC chemokine-driven signaling has been previously attempted by employing various antagonists against CXCR1 and CXCR2 receptors, including neutralizing antibodies, small molecules and peptidederived inhibitors. However, these antagonists have shown limited therapeutic effects (Schall, T. J. & Proudfoot, A. E. *Nat Rev Immunol* 11, 355-363 (2011); Szekanecz, Z. & Koch, A. E. *Nat Rev Rheumatol* 12, 5-13 (2016)). Failures of such receptor-based therapies have been attributed to (i) difference between the orthologous rodent (pre-clinical) and human (clinical systems); and (ii) the extremely high doses of antagonist required to guarantee continuous receptor occupancy, such that all receptors in the body are antagonized (Id.).

**[0168]** Accordingly, the present disclosure provides multispecific variable regions, and isolated monoclonal antibodies, or antigen binding fragments thereof, that bind to the ELR+ CXC chemokine ligands themselves. In some embodiments, the multispecific variable regions, and isolated monoclonal antibodies, or antigen binding fragments thereof, described herein, bind to and inhibit or reduce the activity of the ELR+ CXC chemokine ligands.

**[0169]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21. In some embodiments, the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 21.

**[0170]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22. In some embodiments, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 22.

**[0171]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21, and wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**[0172]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in:

[0173] (a) SEQ ID NOs: 1 and 2, respectively;

[0174] (b) SEQ ID NOs: 11 and 12, respectively; or

[0175] (c) SEQ ID NOs: 21 and 22, respectively.

**[0176]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises a heavy chain variable region and light chain variable region comprising amino acid sequences having 90% identity to the amino acid sequences set forth in:

[0177] (a) SEQ ID NOs: 1 and 2, respectively;

[0178] (b) SEQ ID NOs: 11 and 12, respectively; or

[0179] (c) SEQ ID NOs: 21 and 22, respectively.

**[0180]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises heavy and light chain CDRs selected from the group consisting of:

**[0181]** (a) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively;

**[0182]** (b) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 15, 16 and 17, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 18, 19 and 20, respectively; and

**[0183]** (c) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**[0184]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively.

**[0185]** In some embodiments, the multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**[0186]** In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human CXCL1, human CXCL2, human CXCL3, human CXCL5, human CXCL6, human CXCL7, human CXCL8, murine CXCL1, murine CXCL2, murine CXCL3, murine CXCL5, murine CXCL7, or any combination thereof.

[0187] In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to at least two ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to at least four ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least four ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to at least five ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to at least six ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least seven ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least eight ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least nine ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least ten ELR+ CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least eleven ELR+ CXC chemokines. In some embodiments,

a multispecific variable region, or isolated monoclonal antibody provided herein, binds to at least twelve ELR+ CXC chemokines.

**[0188]** In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human CXCL1, human CXCL2, human CXCL3, and murine CXCL1. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human CXCL1, human CXCL5, human CXCL8, murine CXCL1, murine CXCL2 and murine CXCL5. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human CXCL2, and murine CXCL5. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human CXCL1, human CXCL2, human CXCL3, human CXCL5, human CXCL6, human CXCL7, human CXCL8, murine CXCL1, murine CXCL2, murine CXCL3 and murine CXCL1, murine CXCL2, murine CXCL3, and murine CXCL5.

**[0189]** In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human ELR+CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to murine ELR+CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to murine ELR+CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human and murine ELR+CXC chemokines. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, binds to human and murine ELR-CXC chemokines (e.g., murine CXCL4, human CXCL10 and human CXCL11).

[0190] In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, inhibits or reduces binding of an ELR+ CXC chemokine of interest to its cognate receptor. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, inhibits or reduces binding of an ELR+ CXC chemokine of interest to CXCR2. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, inhibits or reduces binding of an ELR+ CXC chemokine of interest CXCR1. In some embodiments, a multispecific variable region, or isolated monoclonal antibody, or antigen binding fragment thereof, provided herein, inhibits or reduces binding of an ELR+ CXC chemokine of interest to CXCR1 and CXCR2.

[0191] Fusion Protein

**[0192]** In some embodiments, the present disclosure provides fusion proteins comprising a multispecific variable region (e.g., scFv) described herein, operably coupled to a polymer. Examples of polymers suitable for use in the fusion proteins described herein, are provided in Strohl, W. R. *BioDrugs*, Vol. 29: 215-239 (2015), herein incorporated by reference in its entirety. The coupling of a polymer to multispecific variable region, either covalently or non-covalently, enhances the solubility and stability of the multispecific variable region.

**[0193]** Moreover, in some embodiments, the conjugating of a polymer to a multispecific variable region extends the pharmacokinetic profile (e.g., serum half-life) of the multispecific variable region. In some embodiments, the serum

half-life of a fusion protein described herein is increased relative to the multispecific variable region alone. In some embodiments, the serum half-life of a fusion protein described herein is at least 20, 40, 60, 80, 100, 120, 150, 180, 200, 400, 600, 800, or 1000% longer relative to the multispecific variable region alone. In certain embodiments, the serum half-life of a fusion protein described herein is at least 1.5-fold, 2-fold, 2.5-fold, 3-fold, 3.5 fold, 4-fold, 4.5-fold, 5-fold, 6-fold, 7-fold, 8-fold, 10-fold, 12-fold, 13-fold, 15-fold, 17-fold, 20-fold, 22-fold, 25-fold, 27-fold, 30-fold, 35-fold, 40-fold, or 50-fold greater than the serum half-life of the multispecific variable region alone. In certain embodiments, the serum half-life of a fusion protein described herein is at least 10 hours, 15 hours, 20 hours, 25 hours, 30 hours, 35 hours, 40 hours, 50 hours, 60 hours, 70 hours, 80 hours, 90 hours, 100 hours, 110 hours, 120 hours, 130 hours, 135 hours, 140 hours, 150 hours, 160 hours, or 200 hours. [0194] In some embodiments, the polymer is an albumin moiety (e.g., serum albumin). In some embodiments, the polymer is an Fc domain. In some embodiments, the polymer is polyethylene glycol (PEG). In some embodiments, the polymer is transferrin. In some embodiments, the polymer is a serum immunoglobulin binding protein. In some embodiments, the polymer is an albumin binding moiety.

#### Serum Albumin

**[0195]** In some embodiments, the fusion protein comprises a multispecific variable region (e.g., scFv) described herein, operably coupled to an albumin moiety, or fragment thereof. Suitable albumins for use in the fusion proteins can be from human, primate, rodent, bovine, equine, donkey, rabbit, goat, sheep, dog, chicken or pig. In some embodiments, the albumin is a serum albumin, for example, a human serum albumin, primate serum albumin (e.g., chimpanzee serum albumin, gorilla serum albumin), rodent serum albumin, mouse serum albumin and rat serum albumin, bovine serum albumin, equine serum albumin, donkey serum albumin, rabbit serum albumin, goat serum albumin, sheep serum albumin, dog serum albumin, chicken serum albumin, and pig serum albumin.

**[0196]** Serum albumin exploits the FcRn receptor to achieve long half-life in circulation but its plasma persistence is still shorter than full length monoclonal antibodies, thus avoiding "buffering" effects associated with the use of full-length antibody-based strategies (Sand, K. M. et al *Front Immunol* 5, 682 (2014); Mihara, M. e al *Immunology* 74, 55-59 (1991); O'Hear, C. E. & Foote, J. *Proc Natl Acad Sci USA* 102, 40-44 (2005); Haringman, J. J. et al *Arthritis and Rheumatism* 54, 2387-2393 (2006)). Unlike an antibody, serum albumin does not find the FcyR receptors expressed on the surface of immune system cells, thus eluding extra immune system activation and inflammation mediated by antibody-dependent cell-mediated cytotoxicity (ADCC).

**[0197]** In some embodiments, the fusion protein comprises a human serum albumin (HSA), or variants or fragments thereof, such as those disclosed in U.S. Pat. No. 5,876,969, WO 2011/124718, WO 2013/075066, and WO 2011/0514789. In some embodiments, the serum albumin moiety used in the fusion protein described herein, has sequence identity to the sequence of wild-type HSA as set forth in SEQ ID NO: 171. of at least 50%, such as at least 60%, at least 70%, at least 80%, at least 85%, at least 86%,

at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%.

**[0198]** In some embodiments, the fusion protein comprises a mouse serum albumin (MSA), or variants or fragments thereof. In some embodiments, the serum albumin moiety used in the fusion protein described herein, has sequence identity to the sequence of wild-type MSA as set forth in SEQ ID NO: 173. of at least 50%, such as at least 60%, at least 70%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%.

[0199] In some embodiments, the number of alternations, e.g., substitutions, insertions, or deletions in the albumin variants of the present disclosure is 1-20, e.g., 1-10, 1-5, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 alterations compared to the corresponding wild-type albumin (e.g., HSA or MSA). [0200] In addition to wild-type albumin, albumin variants are considered applicable as fusion partners with the multispecific variable regions (e.g., scFv) of the disclosure. Non-limiting examples of such variants include one or more alterations (e.g., substitutions, deletions, or insertions) in one or more positions corresponding to positions 417, 440, 464, 490, 492, 493, 494, 495, 496, 499, 500, 501, 503, 504, 505, 506, 510, 535, 536, 537, 538, 540, 541, 542, 550, 573, 574, 575, 577, 578, 579, 580, 581, 582 and 584 of HSA (SEQ ID NO: 171). In some embodiments, a variant comprises an alteration of at least one of these positions, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or all of these positions. The substitution(s) may be any substitution(s) where the amino acid in the natural albumin sequence is substituted with a different amino acid selected among the remaining 19 natural occurring amino acids, provided that the substitution(s) increases the half-life of the polypeptide it is fused or conjugated to relative to the polypeptide not fused to the variant or a polypeptide fused to the wild-type albumin. Exemplary variants with altered serum half-life and/or binding to FcRn are those that include one or more of the following amino acid substitutions in HSA (SEQ ID NO: 171), as disclosed in U.S. Published Application No. 2012-0220530: Q417A, Q417H, H440Q, H464O, A490D, E492G, E492T, E492P, E492H, V493P, V493L, D494N, D494Q, D494A, D494E, D494P, E495Q, E495A, T496A, P499A, K500E, K500G, K500A, K500S, K500C, K500P, K500H, K500F, K500N, K500W, K500T, K500M, K500Y, K500V, K500Q, K500L, K500I, K500R, E501A, E501P, E501Q, N503K, N503D, E503H, A504E, E505K, E505D, T506F, T506S, H510Q, H535Q, K536A, P537A, K538A, K538H, T540S, K541A, K541D, K541G, K541N, K541E, E542P, E542D, D550N, K573Y, K573W, K573P, K573H, K573F, K573V, K573I, K573T, K573N, K573S, K573G, K573M, K573C, K573A, K573E, K573Q, K573R, K573L, K573D, K574N, Q580K, L575F, A577T, A577E, A578R, A578S, S579C, S579T, Q580K, A581D, A582T, G584A (the contents of which are incorporated herein by reference). In particular embodiments, the variant has position 573 of HSA (SEQ ID NO: 171) substituted with proline (P), tryptophan (W), or tyrosine (Y). In some embodiments, the variant comprises multiple alterations, such as substitutions, at positions corresponding to 494 and 496; 492 and 493; 494 and 417; 492 and 503; 492 and 573 (e.g., E492G+K573P, E492G+K573A); and 492, 503, and 573 (e.g., E492G+N503H+K573P). It should be understood that variants containing any alteration (e.g., substitution, insertion, deletion) at any one of the above positions of HSA (SEQ ID NO: 171), or at any other position(s), are suitable for use in the fusion proteins described herein.

[0201] In some embodiments, the albumin variant has an increased serum half-life compared to a wild-type albumin. Albumin variants with increased serum half-life, as disclosed in WO2011/051489, include E492G, K500R, N503H, N503K, D550E, K573Y, K573W, K573P, K573H, K573F, K573V, K573I, K573T, K573N, K573S, K573G, K573M, K573C, K573A, K573E, K573Q, K573R, K573L, K573D, K574N, O580K, E492G+N503K, E492G+N503H, E492G+K573A, E492G+K573P, E492G+N503K+K573P, E492G+N503H+K573P, E492G+N503K+K573A K573P+ L575F+G584A, K573P+A578S+S579T+G584A, K573P+ A577E+A578S+Q580K+A582T, K573P+K574N+A577T+ A578R+S579C+O580K+A581D+G584A. and E492H+ E501P+N503H+E505D+T506S+T540S+K541E. It will be evident to the skilled artisan that variants with other amino acid substitutions or combinations of amino acid substitutions can be readily tested with routine methods to determine whether they exhibit increased serum half-life.

**[0202]** Some natural variants of albumin also exhibit increased serum half-life, and are suitable for use in the fusion proteins described herein. Such natural HSA variants with increased serum half-life are known in the art, such as E501K, E570K (Iwao et al. 2007, *B. B. A. Proteins and Proteomics* 1774, 1582-90), E505K (Gallino et al., supra), K536E, K574N (Minchiotti et al., *Biochim Biophys Acta* 1987:916:411-418), D550G (Takahashi et al., *PNAS* 1987: 84:4413-7), and D550A (Carlson et al., *PNAS* 1992:89: 8225-9).

[0203] In some embodiments, the variant albumin has an amino acid substitution that increases the affinity of the albumin to FcRn, which correlates with increased serum half-life. Such amino acid substitutions include, but are not limited to, HSA with K573P (i.e., lysine at position 573 substituted with a proline). Routine methods, such as surface plasmon resonance (SPR), as disclosed in WO2011/051489, can be used to determine whether a particular albumin variant exhibits increased affinity to FcRn relative to the corresponding wild-type albumin. It will be evident to the skilled artisan that increased affinity to FcRn can be determined by comparing the binding constants KD of the albumin variant and wild-type albumin. In the context of the present disclosure, variant albumins having a KD that is lower than the KD for natural HSA is considered to have a higher plasma half-life than HSA.

**[0204]** In some embodiments, it may be desirable for the variant albumin, or fragment thereof, to decrease the serum half-life of a fusion protein. Such variant albumins, or fragments thereof, may decrease the binding of the fusion proteins to FcRn relative to non-albumin fused multispecific variable regions in which albumin is the corresponding wild-type albumin. Fusion proteins with decreased serum half-lives, e.g., those with decreased FcRn binding affinity, are useful, for example, for administration to a mammal where a shortened circulation time may be advantageous, e.g., for in vivo diagnostic imaging or in situations where the starting polypeptide has toxic side effects when present in the circulation for prolonged periods. Albumin variants with decreased FcRn binding affinity are also less likely to cross the placenta and, thus, are also useful in the treatment of

diseases or disorders in pregnant women. In addition, other applications in which reduced FcRn binding affinity may be desired include those applications in which localization in the brain, kidney, and/or liver is desired. In some embodiments, the fusion proteins described herein exhibit reduced transport across the epithelium of kidney glomeruli from the vasculature. In some embodiments, the fusion proteins described herein exhibit reduced transport across the blood brain barrier (BBB) from the brain, into the vascular space. In some embodiments, a fusion protein with altered FcRn binding comprises at least one albumin domain (e.g., domain III of HSA) having one or more amino acid substitutions within the "FcRn binding region" of an albumin domain. Exemplary albumin variants that exhibit decreased serum half-life are disclosed in, e.g., WO2011/124718, and include Q417A, H464Q, D494N, D494Q, D494A, E495Q, E495A, T496A, P499A, K500E, K500G, K500D, K500A, K500S, K500C, K500P, K500H, K500F, K500N, K500W, K500T, K500M, K500Y, K500V, K500Q, K500L, K500I, K500R, D500N, E501A, E501Q, N503K, N503D, H510Q, H535Q, K536A, P537A, K541G, K541D, K541A, K541N, E492T+N503D, E492G+V493P, D494E+Q417H, E495Q+ T496A, D494N+E495Q+T496A, E492G+K538H+K541N+ E542D, E492G+V493P+K538H+K541N+E542D, A490D+ E492T+V493L+E501P+E503D+A504E+E505K+T506F+ K541D. Exemplary natural albumin variants that exhibit decreased serum half-life include D494N (Peach et al., Biochim Biophys Acta 1991; 1097:49-54), and K541E and K560E (Iwao et al., B. B. A. Proteins and Proteomics 2007; 1774:1582-90).

[0205] One or more positions of albumin, or a variant or fragment thereof, can be altered to provide reactive surface residues for, e.g., conjugation with a multispecific variable region. Exemplary positions in HSA (SEQ ID NO: 171) that can be altered to provide conjugation competent cysteine residues include, but are not limited to, those disclosed in WO2010/092135, such as, D1C, A2C, T79C, E82C, E86C, D121C, D129C, S270C, A364C, A504C, E505C, D549C, D562C, A578C, A579C, A581C, L585C, and L595C. Alternatively a cysteine residue may be added to the N or C terminus of albumin. Methods suitable for producing conjugation competent albumin, or a variant or peptide thereof, as well as covalently linking albumin, or a variant or fragment thereof, with a conjugation partner or partners (e.g., a multispecific variable region) are routine in the art and disclosed in, e.g., WO2010/092135 and WO 2009/ 019314. In some embodiments, the conjugates may conveniently be linked via a free thiol group present on the surface of HSA (amino acid residue 34 of mature HSA) using art-recognized methods.

**[0206]** In addition to the albumin or variants thereof described supra, fragments of albumin, or fragments of variants thereof, are suitable for use as the albumin component of the fusion proteins described herein. Exemplary albumin fragments that are suitable for use in the fusion proteins are disclosed in WO 2011/124718. A fragment of albumin (e.g., a fragment of HSA) will typically be at least 20 amino acids in length, such as at least 40 amino acids, at least 60 amino acids, at least 100 amino acids, at least 150 amino acids, at least 200 amino acids, or at least 500 amino acids in length, and will alter (e.g.,

increase) the serum half-life of the polypeptide it is fused to (e.g., multispecific variable region) relative to the non-fused polypeptide.

[0207] In some embodiments, a fragment may comprise at least one whole sub-domain of albumin. Domains of HSA have been expressed as recombinant proteins (Dockal et al., JBC 1999; 274:29303-10), where domain I was defined as consisting of amino acids 1-197 (SEQ ID NO: 175), domain II was defined as consisting of amino acids 189-385 (SEQ ID NO: 176), and domain III was defined as consisting of amino acids 381-585 (SEQ ID NO: 177) of HSA (SEQ ID NO: 171). Partial overlap of the domains occurs given the extended  $\alpha$ -helix structure (h10-h1) which exists between domains I and II, and between domains II and III (Peters, 1996, op. cit, Table 2-4). HSA also comprises six subdomains (sub-domains IA, IB, NA, NB, INA and NIB). Sub-domain IA comprises amino acids 6-105, sub-domain IB comprises amino acids 120-177, sub-domain NA comprises amino acids 200-291, sub-domain NB comprises amino acids 316-369, sub-domain INA comprises amino acids 392-491 and sub-domain NIB comprises amino acids 512-583 of SEQ ID NO: 171.

[0208] A fragment may comprise a whole or part of one or more domains or sub-domains as defined above, or any combination of those domains and/or sub-domains. A fragment may comprise or consist of at least 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% of an albumin or of a domain of an albumin, or a variant or fragment thereof. Additionally, single or multiple heterologous fusions comprising any of the above; or single or multiple heterologous fusions to albumin, or a variant or fragment of any of these may be used. Such fusions include albumin N-terminal fusions, albumin C-terminal fusions and co-N-terminal and C-terminal albumin fusions as exemplified by WO 01/79271. In some embodiments, the fragment of albumin or variant thereof retains the ability to bind to FcRn. In some embodiments, the fusion proteins contain domain III of albumin, or a variant thereof. In some embodiments, the fusion proteins contain domain III of albumin and an additional domain selected from the group consisting of domain I, domain II, and domain III. In some embodiments, the fusion proteins contain domains I, II, and III of albumin.

**[0209]** In certain embodiments, the fusion protein comprises a serum albumin binding protein such as those described in US2005/0287153, US2007/0003549, US2007/0178082, US2007/0269422, US2010/0113339, WO2009/083804, and WO2009/133208, which are herein incorporated by reference in their entirety.

#### Fc Fragments

**[0210]** In some embodiments, the fusion protein comprises a multispecific variable region described herein, operably coupled to an Fc domain. In some embodiments, the Fc domain comprises the amino acid sequence set forth in SEQ ID NO: 174. It will be understood by those in the art that epitope tags corresponding to 6x his tag on the fusion proteins are optional. The Fc domain does not contain a variable region that binds to antigen. Fc domains useful for producing the fusion proteins disclosed herein may be obtained from a number of different sources. In certain embodiments, an Fc domain of the fusion protein is derived from a human immunoglobulin. In certain embodiments, the Fc domain is from a human IgG1 constant region (SEQ ID NO: 172). The Fc domain of human IgG1 is set forth in SEQ

ID NO: 174. It is understood, however, that the Fc domain may be derived from an immunoglobulin of another mammalian species, including for example, a rodent (e.g. a mouse, rat, rabbit, guinea pig) or non-human primate (e.g. chimpanzee, macaque) species. Moreover, the Fc domain or portion thereof may be derived from any immunoglobulin class, including IgM, IgG, IgD, IgA, and IgE, and any immunoglobulin isotype, including IgG1, IgG2, IgG3, and IgG4.

**[0211]** In some embodiments, a fusion protein includes a mutant Fc domain. In some embodiments, a fusion protein includes a mutant, IgG1 Fc domain. In some embodiments, a mutant Fc domain comprises one or more mutations in the hinge, CH2, and/or CH3 domains. In some embodiments, a mutant Fc domain includes a D265A mutation.

[0212] A variety of Fc domain gene sequences (e.g., mouse and human constant region gene sequences) are available in the form of publicly accessible deposits. Constant region domains comprising an Fc domain sequence can be selected lacking a particular effector function and/or with a particular modification to reduce immunogenicity. Many sequences of antibodies and antibody-encoding genes have been published and suitable Fc domain sequences (e.g. hinge, CH2, and/or CH3 sequences, or portions thereof) can be derived from these sequences using art recognized techniques. The genetic material obtained using any of the foregoing methods may then be altered or synthesized to obtain polypeptides suitable for use in the methods disclosed herein. It will further be appreciated that the scope of this invention encompasses alleles, variants and mutations of constant region DNA sequences.

[0213] Fc domain sequences can be cloned, e.g., using the polymerase chain reaction and primers which are selected to amplify the domain of interest. To clone an Fc domain sequence from an antibody, mRNA can be isolated from hybridoma, spleen, or lymph cells, reverse transcribed into DNA, and antibody genes amplified by PCR. PCR amplification methods are described in detail in U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; 4,965,188; and in, e.g., "PCR Protocols: A Guide to Methods and Applications" Innis et al. eds., Academic Press, San Diego, Calif. (1990); Ho et al. 1989. Gene 77:51; Horton et al. 1993. Methods Enzymol. 217:270). PCR may be initiated by consensus constant region primers or by more specific primers based on the published heavy and light chain DNA and amino acid sequences. As discussed above, PCR also may be used to isolate DNA clones encoding the antibody light and heavy chains. In this case the libraries may be screened by consensus primers or larger homologous probes, such as mouse constant region probes. Numerous primer sets suitable for amplification of antibody genes are known in the art (e.g., 5' primers based on the N-terminal sequence of purified antibodies (Benhar and Pastan. 1994. Protein Engineering 7: 1509); rapid amplification of cDNA ends (Ruberti, F. et al. 1994. J. Immunol. Methods 173:33); antibody leader sequences (Larrick et al. Biochem Biophys Res Commun 1989; 160: 1250). The cloning of antibody sequences is further described in Newman et al., U.S. Pat. No. 5,658,570, filed Jan. 25, 1995, which is herein incorporated by reference.

**[0214]** Fusion proteins disclosed herein may comprise one or more Fc domains (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more Fc domains). In certain embodiments, the Fc domains may be of different types. In certain embodiments, at least one Fc

domain present in the fusion protein comprises a hinge domain or portion thereof. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain which comprises at least one CH2 domain or portion thereof. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain which comprises at least one CH3 domain or portion thereof. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain which comprises at least one CH4 domain or portion thereof. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain which comprises at least one hinge domain or portion thereof and at least one CH2 domain or portion thereof (e.g, in the hinge-CH2 orientation). In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain which comprises at least one CH2 domain or portion thereof and at least one CH3 domain or portion thereof (e.g., in the CH2-CH3 orientation). In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprising at least one hinge domain or portion thereof, at least one CH2 domain or portion thereof, and least one CH3 domain or portion thereof, for example in the orientation hinge-CH2-CH3, hinge-CH3-CH2, or CH2-CH3-hinge.

**[0215]** In certain embodiments, the fusion protein comprises at least one complete Fc region derived from one or more immunoglobulin heavy chains (e.g., an Fc domain including hinge, CH2, and CH3 domains, although these need not be derived from the same antibody). In certain embodiments, the fusion protein comprises at least two complete Fc domains derived from one or more immunoglobulin heavy chains. In certain embodiments, the complete Fc domain is derived from a human IgG immunoglobulin heavy chain (e.g., human IgG1).

**[0216]** In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprising a complete CH3 domain. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprising a complete CH2 domain. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprising at least a CH3 domain, and at least one of a hinge region, and a CH2 domain. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprising a hinge and a CH3 domain. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprising a hinge and a CH3 domain. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain comprises at least one Fc domain comprises at least one Fc domain is derived from a human IgG immunoglobulin heavy chain (e.g., human IgG1).

**[0217]** The constant region domains or portions thereof making up an Fc domain of the fusion protein disclosed herein may be derived from different immunoglobulin molecules. For example, a fusion protein disclosed herein may comprise a CH2 domain or portion thereof derived from an IgG1 molecule and a CH3 region or portion thereof derived from an IgG3 molecule. In another example, the fusion protein comprises an Fc domain comprising a hinge domain derived, in part, from an IgG1 molecule and, in part, from an IgG3 molecule. As set forth herein, it will be understood by one of ordinary skill in the art that an Fc domain may be altered such that it varies in amino acid sequence from a naturally occurring antibody molecule.

**[0218]** In certain embodiments, the fusion protein disclosed herein lacks one or more constant region domains of a complete Fc region, i.e., they are partially or entirely deleted. In certain embodiments, the fusion protein disclosed herein will lack an entire CH2 domain. In certain embodiments, the fusion protein disclosed herein comprise CH2 domain-deleted Fc regions derived from a vector (e.g., from IDEC Pharmaceuticals, San Diego) encoding an IgG1 human constant region domain (see, e.g., WO02/060955A2 and WO02/096948A2). This exemplary vector is engineered to delete the CH2 domain and provide a synthetic vector expressing a domain-deleted IgG1 constant region. It will be noted that these exemplary constructs are preferably engineered to fuse a binding CH3 domain directly to a hinge region of the respective Fc domain.

**[0219]** In other constructs it may be desirable to provide a peptide spacer between one or more constituent Fc domains. For example, a peptide spacer may be placed between a hinge region and a CH2 domain and/or between a CH2 and a CH3 domain. For example, compatible constructs could be expressed wherein the CH2 domain has been deleted and the remaining CH3 domain (synthetic or unsynthetic) is joined to the hinge region with a 1-20, 1-10, or 1-5 amino acid peptide spacer. Such a peptide spacer may be added, for instance, to ensure that the regulatory elements of the constant region domain remain free and accessible or that the hinge region remains flexible. Preferably, any linker peptide compatible used in the instant invention will be relatively non-immunogenic and not prevent proper folding of the Fc.

#### Modified Fc Domains

**[0220]** In certain embodiments, an Fc domain employed in the fusion protein disclosed herein is altered or modified, e.g., by amino acid mutation (e.g., addition, deletion, or substitution). As used herein, the term "Fc domain variant" refers to an Fc domain having at least one amino acid modification, such as an amino acid substitution, as compared to the wild-type Fc from which the Fc domain is derived. For example, wherein the Fc domain is derived from a human IgG1 antibody, a variant comprises at least one amino acid mutation (e.g., substitution) as compared to a wild type amino acid at the corresponding position of the human IgG1 Fc region.

**[0221]** In certain embodiments, the Fc variant comprises a substitution at an amino acid position located in a hinge domain or portion thereof. In certain embodiments, the Fc variant comprises a substitution at an amino acid position located in a CH2 domain or portion thereof. In certain embodiments, the Fc variant comprises a substitution at an amino acid position located in a CH3 domain or portion thereof. In certain embodiments, the Fc variant comprises a substitution at an amino acid position located in a CH3 domain or portion thereof. In certain embodiments, the Fc variant comprises a substitution at an amino acid position located in a CH3 domain or portion thereof.

**[0222]** In certain embodiments, the fusion protein disclosed herein comprises an Fc variant comprising more than one amino acid substitution. The fusion protein disclosed herein may comprise, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid substitutions. Preferably, the amino acid substitutions are spatially positioned from each other by an interval of at least 1 amino acid position or more, for example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid positions or more. More preferably, the engineered amino acids are spatially positioned apart from each other by an interval of at least 5, 10, 15, 20, or 25 amino acid positions or more.

[0223] In some embodiments, an Fc domain includes changes in the region between amino acids 234-238, including the sequence LLGGP at the beginning of the CH2 domain. In some embodiments, an Fc variant alters Fc mediated effector function, particularly ADCC, and/or decrease binding avidity for Fc receptors. In some aspects, sequence changes closer to the CH2-CH3 junction, at positions such as K322 or P331 can eliminate complement mediated cytotoxicity and/or alter avidity for FcR binding. In some embodiments, an Fc domain incorporates changes at residues P238 and P331, e.g., changing the wild type prolines at these positions to serine. In some embodiments, alterations in the hinge region at one or more of the three hinge cysteines, to encode CCC, SCC, SSC, SCS, or SSS at these residues can also affect FcR binding and molecular homogeneity, e.g., by elimination of unpaired cysteines that may destabilize the folded protein.

[0224] Other amino acid mutations in the Fc domain are contemplated to reduce binding to the Fc gamma receptor and Fc gamma receptor subtypes. For example, mutations at positions 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 279, 280, 283, 285, 298, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 312, 315, 322, 324, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 356, 360, 373, 376, 378, 379, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439 of the Fc region can alter binding as described in U.S. Pat. No. 6,737,056, issued May 18, 2004, incorporated herein by reference in its entirety. This patent reported that changing Pro331 in IgG3 to Ser resulted in six fold lower affinity as compared to unmutated IgG3, indicating the involvement of Pro331 in Fc gamma RI binding. In addition, amino acid modifications at positions 234, 235, 236, and 237, 297, 318, 320 and 322 are disclosed as potentially altering receptor binding affinity in U.S. Pat. No. 5,624,821, issued Apr. 29, 1997 and incorporated herein by reference in its entirety.

[0225] Further mutations contemplated for use include, e.g., those described in U.S. Pat. App. Pub. No. 2006/ 0235208, published Oct. 19, 2006 and incorporated herein by reference in its entirety. This publication describes Fc variants that exhibit reduced binding to Fc gamma receptors, reduced antibody dependent cell-mediated cytotoxicity, or reduced complement dependent cytotoxicity, that comprise at least one amino acid modification in the Fc region. including 232G, 234G, 234H, 235D, 235G, 235H, 2361, 236N, 236P, 236R, 237K, 237L, 237N, 237P, 238K, 239R, 265G, 267R, 269R, 270H, 297S, 299A, 299I, 299V, 325A, 325L, 327R, 328R, 329K, 3301, 330L, 330N, 330P, 330R, and 331L (numbering is according to the EU index), as well as double mutants 236R/237K, 236R/325L, 236R/328R, 237K/325L, 237K/328R, 325L/328R, 235G/236R, 267R/ 269R, 234G/235G, 236R/237K/325L, 236R/325L/328R, 235G/236R/237K, and 237K/325L/328R. Other mutations contemplated for use as described in this publication include 227G, 234D, 234E, 234G, 234I, 234Y, 235D, 235I, 235S, 236S, 239D, 246H, 255Y, 258H, 260H, 2641, 267D, 267E, 268D, 268E, 272H, 272I, 272R, 281D, 282G, 283H, 284E, 293R, 295E, 304T, 324G, 324I, 327D, 327A, 328A, 328D, 328E, 328F, 328I, 328M, 328N, 328Q, 328T, 328V, 328Y, 3301, 330L, 330Y, 332D, 332E, 335D, an insertion of G between positions 235 and 236, an insertion of A between positions 235 and 236, an insertion of S between positions 235 and 236, an insertion of T between positions 235 and 236, an insertion of N between positions 235 and 236, an

insertion of D between positions 235 and 236, an insertion of V between positions 235 and 236, an insertion of L between positions 235 and 236, an insertion of G between positions 235 and 236, an insertion of A between positions 235 and 236, an insertion of S between positions 235 and 236, an insertion of T between positions 235 and 236, an insertion of N between positions 235 and 236, an insertion of D between positions 235 and 236, an insertion of V between positions 235 and 236, an insertion of L between positions 235 and 236, an insertion of G between positions 297 and 298, an insertion of A between positions 297 and 298, an insertion of S between positions 297 and 298, an insertion of D between positions 297 and 298, an insertion of G between positions 326 and 327, an insertion of A between positions 326 and 327, an insertion of T between positions 326 and 327, an insertion of D between positions 326 and 327, and an insertion of E between positions 326 and 327 (numbering is according to the EU index). Additionally, mutations described in U.S. Pat. App. Pub. No. 2006/0235208 include 227G/332E, 234D/332E, 234E/332E, 234Y/332E, 234I 332E, 234G/332E, 235I/332E, 2358/ 332E, 235D/332E, 235E/332E, 236S/332E, 236A/332E, 236S/332D, 236A/332D, 239D/268E, 246H/332E, 255Y/ 332E, 258H/332E, 260H/332E, 264I 332E, 267E/332E, 267D/332E, 268D/332D, 268E/332D, 268E/332E, 268D/ 332E, 268E/330Y, 268D/330Y, 272R/332E, 272H/332E, 283H/332E, 284E/332E, 293R/332E, 295E/332E, 304T/ 332E, 324I 332E, 324G/332E, 324I/332D, 324G/332D, 327D/332E, 328A/332E, 328T/332E, 328V/332E, 328I 332E, 328F/332E, 328Y/332E, 328M/332E, 328D/332E, 328E/332E, 328N/332E, 328Q/332E, 328A/332D, 328T/ 332D, 328V/332D, 328I 332D, 328F/332D, 328Y/332D, 328M/332D, 328D/332D, 328E/332D, 328N/332D, 328Q/ 332D, 330L/332E, 330Y/332E, 330I 332E, 332D/330Y, 335D/332E, 239D/332E, 239D/332E/330Y, 239D/332E/ 330L, 239D/332E/330I, 239D/332E/268E, 239D/332E/ 268D, 239D/332E/327D, 239D/332E/284E, 239D/268E/ 330Y, 239D/332E/268E/330Y, 239D/332E/327A, 239D/ 332E/268E/327A, 239D/332E/330Y/327A, 332E/330Y/268 E/327A, 239D/332E/268E/330Y/327A, Insert G>297-298/ 332E, Insert A>297-298/332E, Insert S>297-298/332E, Insert D>297-298/332E, Insert G>326-327/332E, Insert A>326-327/332E, Insert T>326-327/332E, Insert D>326-327/332E, Insert E>326-327/332E, Insert G>235-236/332E, Insert A>235-236/332E, Insert S>235-236/332E, Insert T>235-236/332E, Insert N>235-236/332E, Insert D>235-236/332E, Insert V>235-236/332E, Insert L>235-236/332E, Insert G>235-236/332D, Insert A>235-236/332D, Insert S>235-236/332D, Insert T>235-236/332D, Insert N>235-236/332D, Insert D>235-236/332D, Insert V>235-236/ 332D, and Insert L>235-236/332D (numbering according to the EU index) are contemplated for use. The mutant L234A/ L235A is described, e.g., in U.S. Pat. App. Pub. No. 2003/ 0108548, published Jun. 12, 2003 and incorporated herein by reference in its entirety. In embodiments, the described modifications are included either individually or in combination. In certain embodiments, the mutation is D265A in human IgG1.

**[0226]** In certain embodiments, the fusion protein disclosed herein comprises an amino acid substitution to an Fc domain which alters antigen-independent effector functions of the polypeptide, in particular the circulating half-life of the polypeptide. **[0227]** In certain embodiments, the fusion protein disclosed herein comprises an Fc variant comprising an amino acid substitution which alters the antigen-dependent effector functions of the polypeptide, in particular ADCC or complement activation, e.g., as compared to a wild type Fc region. Such fusion proteins exhibit decreased binding to FcR gamma when compared to wild-type polypeptides and, therefore, mediate reduced effector function. Fc variants with decreased FcR gamma binding affinity are expected to reduce effector function, and such molecules are also useful, for example, for treatment of conditions in which target cell destruction is undesirable, e.g., where normal cells may express target molecules, or where chronic administration of the polypeptide might result in unwanted immune system activation.

**[0228]** In certain embodiments, the fusion protein exhibits altered binding to an activating Fc $\gamma$ R (e.g. Fc $\gamma$ I, Fc $\gamma$ IIa, or Fc $\gamma$ RIIIa). In certain embodiments, the fusion protein exhibits altered binding affinity to an inhibitory Fc $\gamma$ R (e.g. Fc $\gamma$ RIIb). Exemplary amino acid substitutions which altered FcR or complement binding activity are disclosed in International PCT Publication No. WO05/063815 which is incorporated by reference herein.

[0229] The fusion protein disclosed herein may also comprise an amino acid substitution which alters the glycosylation of the fusion protein. For example, the Fc domain of the fusion protein may comprise an Fc domain having a mutation leading to reduced glycosylation (e.g., N- or O-linked glycosylation) or may comprise an altered glycoform of the wild-type Fc domain (e.g., a low fucose or fucose-free glycan). In certain embodiments, the fusion protein has an amino acid substitution near or within a glycosylation motif, for example, an N-linked glycosylation motif that contains the amino acid sequence NXT or NXS. Exemplary amino acid substitutions which reduce or alter glycosylation are disclosed in WO05/018572 and US2007/ 0111281, the contents of which are incorporated by reference herein. In certain embodiments, the fusion protein disclosed herein comprises at least one Fc domain having engineered cysteine residue or analog thereof which is located at the solvent-exposed surface. In certain embodiments, the fusion protein disclosed herein comprise an Fc domain comprising at least one engineered free cysteine residue or analog thereof that is substantially free of disulfide bonding with a second cysteine residue. Any of the above engineered cysteine residues or analogs thereof may subsequently be conjugated to a functional domain using art-recognized techniques (e.g., conjugated with a thiolreactive heterobifunctional linker).

**[0230]** In certain embodiments, the fusion protein disclosed herein may comprise a genetically fused Fc domain having two or more of its constituent Fc domains independently selected from the Fc domains described herein. In certain embodiments, the Fc domains are the same. In certain embodiments, at least two of the Fc domains are different. For example, the Fc domains of the fusion protein disclosed herein comprise the same number of amino acid residues or they may differ in length by one or more amino acid residues (e.g., by about 5 amino acid residues, about 10 residues, about 15 residues, about 20 residues, about 30 residues, about 40 residues, or about 50 residues). In certain embodiments, the Fc domains of the fusion protein disclosed herein may differ in sequence at one or more amino acid positions. For

example, at least two of the Fc domains may differ at about 5 amino acid positions (e.g., 1, 2, 3, 4, or 5 amino acid positions), about 10 positions, about 15 positions, about 20 positions, about 30 positions, about 40 positions, or about 50 positions).

#### Polyethylene Glycol (PEG)

**[0231]** In certain embodiments, a fusion protein disclosed herein comprises a polyethylene glycol (PEG) domain. PEGylation is well known in the art to confer increased circulation half-life to proteins. Methods of PEGylation are well known and disclosed in, e.g., U.S. Pat. Nos. 7,610,156, 7,847,062, all of which are hereby incorporated by reference.

[0232] PEG is a well-known, water soluble polymer that is commercially available or can be prepared by ring-opening polymerization of ethylene glycol according to methods well known in the art (Sandler and Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, pages 138-161). The term "PEG" is used broadly to encompass any polyethylene glycol molecule, without regard to size or to modification at an end of the PEG, and can be represented by the formula:  $X-0(CH_2CH_20)_{n-1}CH_2CH_2OH$ , where n is 20 to 2300 and X is H or a terminal modification, e.g., a C<sub>1-4</sub> alkyl. In certain embodiments, the PEG suitable for use in the methods disclosed herein terminates on one end with hydroxy or methoxy, i.e., X is H or CH3 ("methoxy PEG"). PEG can contain further chemical groups which are necessary for binding reactions; which results from the chemical synthesis of the molecule; or which is a spacer for optimal distance of parts of the molecule. In addition, such a PEG can consist of one or more PEG side-chains which are linked together. PEGs with more than one PEG chain are called multiarmed or branched PEGs. Branched PEGs can be prepared, for example, by the addition of polyethylene oxide to various polyols, including glycerol, pentaerythriol, and sorbitol. For example, a four-armed branched PEG can be prepared from pentaerythriol and ethylene oxide. Branched PEG are described in, for example, EP-A 0 473 084 and U.S. Pat. No. 5,932,462, both of which are hereby incorporated by reference. One form of PEGs includes two PEG side-chains (PEG2) linked via the primary amino groups of a lysine (Monfardini et al., Bioconjugate Chem 1995; 6:62-9).

[0233] In certain embodiments, the fusion protein comprising PEG is produced by site-directed pegylation, particularly by conjugation of PEG to a cysteine moiety at the N- or C-terminus. A PEG moiety may also be attached by other chemistry, including by conjugation to amines. PEG conjugation to peptides or proteins generally involves the activation of PEG and coupling of the activated PEGintermediates directly to target proteins/peptides or to a linker, which is subsequently activated and coupled to target proteins/peptides (see Abuchowski et al., JBC 1977; 252: 3571 and JBC 1977; 252:3582, and Harris et. al., in: Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications; (J. M. Harris ed.) Plenum Press: New York, 1992; Chap. 21 and 22). A variety of molecular mass forms of PEG can be selected, e.g., from about 1,000 Daltons (Da) to 100,000 Da (n is 20 to 2300), for conjugating to the variable region. The number of repeating units "n" in the PEG is approximated for the molecular mass described in Daltons. It is preferred that the combined molecular mass of PEG on an activated linker is suitable for pharmaceutical use. Thus, in one embodiment, the molecular mass of the PEG molecules does not exceed 100,000 Da. For example, if three PEG molecules are attached to a linker, where each PEG molecule has the same molecular mass of 12,000 Da (each n is about 270), then the total molecular mass of PEG on the linker is about 36,000 Da (total n is about 820). The molecular masses of the PEG attached to the linker can also be different, e.g., of three molecules on a linker two PEG molecules can be 5,000 Da each (each n is about 110) and one PEG molecule can be 12,000 Da (n is about 270).

[0234] One skilled in the art can select a suitable molecular mass for PEG, e.g., based on how the fusion protein comprising PEG will be used therapeutically, the desired dosage, circulation time, resistance to proteolysis, immunogenicity, and other considerations. For a discussion of PEG and its use to enhance the properties of proteins, see N. V. Katre, Advanced Drug Delivery Reviews 1993; 10:91-114. [0235] In certain embodiments, PEG molecules may be activated to react with amino groups on the variable region, such as with lysines (Bencham C. O. et al., Anal. Biochem., 131, 25 (1983); Veronese, F. M. et al., Appl. Biochem., 11, 141 (1985); Zalipsky, S. et al., Polymeric Drugs and Drug Delivery Systems, adrs 9-110 ACS Symposium Series 469 (1999); Zalipsky, S. et al., Europ. Polym. J., 19, 1177-1183 (1983); Delgado, C. et al., Biotechnology and Applied Biochemistry, 12, 119-128 (1990)).

[0236] In certain embodiments, carbonate esters of PEG are used to form the fusion protein. N,N'-disuccinimidylcarbonate (DSC) may be used in the reaction with PEG to form active mixed PEG-succinimidyl carbonate that may be subsequently reacted with a nucleophilic group of a linker or an amino group of the variable region (see U.S. Pat. Nos. 5,281,698 and 5,932,462). In a similar type of reaction, 1,1'-(dibenzotriazolyl)carbonate and di-(2-pyridyl)carbonate may be reacted with PEG to form PEG-benzotriazolyl and PEG-pyridyl mixed carbonate (U.S. Pat. No. 5,382, 657), respectively. Generation of a fusion protein comprising PEG can be performed according to the methods of the state of the art, for example by reaction of the variable region with electrophilically active PEGs (Shearwater Corp., USA, www.shearwatercorp.com). Preferred PEG reagents suitable for use in the methods disclosed herein are, e.g., N-hydroxysuccinimidyl propionates (PEG-SPA), butanoates (PEG-SBA), PEG-succinimidyl propionate or branched N-hydroxysuccinimides such as mPEG2-NHS (Monfardini, C, et al., Bioconjugate Chem. 6 (1995) 62-69).

**[0237]** In certain embodiments, PEG molecules may be coupled to sulfhydryl groups on the variable region (Sartore, L., et al., Appl. Biochem. Biotechnol., 27, 45 (1991); Morpurgo et al., Biocon. Chem., 7, 363-368 (1996); Goodson et al., Bio/Technology (1990) 8, 343; U.S. Pat. No. 5,766,897). U.S. Pat. Nos. 6,610,281 and 5,766,897 describe exemplary reactive PEG species that may be coupled to sulfhydryl groups.

**[0238]** In certain embodiments where PEG molecules are conjugated to cysteine residues native to the variable region, whereas in certain embodiments, one or more cysteine residues are engineered into the variable region. Mutations may be introduced into the coding sequence of the variable region to generate cysteine residues. This might be achieved, for example, by mutating one or more amino acid residues to cysteine. Preferred amino acids for mutating to a cysteine residue include serine, threonine, alanine and other hydrophilic residues. Preferably, the residue to be mutated to

cysteine is a surface-exposed residue. Algorithms are wellknown in the art for predicting surface accessibility of residues based on primary sequence or a protein.

**[0239]** In certain embodiments, the fusion protein comprising PEG comprises one or more PEG molecules covalently attached to a linker.

[0240] In certain embodiments, the variable region is pegylated at the C-terminus. In certain embodiments, a protein is pegylated at the C-terminus by the introduction of C-terminal azido-methionine and the subsequent conjugation of a methyl-PEG-triarylphosphine compound via the Staudinger reaction. This C-terminal conjugation method is described in Cazalis et al., C-Terminal Site-Specific PEGylation of a Truncated Thrombomodulin Mutant with Retention of Full Bioactivity, Bioconjug Chem. 2004; 15(5): 1005-1009. Monopegylation of the variable region can also be achieved according to the general methods described in WO 94/01451. WO 94/01451 describes a method for preparing a recombinant polypeptide with a modified terminal amino acid alpha-carbon reactive group. The steps of the method involve forming the recombinant polypeptide and protecting it with one or more biologically added protecting groups at the N-terminal alpha-amine and C-terminal alphacarboxyl. The polypeptide can then be reacted with chemical protecting agents to selectively protect reactive side chain groups and thereby prevent side chain groups from being modified. The polypeptide is then cleaved with a cleavage reagent specific for the biological protecting group to form an unprotected terminal amino acid alpha-carbon reactive group. The unprotected terminal amino acid alpha-carbon reactive group is modified with a chemical modifying agent. The side chain protected terminally modified single copy polypeptide is then deprotected at the side chain groups to form a terminally modified recombinant single copy polypeptide. The number and sequence of steps in the method can be varied to achieve selective modification at the Nand/or C-terminal amino acid of the polypeptide.

**[0241]** The ratio of variable region to activated PEG in the conjugation reaction can be from about 1:0.5 to 1:50, between from about 1:1 to 1:30, or from about 1:5 to 1:15. Various aqueous buffers can be used to catalyze the covalent addition of PEG to the variable region, or variants thereof. In certain embodiments, the pH of a buffer used is from about 7.0 to 9.0. In certain embodiments, the pH is in a slightly basic range, e.g., from about 7.5 to 8.5. Buffers having a pKa close to neutral pH range may be used, e.g., phosphate buffer.

**[0242]** Conventional separation and purification techniques known in the art can be used to purify the fusion protein comprising PEG, such as size exclusion (e.g. gel filtration) and ion exchange chromatography. Products may also be separated using SDS-PAGE. Products that may be separated include mono-, di-, tri- poly- and un-pegylated variable regions as well as free PEG. The percentage of mono-PEG conjugates can be controlled by pooling broader fractions around the elution peak to increase the percentage of mono-PEG in the composition.

**[0243]** In certain embodiments, the fusion protein comprising PEG contains one, two or more PEG moieties. In certain embodiments, the PEG moiety(ies) are bound to an amino acid residue which is on the surface of the protein and/or away from the surface that contacts the chemokine of interest. In certain embodiments, the combined or total molecular mass of PEG in the fusion protein comprising PEG is from about 3,000 Da to 60,000 Da, optionally from about 10,000 Da to 36,000 Da. In certain embodiments, PEG of the fusion protein is a substantially linear, straight-chain PEG.

[0244] In certain embodiments, the fusion protein comprising PEG will preferably retain at least 25%, 50%, 60%, 70%, 80%, 85%, 90%, 95% or 100% of the biological activity associated with the unmodified protein. In certain embodiments, biological activity refers to the ability to bind the chemokine(s) of interest. The serum clearance rate of the fusion protein comprising PEG may be decreased by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or even 90%, relative to the clearance rate of the variable region alone. The fusion protein comprising PEG may have a circulation half-life  $(t^{\hat{}})$  which is enhanced relative to the half-life of the variable region alone. The half-life of the fusion protein comprising PEG, or variants thereof, may be enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400% or 500%, or even by 1000% relative to the half-life of the variable region alone. In certain embodiments, the protein half-life is determined in vitro, such as in a buffered saline solution or in serum. In certain embodiments, the protein half-life is an in vivo circulation half-life, such as the half-life of the protein in the serum or other bodily fluid of an animal.

#### Other Polymers

**[0245]** In certain embodiments, the fusion protein comprises transferrin, as disclosed in U.S. Pat. Nos. 7,176,278 and 8,158,579, which are herein incorporated by reference in their entirety.

**[0246]** In certain embodiments, the fusion protein comprises a serum immunoglobulin binding protein such as those disclosed in US2007/0178082, which is herein incorporated by reference in its entirety.

**[0247]** In certain embodiments, the fusion protein comprises a fibronectin (Fn)-based scaffold domain protein that binds to serum albumin, such as those disclosed in US2012/0094909, which is herein incorporated by reference in its entirety. Methods of making fibronectin-based scaffold domain proteins are also disclosed in US2012/0094909. A non-limiting example of a Fn3-based extended-PK group is Fn3(HSA), i.e., a Fn3 protein that binds to human serum albumin.

**[0248]** In some embodiments, the fusion protein comprises an XTEN moiety. An XTEN moiety comprises amino acid residues A, E, G, P, S and T. In some embodiments, an XTEN moiety ranges from 36 to 288 amino acid residues in length. Exemplary XTEN moieties are described in WO 2011/123830; Schellenberger V. et al., *Nat Biotechnol*. Vol. 27: 1186-90 (2009); and Geething N C. Et al *PLos One Vol*. 5: e10175 (2010), each of which is herein incorporated by reference in its entirety.

**[0249]** In some embodiments, the fusion protein comprises an ELP moiety. An ELP moiety is a repeating peptide unit containing sequences commonly found in elastin. The ELP sequence contains repeats of V-P-G-x-G, wherein x is any amino acid except proline. ELP moieties can be degraded over time by human elastases, thereby making them biologically degradable. Examples of ELP moieties are described in, Floss, D M. et al *Trends Biotechnol. Vol.* 26:

489-501 (2013); and Floss, D M. et al, Hoboken: Wiley, p. 372-98 (2013), each of which is herein incorporated by reference.

**[0250]** In some embodiments, the fusion protein comprises a polymer of repeating amino acids proline, alanine and serine (i.e., PAS moiety). In some embodiments, a PAS moiety comprise 100-20 repeats in length. Exemplary PAS moieties are described in Huang, C. *Curr Opin Biotechnol Vol.* 20: 692-9 (2009), herein incorporated by reference.

#### Linkers

**[0251]** In some embodiments, the multispecific variable region is operably coupled to a polymer (e.g., serum albumin) via a linker. In some embodiments, the fusion protein includes a plurality of linker domains. In some embodiments, the linker domain is a polypeptide linker. In some embodiments, it is desirable to employ a polypeptide linker to fuse a polymer (e.g., serum albumin) with a multispecific variable region to form a fusion protein described herein.

**[0252]** In some embodiments, the fusion proteins employ a polypeptide linker to join any two or more domains in frame in a single polypeptide chain. In some embodiments, the two or more domains may be independently selected from any of the polymers (e.g., serum albumin), or variants or fragments thereof, or multispecific variable regions discussed herein.

[0253] Linkers suitable for fusing the multispecific variable region to the polymer (e.g., serum albumin) are well known in the art, and are disclosed in, e.g., US2010/0210511 US2010/0179094, and US2012/0094909, which are herein incorporated by reference in its entirety. Exemplary linkers include gly- ser polypeptide linkers, glycine-proline polypeptide linkers, and proline-alanine polypeptide linkers, the Fc interlinker from human IgG1  $C_{H2}$  residues 297-322: NSTYRVVSVLTVLHQDWLNGKEYKCK, and the HSA interlinker from the D3 domain of human serum albumin: FQNALLVRYTKKVPQVSTPTLVEVS. See Fang et al., Chines. Sci. Bull., 2003, 48:1912-1918, incorporated by reference in its entirety. Other linkers are provided, for example, in U.S. Pat. Nos. 5,525,491; Alfthan et al., Protein Eng., 1995, 8:725-731; Shan et al., J. Immunol., 1999, 162:6589-6595; Newton et al., Biochemistry, 1996, 35:545-553: Megeed et al.: Biomacromolecules, 2006, 7:999-1004: and Perisic et al., Structure, 1994, 12:1217-1226; each of which is incorporated by reference in its entirety. In certain embodiments, the linker is a gly-ser polypeptide linker, i.e., a peptide that consists of glycine and serine residues.

[0254] Exemplary gly-ser polypeptide linkers comprise the amino acid sequence Ser(Gly<sub>4</sub>Ser)n. In certain embodiments, n=1. In certain embodiments, n=2. In certain embodiments, n=3, i.e., Ser(Gly<sub>4</sub>Ser)3. In certain embodiments, n=4, i.e., Ser(Gly<sub>4</sub>Ser)4. In certain embodiments, n=5. In certain embodiments, n=6. In certain embodiments, n=7. In certain embodiments, n=8. In certain embodiments, n=9. In certain embodiments, n=10. Another exemplary gly-ser polypeptide linker comprises the amino acid sequence Ser (Gly<sub>4</sub>Ser)n. In certain embodiments, n=1. In certain embodiments, n=2. In certain embodiments, n=3. In certain embodiments, n=4. In certain embodiments, n=5. certain embodiments, n=6. Another exemplary gly-ser polypeptide linker comprises (Gly<sub>3</sub>Ser)n. In certain embodiments, n=1. In certain embodiments, n=2. In certain embodiments, n=3. In certain embodiments, n=4. In certain embodiments, n=5. In certain embodiments n=6.

[0255] In some embodiments, the polypeptide linker is synthetic. As used herein, the term "synthetic" with respect to a polypeptide linker includes peptides (or polypeptides) which comprise an amino acid sequence (which may or may not be naturally occurring) that is linked in a linear sequence of amino acids to a sequence (which may or may not be naturally occurring) to which it is not naturally linked in nature. For example, the polypeptide linker may comprise non-naturally occurring polypeptides which are modified forms of naturally occurring polypeptides (e.g., comprising a mutation such as an addition, substitution or deletion) or which comprise a first amino acid sequence (which may or may not be naturally occurring). Polypeptide linkers may be employed, for instance, to ensure that the variable region, or a variant or fragment thereof, is juxtaposed to ensure proper folding and formation of a functional variable region, or a variant or fragment thereof. Polypeptide linkers may be employed, for instance, to ensure that the polymer (e.g., serum albumin moiety), or a variant or fragment thereof, is juxtaposed to ensure proper folding and formation of a functional polymer (e.g., serum albumin moiety), or a variant or fragment thereof. Preferably, a polypeptide linker will be relatively non-immunogenic and not inhibit any noncovalent association among monomer subunits of a binding protein.

**[0256]** In certain embodiments, the fusion protein comprising a multispecific variable region and a polymer employs a polypeptide linker to join any two or more domains in frame in a single polypeptide chain.

**[0257]** Other linkers that are suitable for use in a fusion protein are known in the art, for example, the serine-rich linkers disclosed in U.S. Pat. No. 5,525,491, the helix forming peptide linkers (e.g., A(EAAAK)nA (n=2-5)) disclosed in Arai et al. (*Protein Eng* 2001; 14:529-32), and the stable linkers disclosed in Chen et al. (*Mol Pharm* 2011; 8:457-65), i.e., the dipeptide linker LE, a thrombin-sensitive disulfide cyclopeptide linker, and the alpha-helix forming linker LEA(EAAAK)4ALEA(EAAAK)4ALE.

[0258] In some embodiments, a polypeptide linker for use in the fusion protein described herein, comprises a biologically relevant peptide sequence or a sequence portion thereof. For example, a biologically relevant peptide sequence may include, but is not limited to, sequences derived from an anti-rejection or anti-inflammatory peptide. Said anti-rejection or anti-inflammatory peptides may be selected from the group consisting of a cytokine inhibitory peptide, a cell adhesion inhibitory peptide, a thrombin inhibitory peptide, and a platelet inhibitory peptide. In some embodiments, a polypeptide linker comprises a peptide sequence selected from the group consisting of an IL-1 inhibitory or antagonist peptide sequence, an erythropoietin (EPO)-mimetic peptide sequence, a thrombopoietin (TPO)mimetic peptide sequence, G-CSF mimetic peptide sequence, a TNF-antagonist peptide sequence, an integrinbinding peptide sequence, a selectin antagonist peptide sequence, an anti-pathogenic peptide sequence, a vasoactive intestinal peptide (VIP) mimetic peptide sequence, a calmodulin antagonist peptide sequence, a mast cell antagonist, a SH3 antagonist peptide sequence, an urokinase receptor (UKR) antagonist peptide sequence, a somatostatin or cortistatin mimetic peptide sequence, and a macrophage and/or T-cell inhibiting peptide sequence. Exemplary peptide sequences, any one of which may be employed as a polypeptide linker, are disclosed in U.S. Pat. No. 6,660,843, which is incorporated by reference herein.

**[0259]** Other exemplary linkers include GS linkers (i.e., (GS)n), GGSG linkers (i.e., (GGSG)n), GSAT linkers, SEG linkers, and GGS linkers (i.e., (GGSGGS)n), wherein n is a positive integer (e.g., 1, 2, 3, 4, or 5). Other suitable linkers for use in fusion proteins can be found using publicly available databases, such as the Linker Database (ibi.vu.nl/ programs/linkerdbwww). The Linker Database is a database of inter-domain linkers in multi-functional enzymes which serve as potential linkers in novel fusion proteins (see, e.g., George et al., *Protein Engineering* 2002; 15:871-9).

[0260] It will be understood that variant forms of these exemplary polypeptide linkers can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence encoding a polypeptide linker such that one or more amino acid substitutions, additions or deletions are introduced into the polypeptide linker. Mutations may be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. [0261] Polypeptide linkers are at least one amino acid in length and can be of varying lengths. In one embodiment, a polypeptide linker is from about 1 to about 50 amino acids in length. As used in this context, the term "about" indicates +/- two amino acid residues. Since linker length must be a positive integer, the length of from about 1 to about 50 amino acids in length, means a length of from 1 to 48-52 amino acids in length. In another embodiment, a polypeptide linker is from about 10-20 amino acids in length. In another embodiment, a polypeptide linker is from about 15 to about 50 amino acids in length.

**[0262]** In another embodiment, a polypeptide linker is from about 20 to about 45 amino acids in length. In another embodiment, a polypeptide linker is from about 15 to about 25 amino acids in length. In another embodiment, a polypeptide linker is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, or 61 or more amino acids in length.

**[0263]** Polypeptide linkers can be introduced into polypeptide sequences using techniques known in the art. Modifications can be confirmed by DNA sequence analysis. Plasmid DNA can be used to transform host cells for stable production of the polypeptides produced.

## **Exemplary Fusion Proteins**

**[0264]** The fusion proteins of the disclosure are modular and can be configured to incorporate various individual domains. For example, in some embodiments, the fusion protein includes a multispecific variable region comprising the heavy and light chain variable regions set forth in SEQ ID NOs: 1 and 2, respectively. In some embodiments, the fusion protein includes a multispecific variable region comprising the heavy and light chain variable regions set forth in SEQ ID NOs: 11 and 12, respectively. In some embodiments, the fusion protein includes a multispecific variable region comprising the heavy and light chain variable regions set forth in SEQ ID NOs: 21 and 22, respectively.

**[0265]** In some embodiments, the multispecific variable region comprises amino acid substitutions that result in the formation of a cysteine bridge, useful for stabilization of the fusion protein. In some embodiments, the multispecific variable region comprises a heavy chain variable region

comprising the amino acid substitutions G44C, E44C, or Q105C (Kabat numbering). In some embodiments, the multispecific variable region comprises a light chain variable region comprising the amino acid substitutions A43C or Q100C (Kabat numbering). In some embodiments, the multispecific variable region comprises a heavy chain variable region comprising amino acid substitution E44C, and a light chain variable region comprising amino acid substitution Q100C. In some embodiments, the multispecific variable region comprises a heavy chain variable region comprising amino acid substitution G44C, and a light chain variable region comprising amino acid substitution Q100C. In some embodiments, the multispecific variable region comprises a heavy chain variable region comprising amino acid substitution Q105C, and a light chain variable region comprising amino acid substitution A43C.

[0266] In some embodiments, the fusion protein includes the HSA set forth in SEQ ID NO: 171. In some embodiments, the fusion protein includes the MSA set forth in SEQ ID NO: 173. In some embodiments, the fusion protein includes the (Gly<sub>4</sub>Ser)<sub>3</sub> linker domain set forth in SEQ ID NO: 178. In some embodiments, the fusion protein includes the secretory leader sequence set forth in SEQ ID NO: 179. In some embodiments, the fusion protein includes the His tag set forth in SEQ ID NO: 181. It will be understood to the skilled artisan that these individual domains can be operably coupled to each other in any order form a fusion protein that is active (e.g., reduces or inhibits the binding of an ELR+ CXC chemokine to its cognate receptor). For example, as detailed in the specific examples below, the multispecific variable region comprising the heavy and light chain variable regions set forth in SEQ ID NOs: 1 and 2, is operably coupled to MSA. In another example, the multispecific variable region is operably coupled to MSA via a (Gly<sub>4</sub>Ser)<sub>3</sub> linker domain. In yet another example, the fusion protein comprises the secretory leader sequence set forth in SEQ ID NO: 179.

[0267] In some embodiments, a fusion protein comprises a multispecific variable region coupled to a wild-type albumin. In some embodiments, the fusion protein comprises a secretory leader sequence, followed by a wild-type MSA, operably coupled via a (Gly<sub>4</sub>Ser)<sub>3</sub> linker domain to a multispecific variable region comprising heavy and light chain variable regions set forth in SEQ ID NOs: 1 and 2, respectively, operably coupled via a (Gly<sub>4</sub>Ser) linker domain to a His-tag (e.g., SEQ ID NO: 95). In some embodiments, the multispecific variable region comprises the amino acid substitution Q100C within the light chain variable region, and the amino acid substitution G44C within the heavy chain variable region (SEQ ID NO: 98; Kabat numbering). In some embodiments, the multispecific variable region comprises the amino acid substitution A43C within the light chain variable region, and the amino acid substitution Q105C within the heavy chain variable region (SEQ ID NO: 99; Kabat numbering). In one embodiments, the fusion protein lacks the leader sequence and the His-tag (SEQ ID NOs: 160, 163 and 164).

**[0268]** In some embodiments, the fusion protein comprises a secretory leader sequence, followed by a wild-type MSA, operably coupled via a  $(Gly_4Ser)_3$  linker domain to a multispecific variable region comprising heavy and light chain variable regions set forth in SEQ ID NOs: 11 and 12, respectively, operably coupled via a  $(Gly_4Ser)$  linker domain to a His-tag (e.g., SEQ ID NO: 96). In some embodiments,

the multispecific variable region comprises the amino acid substitution Q100C within the light chain variable region, and the amino acid substitution E44C within the heavy chain variable region (SEQ ID NO: 100; Kabat numbering). In some embodiments, the multispecific variable region comprises the amino acid substitution A43C within the light chain variable region, and the amino acid substitution Q105C within the heavy chain variable region (SEQ ID NO: 101; Kabat numbering). In one embodiments, the fusion protein lacks the leader sequence and the His-tag (SEQ ID NOs: 161, 165 and 166).

[0269] In some embodiments, the fusion protein comprises a secretory leader sequence, followed by a wild-type MSA, operably coupled via a (Gly<sub>4</sub>Ser)<sub>3</sub> linker domain to a multispecific variable region comprising heavy and light chain variable regions set forth in SEQ ID NOs: 21 and 22, respectively, operably coupled via a (Gly<sub>4</sub>Ser) linker domain to a His-tag (e.g., SEQ ID NO: 97). In some embodiments, the multispecific variable region comprises the amino acid substitution Q100C within the light chain variable region, and the amino acid substitution G44C within the heavy chain variable region (SEQ ID NO: 104; Kabat numbering). In some embodiments, the multispecific variable region comprises the amino acid substitution A43C within the light chain variable region, and the amino acid substitution Q105C within the heavy chain variable region (SEQ ID NO: 105; Kabat numbering). In one embodiments, the fusion protein lacks the leader sequence and the His-tag (SEQ ID NO: 162, 169 and 170).

**[0270]** In some embodiments, the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 95. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 83. In some embodiments, the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 96. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 84. In some embodiments, the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 84. In some embodiments, the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 97. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 97. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 86.

**[0271]** In some embodiments, the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 160. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 149. In some embodiments, the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 161. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 150. In some embodiments, the fusion protein acid sequence set forth in SEQ ID NO: 150. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 162. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 162. In some embodiments, the fusion protein is encoded by the nucleic acid set forth in SEQ ID NO: 151.

Methods of Making Multispecific Variable Regions and Antibodies

**[0272]** The disclosure also provides methods for producing any of the multispecific variable regions, and isolated monoclonal antibodies, or antigen binding fragments thereof, that bind more than one ELR+ CXC chemokine (e.g., at least two, at least three, at least four, at least five, at least six, at least seven), described herein. In some embodiments, the final processed and active form of an ELR+ CXC chemokine protein is used in the methods described herein. **[0273]** In some embodiments, the methods described herein can involve, or be used in conjunction with, e.g.,

phage display technologies, bacterial display, yeast surface display, eukaryotic viral display, mammalian cell display, and cell-free (e.g., ribosomal display) antibody screening techniques (see, e.g., Etz et al. (2001) *J Bacteriol* 183:6924-6935; Cornelis (2000) *Curr Opin Biotechnol* 11:450-454; Klemm et al. (2000) *Microbiology* 146:3025-3032; Kieke et al. (1997) *Protein Eng* 10:1303-1310; Yeung et al. (2002) *Biotechnol Prog* 18:212-220; Boder et al. (2000) *Methods Enzymology* 328:430-444; Grabherr et al. (2001) *Comb Chem High Throughput Screen* 4:185-192; Michael et al. (1995) *Gene Ther* 2:660-668; Pereboev et al. (2001) *J Virol* 75:7107-7113; Schaffitzel et al. (1999) *J Immunol Methods* 231:119-135; and Hanes et al. (2000) *Nat Biotechnol* 18:1287-1292).

[0274] Methods for identifying multispecific variable regions and/or antibodies using various phage display methods are known in the art. In phage display methods, functional variable region domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. Such phage can be utilized to display antigen-binding domains, such as Fab, Fv, or disulfide-bond stabilized Fv antibody fragments, expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage used in these methods are typically filamentous phage such as fd and M13. The antigen binding domains are expressed as a recombinantly fused protein to any of the phage coat proteins pIII, pVIII, or pIX. See, e.g., Shi et al. (2010) JMB 397:385-396. Examples of phage display methods that can be used to make the immunoglobulins, or fragments thereof, described herein include those disclosed in Brinkman et al. (1995) J Immunol Methods 182:41-50; Ames et al. (1995) J Immunol Methods 184:177-186; Kettleborough et al. (1994) Eur J Immunol 24:952-958; Persic et al. (1997) Gene 187:9-18; Burton et al. (1994) Advances in Immunology 57:191-280; and PCT publication nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/11236, WO 95/15982, and WO 95/20401. Suitable methods are also described in, e.g., U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108.

[0275] In some embodiments, the methods described herein further comprise prioritizing crossreactivity over affinity using directed co-evolution, described in further detail in the Examples. For example, using yeast surface display methods described above, output of each cycle of selection is exposed to a diverse array of antigens of interest (e.g., ELR+ CXC chemokines) in the following cycle. In some embodiments, methods that improve both the binding and affinity of variable regions and antibodies are used. Specifically, a high degree of genetic diversity in the antibody encoding genes can be created using error-prone PCR amplification. Binding affinity can be increased by allowing mutants to evolve through consecutive cycles of equilibrium-based selection using decreasing concentrations of the antigens of interest (e.g., ELR+ CXC chemokines). Concurrently, crossreactivity is increased by exposing the outputs of each cycle of affinity selection towards a different antigen of interest (e.g., different ELR+ CXC chemokine) in the following cycle of selection. Variants whose affinity and crossreactivity towards multiple antigens of interest (e.g., ELR+ CXC chemokines) that are higher than their respective parental clones are collected.

[0276] A subpopulation of multispecific variable regions and/or antibodies screened using the above methods can be characterized for their specificity and binding affinity for particular antigens (e.g., chemokines, e.g., ELR+ CXC chemokines) using any immunological or biochemical based method known in the art. For example, specific binding of a multispecific variable region or antibody to a chemokine, may be determined for example using immunological or biochemical based methods such as, but not limited to, an ELISA assay, SPR assays, immunoprecipitation assay, affinity chromatography, and equilibrium dialysis as described above. Immunoassays which can be used to analyze immunospecific binding and cross-reactivity of the antibodies include, but are not limited to, competitive and non-competitive assay systems using techniques such as Western blots, RIA, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, immunodiffusion assays, agglutination assays, complementfixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art.

**[0277]** In embodiments where the selected CDR amino acid sequences are short sequences (e.g., fewer than 10-15 amino acids in length), nucleic acids encoding the CDRs can be chemically synthesized as described in, e.g., Shiraishi et al. (2007) *Nucleic Acids Symposium Series* 51(1):129-130 and U.S. Pat. No. 6,995,259. For a given nucleic acid sequence encoding an acceptor antibody, the region of the nucleic acid sequence encoding the CDRs can be replaced with the chemically synthesized nucleic acids using standard molecular biology techniques. The 5' and 3' ends of the chemically synthesized nucleic acids can be synthesized to comprise sticky end restriction enzyme sites for use in cloning the nucleic acids into the nucleic acid encoding the variable region of the donor antibody.

[0278] In some embodiments, the antibodies described herein comprise an altered heavy chain constant region that has reduced (or no) effector function relative to its corresponding unaltered constant region. Effector functions involving the constant region of the antibody may be modulated by altering properties of the constant or Fc region. Altered effector functions include, for example, a modulation in one or more of the following activities: antibodydependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), apoptosis, binding to one or more Fc-receptors, and pro-inflammatory responses. Modulation refers to an increase, decrease, or elimination of an effector function activity exhibited by a subject antibody containing an altered constant region as compared to the activity of the unaltered form of the constant region. In particular embodiments, modulation includes situations in which an activity is abolished or completely absent.

**[0279]** An altered constant region with altered FcR binding affinity and/or ADCC activity and/or altered CDC activity is a polypeptide which has either an enhanced or diminished FcR binding activity and/or ADCC activity and/or CDC activity compared to the unaltered form of the constant region. An altered constant region which displays increased binding to an FcR binds at least one FcR with greater affinity than the unaltered polypeptide. An altered constant region which displays decreased binding to an FcR binds at least one FcR with lower affinity than the unaltered form of the constant region. Such variants which display decreased binding to an FcR may possess little or no appreciable binding to an FcR, e.g., 0 to 50% (e.g., less than 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1%) of the binding to the FcR as compared to the level of binding of a native sequence immunoglobulin constant or Fc region to the FcR. Similarly, an altered constant region that displays modulated ADCC and/or CDC activity may exhibit either increased or reduced ADCC and/or CDC activity compared to the unaltered constant region. For example, in some embodiments, the antibody comprising an altered constant region can exhibit approximately 0 to 50% (e.g., less than 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1%) of the ADCC and/or CDC activity of the unaltered form of the constant region. An antibody described herein comprising an altered constant region displaying reduced ADCC and/or CDC may exhibit reduced or no ADCC and/or CDC activity.

**[0280]** In some embodiments, an antibody described herein exhibits reduced or no effector function. In some embodiments, an antibody comprises a hybrid constant region, or a portion thereof, such as a G2/G4 hybrid constant region (see e.g., Burton et al. (1992) *Adv Immun* 51:1-18; Canfield et al. (1991) *J Exp Med* 173:1483-1491; and Mueller et al. (1997) *Mol Immunol* 34(6):441-452). See above.

[0281] In some embodiments, an antibody may contain an altered constant region exhibiting enhanced or reduced complement dependent cytotoxicity (CDC). Modulated CDC activity may be achieved by introducing one or more amino acid substitutions, insertions, or deletions in an Fc region of the antibody. See, e.g., U.S. Pat. No. 6,194,551. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved or reduced internalization capability and/or increased or decreased complement-mediated cell killing. See, e.g., Caron et al. (1992) J Exp Med 176:1191-1195 and Shopes (1992) Immunol 148:2918-2922; PCT publication nos. WO 99/51642 and WO 94/29351; Duncan and Winter (1988) Nature 322:738-40; and U.S. Pat. Nos. 5,648,260 and 5,624,821.

**[0282]** It is understood that the above methods can also be used to determine if, e.g., a multispecific variable region does not bind to full length chemokines, e.g., ELR+ CXC chemokines. The above methods can also be used to determine if a multispecific variable region or antibody that specifically binds to more than one ELR+ CXC chemokine also reduces or inhibits the interaction between the chemokines and their cognate receptors (e.g., CXCR1 and CXCR2).

#### Methods of Making Fusion Proteins

**[0283]** The fusion proteins described herein largely may be made in transformed or transfected host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the polypeptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the polypeptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

[0284] The disclosure also provides a vector capable of expressing the polypeptides in an appropriate host. The vector comprises the DNA molecule that codes for the polypeptides operably coupled to appropriate expression control sequences. Methods of affecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal nuclease domains, start signals, stop signals, cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation. The nucleic acid molecules described above can be contained within a vector that is capable of directing their expression in, for example, a cell that has been transduced with the vector. Accordingly, in addition to polypeptide mutants, expression vectors containing a nucleic acid molecule encoding a mutant and cells transfected with these vectors are among the certain embodiments.

[0285] Vectors suitable for use include T7-based vectors for use in bacteria (see, for example, Rosenberg et al., Gene 56: 125, 1987), the pMSXND expression vector for use in mammalian cells (Lee and Nathans, J. Biol. Chem. 263: 3521, 1988), and baculovirus-derived vectors (for example the expression vector pBacPAKS from Clontech, Palo Alto, Calif.) for use in insect cells. The nucleic acid inserts, which encode the polypeptide of interest in such vectors, can be operably linked to a promoter, which is selected based on, for example, the cell type in which expression is sought. For example, a T7 promoter can be used in bacteria, a polyhedrin promoter can be used in insect cells, and a cytomegalovirus or metallothionein promoter can be used in mammalian cells. Also, in the case of higher eukaryotes, tissue-specific and cell type-specific promoters are widely available. These promoters are so named for their ability to direct expression of a nucleic acid molecule in a given tissue or cell type within the body. Skilled artisans are well aware of numerous promoters and other regulatory elements which can be used to direct expression of nucleic acids.

**[0286]** In addition to sequences that facilitate transcription of the inserted nucleic acid molecule, vectors can contain origins of replication, and other genes that encode a selectable marker. For example, the neomycin-resistance (neo') gene imparts G418 resistance to cells in which it is expressed, and thus permits phenotypic selection of the transfected cells. Those of skill in the art can readily determine whether a given regulatory element or selectable marker is suitable for use in a particular experimental context.

**[0287]** Viral vectors that are suitable for use include, for example, retroviral, adenoviral, and adeno-associated vectors, herpes virus, simian virus 40 (SV40), and bovine papilloma virus vectors (see, for example, Gluzman (Ed.), Eukaryotic Viral Vectors, CSH Laboratory Press, Cold Spring Harbor, N.Y.).

**[0288]** The resulting vector having the DNA molecule thereon is used to transform or transfect an appropriate host. This transformation or transfection may be performed using methods well known in the art.

**[0289]** Any of a large number of available and well-known host cells may be used. The selection of a particular host is dependent upon a number of factors recognized by the art.

These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of transformation or transfection, ease of recovery of the peptides, expression characteristics, biosafety and costs. A balance of these factors must be struck with the understanding that not all hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines, useful microbial hosts include bacteria (such as *E. coli*), yeast (such as *Saccharo-myces*) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

**[0290]** Next, the transformed or transfected host is cultured and purified. Host cells may be cultured under conventional fermentation or culture conditions so that the desired compounds are expressed. Such fermentation and culture conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

**[0291]** Prokaryotic or eukaryotic cells that contain and express a nucleic acid molecule that encodes a polypeptide mutant are also suitable for use. A cell is a transfected cell, i.e., a cell into which a nucleic acid molecule, for example a nucleic acid molecule encoding a mutant polypeptide, has been introduced by means of recombinant DNA techniques. The progeny of such a cell are also considered suitable for use in the methods disclosed herein.

**[0292]** The precise components of the expression system are not critical. For example, a polypeptide can be produced in a prokaryotic host, such as the bacterium *E. coli*, or in a eukaryotic host, such as an insect cell (e.g., an Sf21 cell), or mammalian cells (e.g., COS cells, NIH 3T3 cells, or HeLa cells). These cells are available from many sources, including the American Type Culture Collection (Manassas, Va.). In selecting an expression system, it matters only that the components are compatible with one another. Artisans or ordinary skill are able to make such a determination. Furthermore, if guidance is required in selecting an expression system, skilled artisans may consult Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, New York, N.Y., 1993) and Pouwels et al. (Cloning Vectors: A Laboratory Manual, 1985 Suppl. 1987).

**[0293]** The expressed polypeptides can be purified from the expression system using routine biochemical procedures, and can be used, e.g., as therapeutic agents, as described herein.

**[0294]** The fusion proteins may also be made by synthetic methods. For example, solid phase synthesis techniques may be used. Suitable techniques are well known in the art, and include those described in Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al., *Biochem Intl* 1985; 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides. Compounds that contain derivatized peptides or which contain non-peptide groups may be synthesized by well-known organic chemistry techniques.

**[0295]** Other methods are of molecule expression/synthesis are generally known in the art to one of ordinary skill.

#### Modification of Polypeptides

**[0296]** The polypeptides described herein (e.g., fusion proteins, or antibodies or antigen-binding fragments thereof) can be modified following their expression and purification. The modifications can be covalent or non-covalent modifications. Such modifications can be introduced into the polypeptides by, e.g., reacting targeted amino acid residues of the polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. Suitable sites for modification can be chosen using any of a variety of criteria including, e.g., structural analysis or amino acid sequence analysis of the antibodies or fragments.

[0297] In some embodiments, the polypeptides can be conjugated to a heterologous moiety. The heterologous moiety can be, e.g., a heterologous polypeptide, a therapeutic agent (e.g., a toxin or a drug), or a detectable label such as, but not limited to, a radioactive label, an enzymatic label, a fluorescent label, a heavy metal label, a luminescent label, or an affinity tag such as biotin or streptavidin. Suitable heterologous polypeptides include, e.g., an antigenic tag (e.g., FLAG (DYKDDDDK (SEQ ID NO: 180)), polyhistidine (6-His; HHHHHH (SEQ ID NO: 181), hemagglutinin (HA; YPYDVPDYA (SEQ ID NO: 182)), glutathione-Stransferase (GST), or maltose-binding protein (MBP)) for use in purifying the antibodies or fragments. Heterologous polypeptides also include polypeptides (e.g., enzymes) that are useful as diagnostic or detectable markers, for example, luciferase, a fluorescent protein (e.g., green fluorescent protein (GFP)), or chloramphenicol acetyl transferase (CAT). Suitable radioactive labels include, e.g., <sup>32</sup>P, <sup>33</sup>P <sup>14</sup>C, <sup>125</sup>I, <sup>131</sup>I, <sup>35</sup>S, and <sup>3</sup>H. Suitable fluorescent labels include, without limitation, fluorescein, fluorescein isothiocvanate (FITC), green fluorescent protein (GFP), DyLight<sup>™</sup> 488, phycoerythrin (PE), propidium iodide (PI), PerCP, PE-Alexa Fluor® 700, Cy5, allophycocyanin, and Cy7. Luminescent labels include, e.g., any of a variety of luminescent lanthanide (e.g., europium or terbium) chelates. For example, suitable europium chelates include the europium chelate of diethylene triamine pentaacetic acid (DTPA) or tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Enzymatic labels include, e.g., alkaline phosphatase, CAT, luciferase, and horseradish peroxidase.

**[0298]** Two proteins (e.g., an antibody and a heterologous moiety) can be cross-linked using any of a number of known chemical cross linkers. Examples of such cross linkers are those which link two amino acid residues via a linkage that includes a "hindered" disulfide bond. In these linkages, a disulfide bond within the cross-linking unit is protected (by hindering groups on either side of the disulfide bond) from reduction by the action, for example, of reduced glutathione or the enzyme disulfide reductase. One suitable reagent, 4-succinimidyloxycarbonyl- $\alpha$ -methyl- $\alpha$ (2-pyridyldithio)

toluene (SMPT), forms such a linkage between two proteins utilizing a terminal lysine on one of the proteins and a terminal cysteine on the other. Heterobifunctional reagents that cross-link by a different coupling moiety on each protein can also be used. Other useful cross-linkers include, without limitation, reagents which link two amino groups (e.g., N-5-azido-2-nitrobenzoyloxysuccinimide), two sulfhydryl groups (e.g., 1,4-bis-maleimidobutane), an amino group and a sulfhydryl group (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester), an amino group and a carboxyl group (e.g., 4-[p-azidosalicylamido]butylamine), and an amino group and a guanidinium group that is present in the side chain of arginine (e.g., p-azidophenyl glyoxal monohydrate).

[0299] In some embodiments, a radioactive label can be directly conjugated to the amino acid backbone of the polypeptide. Alternatively, the radioactive label can be included as part of a larger molecule (e.g., 125I in meta-[<sup>125</sup>I]iodophenyl-N-hydroxysuccinimide ([<sup>125</sup>I]mIPNHS) which binds to free amino groups to form meta-iodophenyl (mIP) derivatives of relevant proteins (see, e.g., Rogers et al. (1997) J Nucl Med 38:1221-1229) or chelate (e.g., to DOTA or DTPA) which is in turn bound to the protein backbone. Methods of conjugating the radioactive labels or larger molecules/chelates containing them to the polypeptides described herein are known in the art. Such methods involve incubating the proteins with the radioactive label under conditions (e.g., pH, salt concentration, and/or temperature) that facilitate binding of the radioactive label or chelate to the protein (see, e.g., U.S. Pat. No. 6,001,329).

**[0300]** Methods for conjugating a fluorescent label (sometimes referred to as a "fluorophore") to a protein (e.g., an antibody) are known in the art of protein chemistry. For example, fluorophores can be conjugated to free amino groups (e.g., of lysines) or sulfhydryl groups (e.g., cysteines) of proteins using succinimidyl (NHS) ester or tetrafluorophenyl (TFP) ester moieties attached to the fluorophores. In some embodiments, the fluorophores can be conjugated to a heterobifunctional cross-linker moiety such as sulfo-SMCC. Suitable conjugation methods involve incubating a polypeptide, with the fluorophore to the protein. See, e.g., Welch and Redvanly (2003) "Handbook of Radiopharmaceuticals: Radiochemistry and Applications," John Wiley and Sons (ISBN 0471495603).

**[0301]** In some embodiments, the polypeptides can be modified, e.g., with a moiety that improves the stabilization and/or retention of the polypeptides in circulation, e.g., in blood, serum, or other tissues. For example, the polypeptide can be PEGylated as described in, e.g., Lee et al. (1999) *Bioconjug Chem* 10(6): 973-8; Kinstler et al. (2002) *Advanced Drug Deliveries Reviews* 54:477-485; and Roberts et al. (2002) *Advanced Drug Deliveries Reviews* 54:479-476 or HESylated (Fresenius Kabi, Germany; see, e.g., Pavisié et al. (2010) *Int J Pharm* 387(1-2):110-119). The stabilization moiety can improve the stability, or retention of, the polypeptide by at least 1.5 (e.g., at least 2, 5, 10, 15, 20, 25, 30, 40, or 50 or more) fold.

**[0302]** In some embodiments, the polypeptides described herein can be glycosylated. In some embodiments, a polypeptide described herein can be subjected to enzymatic or chemical treatment, or produced from a cell, such that the polypeptide has reduced or absent glycosylation. Methods for producing polypeptides with reduced glycosylation are known in the art and described in, e.g., U.S. Pat. No. 6,933,368; Wright et al. (1991) *EMBO J* 10(10):2717-2723; and Co et al. (1993) *Mol Immunol* 30:1361.

Pharmaceutical Compositions and Modes of Administration

**[0303]** In certain embodiments, the invention provides for a pharmaceutical composition comprising a fusion protein, or an isolated monoclonal antibody, or antigen binding fragment thereof, described herein, with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0304] In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, the formulation material(s) are for s.c. and/or I.V. administration. In certain embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolality, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-betacyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company (1995). In certain embodiments, the formulation comprises PBS; 20 mM NaOAC, pH 5.2, 50 mM NaCl; and/or 10 mM NAOAC, pH 5.2, 9% Sucrose. In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, Remington's Pharmaceutical Sciences, supra. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the fusion protein, or isolated monoclonal antibody, or antigen binding fragment, described herein.

**[0305]** In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, in certain embodiments, a suitable vehicle or carrier can be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. In certain embodiments, the saline comprises isotonic phosphate-buffered saline. In certain embodiments, neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In certain embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5,

or acetate buffer of about pH 4.0-5.5, which can further include sorbitol or a suitable substitute therefore. In certain embodiments, a composition comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, described herein, can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's Pharmaceutical Sciences, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, a composition comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, described herein, can be formulated as a lyophilizate using appropriate excipients such as sucrose.

**[0306]** In certain embodiments, the pharmaceutical composition can be selected for parenteral delivery. In certain embodiments, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the ability of one skilled in the art.

**[0307]** In certain embodiments, the formulation components are present in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0308] In certain embodiments, when parenteral administration is contemplated, a therapeutic composition can be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, described herein, in a pharmaceutically acceptable vehicle. In certain embodiments, a vehicle for parenteral injection is sterile distilled water in which a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, described herein, are formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable micro spheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that can provide for the controlled or sustained release of the product which can then be delivered via a depot injection. In certain embodiments, hyaluronic acid can also be used, and can have the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices can be used to introduce the desired molecule.

**[0309]** In certain embodiments, a pharmaceutical composition can be formulated for inhalation. In certain embodiments, a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, can be formulated as a dry powder for inhalation. In certain embodiments, an inhalation solution comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, can be formulated with a propellant for aerosol delivery. In certain embodiments, solutions can be nebulized. Pulmonary administration is further described in PCT application No. PCT/US94/ 001875, which describes pulmonary delivery of chemically modified proteins.

**[0310]** In certain embodiments, it is contemplated that formulations can be administered orally. In certain embodiments, a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, that is administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as

tablets and capsules. In certain embodiments, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. In certain embodiments, at least one additional agent can be included to facilitate absorption of the fusion protein, or isolated monoclonal antibody, or antigen binding fragment. In certain embodiments, diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

**[0311]** In certain embodiments, a pharmaceutical composition can involve an effective quantity of the fusion protein, or isolated monoclonal antibody, or antigen binding fragment, in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. In certain embodiments, by dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. In certain embodiments, suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0312] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, in sustained- or controlleddelivery formulations. In certain embodiments, techniques for formulating a variety of other sustained- or controlleddelivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT Application No. PCT/US93/00829 which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In certain embodiments, sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (U.S. Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., Biopolymers, 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer et al., J. Biomed. Mater. Res., 15: 167-277 (1981) and Langer, Chem. Tech., 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., supra) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). In certain embodiments, sustained release compositions can also include liposomes, which can be prepared by any of several methods known in the art. See, e.g., Eppstein et al, Proc. Natl. Acad. Sci. USA, 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143,949.

**[0313]** The pharmaceutical composition to be used for in vivo administration typically is sterile. In certain embodiments, this can be accomplished by filtration through sterile filtration membranes. In certain embodiments, where the composition is lyophilized, sterilization using this method can be conducted either prior to or following lyophilization and reconstitution. In certain embodiments, the composition for parenteral administration can be stored in lyophilized form or in a solution. In certain embodiments, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

**[0314]** In certain embodiments, once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. In certain embodiments, such formulations can be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration.

**[0315]** In certain embodiments, kits are provided for producing a single-dose administration unit. In certain embodiments, the kit can contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are included.

**[0316]** In certain embodiments, the effective amount of a pharmaceutical composition comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, are being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

[0317] In certain embodiments, the frequency of dosing will take into account the pharmacokinetic parameters of a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, in the formulation used. In certain embodiments, a clinician will administer the composition until a dosage is reached that achieves the desired effect. In certain embodiments, the composition can therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. In certain embodiments, appropriate dosages can be ascertained through use of appropriate dose-response data.

**[0318]** In certain embodiments, the route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intranuscular, subcutaneously, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device. In certain embodiments, individual elements of the combination therapy may be administered by different routes.

**[0319]** In certain embodiments, the composition can be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion,

timed-release bolus, or continuous administration. In certain embodiments, it can be desirable to use a pharmaceutical composition comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, in an ex vivo manner. In such instances, cells, tissues and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, after which the cells, tissues and/or organs are subsequently implanted back into the patient.

[0320] In certain embodiments, a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptides. In certain embodiments, such cells can be animal or human cells, and can be autologous, heterologous, or xenogeneic. In certain embodiments, the cells can be immortalized. In certain embodiments, in order to decrease the chance of an immunological response, the cells can be encapsulated to avoid infiltration of surrounding tissues. In certain embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

## Kits

**[0321]** A kit can include a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, as disclosed herein, and instructions for use. The kits may comprise, in a suitable container, a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, one or more controls, and various buffers, reagents, enzymes and other standard ingredients well known in the art.

**[0322]** The container can include at least one vial, well, test tube, flask, bottle, syringe, or other container means, into which a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, may be placed, and in some instances, suitably aliquoted. Where an additional component is provided, the kit can contain additional containers into which this component may be placed. The kits can also include a means for containing a fusion protein, or isolated monoclonal antibody, or antigen binding fragment, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits can include labeling with instructions for use and/or warnings.

### Methods of Treatment

**[0323]** The compositions described herein are useful in, inter alia, methods for treating or preventing a variety of autoimmune and related disorders, allergy, inflammation, and/or graft or transplant rejection in a subject. The compositions can be administered to a subject, e.g., a human subject, using a variety of methods that depend, in part, on the route of administration. The route can be, e.g., intravenous injection or infusion (IV), subcutaneous injection (SC), intraperitoneal (IP) injection, intramuscular injection (IM), or intrathecal injection (IT). The injection can be in a bolus or a continuous infusion.

[0324] Administration can be achieved by, e.g., local infusion, injection, or by means of an implant. The implant can be of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. The implant can be configured for sustained or periodic release of the composition to the subject. See, e.g., U.S. Patent Application Publication No. 20080241223; U.S. Pat. Nos. 5,501,856; 4,863,457; and 3,710,795; EP488401; and EP 430539, the disclosures of each of which are incorporated herein by reference in their entirety. The composition can be delivered to the subject by way of an implantable device based on, e.g., diffusive, erodible, or convective systems, e.g., osmotic pumps, biodegradable implants, electrodiffusion systems, electroosmosis systems, vapor pressure pumps, electrolytic pumps, effervescent pumps, piezoelectric pumps, erosion-based systems, or electromechanical systems.

**[0325]** In some embodiments, a fusion protein, or antibody or antigen-binding fragment thereof, is therapeutically delivered to a subject by way of local administration.

[0326] A suitable dose of a fusion protein, or antibody or antigen-binding fragment thereof described herein, which dose is capable of treating or preventing autoimmune and related disorders in a subject, can depend on a variety of factors including, e.g., the age, sex, and weight of a subject to be treated and the particular inducer compound used. For example, a different dose of a whole antibody may be required to treat a subject with autoimmune disease as compared to the dose of a fusion protein required to treat the same subject. Other factors affecting the dose administered to the subject include, e.g., the type or severity of the autoimmune disorder. For example, a subject having rheumatoid arthritis may require administration of a different dosage than a subject with Guillain-Barre syndrome. Other factors can include, e.g., other medical disorders concurrently or previously affecting the subject, the general health of the subject, the genetic disposition of the subject, diet, time of administration, rate of excretion, drug combination, and any other additional therapeutics that are administered to the subject. It should also be understood that a specific dosage and treatment regimen for any particular subject will also depend upon the judgment of the treating medical practitioner (e.g., doctor or nurse). Suitable dosages are described herein.

[0327] A pharmaceutical composition can include a therapeutically effective amount of a fusion protein, or antibody or antigen-binding fragment thereof described herein. Such effective amounts can be readily determined by one of ordinary skill in the art based, in part, on the effect of the administered antibody, or the combinatorial effect of the antibody and one or more additional active agents, if more than one agent is used. A therapeutically effective amount of an antibody or fragment thereof described herein can also vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody (and one or more additional active agents) to elicit a desired response in the individual, e.g., reduction in tumor growth. For example, a therapeutically effective amount of a fusion protein can inhibit (lessen the severity of or eliminate the occurrence of) and/or prevent a particular disorder, and/or any one of the symptoms of the particular disorder known in the art or described herein. A therapeutically effective amount is also one in which any toxic or detrimental effects of the composition are outweighed by the therapeutically beneficial effects.

**[0328]** Suitable human doses of any of the fusion proteins, or antibodies or fragments thereof described herein can further be evaluated in, e.g., Phase I dose escalation studies. See, e.g., van Gurp et al. (2008) *Am J Transplantation* 8(8):1711-1718; Hanouska et al. (2007) *Clin Cancer Res* 13(2, part 1):523-531; and Hetherington et al. (2006) *Antimicrobial Agents and Chemotherapy* 50(10): 3499-3500.

**[0329]** In some embodiments, the composition contains any of the fusion proteins, or antibodies or antigen-binding fragments thereof described herein and one or more (e.g., two, three, four, five, six, seven, eight, nine, 10, or 11 or more) additional therapeutic agents such that the composition as a whole is therapeutically effective. For example, a composition can contain a fusion protein described herein and an anti-inflammatory agent, wherein the fusion protein and agent are each at a concentration that when combined are therapeutically effective for treating or preventing autoimmune and related disorders (e.g., rheumatoid arthritis) in a subject.

[0330] Toxicity and therapeutic efficacy of such compositions can be determined by known pharmaceutical procedures in cell cultures or experimental animals (e.g., animal models of any of the cancers described herein). These procedures can be used, e.g., for determining the  $LD_{50}$  (the dose lethal to 50% of the population) and the  $ED_{50}$  (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio  $LD_{50}/ED_{50}$ . A fusion protein, or antibody or antigen-binding fragment thereof that exhibits a high therapeutic index is preferred. While compositions that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue and to minimize potential damage to normal cells and, thereby, reduce side effects.

[0331] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such fusion proteins, or antibodies or antigen-binding fragments thereof lies generally within a range of circulating concentrations of the antibodies or fragments that include the  $ED_{50}$  with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For a fusion protein described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the fusion protein which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. In some embodiments, e.g., where local administration (e.g., to the eye or a joint) is desired, cell culture or animal modeling can be used to determine a dose required to achieve a therapeutically effective concentration within the local site.

**[0332]** In some embodiments, the methods can be performed in conjunction with other therapies for autoimmune and related diseases. For example, the composition can be administered to a subject at the same time, prior to, or after, radiation, surgery, targeted or cytotoxic chemotherapy, antiinflammatory therapy, steroid therapy, chemoradiotherapy, hormone therapy, immunotherapy, immunosuppressive therapy, antithyroid therapy, antibiotic therapy, gene therapy, cell transplant therapy, precision medicine, genome editing therapy, or other pharmacotherapy.

**[0333]** The compositions described herein (e.g., fusion protein compositions) can be used to treat graft rejection and/or a variety of allergy or autoimmune disorders such as, but not limited to, Crohn's disease, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, Goodpasture's syndrome, T-cell mediated hepatitis, graft vs. host disease, autoimmune uveitis, and/or autoimmune diabetes.

[0334] In some embodiments, a fusion protein, or an antibody or an antigen-binding fragment thereof described herein can be administered to a subject as a monotherapy. Alternatively, as described above, the fusion protein, or the antibody or fragment thereof can be administered to a subject as a combination therapy with another treatment, e.g., another treatment for an autoimmune or related disease. For example, the combination therapy can include administering to the subject (e.g., a human patient) one or more additional agents that provide a therapeutic benefit to a subject who has, or is at risk of developing, an autoimmune or related diseases. In some embodiments, a fusion protein, or an antibody and the one or more additional active agents are administered at the same time. In other embodiments, the fusion protein, or antibody or antigen binding fragment thereof is administered first in time and the one or more additional active agents are administered second in time. In some embodiments, the one or more additional active agents are administered first in time and the fusion protein, or antibody or antigen binding fragment thereof is administered second in time.

**[0335]** A fusion protein, or an antibody or an antigenbinding fragment thereof described herein can replace or augment a previously or currently administered therapy. For example, upon treating with a fusion protein, or an antibody or antigen-binding fragment thereof, administration of the one or more additional active agents can cease or diminish, e.g., be administered at lower levels. In some embodiments, administration of the previous therapy can be maintained. In some embodiments, a previous therapy will be maintained until the level of the fusion protein, or the antibody reaches a level sufficient to provide a therapeutic effect. The two therapies can be administered in combination.

[0336] Monitoring a subject (e.g., a human patient) for an improvement in an autoimmune or related disease, as defined herein, means evaluating the subject for a change in a disease parameter, e.g., a reduction in inflammation. In some embodiments, the evaluation is performed at least one (1) hour, e.g., at least 2, 4, 6, 8, 12, 24, or 48 hours, or at least 1 day, 2 days, 4 days, 10 days, 13 days, 20 days or more, or at least 1 week, 2 weeks, 4 weeks, 10 weeks, 13 weeks, 20 weeks or more, after an administration. The subject can be evaluated in one or more of the following periods: prior to beginning of treatment; during the treatment; or after one or more elements of the treatment have been administered. Evaluation can include evaluating the need for further treatment, e.g., evaluating whether a dosage, frequency of administration, or duration of treatment should be altered. It can also include evaluating the need to add or drop a selected

therapeutic modality, e.g., adding or dropping any of the treatments for an autoimmune ore related disease described herein.

[0337] As ELR+ CXC chemokines are responsible for inducing neutrophil infiltration to sites of inflammation, in some embodiments a fusion protein or an antibody or an antigen-binding fragment thereof described herein, is administered to prevent or block neutrophil infiltration in a subject with an autoimmune disorder. In some embodiments, the fusion protein or antibody, or antigen-binding fragment thereof, prevents or blocks infiltration of neutrophils into the synovial fluid of arthritic joints. Methods of measuring neutrophil infiltration are known in the art. For example, bodily fluid from a subject (e.g., synovial fluid) is collected, cells are isolated and stained with a neutrophil cell marker (e.g., Ly6G), and assessed via flow cytometry. Exemplary methods are described in Mivabe, Y., Kim, N. D., Miyabe, C. & Luster, A. D. Studying Chemokine Control of Neutrophil Migration In Vivo in a Murine Model of Inflammatory Arthritis. Methods in enzymology 570, 207-231 (2016), herein incorporated by reference.

#### **EXAMPLES**

**[0338]** While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the disclosure.

Materials and Methods

Cloning of CXC Chemokines for Mammalian Cell Line Expression

**[0339]** Human and murine CXC chemokines undergo proteolysis in vivo resulting in molecules with altered structure and tuned activity. To avoid that in vitro engineered crossreactive binders might not be able to block the mature form in vivo, the final processed and active form of the protein was cloned and produced. The CXC chemokines were produced in mammalian cell lines thus avoiding refolding procedures while preserving their native structure and activity. CXCL chemokines were cloned as C-terminal fusion of the immunoglobulin fragment crystallizable (Fc) domain (<sup>N</sup>Fc-CXCL<sup>C</sup>) and as N-terminal fusion of the murine serum albumin (SA) protein (<sup>N</sup>CXCL-SA<sup>C</sup>). All mammalian expression vectors were based on gWiz (Genlantis) containing an optimized human cytomegalovirus (CMV) promoter and a Kanamycin antibiotic resistance gene (Kan).

**[0340]** Constructs for expression of <sup>*N*</sup>Fc-CXCL<sup>*C*</sup> fusion proteins were generated by using a modified Pfu DNA polymerase-mediated site-directed mutagenesis protocol (Geiser, M., Cebe, R., Drewello, D. & Schmitz, R. Integration of PCR fragments at any specific site within cloning vectors without the use of restriction enzymes and DNA ligase. *Biotechniques* 31, 88-90, 92 (2001)). PfuUltra II Fusion HS DNA Polymerase was obtained from Agilent Technologies, DpnI enzyme from New England BioLabs and the oligonucleotide primers from Integrated DNA Tech-

nologies. The synthetic DNA coding for the active form of three highly diverse human and murine ELR+ CXC chemokines were obtained from GeneArt Gene Synthesis (Thermo Fisher Scientific). Genes were codon-optimized for expression in mammalian cells. A sequence encoding for Gly-Gly dipeptide spacer (G2, <sup>N</sup>GG<sup>C</sup>) followed by a 15 amino acid peptide sequence (AviTag) containing a defined lysine for site-specific biotinylation (<sup>N</sup>GLNDIFEAQKIEWHE<sup>C</sup>) were inserted at the C-terminus of the ELR+ CXC chemokine to obtain <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> synthetic genes. The AviTag sequence for enzymatically biotinylation was placed at the well tolerated C-terminus of the ELR+ CXC chemokines to (i) preserve unaltered the functional N-terminus region, (ii) avoid loss of epitope recognition and (iii) prevent additional structural heterogeneity that could be triggered by performing a chemistry-based amine-reactive succinimidyl esters based biotinylation. The de novo synthesized <sup>N</sup>CXCL-G2- $AviTag^{C}$  synthetic sequences were subsequently inserted into a previously modified gWiz expression vector containing a DNA sequence encoding for a secretory leader peptide sequence ( $^{N}$ MRVPAQLLGLLLLWLPGARC $^{C}$ ), a Fc domain derived from murine IgG2 heavy-chain constant regions CH2 and CH3, followed by a sequence encoding a hexa-histidine tag (His6; <sup>N</sup>HHHHHHC), an eight amino-acid flexible linker (<sup>N</sup>SSGVDLGT<sup>C</sup>) and a Tobacco Etch Virus proteolytic cleavage site (TEV;  $^{N}$ ENLYFQ:A/V<sup>C</sup>) to obtain the final <sup>N</sup>Fc-His6-linker-TEV-CXCL-G2-AviTag<sup>C</sup> fusion proteins (FIG. 1). The His6-tag was inserted between the Fc domain and the TEV cleavage site for further purification steps. The sequence TEV proteolytic cleavage site allowed for a precisely processed N-terminus of the chemokines that was crucial for their activity. All constructs were verified by DNA sequencing (Macrogen) and termed Fc-CXCL fusion proteins (see Table 1 for information about protein accession number SEQ ID NOs: 31-42 for DNA and amino acid sequences).

TABLE 1

CXCL protein (residues/ accession No.)	Construct for expression	Fusion protein
Groa/hCXCL1 (38-107/P09341) ENA-78/hCXCL5 (43-114/P42830) IL-8/hCXCL8 (29-99/P10145) KC/mCXCL1 (28-96/P12850) MIP-2/mCXCL2 (31-100/P10889) LIX/mCXCL5 (48-118/P50228)	$\begin{array}{l} gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ hCXCL1^{38-107}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ hCXCL5^{43-114}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ hCXCL8^{29-99}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ mCXCL1^{28-96}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ mCXCL2^{31-100}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ mCXCL5^{48-118}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ mCXCL5^{48-118}-G_2-AviTag\\ gWiz-LS-Fc(mlgG2)-His_6-linker-TEV-\\ gWiz-LS-Fc(mlgG2)-Fc(m$	<sup>N</sup> Fc- hCXCL1 <sup>C</sup> <sup>N</sup> Fc- hCXCL5 <sup>C</sup> <sup>N</sup> Fc- mCXCL2 <sup>C</sup> <sup>N</sup> Fc- mCXCL2 <sup>C</sup> <sup>N</sup> Fc- mCXCL2 <sup>C</sup> <sup>N</sup> Fc- mCXCL2 <sup>C</sup>

**[0341]** Constructs for expression of <sup>N</sup>CXCL-SA<sup>C</sup> fusion proteins were generated by using DNA assembly methods such as Gibson Assembly (New England BioLabs) and In-Fusion Cloning (Clontech Laboratories, Takara Bio) technologies. PfuUltra II Fusion HS DNA Polymerase (Agilent Technologies) and Herculase II Fusion DNA Polymerase (Agilent Technologies) were used for the PCR amplification of the insert and the vector, respectively. DpnI enzyme was obtained from New England Biolabs and the oligonucleotide primers from Integrated DNA Technologies.

[0342] The synthetic DNA coding for the active protein form of twelve human and murine (ELR+) CXC chemokines and eight human and murine (ELR-) CXC chemokines were obtained from GeneArt Gene Synthesis (Thermo Fisher Scientific). Genes were codon-optimized for expression in mammalian cells. The de novo synthesized  $^{N}CXCL^{C}$  synthetic sequences were subsequently inserted into a previously modified gWiz expression vector containing a DNA sequence encoding for a secretory leader sequence (<sup>N</sup>MRVPAQLLGLLLWLPGARC<sup>C</sup>), a ten amino-acid flexible linker (<sup>N</sup>GGGGSGGGGS<sup>C</sup>), sequence encoding for mouse serum albumin (SA) followed by a sequence encoding for a five amino-acid flexible spacer ( $^{N}GGGGS^{C}$ ) and a hexa-histidine tag (His6; <sup>N</sup>HHHHHH<sup>C</sup>) to obtain <sup>N</sup>CXCL- $(G_4G)_2$ -SA- $G_4$ S-His<sub>6</sub><sup>C</sup> fusion proteins. The process of the leader sequence during the secretory pathway allows for a precisely cleaved N-terminus that is crucial for the activity of the chemokines. Genes encoding <sup>N</sup>CXCL(G<sub>4</sub>G)<sub>2</sub>-SA-G4S-His<sub>6</sub><sup>C</sup> fusion proteins were further sub-cloned into a new gWiz expression vector via Sail-HF (New England BioLabs) and MauBI (Thermo Fisher Scientific) restriction enzymes. All constructs were verified by DNA sequencing (Macrogen) and termed <sup>N</sup>CXCL-SA<sup>C</sup> fusion proteins (see Table 2 for information about protein accession number and SEQ ID NOs: 43-82 for DNA and amino-acid sequences).

TABLE 2

Expression and Purification of Fc Fusion Proteins

[0343] Fc fusion proteins  $^{N}$ Fc-CXCL<sup>C</sup> were expressed by transient transfection of suspension-adapted human embryonic kidney (HEK-293) cells. Protein production was performed either in house using FreeStyle 293 Expression System (Thermo Fisher Scientific) or outsourced to the Protein Expression Core Facility (PECF) of the Life Science Faculty of the EPFL, as described previously (Angelini, A. et al. Bicyclic peptide inhibitor reveals large contact interface with a protease target. ACS Chem Biol 7, 817-821 (2012); Angelini, A. et al. Chemical macrocyclization of peptides fused to antibody Fc fragments. Bioconjug Chem 23, 1856-1863 (2012); Zhu, E. F. et al. Synergistic innate and adaptive immune response to combination immunotherapy with anti-tumor antigen antibodies and extended serum half-life IL-2. Cancer Cell 27, 489-501 (2015)). At the end of the 7-day phase production, cells were harvested by centrifugation at 15,000×g for 30 minutes at 4° C. on an Avanti JXN-26 Centrifuge (Beckman Coulter). Any additional cell debris was removed from the medium by filtration through 0.22-µm PES membrane filters (Thermo Fisher Scientific) and the clarified medium diluted with 1/10 volume 10× PBS pH 7.4.

CXCL protein (residues/		Fusion
accession No.)	Construct for expression	protein
Groa/hCXCL1 (35-107/P09341)	gWiz-LS-hCXCL1 <sup>35-107</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL1-SA $^{C}$
Groß/hCXCL2 (35-107/P19875)	gWiz-LS-hCXCL2 <sup>35-107</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}\mathrm{hCXCL2}\text{-}\mathrm{SA}^{C}$
Groy/hCXCL3 (35-107/P19876)	gWiz-LS-hCXCL3 <sup>35-107</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}hCXCL3-SA^{C}$
PF-4/hCXCL4 (32-101/P02776)	gWiz-LS-hCXCL4 <sup>32-101</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL4-SA $^{C}$
ENA-78/hCXCL5 (44-114/ P42830)	gWiz-LS-hCXCL5 <sup>44-114</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL5-SA $^{C}$
GCP-2/hCXCL6 (43-114/P80162)	gWiz-LS-hCXCL6 <sup>43-114</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL6-SA $^{C}$
NAP-2/hCXCL7 (59-121/P02775)	gWiz-LS-hCXCL7 <sup>59-121</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL7-SA $^{C}$
IL-8/hCXCL8 (28-99/P10145)	gWiz-LS-hCXCL8 <sup>28-99</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL8-SA $^{C}$
MIG/hCXCL9 (23-125/Q07325)	gWiz-LS-hCXCL9 <sup>23-125</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	$^{N}$ hCXCL9-SA $^{C}$
IP-10/hCXCL10-SA (22-98/	gWiz-LS-hCXCL10 <sup>22-98</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-	NhCXCL10-
P02778)	(Gly <sub>4</sub> Ser)-His <sub>6</sub>	$SA^{C}$
I-TAC/hCXCL11-SA (22-94/	gWiz-LS-hCXCL11 <sup>22-94</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-	<sup>N</sup> hCXCL11-
O14625)	(Gly <sub>4</sub> Ser)-His <sub>6</sub>	$SA^C$
KC/mCXCL1-SA (25-96/P12850)	gWiz-LS-mCXCL1 <sup>25-96</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL1- SA <sup>C</sup>
MIP-2/mCXCL2-SA (28-100/ P10889)	gWiz-LS-mCXCL2 <sup>28-100</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL2- SA <sup>C</sup>
DCIP-1/mCXCL3-SA (28-100/ Q6W5C0)	gWiz-LS-mCXCL3 <sup>28-100</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL3- SA <sup>C</sup>
Pf-4/mCXCL4-SA (30-105/ Q9Z126)	gWiz-LS-mCXCL4 <sup>30-105</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL4- SA <sup>C</sup>
LIX/mCXCL5-SA (48-118/ P50228)	gWiz-LS-mCXCL5 <sup>48-118</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL5- SA <sup>C</sup>
Nap-2/mCXCL7-SA (48-113/ Q9EQI5)	gWiz-LS-mCXCL7 <sup>48-113</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL7- SA <sup>C</sup>
Mig/mCXCL9-SA (22-126/ Pl8340)	gWiz-LS-mCXCL9 <sup>22-126</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA-(Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL9- SA <sup>C</sup>
Ip-10/mCXCL10-SA (22-98/ P17515)	$gWiz-LS-mCXCL10^{22-98}-(Gly_4Ser)_2$ -mouse SA-(Gly_4Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL10- SA <sup>C</sup>
I-Tac/mCXCL11-SA (22-100/ Q9JHH5)	gWiz-LS-mCXCL11 <sup>22-100</sup> -(Gly <sub>4</sub> Ser) <sub>2</sub> -mouse SA- (Gly <sub>4</sub> Ser)-His <sub>6</sub>	<sup>N</sup> mCXCL11- SA <sup>C</sup>

[0344] Recombinant Fc fusions were captured on a rProtein A Sepharose Fast Flow resin (GE Healthcare), packed on a glass Econo-Column Chromatography column (Bio-Rad), that was previously equilibrated with 10 column volumes (CVs) of 1×PBS pH 7.4. The filter culture media was passed through the resin at a flow rate of approximately 2.5 mL/min at room temperature. The resin was then extensively washed with 10 CVs of 1×PBS pH 7.4 and the recombinant Fc fusions eluted in a single peak by applying 10 CVs of elution Buffer E (50 mM Glycine-HCl, pH 2.7). 2 CVs of neutralizing Buffer N (1 M Tris-HCl pH 8.5) were then immediately added to the eluted Fc fusion proteins to prevent protein denaturation. Eluted Fc fusions were diluted twice with 1×PBS pH 7.4 and concentrated by using 10000 NMWL Amicon Ultra-15 ultrafiltration devices (Millipore) at 4000× g and 4° C. on a Allegra X14R centrifuge (Beckman Coulter). The concentrated Fc fusion proteins were further subjected to size-exclusion chromatography (SEC) by using a Hiprep 26/10 desalting column (GE Healthcare) connected to an AKTApurifier system (GE Healthcare) equilibrated with Buffer T (50 mM Tris-HCl, 100 mM NaCl, 0.5 mM EDTA, pH 8.0). Purified Fc fusion proteins <sup>N</sup>Fc- $CXCL^{C}$  in Buffer T were further concentrated to 2 mg/mL by using 10000 NMWL Amicon Ultra-15 ultrafiltration devices (Millipore) at 4000×g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter) and cleaved by using recombinant TEV protease (0.5 mg/mL). Fc fusion:TEV at a molar ratio of 100:1 were incubated at 4° C. for up to 24 hours in a cleavage Buffer T supplemented with a 10:1 ratio of reduced (GSH) to oxidized (GSSG) L-glutathione (50 mM Tris-HCl, 100 mM NaCl, 0.5 mM EDTA, 3 mM GSH, 0.3 mM GSSG, pH 8.0) and complete protease inhibitor cocktail (Roche).

[0345] The further separation of matured cleaved CXC chemokines from the (i) Fc domain, (ii) un-cleaved Fc-CXCL fusion and (iii) recombinant TEV-His6 protease was performed by loading the cleavage mixture on a Ni Sepharose excel affinity resin (GE Healthcare), packed on a glass Econo-Column Chromatography column (Bio-Rad), that was previously equilibrated with 10 CVs of Buffer X (50 mM sodium phosphate, 500 M NaCl, pH 8.0). The mixture was passed through the resin at a flow rate of approximately 1 mL/min at room temperature and the flow-through containing cleaved <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins collected. The purified <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins were further concentrated by using a 3000 NMWL Amicon Ultra-15 ultrafiltration devices (Millipore) at 4000x g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter) and subjected to SEC by using a HiLoad 16/600 Superdex 75 prep-grade column (GE Healthcare) equilibrated with biotinylation Buffer R (50 mM Bicine, pH 8.3) on an AKTApurifier system (GE Healthcare). Purified <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins in Buffer R were then concentrated to approximately 100 µM by using 3000 NMWL Amicon Ultra-4 ultrafiltration devices (Millipore) at 4000× g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter).

**[0346]** Biotinylation of <sup>*N*</sup>CXCL-G2-AviTag<sup>*C*</sup> proteins was performed by using BirA enzyme (Avidity) according to manufacturer's guidelines. Briefly, enzymatic reaction included 50 nmol <sup>*N*</sup>CXCL-G2-AviTag<sup>*C*</sup> protein in Buffer R, 12  $\mu$ g of recombinant BirA enzyme (3 mg/mL; Avidity), 50  $\mu$ M d-biotin, 10 mM ATP pH 7.2 and 10 mM MgOAc for a total volume of 1 mL. To ensure complete biotinylation, the reaction was incubated at 4° C. for 48 hours with gentle

shacking and jumped started every 12 hours by adding  $50 \,\mu\text{L}$  of Biomix-A (500 mM Bicine, pH 8.3; Avidity) and  $50 \,\mu\text{L}$  of Biomix-B (100 mM ATP, 100 mM MgOAc, 500  $\mu\text{M}$  d-biotin; Avidity) to the reaction mix. These conditions were sufficient for complete quantitative reaction yielding one product with expected molecular mass ( $\Delta$ mass=226 Da).

[0347] Biotinylated <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins were further purified by using either reversed-phase high performance liquid chromatography (RP-HPLC) or SEC. RP-HPLC was performed on a Vydac C18 column (Grace & Co.) connected to a Waters HPLC system (Waters). A flow rate of 1 mL/min and a linear gradient was applied with a mobile phase composed of eluant A (99.9% v/v H2O and 0.1% v/v TFA) and eluant B (99.9% v/v ACN and 0.1% v/v TFA). This step efficiently removed unbound small molecules such as free biotin and ATP along with the BirA enzyme. Purified and biotinylated <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins were lyophilized, dissolved in 1×PBS pH 7.4 to a final protein concentration of approximately 100 µM, flash frozen in liquid nitrogen and stored at -80° C. Alternatively, biotinylated <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins were purified by SEC using a Superdex 75 10/300 GL column (GE Healthcare) equilibrated with 1×PBS pH 7.4 and connected to an AKTApurifier system (GE Healthcare).

[0348] The final purified and biotinylated proteins were further concentrated by using 3000 NMWL Amicon Ultra-0.5 centrifugal filter units (Millipore) at 14000× g and 4° C. on a Eppendorf 5702R centrifuge (Eppendorf) to a final protein concentration of approximately 100 µM, flash frozen in liquid nitrogen and stored at -80° C. After purification, the yield of pure and biotinylated <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins ranged from 1 to 5 mg/L of culture. Molecular weights were confirmed by reducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) using NuPAGE 4-12% Bis-Tris Gels (Thermo Fisher Scientific) in 2-(N-morpholino)ethanesulfonic acid (MES) buffer followed by SimplyBlue SafeStain (Thermo Fisher Scientific) and imaged on the Typhoon Trio imager (GE Healthcare). Biotinylated <sup>N</sup>CXCL-G2-AviTag<sup>C</sup> proteins migrated a single band in SDS-PAGE, with apparent molecular masses of about 8-10 kDa.

#### Mass Spectrometric Analysis

**[0349]** The molecular mass of each ELR+ CXC chemokine before and after biotinylation was determined with electrospray ionization mass spectrometry (ESI-MS) performed on a quadrupole time-of-flight mass spectrometer (Q-TOF) coupled to a  $C^3$  or  $C^8$  reversed phase HPLC column for desalting of protein samples. Both LC-MS Agilent 6520 ESI-Q-TOF (Agilent Technologies) and Waters LCT ESI-Q-TOF (Waters) systems, operated in a positive ionization mode, were used. Data were acquired, processed, and analyzed using the Agilent MassHunter (Agilent Technologies) or the MassLynx (Waters) software package. Mass spectrometry (i) confirmed the corrected mass of the purified biotinylated chemokines and (ii) showed that no un-biotinylated protein remains in the final sample.

Selection of Crossreactive Binders from a Naïve Library of Synthetic scFv Displayed on the Surface of Yeast

**[0350]** Crossreactive protein binders to human and murine ELR+ CXC chemokines based on the synthetic antibody single-chain variable fragment scaffold (scFv) were isolated using standard yeast surface display technology as previ-

ously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. *Methods Mol Biol* 1319, 3-36 (2015)). The yeast-displayed synthetic antibody naïve library "G" was constructed using homologous recombination-based methods as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. *Methods Mol Biol* 1319, 3-36 (2015); Van Deventer, J. A., Kelly, R. L., Rajan, S., Wittrup, K. D. & Sidhu, S. S. A switchable yeast display/secretion system. *Protein Eng Des Sel* 28, 317-325 (2015)). The library was constructed to display the synthetic scFv variants on the surface of yeast as C-terminal fusion of the a-agglutinin Aga2 protein ( $_{N}CXCL$ -Aga2p<sup>C</sup>).

**[0351]** Yeast surface display vectors were based on pCT-CON backbone and included a secretory leader sequence (<sup>N</sup>MQLLRCFSIFSVIASVLA<sup>C</sup>), a sequence encoding for the Aga2p protein, a sequence encoding for the influenza hemagglutinin epitope tag (HA; <sup>N</sup>YPYDVPDYA<sup>C</sup>), a fifteen amino-acid flexible linker (<sup>N</sup>GGGGSGGGGGGGGGGGGGC<sup>C</sup>), a sequence encoding for the synthetic scFv in the light (V<sub>L</sub>) to heavy (V<sub>H</sub>) chain orientation, separated by another fifteen amino-acid flexible linker (<sup>N</sup>GTTAASGSSGGSSSGA<sup>C</sup>). A sequence encoding for c-myc epitope tag (c-myc; <sup>N</sup>EQKLI-SEEDLQ<sup>C</sup>) was inserted at the C-terminus of the gene encoding the scFv to obtain<sup>N</sup>Aga2p-HA-(G<sub>4</sub>S)3-V<sub>L</sub>-linker-V<sub>H</sub><sup>-</sup>c-myc<sup>C</sup> fusion proteins.

[0352] Yeast display selection was performed by using an amount of yeast cells at least ten-fold larger than (i) the initial estimated naïve library size (1×109 unique clones) or (ii) the number of cells isolated from the previous round of either magnetic bead screening or flow cytometry sorting. The yeast cells display naïve library were grown in SD-CAA medium at 30° C. with shacking (250 rpm) and surface protein expression induced in galactose-containing SG-CAA media for 20 hours at 20° C. with shacking (250 rpm) as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). Before positive selection, yeast populations  $(1 \times 10^{10})$  underwent three sequential cycles of "negative" selection using uncoated Dynabeads biotin binder magnetic beads (Thermo Fisher Scientific). Ten-fold diversity library depleted of streptavidin-coated beads binders was screened against highly diverse human (hCXCL1, hCXCL5 and hCXCL8) and murine (mCXCL1, mCXCL1 and mCXCL5) biotinylated ELR+ CXC chemokines captured on magnetic beads. Two iterative cycles of magnetic bead selections followed by four cycles of fluorescence-activated cell sorting (FACS) were applied (FIG. 2B).

**[0353]** Complex positive selection schemes, in which tenfold of the cell output isolated from a pathway was incubated with a diverse ELR+ CXC chemokine target in the following pathway, were performed to force crossreactivity and thus enhance the probabilities of isolating crossreactive protein binders. Each cycle comprised growth of yeast cells, expression of the synthetic antibodies on the surface, binding to the immobilized CXC ELR+ chemokine ligands, washing and expansion of the isolated bound yeast cells as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. *Methods Mol* Biol 1319, 3-36 (2015)). Cells were washed using ice-cold PBSA buffer (1× PBS pH 7.4 supplemented with 0.1% w/v bovine serum albumin fraction V). For FACS, highly crossreactive protein binders were selected using a two-color labeling scheme based on fluorescent-conjugated detection reagents for expression (anti-c-myc epitope tag) and binding to ELR+ CXC chemokine (anti-biotin) at recommended dilutions. Notably, highly avidity magnetic and fluorescently labeled reagents (e.g. streptavidin and neutravidin) saturated with diverse biotinylated ELR+ CXC chemokines were used during the all the six selection cycles.

[0354] The use of highly avid reagents increased the likelihood of isolating crossreactive low affinity binders from the naïve library by exploiting the multivalent interaction between yeast cells and the preloaded target. Sorting was performed on BD FACSAria I and III sorter instruments (BD Biosciences) and data evaluated using FlowJo v.10.0.7 software (Tree Star). After six cycles of iterative selections, DNA plasmid was extracted from isolated yeast cells using Zymoprep Yeast Plasmid Miniprep II Kit (Zymo Research). Extracted DNA plasmids were further amplified in Escherichia coli, purified and used (i) to reveal the amino acid sequence of each selected protein binder by DNA sequencing (Macrogen), (ii) to transform new yeast cells to determine the binding affinity of single protein binder using yeast cell surface titrations, and (iii) as template to prepare mutagenized DNA for further library generation and co-evolution of both binding affinity and crossreactivity, as described below.

Single Antibody Clone Binding Affinity Characterization Using Yeast Surface Titrations

[0355] The equilibrium dissociation constant  $(K_D)$  of each individual selected protein binder towards single CXC chemokines was determined by using yeast surface display titrations as described previously (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). Yeast surface display combined to flow cytometry allowed measurement of K<sub>D</sub> directly on the surface of yeast cells without the need for additional sub-cloning, expression and purification steps that were instead necessary to characterize protein binders clones isolated using alternative display technologies (VanAntwerp, J. J. & Wittrup, K. D. Fine affinity discrimination by yeast surface display and flow cytometry. Biotechnol Prog 16, 31-37 (2000)). Importantly, the  $\mathrm{K}_D$  values measured using such method have been shown to be consistent with values obtained using alternative techniques for examining binding affinities such as Surface Plasmon Resonance (SPR), Bio-Layer Interferometry (BLI) and Kinetic Exclusion Assay (KinExA flow fluorimeter) (Razai, A. et al. Molecular evolution of antibody affinity for sensitive detection of botulinum neurotoxin type A. J Mol Biol 351, 158-169 (2005); Traxlmayr, M. W. et al. Strong Enrichment of Aromatic Residues in Binding Sites from a Charge-Neutralized Hyperthermostable Sso7d Scaffold Library. J Biol Chem (2016)).

**[0356]** In brief, DNA plasmids encoding single protein binder clones were transformed into genetically modified *Saccharomyces cerevisiae* yeast cells (EBY100 strain) using Frozen-EZ Yeast Transformation II Kit (Zymo Research) and plated on selective SD-CAA solid agar media. Individual colonies were inoculated in 5 mL SD-SCAA cultures, grown to mid-log phase (0D600=2-5) in SD-CAA media at 30° C. with shacking (250 rpm). Cells were induced in galactose-containing SG-CAA media for 20 hours at 20° C. with shacking (250 rpm) as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). The binding assays were conducted in 96-well plates (Corning) containing  $1 \times 10^4$  induced cells per well. Non-displaying yeast cells  $(1 \times 10^5)$  were added to each well and mixed to induced cells to ensure (i) proper cell pelleting and (ii) an excess of soluble CXC chemokine target over total number of yeast displayed protein binders (5×10<sup>4</sup> copies of protein/ yeast cell) in solution (Hackel, B. J., Kapila, A. & Wittrup, K. D. Picomolar affinity fibronectin domains engineered utilizing loop length diversity, recursive mutagenesis, and loop shuffling. Journal of molecular biology 381, 1238-1252 (2008)). Yeast cells displaying protein binders were incubated with varying concentration of soluble CXC chemokine fusions (<sup>N</sup>CXCL-SA<sup>S</sup>) bearing the His6 tag and the primary chicken anti-c-myc epitope tag (1:1000) antibody (Gallus Immunotech) overnight at 4° C. with shaking (150 rpm). Twelve to sixteen different concentrations of pure <sup>N</sup>CXCL- $SA^{C}$  fusion proteins, ranging from 10 pM to 10  $\mu$ M, were applied spanning a range of concentrations ten times both above and below the expected  $K_D$  value. After primary incubation, cells were pelleted (2500× g for 5 min at 4° C.) and washed twice with 200 µL ice-cold PBSA buffer. Secondary labeling was performed with goat anti-chicken and mouse anti-His6 epitope tag antibodies conjugated to Alexa Fluor dyes at recommended dilutions.

**[0357]** The 96-well plates were run on a high-throughput plate sampler iQue Screener (IntelliCyt) or individually analyzed on an Accuri C6 Flow Cytometer (BD Accuri Cytometers). Data were evaluated using FlowJo v.10.0.7 software (Tree Star). To ensure that the differences in binding were not due to variations of number of proteins expressed on the surface of yeast cell, the median fluorescence intensity (MFI<sub>*DISP*</sub>) from binding signal (His6 tag) was normalized to the median fluorescence intensity (MFI<sub>*DISP*</sub>) from display signal (c-myc tag). The normalized (binding/display=MFI<sub>*BIND*/MFI<sub>*DISP*</sub>) median fluorescence intensity as a function of CXC chemokine concentration was used to determine the K<sub>D</sub> values for all clones of interest. Values reported here are the results of three independent experiments and are presented as mean (dots)±SE (bars).</sub>

Co-Evolution of Protein Binding Affinity and Crossreactivity by Yeast Surface Display

[0358] Two series of random mutagenesis and FACSbased selections (namely I and II) were applied to improve both the binding affinity and crossreactivity of three crossreactive clones: CK1, CK2 and CK4. Random mutagenesis libraries were generated by error-prone PCR as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). To ensure a mutagenesis rate of approximately 1-2 amino acid mutated residues distributed randomly throughout the entire gene, 1 ng of DNA template encoding the CK1, CK2 and CK4 binders were PCR amplified for 15 cycles using Taq DNA polymerase (New England BioLabs), analogue nucleotides (2 µM 8-oxo-dGTP and 2 µM dPTP) and flanking oligonucleotide primers (forward: 5'-GGAGGCGGTAGCGGAGGCG-

5'-GTCCTCTTCAGAAATAAGCTTTTGTTCGGAT-3'; Integrated DNA Technologies).

reverse:

**[0359]** The mutagenized PCR products were further purified, re-amplified for additional 30 cycles in the absence of analogue nucleotides and combined with SalI-HF, NheI-HF

and BamHI-HI (New England BioLabs) digested pCT-CON vector at a molar ratio of 2.5:1. Pre-mixed DNA linearized vector and PCR insert (1 µm/µL) was electroporated into freshly prepared Saccharomyces cerevisiae EBY100 competent cells, where the full constructs are reassembled via homologous recombination (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). Transformed cultures were recovered and expanded in SD-SCAA. Small portions of transformed cells were serially diluted and titrated on SD-SCAA plates to confirm the final reported library sizes (Table 3). Library quality and diversity was further assessed by sequencing twenty colonies of each library. All clones sequenced from the mutagenized libraries were found to be in the expected format. The yeast cells display mutagenized libraries were grown in SD-CAA medium at 30° C. with shacking (250 rpm) and surface protein expression induced in galactose-containing SG-CAA media for 20 hours at 20° C. with shacking (250 rpm) as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)).

TABLE 3

Library name	Template	Library size
CK1-lib I	CK1	$1.0 \times 10^{8}$
CK2-lib I	CK2	$2.0 \times 10^{8}$
CK4-lib I	CK4	$8.0 \times 10^{7}$
CK1-lib II	CK19	$3.0 \times 10^{8}$
CK2-lib II	CK41	$5.0 \times 10^{8}$
CK4-lib II	CK50	$4.0 \times 10^{8}$

[0360] An amount of yeast cells at least ten-fold larger than the estimated mutagenized libraries size were screened against human (hCXCL1, hCXCL5 and hCXCL8) and murine (hCXCL1, hCXCL2 and hCXCL5) biotinylated ELR+ CXC chemokines using equilibrium-based selection strategies. Six sequential cycles of FACS were applied. Each cycle comprised growth of yeast cells, expression of the binders on the surface, binding to the immobilized CXC ELR+ chemokine ligands, washing and expansion of the isolated bound yeast cells as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). Complex selection schemes, in which ten-fold of the cell output isolated from a pathway was incubated with a diverse ELR+ CXC chemokine target in the following pathway, were performed to force crossreactivity and thus enhance the probabilities of isolating crossreactive protein binders. Decreasing concentrations [C] of biotinylated CXC ELR+ chemokines up to ten-fold below the measured  $K_D$  were used for each round of selection ([C]= $0.1 \times K_D$ ) in order to select for crossreactive clones with improved affinity. Secondary fluorescent-conjugated detection reagents for FACS were constantly alternated to avoid enrichments of clones that could bind to them. Sorting was performed on BD FACSAria I and III sorter instruments (BD Biosciences) and data evaluated using FlowJo v.10.0.7 software (Tree Star). After six cycles of iterative selections, DNA plasmid was extracted from isolated yeast cells and used for further DNA sequencing and single clone characterization as described above.

GAGGGTCGGCTAGC-3';

Combination of Individual Mutations by Site-Directed Mutagenesis

**[0361]** Individual mutations from different protein binders were combined to further enhance affinity and specificity. A third step of site directed mutagenesis (namely III) was applied to combine mutations derived from different CK1 and CK2 lineage-derived clones. Site-directed mutagenesis was performed by whole plasmid PCR using QuikChange site directed mutagenesis kit (Agilent Technologies) and pairs of complementary primers carrying single point mutations (Integrated DNA Technologies). The DNA sequences encoding CK63, CK66 and CK72 (CK1 lineage) and CK108, CK111 and CK119 (CK2 lineage) were used as templates to generate fifteen (CK131-CK145) and thirteen (CK146-CK158) variants, respectively, each including different combinations of CDR and FWR mutations. All constructs were verified by DNA sequencing (Macrogen).

**[0362]** Single mutants were displayed on the surface of *Saccharomyces cerevisiae* strain EBY100 using Frozen-EZ Yeast Transformation II Kit (Zymo Research) and plated on selective SD-CAA solid agar media. Individual colonies were inoculated in 5 mL SD-SCAA cultures, grown to mid-log phase (0D600=2-5) in SD-CAA media at 30° C. with shacking (250 rpm). Cells were induced in galactose-containing SG-CAA media for 20 hours at 20° C. with shacking (250 rpm) as previously described (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. *Methods Mol* Biol 1319, 3-36 (2015)). The equilibrium dissociation constant (K<sub>D</sub>) of each individual clone towards single CXC chemokines was determined by using yeast surface display titrations combined to flow cytometry as described above.

Cloning of Selected Synthetic scFv Fused to Mouse Serum Albumin Protein for Mammalian Cell Line Expression [0363] Selected crossreactive synthetic single light  $(V_L)$ 

and heavy  $(V_H)$  chain antibody variable fragments (scFv) were cloned and expressed in mammalian cells as C-terminal fusion of the murine serum albumin (SA) protein (<sup>N</sup>SA $scFv^{C}$ ). Mammalian expression vectors were based on gWiz (Genlantis). Constructs for expression of  $^{N}$ SA-scFv<sup>C</sup> fusion proteins were generated by using DNA assembly methods such as Gibson Assembly (New England BioLabs) or In-Fusion Cloning (Clontech Laboratories, Takara Bio) technologies. PfuUltra II Fusion HS DNA Polymerase (Agilent Technologies) and Herculase II Fusion DNA Polymerase (Agilent Technologies) were used for the PCR amplification of the insert and the vector, respectively. DpnI enzyme was obtained from New England Biolabs and oligonucleotide primers from Integrated DNA Technologies. The DNA sequences encoding the scFv ( $V_L$ - $V_H$  orientation) CK129, CK138 and CK157 as well as separate  $V_L$  and  $V_H$  domains of CK157 were amplified in a PCR reaction by using the pCT-CON vector as template and following inserted into a previously modified gWiz expression vector containing a DNA sequence encoding for a secretory leader peptide sequence (<sup>N</sup>MDMRVPAQLLGLLLLWLPGARC<sup>C</sup>) followed by a sequence encoding the mouse serum albumin а fifteen amino-acid flexible (SA). linker ( $^{N}$ GGGGSGGGGGGGGGGGGC). A sequence encoding for a five amino-acid flexible linker (<sup>N</sup>GGGGS<sup>C</sup>) followed by a hexa-histidine tag (His6; <sup>N</sup>HHHHHHC) was inserted at the C-terminus of the gene encoding the scFv to obtain the final  $^{N}$ SA-(G<sub>4</sub>S)<sub>3</sub>-scFv-G<sub>4</sub>S-His6<sup>*C*</sup>,  $^{-N}$ SA-(G<sub>4</sub>S)<sub>3</sub>V<sub>*L*</sub>-G<sub>4</sub>S-His6<sup>*C*</sup> and  ${}^{N}SA(G_{4}S)_{3}-V_{H}-His_{6}{}^{C}$  fusion proteins (FIG. 6). In a similar fashion, the control scFv (V<sub>H</sub>-V<sub>L</sub> orientation) targeting the human carcinoembryonic antigen (CEA) (Graff, C. P., Chester, K., Begent, R. & Wittrup, K. D. Directed evolution of an anti-carcinoembryonic antigen scFv with a 4-day monovalent dissociation half-time at 37 degrees C. Protein Eng Des Sel 17, 293-304 (2004)) was fused at the C-terminus of mouse serum albumin. The stability of the each scFv was further improved by connecting the  $V_L$  and  $V_H$  domains via an intermolecular disulfide bond (ds). The addition of stabilizing intermolecular disulfide bridges is reported to increase the percent of monomeric forms by permanently fixing monomer:dimer ratios during the purification steps. Two of the most favorable locations were selected for the introduction of pairs of cysteine residues into each single scFv (dsl: VL100 and VH44; ds2: VL43 and VH105; Kabat numbering system) (Reiter, Y. et al. Stabilization of the Fv fragments in recombinant immunotoxins by disulfide bonds engineered into conserved framework regions. Biochemistry 33, 5451-5459 (1994); Jung, S. H., Pastan, I. & Lee, B. Design of interchain disulfide bonds in the framework region of the Fv fragment of the monoclonal antibody B3. Proteins 19, 35-47 (1994); Weatherill, E. E. et al. Towards a universal disulphide stabilised single chain Fv format: importance of interchain disulphide bond location and vL-vH orientation. Protein Eng Des Sel 25, 321-329 (2012); Kabat, E. A., Wu, T. T., Perry, H., Gottesman, K. and Foeller, C. Sequences of Proteins of Immunological Interest, Edn. Fifth Edition. (1991)) and their relative effects on expression, percent monomer formation and retention of antigen binding compared. Cysteine residues were introduced into each scFv by site-directed mutagenesis using DNA assembly methods such as Gibson-Assembly (New England BioLabs) or In-Fusion Cloning (Clontech Laboratories, Takara Bio) technologies and standard oligonucleotide primers carrying single point mutations (Integrated DNA Technologies). Final genes encoding <sup>N</sup>SA-(G<sub>4</sub>S)<sub>3</sub>scFv-G<sub>4</sub>S-His6<sup>*C*</sup>, <sup>*N*</sup>SA-(G<sub>4</sub>S)<sub>3</sub>-scFv-ds1-G<sub>4</sub>S-His6<sup>*C*</sup>, <sup>*N*</sup>SA-(G<sub>4</sub>S)<sub>3</sub>-scFv-ds2-G<sub>4</sub>S-His6<sup>*C*</sup>, <sup>*N*</sup>SA-(G<sub>4</sub>S)<sub>3</sub>-scFv-ds2-G<sub>4</sub>S-His6<sup>*C*</sup>, <sup>*N*</sup>SA(G<sub>4</sub>S)<sub>3</sub>-V<sub>*L*</sub>-G<sub>4</sub>S-His6<sup>*C*</sup> and <sup>*N*</sup>SA-(G<sub>4</sub>S)<sub>3</sub>-V<sub>*L*</sub>-G<sub>4</sub>S-His6<sup>*C*</sup> fusion proteins were further subcloned into a new gWiz expression vector via NotI-HF and XbaI (New England BioLabs) restriction enzymes. All constructs were verified by DNA sequencing (Macrogen, Cambridge, Mass.) and termed <sup>N</sup>CXCL-SA<sup>C</sup> fusion proteins (see Table 4 for information about protein accession number and SEQ ID NOs: 83-106 for DNA and amino-acid sequences). The serum albumin-antibody fusion formats were used for all in vitro and in vivo studies.

TABLE 4

Fusion protein (code name)	Construct for expression
<sup>N</sup> SA-CK138 <sup>C</sup> (SA138) <sup>N</sup> SA-CK157 <sup>C</sup> (SA157)	gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK138-(Gly <sub>4</sub> Ser)-His <sub>6</sub> gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK157-(Gly <sub>4</sub> Ser)-His <sub>6</sub>

Fusion protein (code name)	Construct for expression
<sup>N</sup> SA-CK129 <sup>C</sup> (SA129) <sup>N</sup> SA-CK138-ds1 <sup>C</sup> (SA138- ds1) <sup>N</sup> SA-CK138-ds2 <sup>C</sup> (SA138- ds2) <sup>N</sup> SA-CK157-ds1 <sup>C</sup> (SA157- ds1) <sup>N</sup> SA-CK157-ds2 <sup>C</sup> (SA157- ds2) <sup>N</sup> SA-CK157-VL <sup>C</sup> (SA157- VL) <sup>N</sup> SA-CK157-VL <sup>C</sup> (SA157- VL)	gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK129-(Gly <sub>4</sub> Ser)-His <sub>6</sub> gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK138-ds1 (V <sub>L</sub> 100 <sup>Q&gt;C</sup> / V <sub>H</sub> 44 <sup>G&gt;C</sup> )-(Gly <sub>4</sub> Ser)-His <sub>6</sub> gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK138-ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )-(Gly <sub>4</sub> Ser)-His <sub>6</sub> gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK157-ds1 (V <sub>L</sub> 100 <sup>Q&gt;C</sup> / V <sub>H</sub> 44 <sup>E&gt;C</sup> )-(Gly <sub>4</sub> Ser)-His <sub>6</sub> gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser) <sub>3</sub> -scFv (V <sub>L</sub> -V <sub>H</sub> ) CK157-ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )-(Gly <sub>4</sub> Ser)-His <sub>6</sub> gWiz-LS-mouse SA-(Gly <sub>4</sub> Ser)-V <sub>L</sub> CK157-HiS <sub>6</sub>
<sup>N</sup> SA-CK157-VH <sup>C</sup> (SA157- VH) <sup>N</sup> SA-CK129-ds1 <sup>C</sup> (SA129- ds1) <sup>N</sup> SA-CK129-ds2 <sup>C</sup> (SA129- ds2) <sup>N</sup> SA-sm3e-ds <sup>C</sup> (SActr)	$\begin{array}{l} \label{eq:gwiz-LS-mouse SA-(Gly_4Ser)-V_H CK157-HiS_6} \\ \mbox{gwiz-LS-mouse SA-(Gly_4Ser)_3-scFv} \ (V_L-V_H) \ CK129-ds1 \ (V_L100^{Q>C/} V_H44^{Q>C})-(Gly_4Ser)-His_6} \\ \mbox{gwiz-LS-mouse SA-(Gly_4Ser)_3-scFv} \ (V_L-V_H) \ CK129-ds2 \ (V_L43^{A>C/} V_H105^{Q>C})-(Gly_4Ser)-His_6} \\ \mbox{gwiz-LS-mouse SA-(Gly_4Ser)_3-scFv} \ (V_H V_L) \ \mbox{sm3E-ds} \ (V_H44^{R>C/} V_L100^{Q>C})-(Gly_4Ser)-His_6} \\ \mbox{gwiz-LS-mouse SA-(Gly_4Ser)-His_6} \\ \mbox{gwiz-LS-mouse SA-(Gly_4Ser)-His_6} \\ \mbox{Wiz-LS-mouse SA-(Gly_4Ser)-His_6} \\ \mbox{gwiz-LS-mouse SA-(Gly_4Ser)-His_6} \\ gwiz-LS-mouse SA-(Gly_4Ser)-His_6$

Expression and Purification of Serum Albumin Fusion Proteins

[0364] Serum albumin (SA) fusion proteins <sup>N</sup>CXCL-SA<sup>C</sup> and  $^{N}SA$ -scFv<sup>C</sup> were expressed by transient transfection of suspension-adapted human embryonic kidney (HEK-293) cells. Protein production was performed either in house using FreeStyle 293 Expression System (Thermo Fisher Scientific) or outsourced to the Protein Expression Core Facility (PECF) of the Life Science Faculty of the EPFL, as described previously (Angelini, A. et al. Bicyclic peptide inhibitor reveals large contact interface with a protease target. ACS Chem Biol 7, 817-821 (2012); Angelini, A. et al. Chemical macrocyclization of peptides fused to antibody Fc fragments. Bioconjug Chem 23, 1856-1863 (2012); Zhu, E. F. et al. Synergistic innate and adaptive immune response to combination immunotherapy with anti-tumor antigen antibodies and extended serum half-life IL-2. Cancer Cell 27, 489-501 (2015)). At the end of the 7-day phase production, cells were harvested by centrifugation at 15,000×g for 30 minutes at 4° C. on an Avanti JXN-26 Centrifuge (Beckman Coulter). Any additional cell debris was removed from the medium by filtration through 0.22-um PES membrane filters (Thermo Fisher Scientific) and the clarified medium diluted with 1/10 volume Buffer A (500 mM sodium phosphate, 5 M NaCl, pH 8.0). Recombinant SA fusions were captured on a Ni Sepharose excel affinity resin (GE Healthcare), packed on a glass Econo-Column chromatography column (Bio-Rad), that was previously equilibrated with 10 CVs of Buffer B (50 mM sodium phosphate, 500 M NaCl, pH 8.0). The medium was passed through the resin at a flow rate of approximately 2.5 mL/min at room temperature. The resin was then extensively washed with 10 CVs of Buffer B and the recombinant SA fusions eluted in a single peak by applying 10 CVs of Buffer C (50 mM sodium phosphate, 500 M NaCl, 500 mM Imidazole, pH 8.0). Eluted SA fusions were following diluted with 10 CVs of Buffer B and concentrated by using 10000 NMWL Amicon Ultra-15 ultrafiltration devices (Millipore) at 4000× g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter). The concentrated SA fusion proteins were further purified by size exclusion chromatography using a HiLoad 16/600 Superdex 200 prep-grade column (GE Healthcare) equilibrated with 1×PBS pH 7.4 on an AKTApurifier system (GE Healthcare). Purified SA fusion proteins in 1×PBS pH 7.4 were following concentrated to 5 mg/ml ( $^{N}$ CXCL-SA $^{C}$ ) and 2 mg/mL ( $^{N}$ SA-scFv $^{C}$ ) final concentration by using 10000 NMWL Amicon Ultra-15 ultrafiltration devices (Millipore) at 4000× g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter).

[0365] Protein concentrations were determined by measuring absorbance at 280 nm using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific). Molecular weights were confirmed by reducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) using NuPAGE 4-12% Bis-Tris Gels (Life Technologies) in 3-(Nmorpholino) propanesulfonic acid (MOPS) buffer followed by SimplyBlue SafeStain (Life Technologies) and imaged on the Typhoon Trio imager (GE Healthcare). All purified SA fusion proteins migrated a single band in SDS-PAGE with an apparent molecular mass of approximately 75 kDa (for <sup>N</sup>CXCL-SA<sup>C</sup>), 80 kDa (<sup>N</sup>SA-V<sub>L</sub><sup>C</sup> or (<sup>N</sup>SA-V<sub>H</sub><sup>C</sup>) and 95 kDa ( $^{N}SA$ -scFv<sup>C</sup>). The monodisperse state of concentrated SA fusion proteins was confirmed by size-exclusion chromatography using a Superdex 200 10/300 GL column (GE Healthcare) connected to an AKTApurifier system and equilibrated with 1×PBS pH 7.4. Purified SA fusion proteins were eluted as a single peak at elution volumes  $(V_e)$  that corresponds to apparent molecular masses ranging between 150 kDa (dimer) and 300 kDa (tetramer) in the case of <sup>N</sup>SA-CXCL<sup>C</sup> fusions while <sup>N</sup>SA-scFv<sup>C</sup> fusions were eluted with Ve that corresponds to apparent molecular masses of about 95 kDa (monomer). Size exclusion chromatography columns and the FPLC system used for purifi-cation of  $^{N}SA$ -scFv<sup>C</sup> fusions for animal studies were pretreated with 1M NaOH to remove endotoxins. Purified <sup>N</sup>SA-scFv<sup>C</sup> fusions were further filtered sterile by passing them through a 0.2 µm syringe filters (Pall Life Sciences) and confirmed to contain minimal levels of endotoxin (<0.1 EU/mL) using the QCL-1000 Limulus Amebocyte Lysate (LAL) chromogenic test following the manufacturer's instructions (Lonza).

Biotinylation of Serum Albumin Fusion Proteins and Commercial Antibodies

**[0366]** Reactive EZ-link sulfo-NHS-LC-biotin (Thermo Fisher Scientific) was dissolved in 1×PBS pH 7.4 to obtain

a final concentration of 10 mM. Protein conjugates containing biotin were prepared by incubating serum albumin fusion proteins (at concentrations of 2 mg/mL in 1×PBS pH 7.4) with ten-fold molar excess of EZ-link sulfo-NHS-LCbiotin for 30 minutes at room temperature. Excess of unreacted or hydrolyzed biotinylation reagent was removed using size-exclusion chromatography with Superdex 200 10/300 GL (GE Healthcare) connected to an AKTApurifier system (GE Healthcare) and equilibrated with buffer 1×PBS pH 7.4. Fractions corresponded to the expected protein pick were pulled and concentrated to a final concentration of 2 mg/mL using 10000 NMWL Amicon Ultra-4 ultrafiltration devices (Millipore) at 4000× g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter). Final protein concentrations were measured using a NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific).

## Display of CXC Chemokine on Surface of Yeast Cells

[0367] The ELR+ and (ELR-) CXC chemokines were displayed on the surface of yeast as N-terminal fusion of the a-agglutinin Aga2 protein (<sup>N</sup>CXCL-Aga2p<sup>C</sup>). Yeast surface display vectors were based on pCT backbone (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. *Methods Mol Biol* 1319, 3-36 (2015)). Constructs for surface display of <sup>N</sup>CXCL-Aga2<sup>C</sup> fusion proteins were generated by using Gibson Assembly (New England BioLabs) or In-Fusion Cloning (Clontech Laboratories, Takara Bio) technologies. PfuUltra II Fusion HS DNA Polymerase (Agilent Technologies) and Herculase II Fusion DNA Polymerase (Agilent Technologies) were used for the PCR

amplification of the insert and the vector, respectively. DpnI enzyme was obtained from New England Biolabs and oligonucleotide primers from Integrated DNA Technologies. The synthetic DNA coding for the active protein form of twelve human and murine ELR+ CXC chemokines and eight human and murine (ELR-) CXC chemokines were obtained from GeneArt Gene Synthesis (Thermo Fisher Scientific). The de novo synthesized genes encoding for the active processed form of each CXC chemokine were subsequently inserted into a previously modified yeast display pCT vector containing a DNA sequence encoding for a secretory leader sequence (<sup>N</sup>MKVLIVLLAIFAALPLA-LAQPVISTTVGSAAEGSLDKR<sup>C</sup>), a three amino-acid flexible spacer (<sup>N</sup>GGG<sup>C</sup>), a sequence encoding for c-myc epitope tag (c-myc; <sup>N</sup>EQKLISEEDLQ<sup>C</sup>) followed by a sequence encoding for the Aga2p protein to obtain <sup>N</sup>CXCL- $(G_3)$ -c-myc-Aga2p<sup>C</sup> fusion proteins. The process of the leader sequence during the secretory pathway allows for a precisely cleaved N-terminus that is crucial for the activity of the mature chemokines. Genes encoding <sup>N</sup>CXCL-(G<sub>3</sub>)c-myc-Aga $2p^{C}$  fusion proteins were further sub-cloned into a new pCT vector via Bpu10I and XhoI (New England BioLabs) restriction enzymes except for MIP-2 for which PstI-HF and XhoI (New England BioLabs) restriction enzymes were used. All constructs were verified by DNA sequencing (Macrogen) and termed  $^{N}$ CXCL-Aga2p<sup>C</sup> fusion proteins (see Table 5 for information about protein accession number and SEQ ID NOs: 107-146 for DNA and amino-acid sequences).

TABLE 5

CXCL protein (residues/		Fusion
accession No.)	Construct for expression	protein
Groα/hCXCL1 (38-107/P09341)	pCHA-LS-hCXCL1 <sup>38-107</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL1-Aga2 <sup>C</sup>
Groβ/hCXCL2 (38-107/P19875)	pCHA-LS-hCXCL2 <sup>38-107</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL2-Aga2 <sup>C</sup>
Groy/hCXCL3 (38-107/P19876)	pCHA-LS-hCXCL3 <sup>38-107</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL3-Aga2 <sup>C</sup>
PF-4/hCXCL4 (32-101/P02776)	pCHA-LS-hCXCL4 <sup>32-101</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL4-Aga2 <sup>C</sup>
ENA-78/hCXCL5 (44-114/P42830)	pCHA-LS-hCXCL5 <sup>44-114</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL5-Aga2 <sup>C</sup>
GCP-2/hCXCL6 (44-114/P80162)	pCHA-LS-hCXCL6 <sup>44-114</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL6-Aga2 <sup>C</sup>
NAP-2/hCXCL7 (59-121/P02775)	pCHA-LS-hCXCL7 <sup>59-121</sup> -G <sub>3</sub> -c-myc- Aga2	$^{N}$ hCXCL7-Aga2 $^{C}$
IL-8/hCXCL8 (29-99/P10145)	pCHA-LS-hCXCL8 <sup>29-99</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> hCXCL8-Aga2 <sup>C</sup>
MIG/hCXCL9 (23-125/Q07325)	pCHA-LS-hCXCL9 <sup>23-125</sup> -G <sub>3</sub> -c-myc- Aga2	$^{N}$ hCXCL9-Aga2 $^{C}$
IP-10/hCXCL10-SA (22-98/P02778)	pCHA-LS-hCXCL10 <sup>22-98</sup> -G <sub>3</sub> -c-myc- Aga2	$^{N}$ hCXCL10-Aga2 $^{C}$
I-TAC/hCXCL11-SA (22-94/O14625)	pCHA-LS-hCXCL11 <sup>22-94</sup> -G <sub>3</sub> -c-myc- Aga2	$^{N}$ hCXCL11-Aga2 $^{C}$
KC/mCXCL1-SA (28-96/P12850)	Aga2 pCHA-LS-mCXCL1 <sup>28-96</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL1-Aga2 <sup>C</sup>
MIP-2/mCXCL2-SA (31-100/P10889)	pCHA-LS-mCXCL2 <sup>31-100</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL2-Aga2 <sup>C</sup>
DCIP-1/mCXCL3-SA (31-100/Q6W5C0)	pCHA-LS-mCXCL3 <sup>31-100</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL3-Aga2 <sup>C</sup>
Pf-4/mCXCL4-SA (30-105/Q9Z126)	Aga2 pCHA-LS-mCXCL4 <sup>30-105</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL4-Aga2 <sup>C</sup>
LIX/mCXCL5-SA (48-118/P50228)	Aga2 pCHA-LS-mCXCL5 <sup>48-118</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL5-Aga2 <sup>C</sup>
Nap-2/mCXCL7-SA (48-113/Q9EQI5)	Aga2 pCHA-LS-mCXCL7 <sup>48-113</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL7-Aga2 <sup>C</sup>

TABLE 5-continued

CXCL protein (residues/ accession No.)	Construct for expression	Fusion protein
Mig/mCXCL9-SA (22-126/P18340)	pCHA-LS-mCXCL9 <sup>22-126</sup> -G <sub>3</sub> -c-myc- Aga2	$^{N}$ mCXCL9-Aga $2^{C}$
Ip-10/mCXCL10-SA (22-98/P17515)	pCHA-LS-mCXCL10 <sup>22-98</sup> -G <sub>3</sub> -c-myc- Aga2	<sup>N</sup> mCXCL10-Aga2 <sup>C</sup>
I-Tac/mCXCL11-SA (22-100/Q9JHH5)	pCHA-LS-mCXCL11 <sup>22-100</sup> -G <sub>3</sub> -c-myc-Aga2	<sup>N</sup> mCXCL11-Aga2 <sup>C</sup>

[0368] The  $^{N}$ CXCL-Aga2p<sup>C</sup> fusion proteins were displayed on the surface of Saccharomyces cerevisiae strain EBY100 using a standard protocol as described previously (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. Methods Mol Biol 1319, 3-36 (2015)). Briefly, EBY100 yeast cells were transformed with pCT vectors encoding  $^{N}$ CXCL-Aga2p<sup>C</sup> fusion proteins using Frozen-EZ Yeast Transformation II Kit (Zymo Research). Cells were grown to mid-log phase in SD-CAA media at 30° C. and induced in galactose-containing media SG-CAA for 20 hours at 2° C. Staining of C-terminus c-myc epitope tag indicated that all the CXC chemokines are expressed well on the surface of yeast (approximately 105 copies per cell, a standard for yeast surface display). The proper folding of yeast displayed CXC chemokines was assessed by measuring binding of some displayed CXC chemokines to a panel of commercial neutralizing antibodies.

## Epitope Mapping by Alanine-Scanning Mutagenesis

[0369] Functional binding residues were identified by alanine-scanning mutagenesis using yeast surface display technology combined to flow cytometry. Yeast surface display has been shown to provide a simple, flexible and robust method for fine resolution epitope mapping of both fulllength or single-domain protein (Chao, G., Cochran, J. R. & Wittrup, K. D. Fine epitope mapping of anti-epidermal growth factor receptor antibodies through random mutagenesis and yeast surface display. J Mol Biol 342, 539-550 (2004); Cochran, J. R., Kim, Y. S., Olsen, M. J., Bhandari, R. & Wittrup, K. D. Domain-level antibody epitope mapping through yeast surface display of epidermal growth factor receptor fragments. J Immunol Methods 287, 147-158 (2004); Levy, R. et al. Fine and domain-level epitope mapping of botulinum neurotoxin type A neutralizing antibodies by yeast surface display. J Mol Biol 365, 196-210 (2007); Mata-Fink, J. et al. Rapid conformational epitope mapping of anti-gp120 antibodies with a designed mutant panel displayed on yeast. J Mol Biol 425, 444-456 (2013)). Alanine was chosen as a standard replacement residue for the identification of functional epitopes because it is found commonly in both buried and exposed positions, and it is present in all type of secondary structures. Moreover, alanine does not impose new hydrogen bonding, or lead to stearic problems, and is therefore less likely to cause misfolding of the protein (Wells, J. A. Systematic mutational analyses of protein-protein interfaces. Methods Enzymol 202, 390-411 (1991); Morrison, K. L. & Weiss, G. A. Combinatorial alanine-scanning. Curr Opin Chem Biol 5, 302-307 (2001)). The commonly bound human ELR+ CXC chemokine hCXCL1 (Groa) was selected for alanine-scanning experiments.

[0370] Tridimensional structural analysis and literature data were combined to identify Groa residues suitable for mutagenesis (Fairbrother, W. J., Reilly, D., Colby, T. J., Hesselgesser, J. & Horuk, R. The solution structure of melanoma growth stimulating activity. J Mol Biol 242, 252-270 (1994); Kim, K. S., Clark-Lewis, I. & Sykes, B. D. Solution structure of GRO/melanoma growth stimulatory activity determined by 1H NMR spectroscopy. J Biol Chem 269, 32909-32915 (1994); Poluri, K. M., Joseph, P. R., Sawant, K. V. & Rajarathnam, K. Molecular basis of glycosaminoglycan heparin binding to the chemokine CXCL1 dimer. J Biol Chem 288, 25143-25153 (2013); Ravindran, A., Sawant, K. V., Sarmiento, J., Navarro, J. & Rajarathnam, K. Chemokine CXCL1 dimer is a potent agonist for the CXCR2 receptor. J Biol Chem 288, 12244-12252 (2013); Sepuru, K. M. & Rajarathnam, K. CXCL1/MGSA Is a Novel Glycosaminoglycan (GAG)-binding Chemokine: STRUC-TURAL EVIDENCE FOR TWO DISTINCT NON-OVER-LAPPING BINDING DOMAINS. J Biol Chem 291, 4247-4255 (2016)). Solvent accessibility of hCXCL1 amino acid residues was determined by using both ASAView (Ahmad, S., Gromiha, M., Fawareh, H. & Sarai, A. ASAView: database and tool for solvent accessibility representation in proteins. BMC Bioinformatics 5, 51 (2004)) and PyMOL (PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC) tools. Structurally buried hydrophobic amino acids (I23, V40, A42, L52, V59, I62 and I63) as well as proline (P20, P31, P33, P54 and P57) and cysteine (C9, C11, C35 and C52) residues that are crucial for overall folding and stability of the chemokine were left unaltered. The wild-type hCXCL1 was displayed on the surface of yeast as the amino terminus fusion of the a-agglutinin Aga2 (<sup>*N*</sup>hCXCL1<sup>*WT*</sup>-Aga2p<sup>*C*</sup>). Gene protein encoding  $^{N}$ hCXCL1 $^{WT}$ -(G<sub>3</sub>)-c-myc-Aga2p<sup>C</sup> fusion protein was subcloned into a new pCT vector via Bpu10I and XhoI (New England BioLabs) restriction enzymes. The obtained pCThCXCL1<sup>WT</sup>-Aga2 vector was used as the template for the site-directed mutagenesis. Mutagenic oligonucleotides were designed to introduce single point mutations at the desired sites and generate fifty-four hCXCL1 variants (pCT-hCXCL1<sup>ALAn</sup>-Aga2, <sup>N</sup>hCXCL1<sup>ALAn-Aga2</sup>p<sup>C</sup>; see SEQ ID NOs: 147 and 148 for DNA and amino acid sequences).

[0371] Binding of wild-type (hCXCL1<sup>WT</sup>) and single alanine mutants (hCXCL1<sup>ALAn</sup>) displayed on the surface of yeast toward soluble SA129, SA138 and SA157\* serum albumin-antibody fusions and two commercial neutralizing antibodies targeting Groa was assessed by using flow cytometry. The wild-type (<sup>N</sup>hCXCL1<sup>WT</sup>-Aga2p<sup>C</sup>) and single alanine mutant (NhCXCL1<sup>ALAn</sup>-Aga2p<sup>C</sup>) fusion proteins were displayed on the surface of *Saccharomyces cerevisiae* strain EBY100 using Frozen-EZ Yeast Transformation II Kit (Zymo Research) as described previously (Angelini, A. et al. Protein Engineering and Selection Using Yeast Surface Display. *Methods Mol Biol* 1319, 3-36 (2015)). Individual colonies were inoculated in 5 mL SD-SCAA cultures, grown to mid-log phase ( $OD_{600}=2-5$ ) in SD-CAA media at 30° C. with shacking (250 rpm) and induced in galactose-containing SG-CAA media for 20 hours at 20° C. with shacking (250 rpm). The binding assays were conducted in 96-well plates (Corning) containing  $1 \times 10^4$  induced cells per well pre-mixed with  $1 \times 10^5$  non-displaying yeast cells.

[0372] The level of expression of single wild-type (hCXCL1<sup>WT</sup>) and alanine mutants (hCXCL1<sup>ALAn</sup>) displayed on the surface of yeast was assessed by staining the C-terminus c-myc epitope tag. Yeast cells displaying wild-type  $(hCXCL1^{WT})$  and single alanine mutants  $(hCXCL1^{ALAn})$ were then incubated with soluble serum albumin-antibody fusions SA129, SA138 and SA157\* bearing the His6 tag and the primary chicken anti-c-myc epitope tag (1:1000) antibody (Gallus Immunotech) overnight at 4° C. with shaking (150 rpm). The binding epitopes of two commercial mouse derived monoclonal antibodies targeting hCXCL1: Ab275 (clone 20326) and Ab276 (clone 31716) were also determined. High quality epitope maps were achieved by performing the assays at concentrations of soluble serum albumin-antibody fusions and antibodies that were equivalent to their  $K_D$  binding values for the wild-type hCXCL1: 2.5 nM for SA129, 100 nM for SA138, 1.5 µM for SA157\*, 0.1 nM for Ab275 and 0.25 nM for Ab276. Concentrations higher or lower than that diminished the sensitivity of the assay and made it difficult to differentiate strong from weak binding signals derived from different mutants. At too high concentrations, all the signals were saturated and showed similar binding whereas at too low concentrations, the noise made it difficult to distinguish strong from weak mutants. After primary incubation, cells were pelleted (2500× g for 5 minutes at 4° C.) and washed twice with 200 µL of ice-cold PBSA buffer. Secondary labeling was performed with goat anti-chicken and either mouse anti-His6 epitope tag or goat anti-mouse antibodies conjugated to Alexa Fluor dyes at recommended dilutions. The 96-well plates were run on a high-throughput plate sampler iQue Screener (IntelliCyt). Data were evaluated using FlowJo v.10.0.7 software (Tree Star).

[0373] To ensure that the differences in binding were not due to variations of number of proteins expressed on the surface of yeast cell, the median fluorescence intensity  $(MFI_{BIND})$  from binding signal (His6 tag or goat anti-mouse antibodies) measured for single wild-type (hCXCL1<sup>WT</sup>) and alanine mutants (hCXCL1<sup>ALAn</sup>) was normalized to the median fluorescence intensity (MFI<sub>DISP</sub>) from display signal (c-myc tag). The normalized (binding/display=MFI<sub>BIND</sub>/  $MFI_{DISP}$  values obtained for each hCXCL1 variant (hCXCL1<sup>ALAn</sup>) were further normalized for the normalized value obtained for the wild-type (hCXCL1<sup>WT</sup>) and plotted as  $(MFI_{BIND}^{ALAn}/MFI_{DISP}^{ALAn})/(MFI_{BIND}^{WT}/MFI_{DISP}^{WT})$  providing a value, ranging from 0.0 to 1.0, that corresponded to the contribution of each amino acid residues upon binding with the corresponding serum albumin fusion or neutralizing antibody (Table 6). Alanine mutants V26, V28, E39, 141 and L44 exhibited an intense loss of binding when incubated with all soluble serum albumin fusion proteins SA129, SA138, SA157\* and neutralizing antibodies Ab275 and Ab276 indicating possible misfolding of the displayed hCXCL1 variants and were therefore excluded. Values reported here are the results of three independent experiments and are presented as mean (dots)  $\pm$ SE (bars).

TABLE 6

Epitope mapping interactions							
	Ab275	Ab276	SA129	SA138	SA157		
strong (0.0-0.25)	G17	L15	Q13	L12	N46		
	T43	G17	L15	N46			
	N46	I18	I18	G47			
	G47	H19	N46	R48			
	R48	N46	G47				
	K49	K61	R48				
		K65					
moderate (0.25-0.5)	R8	Q16	T14	R8	I18		
	L12	K21	G17	T14	H19		
	T14	K45	G32	L15	K21		
	L15	G47	T43	G32	K29		
	Q16	K71	A50	A50	K45		
	I18			L67	G47		
	G32				158		
	K45				K65		
	A50				K71		
weak (0.5-0.75)	Q10	T14	N22	Q13	N22		
	Q13	N22	K45	I18			
	N22	R48	E64	M66			
	N53	A50					
		158					
		<b>K</b> 60					
Total residues	19	18	14	13	11		

Yeast Display and Competitive Fluorescent-Based Binding Assay

**[0374]** A competitive flow cytometry-based binding assay was performed to further validate the identified hCXCL1 binding epitopes in different ELR+ CXC chemokines. The assays were conducted in 96-well plates (Corning) containing  $1\times10^4$  induced cells per well pre-mixed with  $1\times10^5$  non-displaying yeast cells. Yeast cells displaying the ELR+ CXC chemokines hCXCL1, hCXCL5, hCXCL8, mCXCL1 and mCXCL2 were pre-incubated at 4° C. with concentration of soluble un-biotinylated protein serum albumin fusions and neutralizing antibodies ("blocking reagents") that are equals to 100-times their  $K_D$  values ( $C_B$ =100  $K_D$ ). After 90 minutes, soluble biotinylated protein serum albumin fusions and neutralizing antibodies ("detection reagents") were added at concentrations that are equals to their  $K_D$  values ( $C_D$ = $K_D$ ).

[0375] The incubation time was 30 minutes at 4° C. with shacking (150 rpm). The cells were then pelleted at 2500× g for 5 minutes and 4° C. on an Allegra X-14R centrifuge (Beckman Coulter), and washed twice with 200 µL ice-cold PBSA buffer. Secondary labeling was performed at 4° C. by using goat anti-chicken and either streptavidin or goat anti-mouse and anti-rat antibodies conjugated to Alexa Fluor 647 at recommended dilutions. After 30 minutes, the cells were pelleted at 2500× g for 5 minutes and 4° C. on an Allegra X-14R centrifuge (Beckman Coulter), and washed twice with 200 µL ice-cold PBSA buffer. The 96-well plates were run on a high-throughput flow cytometry plate sampler iQue Screener (IntelliCyt). Data were evaluated using FlowJo v.10.0.7 software (Tree Star). To ensure that the differences in binding were not due to variations of number of proteins expressed on the surface of yeast cell, the determined median binding fluorescence intensities (MFI-

 $_{BIND}$ ) were normalized to the median display fluorescence intensities (MFI<sub>DISP</sub>). The obtained normalized binding/ display (MFI<sub>BIND</sub>/MFI<sub>DISP</sub>) values were further normalized to the value obtained in the absence of "blocking reagent" providing a percentage value, ranging from 0 to 100%, that corresponded to the residual binding observed upon blocking with the corresponding un-biotinylated serum albumin fusion or neutralizing antibody. Values reported here are the results of two independent experiments and are presented as mean (dots) ±SE (bars).

Mammalian Cell Culture and Competitive Fluorescence-Based Binding Assay

[0376] The binding of two biotinylated human ELR+ CXC chemokines (hCXCL1 and hCXCL8) to the human CXCR1 and CXCR2 receptors was assessed by using flow cytometry-based binding assay. Human embryonic kidney 293 (HEK293) cells that stably express the human CXCR1 (HEK293-IL8RA) and CXCR2 (HEK293-IL8RB) receptors were used (National Cancer Institute at Frederick, Md.) (Ben-Baruch, A. et al. IL-8 and NAP-2 differ in their capacities to bind and chemoattract 293 cells transfected with either IL-8 receptor type A or type B. Cytokine 9, 37-45 (1997)). Transfected HEK293 cells were maintained in DMEM (Thermo Fisher Scientific) supplemented with 10% v/v FBS (Thermo Fisher Scientific), 1% v/v penicillinstreptomycin (Thermo Fisher Scientific), and 0.8 mg/mL G418 (Thermo Fisher Scientific), and grown to approximately 80% confluence in 75 cm<sup>2</sup> flasks in a humidified incubator and an atmosphere of 95% air, 5% CO<sub>2</sub> at 37° C. Receptor expression levels were determined by flow cytometry using fluorescently labeled monoclonal antibodies against human CXCR1 and CXCR2 receptors on an Accuri C6 Flow Cytometer (BD Accuri Cytometers). Cells were treated with Cell Dissociation Buffer Enzyme Free PBS based buffer (Gibcon), washed twice with cold 1× PBS pH 7.4 and resuspended in cold Cell Binding Assay (CBA) buffer (1× PBS pH 7.4 supplemented with 1% w/v BSA and 0.1% w/v NaN<sub>3</sub>) to a final density of  $1 \times 10^6$  cells/mL. Cells were then aliquoted (100 µL) in 96-well plates (Corning) and individual wells  $(1 \times 10^5$  cells each) were incubated with various concentrations of biotinvlated human ELR+ CXC chemokines (hCXCL1 and hCXCL8) ranging from 0.03 to 300 nM. The incubation time was 30 minutes at 4° C. with shacking (150 rpm). The cells were then pelleted at 600× g for 5 minutes and 4° C. on an Allegra X-14R centrifuge (Beckman Coulter) and washed once with 200 µL ice-cold CBA buffer.

[0377] Specific binding of biotinylated ELR+ CXC chemokines to CXCR receptors was detected by incubating the cells with Alexa Fluor 647-labeled Streptavidin (1:200; Thermo Fisher Scientific) for 30 minutes at 4° C. with shaking. Cells were then pelleted at 600x g for 5 minutes and 4° C. on an Allegra X-14R centrifuge (Beckman Coulter), and washed twice with 200 µL ice-cold CBA buffer. Cells were resuspended in 50 µL (2×103 cell/µL final concentration) of cold CBA buffer and analyzed by flow cytometry on an iQue Screener (IntelliCyt). Data were evaluated using FlowJo v.10.0.7 software (Tree Star). Median fluorescence intensities (MFI) were normalized to the maximal value obtained, expressed as a percentage and plotted as a function of varying ELR+ CXC chemokine concentration. The maximal effective concentrations (EC<sub>50</sub>) were determined by fitting a sigmoidal dose-response curve on GraphPad Prism (GraphPad Software). The same assay was used to assess the ability of crossreactive serum albumin-antibody fusions (SA129, SA138 and SA157\*) and commercial neutralizing antibodies (Ab208 and Ab275, R&D Systems) to compete for binding of biotinylated ELR+ CXC chemokines (hCXCL1 and hCXCL8) to their cognate CXCR1 and CXCR2 receptors.

[0378] HEK293 cell lines expressing human CXCR1 and CXCR2 receptors were incubated with biotinylated hCXCL1 and hCXCL8 chemokines as "agonist", at final concentration equal to EC50 values, in the presence of varying concentrations of "antagonists" (SA129, SA138, SA157\*, Ab208 and Ab275), followed by staining with fluorescently labeled streptavidin. Antagonists were serially diluted in 1×PBS pH 7.4 to obtain final concentrations that cover the range from 0.3 nM to 300 nM. Concentrations ranging from 0.03  $\mu$ M to 30  $\mu$ M were used for the antagonist SA157\*. Median fluorescence intensities (MFI) were normalized to the maximal value obtained, expressed as a percentage and plotted as a function of varying concentrations of "antagonists". The half maximal inhibitory concentration (IC<sub>50</sub>) values were determined by fitting a sigmoidal dose-response curve on GraphPad Prism (GraphPad Software). The  $IC_{50}$  values were further converted to inhibition constants  $K_i$  by using the Cheng-Prusoff equation  $K_i = IC_{50}/I$  $([L]/EC_{50}+1)$  where [L] is the fixed concentration of "agonist" biotinylated ELR+ CXC chemokine and  $EC_{50}$  is the concentration of "agonist" that results in half maximal activation of the receptor. Values reported here are the results of three independent experiments. The  $K_i$  and  $K_D$ values, specified in units of molar concentration (mol/L or M) were converted to the pK<sub>i</sub> and pK<sub>D</sub> scale using pK<sub>i</sub>=- $\log_{10}(K_i)$  and  $pK_D = -\log_{10}(K_D)$ , respectively. Higher values of  $pK_i$  and  $pK_D$  indicate exponentially greater potency. Data are presented as mean (dots)  $\pm$ SE (bars).

Isolation of Neutrophils from Human and Murine Fresh Whole Blood

[0379] Human neutrophils were purified directly from human whole blood by immunomagnetic negative selection using EasySep Direct Human Neutrophil Isolation Kit (STEMCELL Technologies). Whole blood from healthy human volunteers was obtained from Research Blood Components, LLC. Blood was collected in sodium-citrate anticoagulant and provided in EDTA vacutainer collection tubes. Murine neutrophils were isolated directly from mouse bone marrow by immunomagnetic negative selection using EasySep Mouse Neutrophils Enrichment Kit (STEMCELL Technologies). The ends of femur and tibia derived from female C57BL/6 mice (Taconic) were cut and the bone marrow cells flushed using a syringe equipped with a 23-gauge needle. Cell clumps and debris were removed by gently passing the cell suspension through a 70 µm mesh nylon strainer.

**[0380]** Both human and murine neutrophils were then pelleted at 1000× g for 5 minutes at 4° C. on a Allegra X-14R centrifuge (Beckman Coulter), the supernatant discarded and the cells washed by adding ice-cold PBE buffer (1× PBS pH 7.4 supplemented with 2 mM EDTA, 0.5% w/v BSA,  $Ca^{2+}$  and  $Mg^{2+}$  free) to obtain a final cell density of  $10^6$  cells/mL. The washing step was repeated one time more and the washed cells resuspended at  $10^7$  cells/mL in ice-cold PBE buffer. Purity of human neutrophils was assessed by using APC-conjugated anti-human CD16 (clone 3G8, BioLegend), FITC-conjugated anti-human CD66b antibody

(clone G10F5; BioLegend) and PE-conjugated anti-human CD45 antibody (clone HI30, BioLegend). Purity of mouse neutrophils was assessed by using APC-conjugated anti-mouse CD11b (clone M1/70; BioLegend) and PE-conjugated anti-mouse Ly-6G/Ly-6C (Gr-1) (clone RB6-8C5; BioLegend). Purified and labeled human and murine neutrophils were further used for calcium signaling experiments.

Competitive Flow Cytometry-Based Intracellular Free Calcium Mobilization Assay

[0381] The ability of engineered serum albumin fusion antibody to block the capacity of human and murine ELR+ CXC chemokines to signal through CXCR1 and CXCR2 receptors resulting in an increase of the intracellular calcium concentration was tested on both human and murine freshly purified neutrophils, respectively (June, C. H. & Moore, J. S. Measurement of intracellular ions by flow cytometry. Curr Protoc Immunol Chapter 5, Unit 5 5 (2004)). Purified human and murine neutrophils in sterile ice-cold PBE buffer were loaded for 30 minutes at 37° C. in the dark with 2 mM cell permeable ratiometric fluorescent dye Indo-1 AM (Thermo Fisher Scientific) resuspended in 100% v/v dry DMSO to obtain a final concentration of 4  $\mu$ M. Samples of 10<sup>6</sup> cells each were kept aside for autofluorescence measurements and single stained. Indo-1 loaded neutrophils were then pelleted at 1000× g for 5 minutes at 4° C. on a Allegra X-14R centrifuge (Beckman Coulter), the supernatant discarded and the cells washed by adding ice-cold Cell Loading (CL) buffer (1× HBSS, pH 7.4, 0.5% w/v BSA, 1 mM Ca<sup>2+</sup> and 1 mM Mg<sup>2+</sup>) to obtain a final cell density of  $10^7$  cells/mL. The washing step was repeated one time more and the washed cells were resuspended at  $5 \times 10^6$  cells/mL in ice-cold CL buffer. Aliquots of  $10^6$  cells/tube (200 µL) were prepared, individually pre-warmed at 37° C. for 10 minutes and stimulated with varying concentrations of "agonist" ELR+ CXC chemokines ranging from 0.03 to 300 nM.

[0382] Samples were analyzed on a BD LSR II flow cytometer (BD Biosciences). Intracellular calcium levels were measured at 405/30 nm (Indo-1 low) and 485/20 nm (Indo-1 high) emission fluorescence after excitation at 355 nm. Baseline fluorescence was recorded for 60 seconds before the addition of "agonist" ELR+ CXC chemokines and fluorescence measured for an additional 240 seconds. The median fluorescence intensities (MFI) at 405/30 nm and 485/20 nm were recorded, the ratio of two wavelengths calculated (Indo-1 ratio) and plotted as a function of time (seconds). Area under the curve (AUC), calculated as an integral over time, was determined using FlowJo v.10.0.7 software (Tree Star). The obtained values were normalized to the maximal response acquired, expressed as percentage of activity. The maximal effective concentrations  $(EC_{50})$ were determined by fitting a sigmoidal dose-response curve on GraphPad Prism (GraphPad Software).

**[0383]** The same assay was used to assess the ability of "antagonist" serum albumin-antibody fusions SA129, SA138 and SA157\* to antagonize the ELR+ CXC chemokine-mediated receptors activation and downstream intracellular calcium mobilization. Commercial neutralizing antibodies targeting human CXCL1 (Ab275), CXCL5 (Ab654), CXCL8 (Ab208) and murine CXCL1 (Ab453) and CXCL2 (Ab452) were included as positive controls. Indo-1 loaded neutrophils were incubated with hCXCL1, hCXCL5, hCXCL8, mCXCL1 and mCXCL1 chemokines as "agonist", at final concentration equal to EC50 values, in the presence of varying concentrations of "antagonist" serum albumin-antibody fusions and neutralizing antibodies. Antagonists were serially diluted in ice-cold CL buffer to obtain final concentrations that cover the range from 10 pM to 10 µM. Intracellular calcium levels were measured as described above. The obtained values were normalized to the maximal response acquired and expressed as percentage of activity plotted as a function of varying concentrations of "antagonists". Values reported here are the results of three independent experiments. Data are presented as mean (dots) ±SE (bars). The half maximal inhibitory concentration (IC<sub>50</sub>) values were determined by fitting a sigmoidal doseresponse curve on GraphPad Prism (GraphPad Software). The IC<sub>50</sub> values were further converted to inhibition constants K<sub>i</sub> by using the Cheng-Prusoff equation and both pK<sub>i</sub> and  $pK_D$  values determined as described above.

#### Fluorescent Labeling of Serum Albumin Fusion Proteins

[0384] Reactive Alexa Fluor 647 succinimidyl ester (Thermo Fisher Scientific) was dissolved in anhydrous dimethylsulfoxide (DMSO, Sigma-Aldrich) to obtain a final concentration of 10 mg/mL. Protein conjugates containing Alexa Fluor 647 were prepared by incubating proteins (at concentrations of 2 mg/mL in 1×PBS pH 7.4 with 1/10 volume 1 M K<sub>2</sub>HPO<sub>4</sub>, pH 9.0) with two-fold molar excess of Alexa Fluor 647 NHS ester (at 10 mg/mL in DMSO) for 20 minutes at room temperature in the dark. Free dye was removed using size-exclusion chromatography with Superdex 200 10/300 GL (GE Healthcare) connected to an AKTApurifier system (GE Healthcare) and equilibrated with buffer 1× PBS pH 7.4. Fractions corresponded to the expected protein pick were pulled and concentrated to a final concentration of 2 mg/mL using 10000 NMWL Amicon Ultra-4 ultrafiltration devices (Millipore) at 4000× g and 4° C. on a Allegra X-14R centrifuge (Beckman Coulter). Final protein concentrations and degrees of labeling were measured using a NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific). Dye-to-protein ratios ranged from 1.0 to 1.5.

Pharmacokinetic Studies in Mice of Serum Albumin-Antibody Fusions

[0385] All animal studies were approved by the Massachusetts Institute of Technology Division of Comparative Medicine and carried out according to the federal, state, and local regulations. Female C57BL/6 mice (Taconic) were maintained under specific pathogen-free conditions and used at 6-8 weeks of age. A single bolus/dose (1 mg) of each Alexa Fluor 647-labeled  $^{N}SA-scF^{C}$  fusions (2 mg/mL) were injected intraperitoneally (i.p.) at 50 mg/kg into 3 mice. At various time points (immediately after injection and at 0.5, 1, 2, 3, 5, 8, 24, 48, 72, 96, 120, 168 hours post injection) blood was collected into heparin-coated capillary tubes (VWR International) and stored at 4° C. in the dark until sample collection was complete. Plasma was obtained after centrifugation (900×g for 5 minutes) and transferred to new capillary tubes. Standard samples were diluted in plasma collected from untreated mice. Serial dilutions (100 µL/well) of the standards (ranging from 0.3  $pg/\mu L$  to 300  $pg/\mu L)$  and plasma samples were prepared. Protein fusion concentration was determined by measurement of fluorescent intensity using a Typhoon imager (GE Healthcare) after degree of labeling correction. Fluorescence intensity was quantified using ImageJ software (NIH).

[0386] To calculate  $^{N}$ SA-scFv<sup>C</sup> half-lives, fluorescent measurements were quantified by normalization to a standard curve for each antibody. Starting at the max concentration time point (3 hours for all cases), pharmacokinetic profiles were fit in Graphpad Prism using a two phase non-compartmental model of the following format: MFI(t) =Ae<sup>- $\alpha t$ </sup>+Be<sup>- $\beta \alpha$ </sup>. Where A, B,  $\alpha$  and  $\beta$  represent the systemic clearance rates of a given fusion protein. Fast and slow half-lives,  $t_{1/2,\alpha}$  and  $t_{1/2,\beta}$  were calculated as  $ln(2)/\alpha$  and  $\ln(2)/\beta$ , respectively. The total clearance (CL) was calculated by dividing the total dose by the AUC from 0 to infinity. Fits for the three mice in each group were averaged to obtain a single pharmacokinetic curve for each <sup>N</sup>SA $scFv^{C}$  fusion, from which total clearance rate and standard error were calculated. Values reported here are the results of triplicate and data are presented as mean (dots) ±SE (bars).

#### Arthritis Induction and Treatment

[0387] All animal studies were approved by the Center for Comparative Medicine (CCM) of the Massachusetts General Hospital (MGH) and carried out according to the federal, state, and local regulations. The inflammatory arthritis serum transfer K/B×N mice model was used (Kouskoff, V. et al. Organ-specific disease provoked by systemic autoimmunity. Cell 87, 811-822 (1996). Mice carrying the KRN T-cell receptor transgene on the C57BL/6 genetic background were mated with NOD mice (Jackson Laboratory) to obtain transgene-positive arthritic K/B×N mice. The presence of the transgene was determined by allele-specific PCR and confirmed by phenotypic assessment. Serum was collected from K/B×N arthritic mice as described (Miyabe, Y., Kim, N. D., Miyabe, C. & Luster, A. D. Studying Chemokine Control of Neutrophil Migration In Vivo in a Murine Model of Inflammatory Arthritis. Methods in enzymology 570, 207-231 (2016)). Experimental arthritis was induced in recipient C57BL/6 by transferring arthritogenic serum containing autoantibodies to the ubiquitous anti-glucose 6-phosphate isomerase (GPI) protein from transgenic 8- to 10-weeks old K/B×N mice to healthy C57BL/6 resulting in synovial pannus formation and both bone and cartilage erosions that mimics the disease that develop spontaneously in transgenic mice. Arthritogenic K/B×N serum (150 μL) was injected intraperitoneally (i.p.) using 26-gauge needle syringe on days 0 and 2 on healthy wild-type C57BL/6 mice (Jackson Laboratory) and disease progress was monitored every other day for 2 weeks as described in the next section.

**[0388]** For the preventative treatment experiments,  $500 \,\mu\text{L}$  of 2 mg/mL serum albumin fusions were injected i.p. daily starting on day 0 and treated every day for a total of 14 continuative days as follows: group 1 (n=10), mice were treated with SA129 (50 mg/Kg in PBS); group 2 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with control serum-albumin fusion (SA<sup>CTR</sup>; 50 mg/Kg in PBS); group 4 (n=10), mice were treated with PBS. For therapeutic treatment, mice were placed into 4 experimental groups so that each group had the same overall clinical score and treated every day for a total of 10 days as follows; Group 1 (n=10), mice were treated with SA129 (50 mg/Kg in PBS); group 2 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with SA138 (50 mg/Kg in PBS); group 3 (n=10), mice were treated with control serum-albumin fusion (fusion fusion fusion

(SA<sup>CTR</sup>; 50 mg/Kg in PBS); group 4 (n=10), mice were treated with PBS. Paw thickness and clinical scores were determined every other day as described previously (Miyabe, Y., Kim, N. D., Miyabe, C. & Luster, A. D. Studying Chemokine Control of Neutrophil Migration In Vivo in a Murine Model of Inflammatory Arthritis. *Methods in enzy-mology* 570, 207-231 (2016)). The clinical arthritis score was calculated for each mouse by summing the scores for the four paws: 0=normal; 1=erythema and swelling of one digit; 2=erythema and swelling of two digits or erythema and swelling of ankle joint; 3=erythema and swelling of more than three digits or swelling of two digits and ankle joint; 4=erythema and severe swelling of the ankle, foot and digits with deformity.

Flow Cytometry Analysis and Quantification of Neutrophils in Synovial Fluid

[0389] The number of neutrophils that accumulated in the synovial fluid were determined using flow cytometry as previously described (Miyabe, Y., Kim, N. D., Miyabe, C. & Luster, A. D. Studying Chemokine Control of Neutrophil Migration In Vivo in a Murine Model of Inflammatory Arthritis. Methods in enzymology 570, 207-231 (2016)). Synovial fluid was obtained from ankle joints of 8- to 10-weeks old C57BL/6 mice (Jackson Laboratory) on day 8 after K/B×N serum injection for all groups. Retrieved synovial fluid cells were resuspended in sterile 1% v/v FCS/ PBS to obtain a final concentration of  $1 \times 10^4$  cells/µL. For flow cvtometry analysis, cells were incubated with anti-FcyRIII/II antibody (clone 2.4G2; BD Bioscience), and following stained with APC-conjugated anti-murine Ly6G antibody (clone 1A8; BioLegend). Flow cytometry was performed with BD LSRFortessa (BD Bioscience) and analyzed with FlowJo v.10.0.7 software (Tree Star). Neutrophils were identified as Ly6G-positive cells in the granulocyte gate of forward and side scatter plots. Values reported here are the results of triplicate and are presented as mean (dots) ±SE (bars).

#### Histology Analysis

[0390] Preventative treated mice (n=3 per group) were sacrificed at day 8 after K/B×N serum injection and paws collected for histology as previously described (Miyabe, Y., Kim, N. D., Miyabe, C. & Luster, A. D. Studying Chemokine Control of Neutrophil Migration In Vivo in a Murine Model of Inflammatory Arthritis. Methods in enzymology 570, 207-231 (2016)). Briefly, paws were fixed in 4% v/v formalin solution overnight and decalcified by treatment with 20% EDTA solution for 2 weeks. Samples were then washed with H<sub>2</sub>O mQ for at least 10 minutes and embedded in paraffin. Sections of 4 µm thickness were stained with Hematoxylin and Eosin (H&E) staining kit (Wako Pure Chemical Industries), mounted by using Mount-Quick mounting medium (Daido Sangyo Co.) and examined by light microscopy. Values reported here are the results of triplicate and are presented as mean (dots) ±SE (bars). Histopathological scoring was performed on H&E stained ankle sections by evaluating both inflammatory cell infiltration and pannus formation as follows. Inflammatory cell infiltration: 0=no change, 1=focal inflammatory cell infiltration, 2=severe and diffuse inflammatory cell infiltration. Pannus formation: 0=no change, 1=pannus formation at one site, 2=pannus formation at two sites, 3=pannus formation at more than three sites. The score of inflammatory cell infiltration and pannus formation were summed to determine a total histopathological score. Visible clinical signs were scored blinded for the origin and treatment of the mice. Because different batches of serum with different potency have been used in different experiments, the measured clinical score values of each experiment were normalized to the maximal value obtained and expressed as a percentage (clinical score %). Values reported here are the results of two independent experiments and are presented as mean (dots)  $\pm$ SE (bars).

## Protein Structure Homology Modeling

**[0391]** The protein structure homology models of selected yeast-displayed antibody single-chain variable fragments CK129, CK138 and CK157 have been generated by using protein structure modeling program MODELLER (Sali, A. & Blundell, T. L. Comparative protein modelling by satisfaction of spatial restraints. *J Mol Biol* 234, 779-815 (1993)) and the three-dimensional structure of a highly homologue synthetic antibody fragment as template (PDB ID: 2KH2) (Wilkinson, I. C. et al. High resolution NMR-based model for the structure of a scFv-IL-1beta complex: potential for NMR as a key tool in therapeutic antibody design and development. *J Biol Chem* 284, 31928-31935 (2009)). Protein structures and models were rendered using PyMOL (PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC).

### Statistical Analysis

**[0392]** All data are presented as mean (dots)  $\pm$ SE (bars). Statistical comparisons were made between each group using one-way analysis of variance (ANOVA) and Graph-Pad Prism (GraphPad Software). P values: \*P<0.05, \*\* P<0.01, \*\*\* P<0.001; \*\*\*\* P<0.0001. ns: non-significant.

## Example 1: Generation of Crossreactive Antibodies that Bind a Diverse Array of ELR+ CXC Chemokines

**[0393]** To evolve highly crossreactive protein binders toward multiple pro-inflammatory ELR+ CXC chemokines,

synthetic single chain variable antibody fragment (scFv) libraries displayed on the surface of yeast were used. Yeast surface display combined with fluorescence-activated cell sorting (FACS) allowed for quantitative selection of protein binders based on both binding affinity and specificity. The synthetic scFv libraries had qualities making them powerful scaffolds for the development of crossreactive binders. Three human (hCXCL1, hCXCL5, and hCXCL8) and three murine (mCXCL1, mCXCL2 and mCXCL5) chemokines were chosen as targets based on their (i) low sequence identity and (ii) proven therapeutic relevance (FIG. 1 and FIG. 2A).

**[0394]** Initially, only one selection pressure was applied, and crossreactivity was prioritized over affinity. To encourage the development of crossreactivity, combinatorial approaches were implemented, in which the output of each cycle of selection was exposed to a diverse array of ELR+CXC chemokines in the following cycle selection (FIG. 2B). The use of highly avid reagents preloaded with ELR+CXC chemokines and constant alternation of the detection reagents favored the isolation of weak crossreactive binders while discouraging the enrichment of clones that recognized detection reagents. Subsequent DNA sequences of individual clones revealed eighteen unique antibody clones with varying amino acid compositions and loop lengths within the complementarity-determining regions (CDRs).

[0395] Selected antibodies exhibited diverse affinities and specificities for soluble ELR+ CXC chemokines (FIG. 2C, Table 7). Of these clones, only four (CK1-CK4) recognized at least three different ELR+ CXC chemokines. The most abundant and crossreactive of these antibodies, CK3, recognized the biotinylation sequence located at the C-terminus of each chemokine, thus explaining its crossreactivity and similar binding affinities (FIG. 2C). In addition to the generation of crossreactive binders, six bi-specific and eight mono-specific antibody clones were isolated (FIG. 2C). The presence of numerous mono- and bi-specific antibodies can be explained by the use of highly avid reagents during the selection process. Taken together, these data showed that crossreactive antibodies generally occurred at lower frequency and with weaker binding affinities compared with the mono- and bi-specific antibodies (FIG. 2C).

TABLE 7

	Binding affinities - $K_D \pm SE (nM)$							
	Groα	ENA-78	IL-8	KC	MIP-2	LIX	MBP	
CK1	>2000	>2000	>2000	N.B.	N.B.	N.B.	N.B.	
CK2	>2000	605 ± 79	N.B.	$481 \pm 80$	$505 \pm 86$	>2000	N.B.	
CK3	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	
CK3*	$562 \pm 88$	448 ± 73	$410 \pm 61$	589 ± 75	445 ± 69	594 ± 81	522 ± 79	
CK4	39.4 ± 7.4	>2000	N.B.	744 ± 93	N.B.	>2000	N.B.	
CK5	>2000	N.B.	>2000	N.B.	N.B.	N.B.	N.B.	
CK6	1675 ± 191	1987 ± 228	N.B.	N.B.	N.B.	N.B.	N.B.	
CK7	N.B.	344 ± 68	N.B.	N.B.	N.B.	>2000	N.B.	
CK8	$382 \pm 73$	N.B.	N.B.	825 ± 98	N.B.	N.B.	N.B.	
CK9	N.B.	N.B.	N.B.	221 ± 49	$278 \pm 41$	N.B.	N.B.	
CK10	28.9 ± 4.5	N.B.	N.B.	801 ± 107	N.B.	N.B.	N.B.	
CK11	425 ± 58	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	
CK12	N.B.	N.B.	N.B.	N.B.	332 ± 57	N.B.	N.B.	
CK13	N.B.	297 ± 98	N.B.	N.B.	N.B.	N.B.	N.B.	
CK14	N.B.	N.B.	N.B.	N.B.	N.B.	269 ± 57	N.B.	
CK15	N.B.	N.B.	N.B.	251 ± 25	N.B.	N.B.	N.B.	

TABLE	7-continued
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	Binding affinities - $K_D \pm SE$ (nM)							
	Groa	ENA-78	IL-8	KC	MIP-2	LIX	MBP	
CK16 CK17 CK18	N.B. N.B. N.B.	102 ± 12 N.B. N.B.	N.B. N.B. 65 ± 6.1	N.B. N.B. N.B.	N.B. N.B. N.B.	N.B. 106 ± 11 N.B.	N.B. N.B. N.B.	

\*= binding affinities measured using biotinylated ELR + CXC chemokines bearing AviTag at C-terminus. N.B. = no binding

#### N.B. = no binding

## Example 2: Use of Two-Pressure Selection Strategies for Molecular Co-Evolution of Antibody Binding Affinity and Crossreactivity

[0396] To further improve both the binding affinity and crossreactivity of CK1, CK2 and CK4 clones, two-pressure selection strategies that encouraged the co-evolution of higher affinity and crossreactivity simultaneously were utilized. Specifically, a high degree of genetic diversity in the antibody-encoding genes was created using error-prone PCR amplification. Then, binding affinity was increased by allowing the mutants to evolve through six consecutive cycles of equilibrium-based selection using decreasing concentrations of ELR+ CXC chemokines. Concomitantly, the development of crossreactivity was forced by exposing the outputs of each cycle of affinity selection towards a different ELR+ CXC chemokine in the following cycle of selection. During this iterative process, variants whose affinity and crossreactivity towards ELR+ CXC chemokines was higher than that of their respective parental clones were exclusively collected.

**[0397]** After two iterative evolutionary processes, each comprising six consecutive cycles of selection, the isolated clones were sequenced and assessed for binding affinity and crossreactivity towards ELR+ CXC chemokines. In addition, when distinct mutations were found scattered across

clones and showed improvement, mutations were combined to investigate the possibility of even further crossreactivity and higher affinity. A summary of the overall co-evolutionary approach, including two iterative evolutionary processes of selection for crossreactivity and affinity (I and II), and a third cycle of combinatorial mutagenesis (III), is shown in FIGS. **2D-2**F.

**[0398]** Implementing these evolutionary processes in this fashion yielded antibodies with significant improvements in affinity and, in most cases, increased crossreactivity toward multiple ELR+ CXC chemokines. For example, the engineered CK138 clone doubled the number of chemokines recognized (i.e., from three to six) and achieved roughly a 30 to 340-fold improvement in affinity toward these chemokines (K<sub>D</sub> values ranging from  $\frac{5}{8}$  to 193 nM) relative to the parental CK1 clones (FIG. 2D; Table 8). Similarly, the CK157 clone retained its crossreactivity toward five targets and added a 20 to 55-fold improvement in affinity ( $K_D$ ) values ranging from 16.9 to 57.1 nM) as compared to the initial CK2 clone (FIG. 2E, Table 9). Finally, while CK129 only retained minimal crossreactivity towards two targets, there was a considerable increase in affinity of 50 and 800-fold toward human Groa ( $K_D$ =0.79 nM) and its mouse homologue KC (K<sub>D</sub>=0.93 nM), respectively (FIG. 2F; Table 10).

TABLE 8

		Binding af	finities - $K_D$	± SE (nM)		
	Groa	ENA-78	IL-8	KC	MIP-2	LIX
CK1	>2000	>2000	>2000	N.B.	N.B.	N.B.
CK19	1262 ± 219	895 ± 72	212 ± 21	931 ± 81	>2000	>2000
CK21	>2000	273 ± 17	144 ± 8.4	$280 \pm 37$	>2000	>2000
CK23	>2000	76.4 ± 5.8	$104 \pm 8.2$	98.3 ± 33.4	>2000	>2000
CK63	>2000	42.9 ± 8.2	$15.2 \pm 3.3$	53.5 ± 9.8	>2000	>2000
CK66	594 ± 39	19.1 ± 1.6	$21.5 \pm 3.6$	$52.5 \pm 8.1$	>2000	>2000
CK72	$120 \pm 10$	$35.1 \pm 2.3$	25.8 ± 3.9	$107 \pm 15$	63.6 ± 9.8	>2000
CK138	61.9 ± 4.1	$5.8 \pm 0.9$	7.4 ± 1.1	$34.8 \pm 3.2$	$36.2 \pm 6.5$	193 ± 22
CK140	64.6 ± 13	$4.9 \pm 0.6$	$8.2 \pm 2.1$	$32.9 \pm 2.8$	$33.2 \pm 7.4$	$197 \pm 10$

TABLE 9

		Binding affin	ities - K	$D \pm SE (nM)$		
	Groa	ENA-78	IL-8	KC	MIP-2	LIX
CK2	>2000	605 ± 79	N.B.	<b>481 ± 8</b> 0	505 ± 86	>2000
CK41	304 ± 44	$220 \pm 65$	N.B.	$143 \pm 14$	75.4 ± 19	429 ± 24
CK43	368 ± 59	$154 \pm 31$	N.B.	$137 \pm 11$	$213 \pm 27$	762 ± 98
CK108	$110 \pm 24$	$40.9 \pm 6.4$	N.B.	39.8 ± 7.5	$40.6 \pm 6.2$	136 ± 19
CK111	62.9 ± 8.4	$35.3 \pm 2.1$	N.B.	$30.5 \pm 2.8$	$23.8 \pm 2.9$	97.8 ± 11
CK119	$56.7 \pm 7.2$	39.3 ± 6.4	N.B.	$29.8 \pm 2.1$	$27.5 \pm 3.8$	$116 \pm 20$

TABLE 9-continued

		Binding affin	ities - K	$L_D \pm SE (nM)$		
	Groα	ENA-78	IL-8	KC	MIP-2	LIX
CK152 CK155 CK157	$48.4 \pm 6.5 \\24.1 \pm 2.2 \\36.2 \pm 4.3$	$25.4 \pm 2.8$ $18.9 \pm 2.5$ $16.9 \pm 1.7$		$17.4 \pm 2.8$ $15.9 \pm 2.4$ $20.6 \pm 4.1$		$53.7 \pm 8.9$

TABLE 10

	Bind	ling affinitio	es - K <sub>D</sub>	± SE (nM)		
	Groa	ENA-78	IL-8	KC	MIP-2	LIX
CK4 CK50 CK56 CK125 CK129	$39.4 \pm 7.4 3.1 \pm 0.5 12.6 \pm 2.5 1.23 \pm 0.2 0.79 \pm 0.1$	>2000 >2000 >2000 >2000 >2000	N.B. N.B. N.B. N.B. N.B.	$744 \pm 93 \\53.8 \pm 3.5 \\108 \pm 4.5 \\1.31 \pm 0.1 \\0.93 \pm 0.1$	N.B. >2000 >2000 >2000 >2000	>2000 >2000 >2000 >2000

**[0399]** Importantly, the sequential order in which the ELR+ CXC chemokine targets were exposed to the antibody mutant libraries was critical to the success of the selection process. Among all the possible selection pathways, improvements in both affinity and crossreactivity were observed only when recombinant genetic libraries were screened in order from lowest to highest affinity chemokines (data not shown). However, this was not applicable to the development of CK129, as its parental clone (CK4) already possessed high initial affinity toward hCXCL1 and mCXCL1, but negligible affinity towards the others.

[0400] Although reaction conditions that allowed, on average, one to two amino-acid mutations per gene were applied, selected clones from each round of sorting showed higher mutation rates (data not shown). The total number of accumulated mutations within both CDRs and framework regions (FWRs) of variable light  $(V_L)$  and heavy  $(V_H)$  chains correlated well with the extent of crossreactivity (data not shown). While the crossreactive antibody CK138 predominantly gathered mutations within the CDRs during the engineering process, CK157 collected numerous mutations within the FWRs (FIGS. 2G and 2H). Both types of mutations were shown to be critical, as reversion of either CDR or FWR mutations to the wild-type amino acids resulted in loss of affinity of CK138 and CK157, respectively, toward ELR+ CXC chemokines (data not shown). Moreover, the FWR mutations were found throughout different clones and cycles of engineering, suggesting strong selection pressure for these residues in conferring high binding crossreactivity and affinity.

**[0401]** Overall, the two-pressure selection approach promoted the evolution of crossreactive binders with improved affinity and revealed the importance of the selection pathway for the achievement of crossreactivity.

## Example 3: Engineered Antibodies Bind a Larger Array of Human and Murine CXC Chemokines

**[0402]** To assess the extent of crossreactivity of the engineered antibodies, their binding affinity towards all human and murine CXC chemokines were characterized. The chemokine panel included twelve human and mouse ELR+CXC chemokines (which share 32-90% sequence identity), and eight human and mouse (ELR-) CXC chemokines

(which share 18-70% sequence identity). The ELR+ CXC chemokines share 20-51% sequence identity with the (ELR-) CXC chemokines.

[0403] To accurately determine the  $K_D$  values of the antibodies for the different chemokines, two complementary configurations of chemokines and antibodies in the context of yeast surface display were utilized. Specifically, titrations using (i) soluble CXC chemokines with yeast-displayed antibodies, and (ii) soluble antibodies with yeast-displayed CXC chemokines, were performed. Exploring both orientations was necessary as some CXC chemokines are known to form oligomers when present in high concentration in solution, leading to undesired multivalent binding phenomena (Wang, X., Sharp, J. S., Handel, T. M. & Prestegard, J. H. Chemokine oligomerization in cell signaling and migration. Prog Mol Biol Transl Sci 117, 531-578 (2013)). The CXC chemokines were expressed as fusions to the N-terminus of mouse serum albumin (SA), and the engineered CK129, CK138 and CK157 binders as single-chain variable fragments (scFv) fused to the C-terminus of SA, which are referred to as SA129, SA138 and SA157\*. SA157\* is denoted with an asterisk as it was produced as separate VL and VH domains and then mixed in equimolar amounts, instead of a single chain with a linker.

[0404] In both orientations, similar crossreactivity of the engineered binders towards CXC chemokines that were not included in the selection cycles was observed (FIG. 3A). Importantly, this was not merely due to non-specific polyreactivity of the engineered binders, as no binding was detected toward a panel of unrelated proteins (data not shown). Yeast-displayed CK129, CK138 and CK157 bind 7, 12 and 16 soluble CXC chemokines, respectively (FIG. 3A). Similarly, the soluble SA129, SA138 and SA157\* bind 4, 11 and 14 yeast-displayed CXC chemokines, respectively (FIG. **3**A). With a few exceptions, the  $K_D$  values determined using SA129, SA138 and SA157\* antibody-fusions with yeastdisplayed CXC chemokines were on average 2- to 5-fold higher than those measured in the opposite arrangement (Table 11). The discrepancy in measured  $K_D$  values and extent of crossreactivity between the two specular orientations was not surprising and may reflect oligomeric CXC chemokines interacting with multiple yeast-displayed antibodies and therefore, mistaking avidity effects as seemingly higher affinity. This phenomenon appeared to be pronounced for (ELR-) CXC chemokines, such as hCXCL10 and hCXCL4, which are known to form highly avid oligomers in solution (Wang, X., Sharp, J. S., Handel, T. M. & Prestegard, J. H. Chemokine oligomerization in cell signaling and migration. Prog Mol Biol Transl Sci 117, 531-578 (2013); Swaminathan, G. J. et al. Crystal structures of oligomeric forms of the IP-10/CXCL10 chemokine. Structure 11, 521-532 (2003); Zhang, X., Chen, L., Bancroft, D. P., Lai, C. K. & Maione, T. E. Crystal structure of recombinant human platelet factor 4. Biochemistry 33, 8361-8366 (1994)).

**[0405]** These data showed that the extent of crossreactivity appeared to correlate both linearly and inversely with binding affinity (FIG. **3**C). SA129, which only recognized four chemokines that share significant sequence identity, displayed relatively high affinity for those targets. In contrast, highly crossreactive SA138 and SA157\* had overall lower binding affinities toward a larger array of targets.

determination of residues that were likely critical for the interaction (FIGS. 4A and 4B).

**[0408]** Identification of the epitopes of two commercially available neutralizing antibodies: highly specific Ab275 (binds only hCXCL1) and the crossreactive Ab276 (binds hCXCL1, hCXCL2 and hCXCL3), were also identified. These epitope maps were then compared to the maps

TABLE 11

				-		
		Binding	affinities - K <sub>r</sub>	<b>±</b> SE (nM)		
	CK129/SA	129	CK13	8/SA138	CK157	/SA157*
			Disp	olay		
	CK129	CXCL	CK138 Solı	CXCL ible	CK157	CXCL
	CXCL	SA129	CXCL	SA138	CXCL	SA157*
Groa	$1.0 \pm 0.1$	$2.7 \pm 0.3$	41.5 ± 4.5	96.7 ± 2.4	61.1 ± 5.6	1433 ± 108
Groβ	$13.9 \pm 1.1$	$43.6 \pm 4.1$	267 ± 38	1591 ± 315	57.9 ± 4.8	853 ± 67
Groy	$5.7 \pm 0.5$	$9.2 \pm 0.9$	349 ± 41	836 ± 130	$53.9 \pm 2.1$	$1034 \pm 87$
ENA-78	>2000	N.B.	$5.8 \pm 0.5$	33.7 ± 2.2	$26.3 \pm 2.3$	$2125 \pm 269$
GCP-2	N.B.	N.B.	$153 \pm 15$	>2000	$46.6 \pm 3.1$	751 ± 88
NAP-2	N.B.	N.B.	N.B.	40.6 ± 1.6	N.B.	N.B.
IL-8	N.B.	N.B.	$6.9 \pm 0.5$	$12.7 \pm 0.9$	N.B.	N.B.
KC	$1.1 \pm 0.1$	$2.9 \pm 0.3$	35.7 ± 3.3	29.4 ± 2.8	$24.3 \pm 1.9$	666 ± 47
MIP-2	>2000	N.B.	$29.1 \pm 4.1$	$14.7 \pm 0.5$	19.9 ± 1.7	591 ± 62
DCIP-1	N.B.	N.B.	$10.9 \pm 1.1$	$31.4 \pm 3.1$	17.4 ± 1.4	2647 ± 264
LIX	>2000	N.B.	$176 \pm 21$	357 ± 33	96.9 ± 6.9	$2018 \pm 169$
Nap-2	N.B.	N.B.	N.B.	N.B.	$13.6 \pm 0.8$	528 ± 53
PF-4	N.B.	N.B.	$167 \pm 28$	N.B.	$112 \pm 5.1$	>20000
MIG	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.
IP-10	N.B.	N.B.	N.B.	N.B.	$45.5 \pm 3.8$	>20000
I-TAC	N.B.	N.B.	N.B.	N.B.	$131 \pm 11$	>20000
Pf-4	N.B.	N.B.	N.B.	N.B.	$17.1 \pm 1.2$	$1770 \pm 119$
Mig	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.
Ip-10	N.B.	N.B.	500 ± 55	N.B.	44.4 ± 3.7	N.B.
I-Tac	N.B.	N.B.	N.B.	N.B.	$124 \pm 13$	N.B.

## Example 4: Recognition of Functional Epitopes by Crossreactive Antibodies

**[0406]** Next, fine epitope mapping using alanine-scanning mutagenesis was performed to identify the residues that were directly involved in the interactions. hCXCL1 was chosen as the model chemokine over other ELR+ CXC chemokines because (i) it is recognized by all the engineered crossreactive binders and (ii) it is well-characterized biochemically. First, three-dimensional structural analysis and literate data was combined to identify hCXCL1 amino acid suitable to mutagenesis. Structurally buried hydrophobic amino acids, proline and cysteine residues were left unaltered, as they are crucial for overall folding and stability of the chemokine.

**[0407]** Fifty-four predicted solvent-exposed hCXCL1 residues were selected, individually mutated to alanine, expressed on the surface of yeast, and screened for decreased binding affinity to the soluble SA129, SA138 and SA157\* serum-albumin antibody fusions. Five mutants that exhibited an intense loss of binding upon incubation with all the binders were excluded as this phenomenon was likely due to protein misfolding and destabilization of the displayed variants. Next, the binding of the remaining forty-nine hCXCL1 mutants towards soluble SA129, SA138 and SA157\* serum albumin antibody-fusions was assessed. Solvent exposed mutations that eliminated or significantly reduced binding affinity were identified, which allowed for

assigned to the engineered binders. Similarly to Ab275 and Ab276, SA129 and SA138 bind motifs along the functional N- and 40s-loops that are known to be crucial for the binding of hCXCL1 to its cognate receptor, CXCR2. In contrast, SA157\* recognized a distinctive epitope and engaged binding with hCXCL1 residues that are more important for the interaction with the glycosaminoglycans (GAGs). These epitope maps were also consistent with the results from a competitive assay (data not shown).

**[0409]** The residues recognized by the highly crossreactive SA138 and SA157\* are conserved among many different chemokines, thus explaining their wide extent of binding crossreactivity. The epitope-mapping data suggested that the degree of crossreactivity inversely correlated with the number of bound residues. The relatively more specific Ab275, Ab276 and SA129 engaged binding with a larger number of hCXCL1 residues than the more crossreactive SA138 and SA157\* binders. (FIG. 4C). In contrast, the binding specificity of SA138 and SA157\* appeared to be achieved through mostly peripheral long-range weak interactions, and interactions with a few preserved prominent structural conserved residues, such as the hot-spot motif NGF. In contrast, Ab275, Ab276 and SA129 appeared to engage chemokines with much stronger interactions (FIG. 4D).

## Example 5: Analysis of Binding of Soluble ELR+ CXC Chemokine Ligands to their Cognate Receptors

[0410] To measure the potential therapeutic efficacy of the crossreactive binders, the ability of SA129, SA138 and SA157\* fusions were tested for their ability to inhibit binding of ELR+ CXC chemokines to their cognate CXCR1 and CXCR2. HEK293 cell lines expressing human CXCR1 and CXCR2 were utilized. Cells were incubated with various concentrations of hCXCL1 and hCXCL8 ligands to determine the half-maximal effective concentrations (EC50) of the interaction. Next, the ability of SA129, SA138 and SA157\* to antagonize the interactions between hCXCL1 and hCXCL8 ligands and their cognate receptors was examined. The engineered binders inhibited the ability of hCXCL1 and hCXCL8 chemokines to bind CXCR1 and CXCR2 receptors in a dose dependent manner to various extents (data not shown). Further, the determined inhibitory constants (Ki) correlated well with the previously reported  $K_D$  values (FIG. 5A). These results show that crossreactive SA129, SA138 and SA157\* fusions can markedly interfere with the binding of ELR+ CXC chemokines to both human CXCR1 and CXCR2 in vitro.

[0411] Next, the ability of the SA129, SA138 and SA157\* fusions to antagonize the activation of ELR+ CXC chemokine receptors was assessed. An intracellular calcium mobilization assay was utilized, wherein the assay was in the presence of human and mouse derived neutrophils activated with human (hCXCL1, hCXCL5, and hCXCL8) and murine (mCXCL1 and mCXCL2) ELR+ CXC chemokines, respectively. First, the EC50 of the chemokines on the neutrophils was determined (0.94±0.2 for hCXCL1; 4.8±0.8 for hCXCL5; 1.29±0.4 for hCXCL8; 0.81±0.9 for mCXCL1; 2.5±0.7 for mCXCL2). Then, changes in intracellular calcium levels were monitored upon pre-incubation of ELR+ CXC chemokines with varying concentrations of SA129, SA138 and SA157\* as antagonists. Commercially available neutralizing monoclonal antibodies were used as a positive control. The assays revealed that the engineered binders exhibited inhibitory activity by preventing binding of the human and murine ligands to the receptor in a dose dependent manner (FIGS. 5B and 5C). Again, the calculated K, values correlated well with the previously determined  $K_{D}$ affinities (FIG. 5D). Taken together, these data provided strong evidence that engineered crossreactive antibodies are potent inhibitors of ELR+ CXC chemokine signaling in vitro and ex vivo, and have the potential to suppress CXCR1 and CXCR2 activation in vivo.

## Example 6: Effect of Crossreactive Serum Albumin-Antibody Fusions on Neutrophil Infiltration In Vivo and Inflammatory Arthritis in Mice

**[0412]** Given the promising results from the inhibitory assays, the inhibitory potency of the engineered fusions in the murine serum transfer K/B×N model of autoantibody-induced arthritis was tested. This model displays clinical and histopathological similarities to human rheumatoid arthritis (Christensen, A. D., Haase, C., Cook, A. D. & Hamilton, J. A. K/B×N Serum-Transfer Arthritis as a Model for Human Inflammatory Arthritis. *Front Immunol* 7, 213 (2016); Ditzel, H. J. The K/B×N mouse: a model of human inflammatory arthritis. *Trends Mol Med* 10, 40-45 (2004); Kouskoff,

V. et al. Organ-specific disease provoked by systemic autoimmunity. Cell 87, 811-822 (1996); Matsumoto, I. et al. How antibodies to a ubiquitous cytoplasmic enzyme may provoke joint-specific autoimmune disease. Nat Immunol 3, 360-365 (2002); Ji, H. et al. Arthritis critically dependent on innate immune system players. Immunity 16, 157-168 (2002)). The levels of ELR+ CXC chemokines are markedly upregulated in the joints of these arthritic mice and neutrophils, that have upregulated CXCR2 in the joint, are the main effector cells, making K/B×N serum transfer-induced arthritis mice an excellent model to test the therapeutic efficacy of the engineered binders (Chou, R. C. et al. Lipid-cytokine-chemokine cascade drives neutrophil recruitment in a murine model of inflammatory arthritis. Immunity 33, 266-278 (2010); Wipke, B. T. & Allen, P. M. Essential role of neutrophils in the initiation and progression of a murine model of rheumatoid arthritis. J Immunol 167, 1601-1608 (2001); Jacobs, J. P. et al. Deficiency of CXCR2, but not other chemokine receptors, attenuates autoantibodymediated arthritis in a murine model. Arthritis and rheumatism 62, 1921-1932 (2010)).

[0413] Serum albumin-antibody fusions were generated to antagonize circulating small ELR+ CXC chemokines in vivo (FIG. 6). In addition to the SA129 and SA138 fusions described above, an irrelevant SA-fusion (SA<sup>CTR</sup>) was used. The negative control SACTR encodes SA fused to an antibody fragment that targets the human carcinoembryonic anigen (CEA), a protein that does not exist in mice. To ensure complete inhibition of all ELR+ CXC chemokines present in circulation, relatively high doses of the engineered fusion proteins was administered (i.e., 50 mg/kg). When injected into mice, SA129, SA138 and SACTR displayed plasma half-lives between 42-47 hours, considerably longer than small synthetic compounds or antibody fragments, but shorter than full length monoclonal antibodies. Despite the high doses of SA129, SA138 and SA<sup>CTR</sup>, the molecules were well tolerated. Treated mice gained weight and exhibited good body condition. Moreover, no signs of splenomegaly as a consequence of neutropenia were detected.

[0414] Initially the ability of crossreactive SA fusions to prevent the manifestation of the inflammatory arthritis in the K/B×N serum transfer model was assessed. Specifically, mice were treated on the same day as the arthritogenic serum was injected and the progression of the disease evaluated by both blinded clinical scores and measurements of ankle thickness. Mice treated with the more crossreactive SA138, which binds all four murine ELR+ CXC chemokines (mCXCL1, mCXCL2, mCXCL3, and mCXCL5), were protected from developing arthritis, with an approximately 80% reduction of clinical score compared with negative controls at the peak of the disease (day 8 after arthritogenic K/B×N serum transfer and disease initiation; FIGS. 7A and 7B). In contrast, the more specific SA129 that recognizes just one murine ELR+ CXC chemokine (mCXCL1) only moderately reduced joint inflammation, with an approximately 30% reduction of clinical score at day 8 (FIGS. 7A and 7B). Mice treated with SA<sup>CTR</sup> showed typical clinical signs of untreated mice that received arthritogenic serum and developed inflammatory arthritis with pronounced joint swelling. There were no differences between mice treated with SACTR or with vehicle (PBS) only (FIGS. 7A and 7B).

**[0415]** Next, the number of synovial fluid neutrophils isolated from the arthritic joints of mice treated with SA129,

SA138 and SACTR fusions was determined. Synovial tissues were harvested at the peak of the disease (day 8 after disease initiation). Mice treated with arthritogenic serum and the broadly crossreactive SA138 had 50- and 70-fold lower levels of infiltrated neutrophils than mice treated with the more specific SA129 and the irrelevant  $SA^{TR}$ , respectively (FIG. 7C). These data were consistent with previous clinical score measurements and resembled those observed using mice deficient in CXCR2 (CXCR2-/-) injected with arthritogenic serum (Chou, R. C. et al. Lipid-cytokine-chemokine cascade drives neutrophil recruitment in a murine model of inflammatory arthritis. Immunity 33, 266-278 (2010); Jacobs, J. P. et al. Deficiency of CXCR2, but not other chemokine receptors, attenuates autoantibody-mediated arthritis in a murine model. Arthritis and rheumatism 62, 1921-1932 (2010)).

**[0416]** Histological analysis and scoring of inflamed ankle sections were also performed. Inflammatory cell infiltration and pannus formation were absent or minimally present in mice treated with the broadly crossreactive SA138 (FIGS. 7D and 7E). Consistent with previous clinical findings, the joints of mice treated with arthritogenic serum and control

SA<sup>CrR</sup> displayed abundant inflammatory cell infiltration and pannus formation. These pathological changes were present, though less pronounced, in mice treated with the more specific SA129 fusion.

[0417] Further, the therapeutic efficacy of crossreactive SA fusion in mice with established arthritis was tested. Arthritic mice were treated 4 days after arthritogenic serum transfer, when joint inflammation had developed. The highly crossreactive SA138 reversed inflammation very quickly and provided a remarkable complete resolution of the disease with an approximately 60% reduction of clinical score and 0.3 mm of ankle thickness over control at the peak of the disease (day 8 after disease initiation; FIGS. 7F and 7G). The specific SA129-treated mice exhibited only a modest reduction of both clinical scores (~25%) and ankle thickness (0.1 mm) at day 8 (FIGS. 7F and 7G). The SA<sup>CrR</sup> and vehicle-treated mice showed no difference in the rate of disease development (FIGS. 7F and 7G). Taken together, these data show that highly crossreactive SA138 fusion efficiently blocked neutrophil infiltration in the synovial tissues, thus preventing and even reversing inflammatory arthritis.

# Table 12: Sequence Summary

SEQ ID NO	Description	Sequence
<b>NO</b>	CK138 V <sub>H</sub>	EVQLVESDGGLVQPGGSLRLSCAASGFNLSYYGMHWVRQA
	amino acid	PGKGLEWVAYIASYPGYTSYADSVKGRFTISADTSKNTAYL
	sequence	QMNSLRAEDTAVYYCARSGYSYSPYYSWFSAGMNYWGQG
		ALVTVSS
2	CK138 V <sub>L</sub>	AIQMTRSPSSLSASVGDRVTITCRASQYHDGSAAWYQQKPG
	amino acid	KAPKLLIYGASYLYSGVPSRFSGSRSGTDFTLTISSLQPEDFA
	sequence	TYYCQQSSYSLITFGQGTKVEIK
3	CK138 V <sub>H</sub>	GAGGTTCAGCTGGTGGAGTCTGACGGTGGCCTGGTGCAGCCAGGG
	nucleic acid	GGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTTCAACCTCTCT
	sequence	TACTACGGTATGCACTGGGTGCGTCAGGCCCCGGGTAAGGGCCTG
		GAATGGGTTGCATACATTGCTTCTTACCCTGGCTACACTTCTTAT
		GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCC
		AAAAACACAGCCTACCTACAAATGAACAGCTTAAGAGCTGAGGAC
		ACTGCCGTCTACTATTGTGCTCGCTCTGGTTACAGTTACTCTCCG
		TATTATTCTTGGTTCTCTGCTGGTATGAACTACTGGGGTCAAGGA
		GCCCTGGTCACCGTCTCCTCG
4	CK138 V <sub>L</sub>	GCTATCCAGATGACCCGGTCCCCGAGCTCCCTGTCCGCCTCTGTG
	nucleic acid	GGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGTACCACGAC
	sequence	GGTTCTGCAGCCTGGTATCAACAGAAACCAGGAAAAGCTCCGAAG
		CTTCTGATTTACGGTGCATCCTACCTCTACTCTGGAGTCCCTTCC
		CGCTTCTCTGGTAGCCGTTCCGGGACGGATTTCACTCTGACCATC
		AGCAGTCTGCAGCCGGAAGACTTCGCAACTTATTACTGTCAGCAA
		TCTTCTTATTCTCTGATCACGTTCGGACAGGGTACCAAGGTGGAG
		АТСААА
5	CK138 V <sub>H</sub>	NLSYYGMH
	CDR1	
6	CK138 V <sub>H</sub>	AYIASYPGYTSY
	CDR2	
7	CK138 V <sub>H</sub>	RSGYSYSPYYSWFSAGMN
	CDR3	
8	CK138 V <sub>L</sub>	QYHDGSA
	CDR1	
9	CK138 V <sub>L</sub>	YGASYL
	CDR2	
10	CK138 V <sub>L</sub>	QSSYSLIT
	CDR3	
11	CK157 V <sub>II</sub>	EVQLVESGGGLVQPGGSLRLSCAASGSNPYYYGGTHWVRQ
	amino acid	APGEELEWVASIGSYPGYTDYADSVKGRFTISADTSKNTAY
	sequence	LQMNSLRAEDTAVYYCARHYYWYDATDYWGQGTLVTVS
		S
12	CK157 V <sub>L</sub>	DIQMTQSPSSLSASVGDRVTITCRASQSYGGVAWYQQKPGK
	amino acid	APKLLIYSASYLYSGVPSRFSGSRSGTDFTLTISSLQPEDFAT

	sequence	YYCQQPSHLITFGQGTEVEIK
13	CK157 V <sub>II</sub>	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGG
	nucleic acid	GGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTCCAACCCCTA
	sequence	TACTACGGTGGTACGCACTGGGTGCGTCAGGCCCCGGGTGAGGA
	1	CTGGAATGGGTTGCATCTATTGGTTCTTACCCTGGCTACACTGA
		TATGCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACA
		TCCAAAAACACAGCCTACCTACAAATGAACAGCTTAAGAGCTGAG
		GACACTGCCGTCTATTATTGTGCTCGCCATTACTACTGGTACGA
		GCTACTGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTC
14	CK157 VL	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGT
11	nucleic acid	GGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGTCTTACGG
	sequence	GGTGTAGCCTGGTATCAACAGAAACCAGGAAAAGCCCCGAAGCT
	sequence	CTGATTTACTCTGCATCCTACCTCTACTCTGGAGTCCCTTCTCG
		TTCTCTGGTAGCCGTTCCGGGACGGATTTCACTCTGACCATCAG
		AGTCTGCAGCCGGAAGACTTCGCAACTTATTACTGTCAGCAACC
15		
15	CK157 V <sub>H</sub>	NPYYYGGTH
17	CDR1	
16	CK157 V <sub>H</sub>	ASIGSYPGYTDY
	CDR2	
17	CK157 V <sub>H</sub>	RHYYWYDATD
	CDR3	
18	CK157 V <sub>L</sub>	QSYGGV
	CDR1	
19	CK157 V <sub>L</sub>	YSASYL
	CDR2	
20	CK157 V <sub>L</sub>	QPSHLIT
	CDR3	
21	CK129 V <sub>H</sub>	EVQLVESGGGLVQPGGSLRLSCAASGFNISSYGSMHWVRQ
	amino acid	APGKGLEWVASIYPYSSSTYYADSVKGRFTISADTSKNTAY
	sequence	LQMNSLRAEDTAVYYCARGYGPWYAYSYFALDYWGQGT
		VTVSS
22	CK129 V <sub>L</sub>	DIQMTQSPSPLSASVGDRVTITCRASQYGGYVAWYQQKPG
	amino acid	KAPKLLIYGASLLYSGVPSRFSGGRSGTDFTLTISSLQPEDFA
	sequence	TYYCQRGHALITFGQGTKVEIE
23	CK129 V <sub>H</sub>	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGG
	nucleic acid	GGCTCACTCCGTTTATCCTGTGCAGCTTCTGGCTTCAACATCTC
	sequence	TCTTACGGTTCTATGCACTGGGTGCGTCAGGCCCCGGGTAAGGG
	bequeilee	CTGGAATGGGTTGCATCTATTTACCCTTACTCTAGCTCTACTTA
		TATGCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACAC
		TCCAAAAACACAGGCCTACCTACAAATGAACAGCTTAAGAGCTGA
		GACACTGCCGTCTATTATTGTGCTCGTGGTTACGGTCCGTGGTA
		GCTTACTCTTACTTCGCTTTGGACTACTGGGGTCAAGGAACCCT
24		GTCACCGTCTCCTCG
24	CK129 V <sub>L</sub>	
	nucleic acid	GGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGTACGGTGG

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	sequence	TACGTAGCCTGGTATCAACAGAAACCAGGAAAAGCTCCGAAGCTT CTGATTTACGGTGCATCCCTTCTCTACTCTGGAGTCCCTTCTCGC TTCTCTGGTGGCCGTTCCGGGGACGGATTTCACTCTGACCATCAGC AGTCTGCAGCCGGAAGACTTCGCAACTTATTACTGTCAGCGAGGT CATGCTCTGATCACGTTCGGACAGGGTACCAAGGTGGAGATCGAA
25	CK129 V <sub>H</sub> CDR1	NISSYGSMH
26	CK129 V <sub>H</sub> CDR2	ASIYPYSSSTYY
27	CK129 V <sub>H</sub> CDR3	RGYGPWYAYSYFALD
28	CK129 V <sub>L</sub> CDR1	QYGGYV
29	CK129 V <sub>L</sub> CDR2	YGASLLY
30	CK129 V <sub>L</sub> CDR3	RGHALIT
31	gWiz-LS- Fc(mIgG2)- His6-linker- TEV- hCXCL1 <sup>38-</sup> <sup>107</sup> -G2- AviTag	ATGASSET00000000000000000000000000000000000
32	gWiz-LS- Fc(mIgG2)- His6-linker- TEV- hCXCL5 <sup>43-</sup> <sup>114</sup> -G <sub>2</sub> - AviTag	ATGAGGGTOCCCCUTCAGCTCCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCA COATGTGAGCCCCAGAGTGCCCCCCCCTGCTCCTGGCTCCCCCCCC

		CCTOCADCACCACAASACATCADTAACAAASACETCACCCTCACCTOCATCATC
		acadoottettacotteccarattectotecceetocaccaatectectac caretaaaactajaacaacajeccaacajecctecaceeticatecetta jeec
		ATSIACAGGAASCICAGASIACAAAASASCAGTIGSSAAAGAGGAAGCOULTIC
		GCCTGUL DAGLIGITODACGAGGAL DEGLACAA ECACUTL ACGACITAAGACCATC NGCCCCCUUUUUGGSIXAACACCATCACCATCACCCTCTCCCCCCTGCATCTC
		GGTACC <b>GAGAACCTGTACTTCCAA</b> GTGCTGCGCGAGCTGAGATGCGTGTGCCTG
		ATCGGCCCCCAGTGCAGCAAGGTGGAAGTGGTGGCCAGCCTGAAGAACGGCAAA
		GAGATCTGCCTGGACCCCGAGGCCCCATTCCTGAAGAAAGTGATCCAGAAGATC
		CTGGACGGCGGCAACAAAGAGAAC <u>GGCGGA</u> GGCCTGAACGACATCTTCGAGGCC CAGAAAATCGAGTGGCACGAG <b>TGATGATAA</b>
33	gWiz-LS-	ATGAGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
	Fc(mIgG2)-	CGALGE GAGOCCAGAGTOCCCA LEACACAGAGUUCCEG LOUTCCAC LOAAAGAG
	His6-linker-	Tereconarsescanteraganersecarnescentrestere
	TEV-	COTCCARAGATICAAGGATGIACTOATGZICTOOOTIGAGCOOCATGGICACATGI
	$hCXCL8^{29-}$	CECUTO PEOCATOR ACCACCA FOACCOCATA COTOCATA E CADOD SUFEL DOTO AACAACCEOCAACTA CACACCACCACACACAACCOCA LA CAC ACCA TA CAAC
	$99-G_2-$	ACTACTODO OFFICIONO ACTOCIÓN CONTRACASE CONTRACASES EN ACTACIÓN DA CASENCIA CONTRACASES
		GECA AGA ATTCA A A BOA A SETO A A CARACTER COMPTCE COMPTCE A
	AviTag	AAAAGUREO EGAAAROOGAURASSOCIAURASAGGTUGASAGGTIATA. G. UTTG
		CCTOCACCAGOAGAAGAGAAGACTAAGAAAGAGTUCAGUCTGACCCGGACCCGGACCATGATC
		ACAGGOTECITACCEGCGAARTEGUTGTGGECEGGAGGEGCAATGGGGGGAGA
		CRAMARACTACARCARCERCORDOUTCCTCCACTCCATCOTTCCTTC
		AFGIAGASCAASCICAGAGIAGAAAAGSGCNCTIGSGAAGAGGAAGCCTITIC
		CCCTCCTCACTCCTCCACCACCACCACCACCACCACCACC
		TOCOGETUTUTGESARCACCATCACCATCACCTCTTCTGGCGTGGATCTG
		GGTACCGAGAACCTGTACTTCCAAGCCAAAGAACTGCGGTGCCAGTGCATCAAG
		ACCTACAGCAAGCCCTTCCACCCCAAGTTCATCAAAGAACTGAGAGTGATCGAG AGCGGCCCTCACTGCGCCCAACACCGAGATCATCGTGAAGCTGAGCGACGGCAGA
		GAGCTGTGCCTGGACCCCCAAAGAAAACTGGGTGCAGCGGGTGGGGAAAAGTTC
		CTGAAGCGGGCCGAGAACAGC <i>GGCGGA</i> GGCCTGAACGACATCTTCGAGGCCCAG
		AAAATCGAGTGGCACGAG <b>TGATGATAA</b>
34	gWiz-LS-	ATGACCCDODDCCTDADCHCCTDODDCHCCCDODHCHCTDODTCCCACCTDCA
	Fc(mIgG2)-	CGATGEGAGOCCAGAGTOCCCN: AACACAGAACCECEGI. OTECCACI: OAAAGAG
	His <sub>6</sub> -linker-	EG LOUCCCA EGOQCAGO EGOAGACO EGOTOGO EGGACCA EGOGLULTI CA LOTTIC
	TEV-	CCTCCAAAGATCAASSATCTACTCATCATCTCCCCCACCCCCCCCCC
		STGTTGTTGATGTGZGCGAGGATGACCCAGZCGUCCAGZTCAGCCGGTUDGTG
	mCXCL1 <sup>28-</sup>	ANDRACOTOCARCHAGAGAGAGOTON DRCAGARA DOCATACAC ROGATTA DARC
	$^{96}$ -G <sub>2</sub> -	A CTACTO COGEGE COTO A SUBCO COCOMPOSA SUACOR GENERAL CALA SUBCIONAL COMPANY
	AviTag	GGCAABBAGELIUAAREGCAABBLOAACAAUABAGCUUECOCALUUCOCALOBAB BARAOOAUCECAAAACCCARABBSUCARTAABAGCTOCACAGGCACAESUOTTG
		COLOCACUACCERARISSI
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		ATOTACASCAACOT CACROTACAAARCACCACTHOOCAAACACCAASUCUUTTO
		GCCTGCTCAGTGGTCCACGAGGGTCTGCACAATCRCCTLACGACTAAGACCATC
		TO DOCKNOT DOCKNAAA CACCATCACCATCATCACTCTTCTGGCGTGGATCTG

		GGTACCGAGAACCTGTACTTCCAAGCCAACGAGCTGCGGTGCCAGTGCCTGCAG ACCATGCCCGCCATCCACCTGAAGAACATCCAGAGCCTCAAGCTCCTGCCCAGC GGCCCTCACTGCACCCAGACCGAAGTGATCGCCACCCTGAAGAACGGCAGAGAG GCCTGCCTGGATCCCGAGGCCCCGGTGCAGAAAATCGTGCAGAAAATGCTG AAGGGCGTGCCCAAG <u>GGCCGGAGGCCTGAACGACATCTTCGAGGCCCAGAAAATCG</u> GAGTGGCACGAGTGATGATAA
35	gWiz-LS- Fc(mIgG2)- His6-linker- TEV- mCXCL2 <sup>31-</sup> <sup>100</sup> -G2- AviTag	ATGACOUTCCCODECTACCTORESCOUTECTOCTECCCODECACCTORA CGATATIGA SCICLAGA STRECOLATIAN CACAGA ACCONTRUIDUT CACAGA STRECOLATION TO COLICCA AGUAL CAACUATE HACIDATION CUUDEL CACCUUGAL COLUMNA AC STREETERA TETERASCER SCATCACCACACO TUURE A TORSULTET TOTE ACCACO TOCCAGA CTACACACO STUCAGA COLUMNA ACCUURE A TORSULTET TREE ACCACO TOCCAGO STREAC ACACO STUCAGA COLUMNA COCUUNI CACACO STUTACAAC AGTACT CTCCCGG STREAC ACACO STUCAGA COLUMNA COCUUNI COCUUNI CACACO STREAC ACCACO TOCCAGO STREAC ACACO STUCAGA COLUMNA COCUUNI COCUUNI CACA ACACO TOCCAGO STREAC ACACO STACACA SAFOCO LOUAL COCUUNI CACA ACACO TOTES AANOCCASACO SCACACA SAFOCO LOUAL COCUUNI CACA ACACO TOTES AANOCCASACO SCACACA SAFOCO STREAC STREACT COUCUAC CACACAGA STREACTICA STREACTICA SCACACO STREAC ACACOCUTETINA COLUMNA CACACASA CACACACA SAFOCO SCACACO STREAC CACOCUTETINA COLUMNA SAFOCACO SCACACO SCACACO SCACACO STREAC ACACOCUTETINA COLUMNA SAFOCACO SCACACO SCACACO SAFOCO SCACA CACOCUTETINA COLUMNA SAFOCACO STREAC ACTO SCOLUCINA CACOCUTETINA STREACT ACACAACACO SCACACO SCACACO SAFOCO SCACA CACOCUTETINA STREACTICA SAFA SACACO SCACACO SAFOCO SCACA CACOCUTETINA STREACT ACACAACACT SCACACO SCACACO SCACACO STREAC COUCUL O LE CUUDI. AAS CACCATCATCATCATCATCATCATCATCACCATCATCACCAC
36	gWiz-LS- Fc(mIgG2)- His6-linker- TEV- mCXCL5 <sup>48-</sup> <sup>118</sup> -G <sub>2</sub> - AviTag	ATGROCHTCCCCCCTCACCTCCTCCCCCCCCCCCCCCCCCCCCC

		AARATCGAGTGGCACGAG <b>TGATGATAA</b>
37		<u>MRVEAQLIGIIIIIWIRGERC</u> UPRVPITQNPCPPLEECPPCEARDIIGGPSVFT
	LS-Fc-His6-	PARI ROVIMI SUSPINITOVIVOVSEDDE OVQI SVEVNIVEVHI AQTQI HREON
	linker-TEV-	STLEVYSALPIQEQCHESCREELCVYMRALESPIERTISKPROPYEAGQVYV
	hCXCL1 <sup>38-</sup>	FEPAREZIKKERSI. KUMI LOPILPARI AVEW ISNOR ERQIMKELA EVILEVU OST.
		my skervças twergelfacevy anglemelatette skelgel <b>herressgvd</b>
	$^{107}$ -G <sub>2</sub> -	GTENLYFQATELRCQCLQTLQGIHPKNIQSVNVKSPGPHCAQTEVIATLKNGR
	AviTag	ACLNPASPIVKKIIEKMLNSDKSN <u>GG</u> GLNDIFEAQKIEWHE
38	LS-Fc-His <sub>6</sub> -	<u>wryf Aglest Lligipgargeer yf i tonf op fi reoff gaappli Sspsyfi.</u>
	linker-TEV-	FERENDVERESESPEVICVVEVSEODEDVÇEVBEVARVEVALAÇEÇTEREDT.
		STERVYSBLETQHQDPHS/KEEKOSVNEPALESPTEKTTSRPREPVBACQVVV
	$hCXCL5^{43}$	PPPA SEMPRATEPS FOOM FIGHT PAR LAVON DEMORTE ONE RELATIVLE OF DEST
	$^{114}$ -G <sub>2</sub> -	WUSKLEVQKSTWEEGSTFACSVVEGTERALITEKTISESTSK <b>HRBBBBSSGVD</b> .
	AviTag	GT <b>ENLYFQ</b> VLRELRCVCLQTTQGVHPKMISNLQVFAIGPQCSKVEVVASLKNG
		EICLDPEAPFLKKVIQRILDGGNKEN <u>GG<b>CINDIFEAQKIEWHE</b></u>
39	LS-Fc-His <sub>6</sub> -	MENEAQUDGILLINDPGARGEDENPHTYNECEPHKEGEPGAAPDLESSEGNEI.
	linker-TEV-	
		STIEVVSAUPTOHOLAMSSKEEKOSVERRATESPTEKTIS SPESVVRAPOVVV
	hCXCL8 <sup>29-</sup>	PPPA SEMERREPORT OWE DOTE PAREAVOWL SEGRET SQUERE LETVED SEGRET
	$^{99}$ -G <sub>2</sub> -	WYSKLEVOKSUWERSSUFACEVVÆGLENRIJTEKU FRESUSK <b>HRHRRHSSGVD</b>
	AviTag	GTENLYFQAKELRCQCIKTYSKPFHPKFIKELRVIESGPHCANTEIIVKLSDG.
		ELCLDPKENWVQRVVEKFLKRAENS <u>GGGINDIFEAQKIEWHE</u>
40	LS-Fc-His <sub>6</sub> -	Mentragilisi illiyile garcare vv fitore ce pi kecipp caap d.e.c.c.p.svat.
10	linker-TEV-	FERIRDVERI SESERVIDVVVDVS SUDEDVÇE SVEVRIVELAÇI, ÇIBREDI.
		STLEVVSALDLQVQDØMSGKEFKORVENBALDSDLEKTUS RDDGVVRADQVMV
		I STITELE SOUTH TO CONTROLE OF DEPENDENCE DE TERET DE TREST DE LE SERVICE DE LE SERVICE DE LE SERVICE DE LE SE
	mCXCL1 <sup>28-</sup>	
		PPPAREMEREEVELOWE JONE PAMEAVOWL SUGPTED STREATVLOSEDOX
	<i>mCXCL1</i> <sup>28-</sup> <sup>96</sup> - <i>G</i> <sub>2</sub> -	PEPARENERERSELORE IGELEAR LAVOWL SEGET SQASKE LATVLESEGGY Mysklevqwstweegs leadovversileralitekt for stor <b>hennen <u>ssgvd</u></b>
	mCXCL1 <sup>28-</sup>	PEPARENERERSELORE IGELEAR LAVOWL SEGET SQASKE LATVLESEGGY Mysklevqwstweegs leadovversileralitekt for stor <b>hennen <u>ssgvd</u></b>
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G2- AviTag	PPPASEMERKEPSELOMELIGEEPAMEAVDWLSNGPTSQNSKGLATVLDSBOGY MYSKLPVQKSTWERGSDFAOSVVHEGLENALITTKIESPSEGK <b>HHHHHH</b> SSGVD GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPK <u>GG</u> GLNDIFEAQXIEWHE
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His <sub>6</sub> -	PPEASEMEREEPSELOMELIGEEPAELAVOWLSNGFTSQASKALATVLDSDGSY MYSRLFYQKSTWERGSDFACOVYERGLABADITEKTESPSEGK <b>HHHHHHS</b> SGVD GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATEKNGR ACLDPEAPLVQKIVQKMEKGVPK <u>GG</u> GENDIFEAQKIEWHE MRYFACLEGELLLWEFGARCEPFYFTDQRPCEFEKECTPCAAPDLEGGFSVFT
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV-	PPPAEEMIKEERSII OMIISPIPAEIAVOWI SHGRTEQAIKALATVIDSOGSY MYSKLEVQKSTWERGSIFAOSVVHUJLERALTTKI I SESIGK <b>HHHHHIS</b> SGVD GT <b>ENLYFQ</b> ANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATIKNGR ACLDPEAPIVQKIVQKMLKGVPK <u>GG</u> GLNDTFTAQKIEWHT MRVPAOLIGILLIMIFGARCEPPVFITORPCTFIKEOPPCAAPDLLGSPSVFT PPKIKDVLMISLSPMVTOVVDVSEODPDVGISWEVDIVEVBLAQTCOREDY
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup>	PPPAEEMIKEEPSILOWIIGFIPAHIAVUWI SNGFTSQAYKALATVIDSNGSY MYSKLEVQKSTWERGSTFACSVVHUGLANALITKIIISESIGK <b>HHHHHH<u>SSGVD</u> GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPK<u>GG</u>GINDIFFEAQKIEWHE MRVPACILGELLLMIFGARCEPPVFITQRPCFFIKEOPPCAAPDLLGGFSVET. PPKIKDVLMISISPMVTCVVDVSEOPPDVGISWEVDINEVELAQTQCBREDVI STLEVVSALFIQWQDWMSGNEFKCAVNNKALPSFIEKTISEFGPVRAPOVYV</b>
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV-	PPEASEMEREEPSELOWEIGEEPAELAVOWLSRGPTSQASKALATVLDSBGSY MYSKLRVQMSTWERGSTFACEVVHEGLABALTTKTEEPSEGK <b>HHHHHHSSGVD</b> GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPK <u>GG</u> GLNDIFEAQXIEWHE MRVPAQLEGELLLMILFGAROEPPVFETQRPCFFEREOPPCAAPDLEGGFSVFT PFKEKDVLMISLSPMVTOVVVDVSEODPDVGESWEVDIVEVBLAQTQTØREDV STLEVVSALFIQHQDWMSGPEFKORVNDRALPSFLEVTTSRFEGPVRAPOVYV PPPAEEMERKEPSETOMETOPEPAELAVOWTSNCRTEQNYRNLATVLDSDCSY
41	<i>mCXCL1</i> <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - <i>AviTag</i> <i>LS-Fc-His6-</i> <i>linker-TEV-</i> <i>mCXCL2</i> <sup>31-</sup> <sup>100</sup> -G <sub>2</sub> -	PPEASEMEREEPSELOMELIGEEPAELAVOWL SEGFTSQASKALATVLDSEGST MYSRLEVQKSTWERGSLFACSVVERGLEBELTTKTEEPSEGK <b>HHHHHHSSGVD</b> GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPKGGGLNDIFTEAQXIEWHT MRVPAQLEGELLLWLPGAROEPPVEIDQEPCEFEKEOPPCAAPDLLGGESVET PPKEKDVLMISLSPMVTOVVVEVSEODPDVGESWEVEEVEVEVELAQTQCBREDV STLEVVSALFIQUQDWESGEEFKOKVNEKALPSFLEKTESAFFGPVRAPOVV PPFASEMEKKEPSETCMETOPEPAELAVOWTSNORTEQNYKHLATVLDSDOSY MYSRLEVQKSTWERGSLFACSVVEGLEBELTKEEPSEGKHHHHHHSSGVD
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup>	PPEASEMEREEPSELOMELIGEEPAELAVOWL SEGFTSQASKALATVLDSEGST MYSRLEVQKSTWERGSLFACSVVERGLEBELTTKTEEPSEGK <b>HHHHHHSSGVD</b> GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPKGGGLNDIFTEAQXIEWHT MRVPAQLEGELLLWLPGAROEPPVEIDQEPCEFEKEOPPCAAPDLLGGESVET PPKEKDVLMISLSPMVTOVVVEVSEODPDVGESWEVEEVEVEVELAQTQCBREDV STLEVVSALFIQUQDWESGEEFKOKVNEKALPSFLEKTESAFFGPVRAPOVV PPFASEMEKKEPSETCMETOPEPAELAVOWTSNORTEQNYKHLATVLDSDOSY MYSRLEVQKSTWERGSLFACSVVEGLEBELTKEEPSEGKHHHHHHSSGVD
	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup> <sup>100</sup> -G <sub>2</sub> - AviTag	PPPAEEMIKEEPSILOWILIGELPAHLAVUWLSNGETSQATKALATVLDSDGSY MYSKLEVQKSTWEEGSDFACSVVHUGLENRLITKTISESDGKHHHHHHSSGVD GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPK <u>GG</u> GINDIFEAQXIEWHE MRYPACILGELLLIMIP GARCEPPVFITQNPCFFIKEOPPCAAPDLLGGFEVET PPKIKDVLMISISPMVTCVVDVSEODPDVGIEWEVDISVETAQTQCBREDY STLEVVSALFIQWQDWMSGDEFKCAVNDKALPSFIEKTISAFFGPVRAPQYY PPFAEEMIKKEPSITCMETOPIPAELAVOWTSNCKTEQNYKHIATVLDSDCSY MYSKLEVQKSTWEEGSDFACSVVHUGLENRIJTKTIERSDGKHHHHHHSSGVD GTENLYFQASELRCQCLKTLPRVDFKNIQSLSVTPPGPHCAQTEVIATLKGGQ VCLDPEAPLVQKIIQKILNKGKAN <u>GG</u> GINDIFEAQXIEWHE
41	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup> <sup>100</sup> -G <sub>2</sub> - AviTag LS-Fc-His6-	PPPAEEMIKEEPSILOWILIGELPAHLAVUWL SNGFTSQATKALATVLDSDGSY MYSKLEVQKSTWERGSTFACSVVHEGLERRITTKTISESEGKHNHNHH <u>SSGVD</u> GTENLYFQANELROQCLQTMAGIHLKNIQSLKVLPSGPHOTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPK <u>GG</u> GLNDIFEAQXIEWHE MRVPAQLEGLILLAWLFGARGEPEVTITQRPOETIKEOPPCAAPDLEGGESVST PPKIKDVLMISLSPMVTOVVVEVSEOPPDVGISWEVREVENSEVETAQTQCBREDT STLEVVSALFIQUQDWMSGEEFKOAVERGALPSFLEXTISAFEGFVRAPOVYV PPFASEMIKKEPSITCHEOPIEPAELAVOWTSNORTEQNYKHLATVLDSDOSY MYSKLEVQKSTWERGSTFACSVVREGLERRITTKTISESEGKHNHNHMSSGVD GTENLYFQASELROQCLKTLPRVDFKNIQSLSVTPPGPHCAQTEVIATLKGGQ VCLDPEAPLVQKIIQKILNKGKAN <u>GG</u> GLNDIFEAQXIEWHE
	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup> <sup>100</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV-	PPPAESMIKEEPSILOWILIGELBALLAVUWLSHGETSQAFKALATVLDSEGSY MYSRLEVQKSTWEEGSLFACSVVHEGLEBBLITTKTIEPSSLGKHHHHHHSSGVD GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPKGGGINDTFEAQXIEWHE MRVPAQLLGILLLWLEGARGEDEVEITOPBCTEFIKEOPPCAAEDLLGGEGVET. PFKIKDVLMISLSEMVTOVVEVSEDDEDVGISWEVENVEVETAQTQCBREDY STLEVVSALFIQUQDWEGEVEKOAVHEGALEEPIEKTIEREEGEVRAPOVV PPPASEMIKKEESITOMETOPIEPAELAVOWTSHORTEQNYKHIATVLDSDOSY MYSRLEVQKSTWEEGSTFACEVERGLEBBLIKKTESESTGKHHHHHHSSGVD GTENLYFQASELRCQCLKTLPRVDFKNIQSLSVTPPGPHCAQTEVIATLKGGQ VCLDPEAPLVQKIIQKILNKGKANGGGINDIFEAQXIEWHE
	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup> <sup>100</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL5 <sup>48-</sup>	PPPAESMIKEEPSILOWIIGELPAELAVUWI SHGPTSQAYKALATVIDSEGSY MYSKLEVQKSTWERGSIDFACSVVHEGLERALITKIIIDESIGKHHHHHHSSGVD GTENLYFQANELRCQCLQTMAGIHIKNIQSIKVIDSGPHCTQTEVIATIKNGR ACIDPEAPIVQKIVQKMIKGVPK <u>GG</u> GINDIFTAQXIEWHT MRVPAQIDGILLIMIEGARCEPPVEITQRPCFFIKEOPPCAAPDLEGGEGVET. PPKIKDVIMISISPMYTOVVDVSEODPDVGISWEVNEVEVELAQIQCGREDY STLEVVSALFIQHQDWMSGEEFKOKVNNRALPSFIEVTISKEFGPVRAPOVYV PPPAEEMIKKEPSITCMITOFIPAELAVOWISHCRTEQNYKHIATVIDSDOSY MYSKLEVQKSTWERGSIDFACSVVHEGIERALITKIIPESIGKHHHHHHSSGVD GTENLYFQASEIRCQCIKTIPRVDFKNIQSISVTPPGPHCAQTEVIATIKGQ VCIDPEAPIVQKIIQKIINKGKAN <u>GG</u> GINDIFEAQXIEWHE
	mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV- mCXCL2 <sup>31-</sup> <sup>100</sup> -G <sub>2</sub> - AviTag LS-Fc-His6- linker-TEV-	PPEASEMERKEPSELOWEIGEPAELAVOWLSHGETSQAFKALATVLDSEGSY MYSRLEVOKSTWERGSLFACSVVHEGLERBELTTKTEEPSEGKHHHHHHSSGVD GTENLYFQANELRCQCLQTMAGIHLKNIQSLKVLPSGPHCTQTEVLATLKNGR ACLDPEAPLVQKIVQKMLKGVPKGGGLNDIFTAQXIEWHT MRYFAQLEGILLLWLFGAROADEVFEDORECEPIKEOPFCAAEDLEGGFSVFF. PFKEKDVLMISLSFMVTOVVDVSEODEDVCISWEVENVEVEDAQUQCBREDVE STLEVVSALFIQUODWSGEUFKONVNERALPSFLEKTESREFSFVRAPOVVV PPFASEMERKEPSEICHEDOFEPAELAVOWTSHCRTEQNYKHLATVLDSDOSY MYSKLEVOKSTWERGSLFAOSVVHEGLERBELTTKTESESLGKHHHHHHSSGVD

43	gWiz-LS-	ATGASSBICCCSSD.CAGCEUCI.96660/BUDDIGC.SUPCIAGC.BUDDAGG.B
	hCXCL1 <sup>35-</sup>	CGARRY GCCTCTGTCGCCACCGAGCTGAGATGCCAGTGCCTGCAGACCCTGC
	107_	GGCATCCACCCCAAGAACATCCAGAGGGTGAACGTGAAGTCCCCTGGCCCCC
	(Gly4Ser)2-	TGCGCCCAGACCGAAGTGATCGCCACCCTGAAGAACGGCCGGAAGGCCTGCC
	mouse SA-	AACCCCGCCAGCCCCATCGTGAAGAAAATCATCGAGAAGATGCTGAACAGCG
		AAGAGCAACGGTGGAGGCGGTAGCGGAGGGTCGCGAACCACACACA
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		GCCTTAGCC <u>GGAGGGGGGGGGGGTTCC</u> CACCATCACCATCACTGATAA
44	gWiz-LS-	ATGAGGE CCCUGULOAGCIUULOGGGUIDOLOCLUUICLOGGUIDOLOCLUUCAEGLU
	$hCXCL2^{35}$	CORRECTCCTCTGGCCACAGAGCTGAGATGCCAGTGCCTCCAGACACTCC
	107_	GGCATCCACCTGAAGAACATCCAGAGCGTGAAAGTGAAGTCCCCTGGCCCCC
		TGCGCCCAGACAGAAGTGATCGCCACCCTGAAGAATGGCCAGAAGGCCTGCC
	$(Gly_4Ser)_2$ -	AACCCCGCCAGCCCTATGGTCAAGAAAATCATCGAGAAGATGCTGAAGAACG
	mouse SA-	AAGAGCAACGGTGGAGGCGGTAGCGGAGGCGGAGGGTCGGAAGGACACACAC
	(Gly4Ser)-	GROATCOCCETCOSTATASTCRTTICCCR-SACASCRITTCAAROOCTISC:

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		COUSAAGAAAUSAAEGELTUULGOAAGAAGAAGAAGAAGAAGAAGUUGAGOOLSUUA
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		CARAACTITIGRAGAGAGAGATITITAAAGAATISGGCAGIAGCICGICTGAGCOAG
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		ANAGTONONAGGAGTOTTOCONTGOTGACOTGGGAATOGCGAGAGGAGAG
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	107	GGCATCCACCTGAAGAACATCCAGAGCGTGAACGTGCGGAGCCCTGGCCCTCAT
	-	TGTGCCCAGACAGAAGTGATCGCCACCCTGAAGAATGGCAAGAAGGCCTGCCT
	$(Gly_4Ser)_2$ -	AACCCCGCCAGCCCTATGGTGCAGAAGATCATCGAGAAGATCCTGAACAAGGGC
	mouse SA-	AGCACCAACGGTGGAGGCGGTAGCGGAGGGGGGGGGCGGAAGCAAABAAGT
	(Gly <sub>4</sub> Ser)-	GAGATUGOODATUGGTATAATGATTEGUGAGAADALTTCAAAGGOODAGTU
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47	gWiz-LS- hCXCL5 <sup>44-</sup>	ATG
	(Gly4Ser)2-	GCCCCATTCCTGAAGAAAGTGATCCAGAAGATCCTGGACGGCGGCAACAAAGAG
	mouse SA-	AACGGTGGAGGCGGTAGCGGAGGCGGGAGGGTCGGBAGGCACACACACCACAC
	(Gly <sub>4</sub> Ser)-	GOULAT DESTAAL GAT LIKREGAGAALAADAT ELUAAASSOL HASLOOL HATT
	His6	GCOPTTUCCARTAUCTCOAGAAATGODOAUACGAPGAGCATGOOAAATUAGTG
	HIS6	CAGGAAGIAACAGACITIGCAAAGACGTGTGTGCGGACGAGCGCGAAC
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		AACIIGGECAAAACCAACIGIGATUELIACGAGAAGCILGGAGAALAIGGAIIC CAAAAIGOOATTUEAGTECGUENOACCUAGAAAGUACUTOAGGEGEOOACCUUR
		AC LOTOSI GGAGGOL GCHAGAAROO LAGGARGAG LGGGCACCAASUGL I G LAUA
		CTINOTSPACATOASPCACTOOSTFCINOTOSPACACTANCTCUCTOSPALICOTO
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		TO TO TO A COMPAREMENT OF COMPAREMENT.
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49	gWiz-LS- hCXCL7 <sup>59-</sup>	ATG
		TTACCO <u>GGAGGGGGGGGGGTTCC</u> CACCATCACCATCAC <b>TGATAA</b>
		SACACCUROTUCICGAOTSAGORTOCASACOTTOUCACUASAUGCAAASAUGC
		STOAT GGATGAOT E UGUACAGE UGUTGGA LACATGE E GCAAGGO E GCUGACAA
		CITROTSASCIAGTSASCAAASCCCAAGSCTACAGGGSASCAACTSAAGAC
		TCTCATATCTCCACACTTCCACASAACACCACAACAACAACAAAAAAAA
		ARVERATE FRANCKARCON FRANCKARCHUSTAR GEFELLER GELEUR FRA GELUARGARACHTAL GELOUCARAGACHTTRAAGUNGAGACHTUCACON I UCA
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		AC ADTT CETGAAGATCAGAGACTGECUT GT GT GGAAGACTAFC DODCTGCAAT
		CCAACTOLOG ISBAGOOLGUAAGAACUTAGGAAGAGTOGOCACUAAGIGITS
		TTCCARATGCCATIOTAGTCCGOTACSCCCAGAASGCAOTCSGCUTCAAS
		AAVAACTTOOTUAAAAOOAACTOTOATUTTIAGOAVAACOTTOJAGAATATOG
		CCCSCRUSCIACESCRUSCRUSCUIGAAUTICRECCUUHECAGARGAGES
		CTICCTARGASTACGAACCCADETCCBAAAGECCTCOCTCARCOCA
		tfgtatgaatattoagaa sacroootsattactoistatoootsitteotsas
		CASCARCTCTSCARCARCISTCCTCASSCCARCONTGTCTTSCTCCCCCACSTT
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		GOCCCCAGAACTECETETACTERCOTGASCECULACAAESAGAEECIISECCCASES
		ACCEPTEATOOSACACTATCESCATCAASTECCCASAAGACATCOTLACTCOTA
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	Hise	STECAGGAAR AACAGAULE GCAAAGACG ISTULEGCCGATEAG LOUGCOGC
	(Gly4Ser)-	ATTWOTTTTCCCAGEATCPCCAGEATGCTCATACGATGCCAEATT
	mouse SA-	ATCCCODATCCCTACATCSTTCGCCACAGAGAGACATTCAAACCCCCCACCCCT
	(Gly4Ser)2-	AAGAACGGTGGAGGCGGTAGCGGAGGCGGAGGGTCGCAAOAACACAAAAAACCC
	114_	GAGGCCCCATTCCTGAAGAAAGTGATCCAGAAGATCCTGGACAGCGGCAACAA
		AAGGTGGAAGTGGTGGCCAGCCTGAAAAACGGAAAACAAGTGTGCCTGGACCC
	$hCXCL6^{43}$	AACCCCAAGACCATCGGCAAGCTCCAGGTGTTCCCTGCCGGCCCTCAGTGCAG
τu	gWiz-LS-	COATCT GTGCTGACCGAGCTGCGGTGCACCTGTCTGAGAGTGACCCTGCGCGT
48		ATGASSGT000050T0AGCH00T966GUH00T60T50T0T966T000A96T30
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<sup>121</sup> _ (Gly4Ser)2-	GAAGTGATTGCCACACTGAAAGACGGCCGGAAGATCTGCCTGGACCCTGACGCC CCCAGAATCAAGAAAATCGTGCAGAAAAAGCTGGGTGGAGGCGGTAGCGGAGGC		
mouse SA- (Gly4Ser)-	GRAGGETCE GARGE ADACARGAGE AGE TO CONCATEGE TATAR FRANT 2553     GARCANNA TO CORAGES CONCATES TO CONTENT CONSIGNATION STATE     LOCTUAL ACGATGAGE A LOUGAA FLAGT CONTENT CONSIGN TATE CONCATES CONSIGNATION ADACATES CONSIGNATIES CONSIGNATIS		
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50 gWiz-LS- hCXCL8 <sup>28-</sup> <sup>99</sup> - (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	ATG AGGETUDDOGOLICADOLOGLIGUDGOLOCTUD. DOLCTUDOLOCICADOLOCIADOLOGLIGUDGOLOCTUD. DOLCTUDOLOCICIDADOLOCIADOLOCICIDIDOLOCICIDADOLOCICIDIDOLOCICIDADOLOCICIDADOLOCICIDADOLOCICIDADOLOCICIDIDOLOCICIDADOLOCICIDIDOLOCICIDADOLOCICIDIDOLOCICIDIDOLOCICIDADOLOCICIDIDOLOCICIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICICIDOLOCICICIDOLOCICICIDOLOCICIDIDOLOCICICIDOLOCICICIDOLOCICICIDOLOCICICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDOLOCICIDIDOLOCICIDOLOCICIDIDOLOCICIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDOLOCICICIDOLOCICIDOLOCICIDOLOCICICIDIDOLOCICICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDIDOLOCICIDOLOCICIDOLOCICICIDOLOCICIDOLOCICICIDOLOCICIDOLOCICICIDOLOCICIDOLOCICICIDO		
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51	gWiz-LS- hCXCL9 <sup>23-</sup> 125_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	CTUBATCAAA DETAILOTO DUCAAACA STITEAA AOUTGACAOUTUCACOUTUCACOUTUCACOUTUCACOUTUCACOUTUCACOUTUCACOUTUCACOUTUCACOUTUCACAO
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52	gWiz-LS- hCXCL10 <sup>22-</sup> 98_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	ATG ADDNECCOUD, CACCIDOL SECCUTORI SCILUTERISCUNDEASE JULA           CAROL STGCCTCTGAGCAGAACCGTGCGGTGCACCTGTATCAGCATCAGCAAC         CAGCCCGTGAACCCCAGAAGCCTGGAAAAGCTGGAAATCATCCCCGCCAGCCA

	CTICCA BATA TOCATTIC CAAA TOCCATTITACITCO DACA COCABAACO. COTO ACCTOTO ACCUCAACTO DUUTO ACCUTUCAACAACO DACCAACAACO COTO ACCTATTIC DACA TTIC OTCAA DATCACA DACTAACO DACCAACAACO TA CERTOTO CAALCO TGATCO TOCAACATCO COCABAA SACODO AST AGUIAAGOALG JEACOAAGUUTELAGUUGALOOC JUUTEBAAA SUCESSOATG TTOTOTO SCTCTGACA STIGATO AS A CATATISTIC CORAAGASTI TAAS SCIDEA ACCTTOTO COTO CACECTIGATA DUI GOACACITICO AGA SAAGA AS COGO ACACT AR STAA CAAR DECTTOTTISTICA COTOFICTAACOACAACOO AACTACACOCAACEC GA SCAACTGAAGACITICA TGACATTICO ACCACTTICO TOGA TACATO TIG AACOCTTOTICACACITICA TGACATTICO ACCACTTICO TOGA TACATO TIG AACOCTTOTICACACITICA TGACATTICO ACCACTTICO TOGA TACATO TIG AACOCTTOTICA CACTTICTICACCTICICO ACCACTTICO TOGA TACATO TIG AACOCTTOTICACACTICICACACTTICO ACCOCTICICACAC
53 gWiz-LS- hCXCL11 <sup>22-</sup> 94_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	ATG ANY LESS TRANSPORTATION TO SERVICE TRANSPORTAGE SERVICE AND AN A SERVICE AND A S

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54	gWiz-LS-	ATG GOOD COORD COMPANY CONTRACTOR
	$mCXCL1^{25}$	GGCATCCACCTGAAGAACATCCAGAGCCTGAAGGTGCTGCCCAGCGGCCCTCA
	$(Gly_4Ser)_2$ -	
	mouse SA-	GATCCCGAGGCCCCCCTGGTGCAGAAAATCGTGCAGAAAATGCTGAAGGGCGT CCCAAGGGTGGAGGCGGTAGCGGAGGCGGAGGGTCGCAASCACACAACAA
	(Gly4Ser)-	ATOSCOCATORE A LAATRA EE LOOCAGAACBACAE EE CAAARSOC LAUL DE ATOSCOTTTTCOCAGTATCTOCAGAAATSCOCATACGAE GACAGOATS
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		GASAAAGDATUSSTOPDATUTSUDDOTUDSAAAATISAAGTOOLOOAGDATISCA
		AAGTTTGGAGAGAGAGOLLTTAAAGCATGGGCAGLAGUL 0510.TEAGOCAGAG TEODOCAETGCTGACTTEGCAGAGAGCATGGGCAEATDGGCAEGAGAGCAAA
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		CIGAACCEIGIUTELCIGCTECALGAGAGACCCCAGTEAGIGASCALELLAU AAGTECTGTAGTEGATCCCCEGGGAAAGCCGGCCATGCTICTCTCCCCCEGA
		GEDEAT GEAACA TATUTCOCCARA GAGT TAXAGOTGAGA COLOCACUTTOCA DOTGATATOT MACACOTT CCACACAA MACAACCAMATIAACAAACAAAC MOC
		CTUBUIGAGO UBIIGAAGCAURAGOOCAAGGOTACAGUGGAGCAAGUGAAGAG GTCATO ATGACTTUBURCACTUBUICCATACATCTTO CAAGCOTO UGACAA
		GACACOUSCI DOTOSACIGACOSTICCAAACOTIGUDACUA GAUROAAA SACOO TURRUC <u>GGAGGGGGGGGGTTCC</u> CACCATCACCATCACTGATAA
55	gWiz-LS-	ATGAGGTCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
	$mCXCL2^{28-}$	CGGGTGGACTTCAAGAACATCCAGAGCCTGAGCGTGACCCCCCCTGGCCCTCA
	- (Gly4Ser)2-	TGTGCCCAGACCGAAGTGATCGCCACCCTGAAGGGCGGCCAGAAAGTGTGCCT
	( <i>Gry45C1)</i> 2 <sup>-</sup>	GACCCCGAGGCCCCCTGGTGCAGAAGATCATCCAGAAGATCCTGAACAAGGG

	mouse SA-	AAGGCCAACGGTGGAGGCGGTAGCGGAGGCGGAGGGTCGUAADDADDADDADT
		URGA TO CUCULATO CONTATI RA TOA TITTO CONCEACIACIACIA CITTO NARO CUCULATO CO
	(Gly4Ser)-	OT VALLECOOT LEEFC COACTA ECTOCA VAAA TOOT DA EAC OAT DAGCA TOO DAAA
	His <sub>6</sub>	TTASTSCAGGAS STAACAGACHUTGCAAAGACGTSTSTUGCCGATGAGTCUGCC
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		TRICCODORGAACTICITTIECTATOCICEODROFRORAL GAGACICODACCORC
		TGTTETSCAGAGEOTGACAAGEAAAGCTEDCTGACODOGAAGCTTEATSGTETS
		ARSSAGAAASCAT LOUTCL CALCTUTCCG LCAGASAA LGAASL SC LCUASL ATG
		ON CRACIPTICON CRONON COUTTINAN CORTINOCON CERMITO DE CUMACO CRO
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		ARACTCARGASCENTCCCCCAPSCICECCTCCCCACAUGACACC
		goggarchtgocarghacatghghgrafaragolggogrolletul ocaguaractg
		CASECULOOT-DIGA BAAADCAC LOTT-DAAGAAAD DUCAC TOT-DUHAOLOA DOHG
		eascalgacaccalgoeescusaroesculgocaulgougeesculuterusas
		GACUASSAAG JURSCAAGASURALGO JUBAGGOGAAGSALGEO LIUCI, GGGCAUG
		TECTTOTATIGAATATECCAAGAAGACACOOTGATEAOTOTGERALOOCUGELGOTO
		ABACE EGUTARGRAFIATGARGCUACLO EGGAAAGEGCTGOGO EGAGGODARE
		COTFCCCCAT-FFACCOCATAGTCCTTFCCCAAGTFCACCCTTTFCTACAARCAG
		COLLAGRACELUSE CAARACKARCEGUE CETTERUSASARCUESGASARA
		GGATTO SAAAFCO SATHORACIH GGOTAGASCOS CARAFCACOTCA SUISTOA
		ACCONARCICIDETSSAGGOTGCASGAAADCIAGGAAGASIGGGOACCAARTOT
		TGLACKCTTOCHGAGGACGGCTGCCHUSTGLGGAGGGCLAHCUSTCUGCA Afoctgaacostgtgtggcctgcctgggaggagacggcccastgaggaggaggaggaggaggaggaggaggaggaggaggag
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		ACAOTTOREAAACATATOTOOCCARACOOTTRACCOCCAGAOOOTTCACOTTO
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		OCTUTTOTONGCICOTONAGCAGAAGOCCAAGOCTACAGOCCAGCAAGO DAAG
		ACTIVICATORA ISAOTTECCACACITECESCATACA ECETOCAA SCOTOCISAC
		AAGGADADO EGUTTO ECCACITGA99G JOUARACO JITETOAC EAGALI90AAAGAD
		SOCITACUC <u>GGAGGGGGGGGGGTTCCCACCATCACCATCACTGATAA</u>
56	gWiz-LS-	ATGACCHECCCCCCCCACCTCCCCCCCCCCCCCCCCCCCCCCC
	$mCXCL3^{28}$	CGGGTGGACTTCGAGACAATCCAGAGCCTGACCGTGACCCCCCCGGCCCTCAC
	100_	TGTACCCAGACAGAAGTGATCGCCACCCTGAAGGACGGCCAGGAAGTGTGCCTG
	(Gly <sub>4</sub> Ser) <sub>2</sub> -	AATCCCCAGGGCCCCAGACTCCAGATCATCAAGAAGATCCTGAAGTCCGGC
	mouse SA-	AAGAGCAGCGGTGGAGGCGGTAGCGGAGGCGGGGGGGCGCAA DOACAOAA DACH CADATCODOCATCOCTATAATCATTTPDGGACGACGACATTTOAAAGCCOTACHC
	(Gly <sub>4</sub> Ser)-	OF SAFEROUTUERCON OTABUUDON SAAAUGOTUS FACON DA SCADOO DAA
		TTAGTGOAGGANGTAAOAGACTUTGOAAAGAOGTGIGIUGOOGAIGAGTCUGCC
	His <sub>6</sub>	GOCEACUSTGE CAAR POOCHTC ACA CTUTTUT DE ESTAR SUTUTUT SCECCETT
		CCARACCECCEURARAC LETURE GRACTORE E GECTRAL CARRACAGAG
		CCCCARASSAAACCAATCHIIICOUSCAACACAAAGAICACAAACCOCA SCUICCOCA
		CCAPTESAAGGOOASAGGOTGASSCOATGUSCACOTOETEEAAGGAAAAOODA ACCAOOUUEAURGGACACDATTUSCAUGAASEEGCOAGAEGACATOCUEADTTO
		TALESCOULAGA ACTIVITACE A TROUGACE CENCRAL SAGALECTRALE EC TALESCOULAGA ACTIVITACE A TROUESAGUE CENCRAL SAGALECTRACE CAG
		TRUES CLASSOC BACAAGGAASCESCORACCCCAACOLEGATER. SEC

		CAGAACTIIIGAGAGAGAGAGAGAGACTIIIGAAGAATGGGCAGTASCICGTCUGAGCAG
		ACATTOCOCAATGOUGACUTTOCEGAAATCACCAAATEGCAAAAGACUUGAOO AAAGECAACAAGACUGOLGOCATGOLGACCUUGGAATGOGOAGAUGACAGG
		GOGGAACTTGOOAAGTACALGLGTGAAAACCAGGOOACLATCLOOAGCAAACLG CASACTTOOTOCCATGAACCACTOTTGAACAAAOCCCACTOTSTTACTOA SCTG CASCALGACACCALGOOTGCTGATOTGCCTGOOALTGCLGOTGATTTCTLGALGAG CAGCALGACACCALGOOTGCTGATOTGCCTGOOALTGCLGOTGATTTCTTCCT CAGCALGAACTATTGCAAGAACTACTGCTGAGGOOAAGGATOTCTTCCTCCCC CAGCALGAACTATLCCAAGAACACCCCTGALLACTCLGLALCCCLGLLGOTG
		AGACTIGO FARGARER EGRAPOCACIUTISGARASTISCESCOUTGRASCORAT CCTOCO SCRECCTROGCECCOCUTOCTORATITCROCCECCTCURCRACAC CCTRAGASCIUMSECRARACORACTISCETCOCTORATITCROCCECCTCURCRACAC CCTRAGASCIUMSECRARACORACTISCERTUTERACASTASCOTCRESSARATA GGATTCURRACTCURSECURGESSOFECTORACCURGRASGECCTCRESSOF ACODORACTCURSEGURSECEGCAGARACCURGGRASGESTSSOFCACURA FEST
		TOLACACTTOCI GAAGATCAGAGAGTGOCI LUTGL GGAAGACLAI CUGTOL GCA ATOCTGAADOTCUCTOTCTOC CODACGAGAGACCCCCADTCAUTGADDAU CU ACCEAGTGOTGTAGTGGATCCCCDGGTGGAAGACCCCCADTCAUTGADDAU CUT ACCEAGTGGTGTGGTGGAGACCCCCCARAGAGCCCCAGGACCCCCCCCCC
		<ul> <li>CACTUTEA LA JUIGUACACITICOAGAGAAGGAGAAGGAGAALEAAGAACAAAGG</li> <li>GUIUTIGU GAGUITSU GAAGGAQAAGUUUAAGGUIAGASGGAGGAGGAACIIGAAGUUGAAGGUIAGASGGAGGAACIIGAIGAAGUUGAAGGUIAGASGGUIGUIGUIGAG</li> <li>ACTUTUALEGA TCACITICOCCASASTECCTUGATACATUI FECAAGGUIGUIGUICAG</li> </ul>
		AAGAAAACCEGOTTCECGAATGAGGGOAAACCETTGECGACTGAAAGAA SOOLLAGUU <u>GGAGGGGGGGGGTECCAACCAACCACCATCACTGATAA</u>
57	<i>gWiz-LS-</i> <i>mCXCL4<sup>30-</sup></i> <sup>105</sup>	ATG ACCORECCOUNTRACTOR SCCOTORISC CONTRELECTOR SCCOTORAGE CONTRELECTOR SCCOTOR SCCOTOR SCCOTOR SCCOTOR SCCOTOR SCCOTOR SCATTER STRANSPORTS SCCOTOR SCC
	(Gly4Ser)2-	AACGGCCGGAAGATCTGCCTGGACAGACAGGCCCCCTGTACAAGAAAGTGATT AAGAAGATCCTGGAAAGCGGTGGAGGCGGTAGCGGAGGGGGGGG
	mouse SA- (Gly4Ser)-	CASPAGACTCASATCOCCUPTCOCTATAATCATTUSCGACAADAACATTUBAA GOCCTAGTOCUSATIGOCUTTTOCCASTATCTOCASAATGOUCAUACGAUGAG
	His <sub>6</sub>	
		IGUIGUCALE CCARACOLE COTORA A A CERTORE GARUTORE E GARUTO E GUIAUA AAACAACACOCCARACAASCORATCUTTO DE CCARCACACACACACACACOCC AGCOTOCCACCATTUGAA AGOCCAGAGOTES SCOCATOTICACOCCUTURA O
		GAAAAOCCAACOAOCTTTIATGGGACACTATITECATGAAGTTGOOAGAGAGAOAT CCITATITECTATGOOCCCAGAACTTCTTTACTATGCATGAGGAGGTACAATGAGAAT CTGACCCAGTGETG CAGGCTGACAAGGAAAGCTGCCTGACCCCGAA FOTE CATGCTCTCAAGGAGAAACTATICCTTCATCTCCCCTCACAGAATCAA TCA
		<ul> <li>TOCKSTATECASAGETTESSAGAGAGASCTUPTAAASCATEGECASUAGEUCST</li> <li>OTSESCOAGACATEGOOGAATSGOTGACTTEGOAGAAATCAGGAAATUGGOAASCA</li> <li>GACUTGAOCAASSTOAACAASGAGTGCTGCCATGSTGACCTGCCGGAATGCGGC</li> <li>GALGAGAGGCUGAACTEGUGAAGAACCASTGUTGACCAGGCUACLALCTUC</li> <li>ACCAAATEGCAGGCUGGCTGCCGATGAACCASTGUTGAATAACCCCGACTGUCTT</li> </ul>
		AGUAACSEGAGAAUSACEGACEGACEGACEGACEGACEGACEGACEGACEGACEG
		CTOLE OCTUAÇÃO E LOUTAAGAAATAL GAACUUADECE CUAAAAO LOUTODOCE CAAGUCAATO DECOCOCADERTA OCOCERCA OTODEECE CUAACEET CACOOL CTE GTA SA BAGOCTA AGAACEEGO DA AAS CONACESTIGAL OTELE COARAA SCEL
		99ASAADA 1958 TTODANAS TSODA TOTAGITOSCHACADOCA GAAAGOACCI CAGSINUDAACOCCAADICICGUGGAGSCIGOAAGBAACDIAGGAAGAGUGGSC ACCAAGUGHIGIAGADHICCISAAGAICAGAGACIGUUHIGIGIGGAAGACIAT
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		CAUDATUT I AUDAXIERO, EDITATIERO EDITERO EDUCARARAS, DUDUAL COLL TUTROTUTGACARTIGATAL OTIGUACACTICUAGARAAGAGITERAAGCIGARA TECACOTICUACACTOTUATALOTIGUACACTICUAGARAAGAGAAGCAGATIRA AAACAAAGGGOLO E EGUTGAGO EGUTREROCAGAGOCUAAGCOCAAGOCIACAGO CARO EGAGACEGOLO E EGUTREROCIO DECEGACAGOCUAGOCUAGACA EGUTRO A COTICUAGACEGOCUTERROCI <u>GGAGGGGGGGGTTCC</u> CACCACCACCACCACCACCAC TAC
58	<i>gWiz-LS-</i> <i>mCXCL5</i> <sup>48-</sup> 118_	ATGACCTCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
	$(Gly_4Ser)_2$ -	GCCCCCGTGATCAAGAAGATCATCCAGAAGATCCTGGGCAGCGACAAGAAGAA
		GCCGGTGGAGGCGGTAGCGGAGGCGGAGGGTCGCAACACACAC
	mouse SA-	CCCCAT-DEGEATAATGATTTCC-DEGAACAACATTTCCAAASGCCTACTCCTCAT
	(Gly4Ser)-	CCOTTTUCCONTAUCTCOADAARTCOTOAURCOATCAUCATCODAARTUNOT
		UTEOR FGAAAR FAUGERBAAC JEGUL GAC JEUT GARAAACAAGA SUC OGA ACAACCAAR STFFECOTO SPACA CAAR SA TCACARSEC CLOOT JECCACOCATT GARACCAAR STFFECOTO SPACA CAAR SA TCACARSEC JECCACOCACOCA TTUS TGGACACTAE TFECA TGAAR TGCCACARAGEC JECCACACOCAC COACTACTTE TTAC FA TCUTCACACA CATCACATTE TTA AGRAAS CCALOTTE TTUS OF A TCUTCACTAE CAACTAE CATCACCATTE CTACCACA FA TCUTCACCACAA AGACTE STECCACACACTES TO GCACTAR STGCCACTECTOTO STFCACACACACTAE CAACTO TE CACTAE SCACAA TTUS GA SA SA GACOTTET FAA SCO TGCCACACACTAC TO CACCCACA AGA TTUS GA SA SA GACOTTET FAA SCO TGCCACACACTAE CAACTO TE CACTAE SCACAA TTUS GA SA SA GACOTTET FAA SCO TGCCACACACTAE COACTEG COACTAE CAACAA TTUS GA SA SA GACOTTET FAA SCO TGCCACTAE COACTEG COACTAE SCACAAC TCCCAA STGC ACTOTOCATICA CAACACTEG COACACTEG COACTAE SCACAAC TO TCCCACATACACTECT GAACACACACGCCACTAE OF CACCACCES COACTAE AC CACAACGE AT A LOTTE GAACAACCCCCACTTECT I ACTOACCTCOA CA CACACCATGCCT SCACAACACCCCCACTTECT I ACTOACCTCOA CA CACTCCCATGCCT SCACAACCCCCACTTECT I ACTOACCTCOA CAC CACTCCCATGCCT SCACACACCCCCACTTECT I ACTOACCTCOACCTCCA CACTCCCATGCCT SCACACACCCCCACTTECT I ACTOACCTCCT COACCTCCT CACAACTAE I SCACACCCCC TGA TTACTOTOTTET TTS JEGACACCECCACTTUTT TR JEGACAACTACCACTOTO TE SCACACACTCCCCACTTECT TO TGCCACACTCCTT CACAACTAE CACACACCCCCCTTECT TTACTOTOTTET ACTOACTTCCT SCACACTECTUTT TR JEGACAACTACCACTOTO TE SCACACACTCCCCACTTECT TA CAACACTCC TAC AACTTOTTCAAAACCACCTOTOTTET SCACACTTECT COACCTCCT STACAACACCCCCCACTTCCT STACAACACCCCCCACTTCCT STACAACACCCCCACTTCCT STACAACACCCCCACTTCCT STACAACACCCCCACTTCCT STACAACACCCCCACTTCCT STACAACACCCCCACTTCCT SCACACTTCCT SCACACTCCTTCCT STACACTTCCT SCACACTCCCCACTTCCT STACACTTCCT SCACACTTCCT SCACTTCCT SCACACTTCCT SCACTTCCT SCACT
		SOC <u>GGAGGGGGGGGTTCC</u> CACCATCACCATCACTGATAA
59	gWiz-LS- mCXCL7 <sup>48-</sup> 113_	ATGACCTTCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
	(Gly4Ser)2-	CCTGGCGTGAAGCGGATCGTGATGAAGATTCTGGAAGGCTACGGTGGAGGCGG
	1 ( 01) 4001 12	AGCGGAGGCGGAGGGTCG (MACCACACACACACACACACCCCCCATCA

	(Gly4Ser)- His6	CFCCACABAFCUTCATACCATCASCAUCCCAAAFDACTOCACABCDACACACC TEUGOAASGACGTGUTUTGOOGAFSAGTOFGUCGOCAACTUPACAASTCOOTT CRCACTUTUTGGAGAFAAGTUTUTGUCGATACCTUCGTGABAACTAT
		GUI GAACTEGO I GACTEGU, GI ACCAGAGALAAGAGGOOOGAGAGGAGACGAGATEGU I I C UTGOAACGUGAGGA, ISUGAACCCUGUDO I GCUGUCA I LUGAAGGOCGAGA FOI I CA-SECCATEGO CACCTEGUT TAAGGAGAACCCGAADUACCTTATICCCCAGA TAT TI SCATGAGGA STACCAETEG GAUTOT GECUCAGT STISU GOAGAGCUDOU JTAC TA USCITGAGGA STACCAETEG GAUGUT GAUCAGAGAAG CAUL GGUI CHA IC USTU OG I CAUGAGA I GAUGTEGO I COAGTA I GOAGAGA AG CAUL GGUI CAU IC USTU OG I CAUGAGA SACTEGO AG CUCAGTA I GOAGAGA AG CAUL GGUI CAU IC USTU OG I CAUGAGA CAUGUCAGGA CAUGUAAAG CAUL GO I COAGTA CUCAGAAAT CUCAGAAAT CUCAGAATAT GAGAAAAG CAUL GUI CUCAGAAAG U TU CUCAGAAGT CUCAGAAT TA CAU IT ILAAASCAT COODAST ACOTO SU CUCAGGACAGAGGO AG UTTE COAGAGT CAUGUCAGAA CITGE I GAAGAAGGCUUCU I GUI CUCAGGACGACUAGAGCU I GACACCAULCU GO I CAUCT COCOTO SCATTU OT PUT GATTU CUT CAUCAGCAU ISUU ACGCUUG I GAUCUCO TGATTACTET GUI CUT CUT CAUCAGCAU I SUU ACGCUUG GUI COCOTO SCATTU OT PUT CAUCAGGO ULAACTU UCUCAGAAAT TUGAA GOUTT GUI GGAAGAGEI GUI UUGU I GUAGUCUA I CUTU COCA I SUU ACGCUUG GUI COCOTO ATTACTET GUI CUCAGAGACUTAGGACUTI GOTAG GAUAAT TUGAT GUI DGOTT GUI GUAGAGACUT UCUCUU I GUI GUAGUCUAAGAACUTU CUT GAAGAAT TUGAT GUI DGOTT GUI CUCAGAGACUT UCUCUU I GUI GUAGUCUAAGACUTU CUCAGAAAT TUGAC GUI DGOTT GUI CUCAGAGACUT UCUCUU I GUI GUAACACUTAGGAU CUU GUI DGOTT GUI CUCAGAGACUT UCUCUU I GUI CUTU CUCAGAACUTU CUCUAGAACUTU CUCUU GUI DGOTT GUI CUCUUGU I GAUGUCUUCUU I GUI CUCUUAACUTU CUCUUAACUTU CUCUUAACUTU CUCUUU GUI DGOTT GUI CUCUUU I GUI CUCUUU I GUI CUCUUU I GUI CUCUUUU GUI DGOTT GUI CUCUUUU I GUI CUCUUUU I GUI CUCUUUUUUUUUU
		<u>TCC</u> CACCATCACCACCATCAC <b>TGATAA</b>
60	gWiz-LS-	ATGAGGELCCCUBULCACCTUULGECCUTUCE GOLIGUTULGECLUUDAGELGUA
	mCXCL9 <sup>22-</sup> 126_ (Gly4Ser)2- mouse SA-	ACCECCAGAAGAAGAAGAAGCCCCAGAGGAACGCCCAGAAAAACGGGGACCAGCAG
	(Gly <sub>4</sub> Ser)-	COSTALATCATTIGGGASAACAACATTICAAACSCCLAGTCCLSADDOCTTT
	His6	TOCCAGDA TOTOCAGAAA COUTOA TA COATA COATGOCA TOCCAAA CIAGD GOA SGAR GTAA CAGAOT UTGO AAAGA COUTGTGT TSOCGA TGA STOT GOOG UCAAO TO I GAC AAA TOODH I CACADI. OH HITTIGGAGA LEAGU I GHGTGOCAH HOGAAACO I CUST GAAAACDA HOCTCARCTCOOTCAUTCOTCA CAAAACARSAGC COCCAAACAARC
		GAAAADTA FOOTUART FOOTUATION FOOTUAR AAASCARDAGU OODRAADAAD GARAGU FA COTUART FOOTUAR FOOTUAR GAAAACCU AADACCU TAAGG CONGAGGU GAGGU ATTAAGGAAGACETCO TTAAGGAAAACCU AADACCU TAAG GGACACUETTI GORUGAAGT FOOUSAGAAGACETCO TTAUTTU ATGODOCUARA CTLO FELAUTALGO LUADOAG LAUGAL GAGATTUL GACCUACL GELOUDUAGAG COUSTACAACCARACCTOO TEACOCO SAAGATTUL GACCUACL GELOUDUAGAG COUSTACAACCARACCTOO TEACOCO SAAGATTUL GACCUACL GELOUDUAGAG COUSTACAACCARACCTOO TEACOCO SAAGTU CATGUS GAATU USA TESSTOUDATUTSI COGTU SGAAATSE SUCCITOTUS GACAUTU COUSAT GAUSS SAGOTTUT BAAGGAUSGO AGAATSE SUCCITOTUS GACUTU CACUAS GAATU USA GAGTGUL GCATGSI, GACUNOL GGAATGU CACUUTGAOCAR ASU CAAUAAG GAGTGUL GCATGSI, GACUNOL GGAATGU CACUUTGAOCARASU CAAUTU COTOCU

		CA DAAA COACTOTT DAAGAAC DOCACTOT DETACTOR OFFICIACION CACACIACIA ALGOOT SCITIS A FOT SCOTGODA DESCIDIOTES FEDEREL GAGGACOCIASIA AGE TWO AAGAACIA COUTGA ELACTOLIGE A LOUDLIGE EGUTGAGAC L'USOLIAAG AAALA EGAAGODA CLOTGGALAA STIGOLIGOGOTGAGOCIAATOO ECOUGA ESC TA DOGCAGACODOT DA TETTO ADOCTOTTOTAGA CACODOTAACAA DETE GTOSAAAAGAACTIGU GALECETE AOGAGA GOCTTOTAGAA CACODOTAACAA DETE GTOSAAAACCAACTIGU GALECETE AOGAGA GOCTTOTAGAACACODOTAACAA DETE GTOSAAAACCAACTIGU GALECETE AOGAGA GOCTTOTAGAACACODOTAACAA DETE GTOSAAAACCAACTIGU GALECETE AOGAGA GOCTTOGAGACACODOTAACAA DETE GTOSAAAACCAACTIGU GALECETE AOGAGA GOCTTOGAGACACODOTAACAA DE GOCATTOTAGOTOGATIGACACCOCACTOCAGGE GETE FONA COUCCAACTIC GEGGAGGO EGGAAGAACCTAGGAACACTIGEGOCACCAACES EEL STACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTIGEGOCACCAACES EEL STACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTIACOCACITICAACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTIACOCACITICAACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTIACOCACITICAACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTICICOCACITICAACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTICICOCACITICICACCITICAACACILICUT GAAGATOAGAGACTIGOO ELISTISTI GGAAGACTICICICICICICACICICICI GTOTOTICICICOCACIGAGACACICCACICICACOCACICICICAACICICICICICIC
		<u>GGGGGCGGTTCC</u> CACCATCACCATCAC <b>TGATAA</b>
61	gWiz-LS- mCXCL10 <sup>22</sup> -98_ (Gly4Ser)2-	ATG ATG ATCCCACTGGCCAGAACCGTGCGGTGCAACTGCATCCACATCGACGAT GGCCCCGTGCGGATGAGAGCCATCGGCAAGCTGGAAATCATCCCCGCCAGCCTG AGCTGCCCCAGAGTGGAAATTATCGCCACCATGAAGAACGACGAGCGGCGGCGG TGCCTGAACCCCGAGAGCAAGACCATCAAGAACCTGATGAAGGCCTTTAGCCAG AAGCGGAGCAAGAGGGCCCCAGGTGGAGGCGGTAGCGGAGGGCGGAGGGTCG
	mouse SA-	CCACRCRACTOR TRICCOCORPOCITATATOATIT COCACARORACA ETTO
	(Gly4Ser)-	Алкавоставлоотся терсорлеля телорлелаловлея тареле
	Hiso	GATGA ACTUTICOGO CEALTO TO A CAA A TO COTTICA ON OT UTTICT OF GEAGALEAG TTG EGUGAL ECCAALCE COGTGA AAAC LATGE EGAGUTGE EGAGUTCE ET ACABARCAACA SECCOARA SAAACCAATGT TTOOT SEAACACAAAACA TOA SAAC COURSE CEGO CREEKTES SA REGOORS & GOTGA GEAAUTGE EGEACTO STTT AR SSAAN AO CRAECA ACTUTIES BARGOORS & GOTGA GEAAUTGE EGEACTO STTT AR SSAAN AO CRAECA ACTUTIES BARGOORS & GOTGA GEAAUTGE EGEACTO CREEKE COURSE CEGO CREEKTES SA REGOORS & GOTGA GEAAUTGE EGEACTO CREEKE CETTO AT FTUTAL GOOCUAG RAOT TUTIETA ATA TSCI GROOP ACA CRAECE CETO CA STTTE DA A FRANKA CONTICOTO CATO FOR CEGO CAACACA CAATGAA CETO CA STTE DO AN FRANKA CONTICOTO CATO FOR CEGO CAACACA CRAETGAA CETO TO A SUCCESSA ACTIFICA ACAA GEAGAGAS CETTO FRANCESCHI ACAA CAA CETO TO ASCONDANTIC COORA TIC COORTING CAADAASTE NOORA HIE GOTA AC AGACTEGACO AAASTE AACAA GEAGTO CITIC CAACAAACTIFICAACAA TO AG CETO TO ASCONDANT COORATIGCI COACTACTIFICAACAAACCOCOL TITE CETO TO ASCONDACTIFICA ACAA GEAGTO CITIC CAACAAACCOCOL TITE CETO TO ASCONDACTIFICAACAA GEACTO CITIC CAACAAACCOCOL TITE CETO TO ASCONDACTIFIC TO COACTACTIFICAACAAACCOCOL TITE CETO AGACTEGACOCOLAACTIFIC COACTACACACTIFICAACAAACCOCOL TITE CETO STRAGOGUS ACCACTIFIC TO COACTACTIFIC ACTAAACCOCOL TITE CETO STRAGOGUS ACCACTIFIC TO COACTACTIFIC TO ACAAACCOCOL TITE CETO STRAGOGUS ACCACTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO ASCONTIFIC TO COACTAG COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC CETO AS FRANCISA ACATTIFIC TO COACTACTIFIC TO COACTACTIFIC TO COACTACTIFIC TO CET

		AACCOPDETCACAAADEACACCEDETECTCCASTCACCCECCAAACCEESTCAC ABAIGCABABACGCETTASCO <u>GGAGGGGGGGGTTCC</u> CACCATCACCACCATCA TGATAA
62	gWiz-LS- mCXCL11 <sup>22</sup> -100_	ATGACODECCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
	(Gly4Ser)2- mouse SA-	TGCCTGGACCCCAGATCCAAGCAGGCCCGGCTGATCATGCAGGCTATCGAGAA AAGAATTTCCTGCGGCGGCAGAACATGGGTGGAGGCGGTAGCGGAGGCGGAGG TCG.SAAGAACAACAAGAACAAGAACAAGGCCGATGGGTGAGAAAAAA
	(Gly4Ser)- His6	CAUTEC AAAGGEET AGTOETGAL TGOETTTL TOODAGTAL OTOEAGAAATGUEE TA CGATGAGEATGECAAATTAGTGAAGGAAGTAATGGEAL OTOEAGAAGESTG OTTGECGATGAGECGAGECGAACTGEGGAAAACTAL OG LGAACLOOC TGG GALAAGLI GI GTGOEALI ECGAGACCI COGTGAAAACTAL OG LGAACLOOC TGG GALAAGLI GI GTGOEALI ECGAGACCI COGTGAAACTAL OG LGAACACCAAGA COCTATAAAAAAAACAACACCOCCAAACCAACCAACTTE DETGCAACACCAACAACA CACAACCECGACCACCACCACCACCACACCCACACCACCACCACCACC
		GUIDROT SE FILIPPETUSAGGACOA SUBARTEU SUBARABADI AT ECTER SUCCEA SAUETO TI CUIDREC COUTO TUTAL PARTE TI CARGA GUIDROT SULTA TUL 9 E LOUDL 9 E EGUIGRARACUTOCI, ARGABATA EGA SUCACE COUTSALTA CASUCI CETEUR GARRAGUUTARRACTI SOTOARACIA OTO UT COUDRATT CASUCI CETEUR GARRAGUUTARRACTI SOTOARACIA OTO UT CA ARA SUACOTORASI EFORACCUCA ACTUTUCET FOR SOCTI ACTU SUI ACACIU CAACACITATE TO TO UT CASUCI CAACIUTUS AGATU AGAGACUSCOLI E LIST CAACACITATE TO TO UT CERATOOU GARCOTO UT CETEUR TO TO UT CEATARACAC CONTO TO TO TO CERATOOU GARCOTO UT CETEUR TO UT CEATARACAC CONTO TO TO TO TO ACTUTARACITATE COUCACACIUS COORAAGOO CONTO TO TO TO TO ACTUTATATO USURCACI TI CURGARASISTE DA SUIDRACAUCITI CACITITI CANTUTISAL ATO USURCACI TI CURGARASISAGAA CAGALLE ABGARCAARCOPOLICUTISAL ATO USURCACI TI CURGARASISAGAA
		ACASCGOACCACACACACACTC DOAT STATCACTT FECACACTT COTODALTAC TOTTESCAAGGCTESCTGACAAGGCACACCTESCTTOTUSACTGACGESTCCAAAGCT OTCACTAGATGCAAAGACGCCTTAGGC <u>GGAGGGGGGGGTTCC</u> CACCATCACCA CATCACTGATAA
63	LS- hCXCL1 <sup>35-</sup> 107_	MRVEAQUECE LEURIE CARC <b>ASVATELRCQCLQTLQGIHPKNIQSVNVKSPGP</b> CAQTEVIATLKNGRKACLNPASPIVKKIIEKMLNSDKSNGGGGSGGGGSEASK ELAEKXNDLGEGEFKGLVLLAFSQTLQEGSDERAELVQEVIDEAKLOVADES ANODASIJETIFGDALCAIPNLREEMGELADCOTKGEPERVECFLQAEDOMPSI
	(Gly4Ser)2-	PFERPEAEACTSPEENPUTFMGRYLHEVAPEUPYFVAPELLYSAEQNEULT
	mouse SA- (Gly4Ser)- His6	COAEADRESOLIPRLEOVKEKALVESVRÖRREGS SIGRFÜJKAR KAWAVARES TEPEADRAEITELATOLITEVIKEOORODELEORDDRAELAATHOENQATISSK QICCOKPELERABOLISEVEROTINPADLEATAADEVROQEVOEDYASAKOVELG
	11136	FENERSER WEDY SVOLUE REALETIVATE ERICCAE AND PACYOTIVE ARE QUEVE

		CTLEEOQREFCVEOYESA LUNRVOLLHEKTEVSEHVTKOCSOS LVERRECESA) TVDET7VEKEFKRETFTERSOLOTUPERERQIKKOTALAELVKAKPESTAEQLE TVMDDFAQELDTOCKAADEDTOFFTEGPULVTROEDALA <u>GGGGS</u> HHHHHH
64	LS- hCXCL2 <sup>35-</sup> 107_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MKYPAQLEGILL.W.EGARCAPLATELRCQCLQTLQGIHLKNIQSVKVKSPGPH CAQTEVIATLKNGQKACLNPASPMVKKIIEKMLKNGKSNGGGGSGGGGSEAHKE ETAHENNELGEQWEKALVITAFSQYLQKCSNEEAKLVQEVTEFAKTOVADEGE ANCEKSLHILFGDKLCALPELRKNYGELAUCOILCETERNECFLQEKDDNPISH PFERFEAEGMCTSEHEUPTTEMGHVIHEVAREUPTYAPELINYAEQVUETTY CCAEADEBSCLIFELDGVKEKALVSSVRQPMNCSSMQLFGTRAFKAWAVARLSG TYPNADFAELTKLAIFLTKVREEGGEDDLLEGAUDRAFLANGMOEAQATTSSKI QTCCUMPLLEEBUCLSEVENDTMPADLEAIAADEVEDGEVCENMAEAROVFLGT FINEYSREHEDTSVELLIKLAKKYEATLERDGAADFAEVSTVCENMAEAROVFLGT FINEYSREHEDTSVELLIKLAKKYEATLERDGAADFAEVSTVCENMAEAROVFLGT FINEYSREHEDTSVELLIKLAKKYEATLERDGAAARFPACYGLVLAEFQEDVER PKNLVETUCULYERLGENGEQMAILVRYTOREDOVSTETLEVEAARREGKAAR CTLEEMGELEOVEDYLGALLERVOLENKTPVGENVERVERFEUCESAA
65	LS- hCXCL3 <sup>35-</sup> 107_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MEVE ACTLOLINIE CARE CASVVTELRCQCLQTLQGTHLKNTQSVNVRSPGPH CAQTEVIATLKNGKKACLNPASPMVQKIIEKILNKGSTNGGGGSGGGGSEABES ETAE RYNDIGEQOPKTEVIIAP SQVLQBOSYDEHAFLVQEVTEPART OVAD GSJ ANODASIJETT FODELCAIPPLEENYGELADOUTKOEREPARTELORIDONPSIJE PERPEABAMOL SEKENPLIERGEVIERVARE BUYETARELLY SAEQYNELLIG COAEADRESOLTEXILDGVLERALVSSVEQRMROSSMQKFGRAAFKARAVAELSG LEPMADEAELIE LAIDILEVNKEOCHGELLECARDEAELAKTHCENQATISSE QTOODEPUTKAACISEVERDTMPADILEAIARDTVEDQEVCKNYAEARDVPLOT FLYETSEE UPDYSVSELERLAELYEAT LEECCAEARPEACYGUVLAEFQDIVEL PKNEVEINCULTERLOEX DE QAATLORYTQRAFQVSTFLEVEARPHLORVDTKO CTILEEDGRIDOVEDYLSAIDENVOLLEEKTPVBENVTKOOSGEVERROFGAT TVDETYVPREFEARTETERSDICTERERQUKEGTALAELYERKEATAEQLE TVDETYVPREFEARTETERSDICTERERQUKEGTALAELYERKEATAEQLE
66	LS- hCXCL4 <sup>32-</sup> 101_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MPVEAQUER LEARDROARCEAEEDGDLQCLCVKTTSQVRPRHITSLEVIKAGE HCPTAQLIATLKNGRKICLDLQAPLYKKIIKKLLESGGGGSGGGGSEAUKSEID ENYRDLCEQEEKGLVLIAESQELQKOSIDERAKIVQEVIEFAKIOVAEESAAG OKSLHTILFCOKLCAIENIRENDCELADOCTEGEPERNECFLQEKDDESIPPED EREAEAMOTSERENPTTEMGUYLREVAEEBEYETAFEILTYAEQXMEILOQCOM EADSESCLTEK LDOVKEKALVSSVPQRMKOSSMQKFCERAEKARAVARLSQTFE NADFAEIITKIATDLCEVNKECONGOLLECADDRAELAUYMOENQACISSKLQTG OKPILLEEAECLSEVEUU MPADLUAL AADEVEUQEVCENXAEAKDVFLGIFID EYSEREDIEN VSILIKLAREVEATLERICCAEANEPACYGTVIAEEQELVEEPKE IVATNOLITEELGEFGEQASIIVRICICAEANEPACYGTVIAEEQELVEEPKE IVATNOLITEELGEFGEQASIIVRICIKAAPESCSSISIVERREDESALTVO ETYVPLEEFKAEIFIFESDICTLEEKTEFVSEHVIKOCSISIVERREDESALTVO ETYVPLEEFKAEIFIFESDICTLEEKTEFVSEHVIKOCSISIVERREDESALTVO ETYVPLEEFKAEIFIFESDICTLEEKTEFVSEHVIKOCSISIVERREDESALTVO ETYVPLEEFKAEIFIFESDICTLEEKTEFVSEHVIKOCSISIVERREDESALTVO
67	LS- hCXCL5 <sup>44-</sup> <sup>114</sup> -	MNYPAQUEGE         GARCIRELRCVCLQTTQGVHPKMISNLQVFAIGPQCSF           VEVVASLKNGKEICLDPEAPFLKKVIQKILDGGNKENGGGGSGGGGSEABEGE           ABPYBOLGEQBFKGLVLIAFGQYLQCCSYDERAEL/VQEVTDEAETCVADESAA

(Gly4Ser)2-CDKS\_LEULECES\_LOAT PHILKEN KIELAFCOUKQEFERRECHLÇERODNPS\_LEFF ERPEREAMOT SPRENT TIPMOR Y DEEVARREP Y FYAREL DYYARQ THE H L QOO mouse SA-ABADKESOLTPKILDOVREKALVSSVR (PREKOSSMOKFOERAPKAWAVARESOTF (Gly<sub>4</sub>Ser)-PNADVARI TELLI I DI TAVIRECORGO I LECADORAR LAKYMORIQAT U SSELQT His<sub>6</sub> CODEULIKAARULSEVERDTEPADLPALAADEVENGEVOKRUARAKDVELUTEL YEYS REPOYSYSLIDESIARAYEA TI EROCAEANPPACYSTYI AEEQDIVEEDA NEVR THE DEVERIOR Y STORALL VEY TO A A POVSTOPTE VERARNE OF VETKOOT. EPROQPLE OVEDVLSALE NEVCLEBERCEVSEBVLRCCSOSE VEPRECESALEV DE LYVPKEE EARTY LEASOLUT LPEERRQIKKO LA LAELVKREF VALASQUNTV MUDEAGEDDICORAADKUIGEBUEGEBLVIRGKURLAGGGGSHRHEER MRYE AQUAGALAR ARCHON PORTONIC CLRVTLRVNPKTIGKLQVFPAGPQCS 68 KVEVVASLKNGKQVCLDPEAPFLKKVIQKILDSGNKKNGGGGGGGGGGGGGGGG LS-TARE PRODUCE OR PACIFIC TARSON LOK OS Y DE BAKLVOZ V TUPART CVAUESAA hCXCL6<sup>43-</sup> NODKSLETEFGDKLCALFNERENGSLADCCTKGEREREGFLGHEDDNFSLER  $114_{-}$ PERFERENCUSFKENETUFACHYLARVARRAPYFYAPELLYZAEQSNEUUTQC (Gly4Ser)2-OR REPORTENT DEVICEDATION OVE GEMKONSKOPPOERAF NAVARU SOT mouse SA-FEMALFAELTK LATELTKVINGE CONCELLE CADERA ELANOMOENQAULISS RLQ TOODAP LUKKAROL SEVERD THPA DEPAILADFVED OF VORMARAED VELOTE (Gly4Ser)-LYEVSPREFOYSVSILLIRIJAKKYEATIJEKCC&EANPPACYCTVLAEFQFLVEEP His<sub>6</sub> RNDVKINOPI, KEKI GEVORQUALLVE KIÇKAPQVSIPIL VEAARDI GEVOLKOC LEPERGRERO ZEOY LOA LEBENTO V SEEVITKOO SOS LIVEREPOESALT VUETYVPEEFKAETEFFESDECTUPSKEAQIKVQTALAEUVKEKDEATASQLAT VEDDAAQMEDI. OOLASDKDI OFSTEDPREVIESUKDALLAGGGGSHHRHRR--MENTRACIDE GENERAL AND GARCAELRCMCIKTTSGIHPKNIQSLEVIGKGTHCNQV 69 LS-EVIATLKDGRKICLDPDAPRIKKIVQKKLGGGGSGGGGSEAEKSELAESYEDLG hCXCL7<sup>59-</sup> SQREKCLV LI AESQN LQKOS (DEBAKL)/QEVITO/AK ( CVADESAANCEKSLIK) I. 121\_ PODELCAIPHLEENYCELADCUTKQEPENECELQEEDDD25LPPERPEAEAM (Gly4Ser)2-CISPRENDIFFERENSEREDIFASIELETIARQNEELLCCARADERC mouse SA-LUPKLOGVESKALVSSYKÇEMELCSSMOKEGEFATKAWAVARESOTEPNADEASE TKLAHDJTKVSKECCEGULLECADORAELAE YMCNOQAL EUSKLQUCCOKPLLE (Gly4Ser)-INHCLGEVENDTEPALEA LAADEVEDQEVOKNYABAKDVDLGTELNEE ARED P His<sub>6</sub> D75V51LEREAEVYEATLEECCAEAEPPACYSTYLLEFOPLYEEPKELVEIDECU IN HIS LORIVER QNATI LVPN DORAPOVSTPITE ZHARKNEOR VOTKOOT LPHDOREP CVEDVESSIENEVOLUNEKTPVSERVIKCOSUSEVERRPUPSALTVEETTVPRE FKAR EFURESDE CELEEKEKQERRQTALAELVKEKPKALA AQLKEVMEOFAQEL DTCCWAADADTCFSTEGEEILVTROADALAGGGGSHHHHHH-- $L\overline{S}$ -MRVPAQUECE DELIVER CARCI**SAKELRCQCIKTYSKPFHPKFIKELRVIESGPHC** 70  $hCXCL8^{28-}$ 99 LAREYNDLGEGRYKGLVLLAFSQYLIGEUSYDEREE UVGEV HOFAKUOVADESAA MODESE HTEFORE CATENEREN MEELAOOUTKOEFERNECFLOORDDDFSEFP (Gly4Ser)2-FURPER EXAMPLES FOR THE WORLD EVALUATE SET AND ADD TO CONTRACT SET AND ADD TO CONT mouse SA-CARADRES CELERALDOV KEKALVSEV ROPHE CESMOKE CE KAS KAWAVA KUSO E (Gly4Ser)-FFREDFARITELATDETEVISKEOCACDLECADDRETEAKYMCENÇACI.SSKLQ His<sub>6</sub> LCCERFILEREARCE SEVERETREADLES LAADEVEEQEVORGMARARDVE LGTF I YEY SREEPON SVSLULKLAALKESTLEACCSESNEDAC MUTVLARE OP I VERF KREVA EBCDE YEMEGEYGEQNA LEVRYEQNAE QVSE PELVEAARREGEVGENCC

		TIPEOQRERCYEDYLSAELBRYJELHERTPYSEHYTRODSCSLVERRPCFSALT VDETYVPEEFKAETFTYESDICTLPEKERQIEVQTALBRU-KERPRATAEQLAT VMDDFAOFLDJCCKAADEDICFSTEOPRE/JRORDALA <u>GGGGS</u> EHERRE
71	LS- hCXCL9 <sup>23-</sup> 115_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MKVPAQLEGELLEVELEGARCTPVVRKGRCSCISTNQGTIHLQSLKDLKQFAPSP SCEKIEIIATLKNGVQTCLNPDSADVKELIKKWEKQVSQKKKQKNGKKHQKKKV LKVRKSQRSRQKKTGGGGSGGGGSEABESELABPYDELGEGBESELVELABSQ ELGEGSYDEBAELVQEVIDPAKLOVADEGAARCDESLEELEEGDELGALPALSEN YGELADCCTEGEPERECFLQAEDDNPFLEPEERPEARAMCTSPRENFTTPMDB YEBEVRPEUPYFYAPELEYYAEQYNETLEGCCAEADRESCETPKLDGVWEKALV SSVRQPMBCSSNQEFUERAEKAWAVARLSQLEFHADEAEITKLAEDLIKVNKEC ORGELEECADDEAELAAYMCENQATISSETQTOCDETTIKRABCEGEVERDTMP ADLFAIAADEVERQEVCENYAEAKDVFLCTELENESKREPDYSVELLEPLASSY BATLERCCAEANPFACYGTVLAEFQPLVEEPENEVEVERDINFKLGEVGFORAI EVRYTQEAUQVSIFLEVEAARALGSVGEKCUTERDQRLEGVEDTESALEPVC LLBEVERQIKEQTAIAELDEVERPOFSALTVDETYVPREPRAETDFRADICT LPEVERGIKEGTAIAELDEVERPARAGELOVEDTAGFLDTCCKAADRDICTS TEGENEVTECKDALA <u>GGGGS</u> HNHNHH-
72	LS- hCXCL10 <sup>22-</sup> 98_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	<u>REVEAULEGE LENERGARCIVPLSRTVRCTCISISNOPVNPRSLEKLETTPASO</u> FCPRVETTATMKKKGEKRCLNPESKATKNLLKAVSKERSKRSPGGGGGGGGSE ANKSETANENNDLGEOUFKOLVLTAFSOVLOKOSNDERAETVOEVUDFAKTOVA UESAANCENSTERTLFOOKLOATEREKENTGELAUOOTECETERRECFLUKKEDIN SELPPFERPEAEANCTSPEERPUTFMGHYTHEVAREFBYNFVARETTNVARQVDE HITGGOARADEEGOLTPELEGVKERALVGSVRORMEUSSMOEFGERAFRAAMMA RISOTPPNADFARTUKLATELTEVRKEOORGDETEOADDFAETAKVMCENOATT SSKLOTCUDERELEERBUISEVERDTMPREDIEATAADFVEDGEVOENYAEAADV YTOTELNEYSERREDSSVSLILERLAKKYRATERVESTOUSSTOTUVEAARRIGEM GTROUTLEEDOGEUVERSTERVERDTMPREDIEATAADVSTOTUVEAARRIGEM GTROUTLEEDOGEUVERSTERVERDTMPREDIEATEVERTOTUVEAARRIGEM GTROUTLEEDOGEUVERSTERVERDTMPRODIEATEVERTOTUVEAARRIGEM GTROUTLEEDOGEUVERSTERTERVERTERVERTOTUVEAARRIGEM GTROUTLEEDOGEUVERSTERTERVERTERVERTOTUVEAARRIGEM GTROUTLEEDOGEUVERSTERTERBOTOTUPERERGERAGTATAELVERVPKATA EQUKTVMEOPAOFILDTOCKAADEETOFSTEICENEVTPOKEATAEAG <del>USENERT</del>
73	LS- hCXCL11 <sup>22-</sup> <sup>94</sup> _ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MRVPAQUECE LELINDE CARCE <b>FPMFKRGRCLCIGPGVKAVKVADIEKASIMYPS</b> N NCDKIEVIITLKENKGQRCLNPKSKQARLIIKKVERKNFGGGGGGGGGGGGSEAHYS ELAFRYNDLGEQHFKGLVLIAF SOYLONGSYDERANDVGEVIDFAKTOVAPESA ANGERSINTIFGORIJCA IPPLRENVGELAO-DUTKGEPERNEGFLQBKDDNPSLP PFERPEAEANGTSPEENPUTFMGNYLHEVAPENPYFYAPEIIYYAEQYNEILTO CGARADEESCLEPELPGVKEKALVSSVRQPMEUSSMGEFGSKAFKAMAVARLSO TPPHADPARITELATIDLITEVNKEGORGDIECADDFAELANYKCENOATISSKI QTCODKPLLERANGLSEVENDTMPADLEAIAADVEDQSVGENAAKDVFLST FINEYSREHPDYSVSELIKLAKKYEATLENCGASHY FEDGYSYCENYAEAKDVFLST FINEYSREHPDYSVSELIKLAKKYEATLENCGASHYFRUSSNGEVGEVERKEVEFGFDYSFR CTLPEDQSEPCVEDYLEALINEVGEFNAILEARASYSEVERCESHVERKEGESAL TVDETYVPREFEASTFFPENSDICTLEENENGTAIAELVENKPKATAEQUK TVDETYVPREFEASTFFPENSDICTLEENENGTAIAELVENKPKATAEQUK
74	LS-	HEYE ALLER WERE APIANEL RCQCLQTMAGIHLKNIQSLKVLPSGPH

	mCXCL1 <sup>25-</sup>	CTQTEVIATLKNGREACLDPEAPLVQKIVQKMLKGVPKGGGGSGGGGSBARKS
	96_	IARTINPLCEQREFICIVI JAFSQYLQKOSYPEBAKLVQEVIDFAKCCVADESAS
	(Gly4Ser)2-	NODKSLETEFODKLCAIPNEPENYCELADCCTRGEPEPNECPIGEKDINPSLE
	mouse SA-	PREPEARANCUSPERNETUFIIGHYLERVARREPIEVAPELLYKAEONNEUUUG CARADKESCLUEKLOSVEEKALVSSVBGRMKUSSMGKFERAENAWAVARUUU
	(Gly4Ser)-	FURMORADULI E GIO FURMALI O DI FUGMENTI DI SUGRE E SUGRE AL MARCANA LOGI FUNADRAS I UKLATOLI KVINAS CUEGLLES SUDRAFI ANYMOENOA I I SISTI (
		TCCPAFLERKARCI SEVERDTREADI PALAADIVEDOEVUVNNARAEDVFLGTE
	His <sub>6</sub>	EVEYSPREGOZSVSILLIRI, PKYPRATI, EKCCAGAN PPACYCTVI, AMPOGEZEE
		ENDWINCH YERI GETGEQUATION YIQKAROVSTETI VEAAFHI GRVGIKOO
		TIPEOREPOYEDYISA ELENY DELENS TPVSEHVIRO OSOSI.VERRPCESALI
		VORTYVPKERKARTFTPESELOUDPEKENQUKKQUALAFEVKENPEAUARÇEN
		VMEDERGELOTICEASERETCESTECPHEVIECECALR <u>GGGGS</u> NNNNNN
75	LS-	NEVEROLEGI LL. SOL GARCAVVASELRCQCLKTLPRVDFKNIQSLSVTPPGPH
	$mCXCL2^{28-}$	CAQTEVIATLKGGQKVCLDPEAPLVQKIIQKILNKGKANGGGGSGGGGSEARC
	100	EIAHEYNDLGEQHFKGLVLHAFSQYLQKCSYDERAKUVQEVTDFAKUMVADE57
	-	ANCEVSIATIESUKLOAIPEERENYGELADOOTEQEPERRECELQEKDOOPSEF
	(Gly4Ser)2-	PFERFEREAMOISPKENFITTFWJHULHEVARPHONFYAPELLINYAEQZNEILIY
	mouse SA-	COREADEESCLIPPELDOVKERALVSSVROPPECSSMORFOFRAFRAMEVARLSO
	(Gly4Ser)-	TPPNADPAGITKLATELTKVHXEOCETDLLECAODRAELARYMCERÇATISSKI
	His <sub>6</sub>	OLCORRETEER ECTLEARED DE VOTBREVER AND
		HINEYSRREPOYSVIELEREAKKYRAILERCOAHABITAOTGIVEARSQPIVE
		PRIEVETIECULY ENLIGENCEPONALLVRY TOLD POVS TETLEVEARELISEVOTEC
		CTLERIOS LPOVENYLSAULREVOLI REATEVSEEVTELOSGELVEEFPCFDAI
		TVDETYVFREFKÆUPTPESDICTLPRKEKQIRGQTALABLVKEKPKATARQLB LVMDDFAQALFFUCKAADEFTUFSIEGENLVLPCEDALA <b>GGGGSHHHHNN</b>
76	LS- mCXCL3 <sup>28-</sup>	MRVPAQLEGITERS PGAFCAVVASELRCQCLNTLPRVDFETIQSLTVTPPGPH
		CTQTEVIATLKDGQEVCLNPQGPRLQIIIKKILKSGKSSGGGGSGGGSEABE
	100_	ELAERYBOLGEGEFKGLVULLAFSQULGEUSYDEBARUVGRVEFFARUVGADE54 ANODASINULFADRIUGAJPBLEEBYGELADCCUKORFESDECFLOEEDDDPSLJ
	$(Gly_4Ser)_2$ -	THE PRODUCT PRODUCT PRODUCT CONTINUES CONTINUES FOR THE PRODUCT OF
	mouse SA-	CCAEADKESOLJTPKLDOVNEKALVSSVFORMKOSSMOKFGERAFKAMAVAFLS(
	(Gly4Ser)-	TE FRADYAET UNLAUDI. TELVEKE OORGELE HOAD DAAET AR THOERDATUS SKI
	His <sub>6</sub>	OT COD KP LEXKAGOLSEVES OTSPADLE AT A XDEVEOOP VCKNYA EAKDYFLOT
		FLYETSPE UP DY SVELLE REALEMEAT LEEUCAE AN PPACYCTVLAEF QP LVEL
		- PREEVE INCOLLABELIGENGEGRAALEVERTEGESTUGVSTERLEVESSERIJGEVOTEG
		CTLPEDQRLECVEDYLSAIDHEVOLLEEKTPVSEHVIKCOSOSDVERRECKSAI
		evdetivereenaeleteesototleesengtregtalaelvaenerataegee
		TYMDDFAQFIDTCCEZADKDTCFSTECPRLVIRCKDALACCCCSHHHHHH
77	LS-	ARVEAGLEGELSERE PARTUTSAGPEESDGDLSCVCVKTISSGIHLKHITSLE
	$mCXCL4^{30-}$	VIKAGRHCAVPQLIATLKNGRKICLDRQAPLYKKVIKKILESGGGGSGGGGS
	105	EKSELARE YNDJGEGEFKGIVL LAFSOFLGECSYDERAED-OEVTOFACTOVAL
	-	SSAAROPSERELFGPRECALPRERSTGELLADUOEKGRESRAROPLQBKDBR
	(Gly4Ser)2-	SEPPEERFEREMUTS PRENPT UPMCHVLBEVARRHPYFYAPELENNASQVNE I
	mouse SA-	LIQUCARADESCI TPALDGVKERALVSSVRORMEUSSNORPGERAFRAVAVAT
	(Gly4Ser)-	LSGTFFNADFABITKLATDUTKVNKECCBCDLLECSPORAELASYMJENGATIS
		SKLQTOCDKPLLRAABCE SEVERDIMPADLES IANDEVEDQEVORMAEAKEVE

	His6	LGUP LYEYSBREOYSVSLLLRLAKKYEATLEKCCABANPPACYOTVLAEFQFI VEEPRALVETBODLYEKLCEYGEQNALLVEYTQKAPQVETFTLVEAAFDLORVO TRUCTLPEOQRLPCVEOYLSAHLNRVULLHEFTPVSEHVTRODSOSLVERPCF SALTVEETYVEEFKAETFTPUSDLOUDPEKERQLEKQUALAEDVKEKEDATAE QLETVMEDEAQFLULOCEASDKELCESTEOPHLYURGKUALAEDVKEKEDATAE -
78	LS- mCXCL5 <sup>48-</sup> <sup>118</sup> (Gly <sub>4</sub> Ser) <sub>2</sub> - mouse SA- (Gly <sub>4</sub> Ser)- His <sub>6</sub>	MPVFAQLECTLLIFTERCARCATELRCVCLTVTPKINPKLIANLEVIPAGPQCPT         VEVIAKLKNQKEVCLDPEAPVIKKIIQKILGSDKKKAGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
79	LS- mCXCL7 <sup>48-</sup> <sup>113</sup> - (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MKVPAQUEGELELINGEGARC IELECCENTISGIPFNSISLVNVYPPGVHCADV         EVIATLKNGQKTCLDPNAPGVKRIVMKILEGYGGGGGGGGGGGGGGGGAANCEVALAHEYN         DISEQBERGEVETAFFQYLQKCSYDERAKTOPTUDFAKTOVADESAANCEVAL         BALLMERNERENGESLADOOIEQGFGGGGGGGGGGGGAANCEVAL         FALMOUKLOALENERENGESLADOOIEQGFFGERAFEAMAVARLSQUPPNEDESEPPERENA         EAMOTAFEENPTTFMSHVLREVAFRHPYSYAPETLYYARQVNETLOQCCAEADE         ESCLIFFEDDGVKERALVSSVRQPMKCSSMQEFGERAFEAMAVARLSQUPPNADF         ALITKLATELLKVAREDOHGDLLECAEDPAELAK/MCENQATLSSELQTODDKP         ILIFFAHOLSEVENDTNPADDPATAADFVEDQEVCENYAFARDVFLOTFLTEMSR         PREPYSVSLLESLAKKTEATLEKOCAEANEPACISTVLAESQEVTEDTINENT         NCLLYERUGENGEGRAFIENVELTVETVEAAENEGEVATACOUTEPENQ         REPVENDENTERVENDUNGENERVELUSSESIVEERVETVENT         REPVENDENTERVENDUNGENDENTERVETVERGENDUNGETVE         REPVENDENTERVENDUNGENTERVENDUNGETVE         PREPVENDENTERVENDUNGENTERVENDUNGETVE         PREPVENDUNGENTERVENDUNGENTERVENDUNGETVE         PREPVENDUNGENTERVENDUNGENTERVENDUNGETVE         PREPVENDUNGENTERVENDUNGENTERVENDUNGENT         PREPVENDUNGENDUNGENUNGENUNGENUNGEN         PREPVENDUNGENDUNGENUNGENUNGENUNGENUNGENUNGENU
80	LS- mCXCL9 <sup>22-</sup> <sup>126_</sup> (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MRVFAOLLGLUUNLEGARCTLVIRNARCSCISTSRGTIHYKSLKDLKQFAPSP         NCNKTEIIATLKNGDQTCLDPDSANVKKLMKEWEKKISQKKKQKRGKHQKNMK         NRKPKTPQSRRSRKTTGGGGSGGGGSEARESEIARAANDEGEOREGEVLEAR         SQMLQEOSYDERARDVQEVIDFARTOVADESAANODASIETTEFØDELCAIPRLE         ENYGELADOOLKQEFEKNEOFLQEKUDRPSLUUFERAEAROLSFEENELIER         ENYGELADOOLKQEFEKNEOFLQEKUDRPSLUUFERAEAROLSFEENELIER         ENYGELADOOLKQEFEKNEOFLQEKUDRPSLUUFERAEAROLSFEENELIER         ENYGELADOOLKQEFEKNEOFLQEKUDRPSLUUFERAEAROLSFEENELIER         ENYGELADOOLKQEFEKNEOFLQEKUDRPSLUUFERAEAROLSFEENELIER         ENYGELADOOLKQEFEKNEOFLQEKUPAROYNELIENELIENEL         GRZUBEVARRHPYFYAFELDYNAROYNELIIOOCAEAUNESOLUPKLDOVIERA         LVSEVARRHPYFYAFELDYNAROYNELIIOOCAEAUNESOLUPKLDOVIERA         LVSEVARRHPYFYAFELDYNAROYNELIIOOCAEAUNESOLUPKLDOVIERA         LVSEVARRHPYFYAFELDYNAROYNELIGTTIYEYSEFEFDDISSELIRAE         KYEAFILEBOOAEANFEADYGEVCRYAEBAKUPELGTTIYEYSEFEFDDISSELIRAELOSYDEQA         KYEAFILEBOOAEANFEADYGEVCRYAEBAKUPELGTTIYEYSEFEFDDISSELIRAELOSYDEQA         KYEAFILEBOOAEANFEADYSEPTIVEARNLOPVCTKOOTLEEDQRLPCVEDYLSAILENR         YCLLBEKEPYSEEVIKOCSGEIVERPEPOPSALTYDEPAQTILOOCEAADKPTO         YCLLBEKEPYSEEVIKOAEAENNREPVATAEQUETVNDEPAQTILOOCEAADKPTO         YCLLBEKEPIKKDAEAENNREPVATAEQUETVNDEPAQTILOOCEAADKPTO         YCLLBEKEPIKKDAEAEAENNREPVATAEQUETVNDEPAQTILOOCEAADKPTO

81	LS- mCXCL10 <sup>22</sup> -98_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	MEVE AQULOLINUM POAP O <b>IPLARTVRONCI HIDDGPVRMA I GKLE I I PASL</b> SCPRVE I I ATMKKNDEQRCLNPESKT I KNIMKAF SQKRSKRAP GGGGSGGGGSE AHES BI AHPYDE LOEQHEE OLVUE AF SQYL QKOSYE BRACLY (BVTDEAE TOVA UESAARODMSURTUF SUKLOA IPMUREN Y GELADOOT NGEPERNEOF LOHKDON PSUEPPER UEREAMOUSE KERP TIPMER I LHEVAR BETEYAPELLY YABOY NE III TQCC ARADREGOUTERIDGVKERA DV SSVRORMKOS SMORE GERAPRAMAVA PL SQYF PRADEAELI, KLA UELTKVREE OUESDLLE OAU DRAELAKYMOENQAT I SSKLOT CODKPLUNEXHOUF EVENDTHE AD DRAI AADE VEDQEVORNYABAREDY FI GI FI YEYSRREEDY SVILLEPERKY EN TUEKOOREANPPACY OTVLAEF OF I VEEPEN UVKUROUD EKUSEY OF QHALEVEN TOKAPONS TYL LVEAARED OF GTECCTUPENOOF DE OVED YUSATI NE VOLL HERTEP VSEHVTEC OSGSLVEERT O FSA LTVDE TYVE REEKAEUP TP HISD I OT LPEKEEC I NROTALABLYKHKERATA EQUKTVMENDER AGELD TOCKAADED TOFS TEGENEV TROUDAL A <u>GGGGS</u> HNEHEN 
82	LS- mCXCL11 <sup>22</sup> -100_ (Gly4Ser)2- mouse SA- (Gly4Ser)- His6	REVEROLDER LELIVIE GARC <b>FLMFKQGRCLCIGPGMKAVKMAE I EKASVI YPSN</b> GCDKVEVI VTMKAHKRQRCLDPRSKQARLIMQAI EKKNFLRRQNMGGGGSGGGG SEAEKSEL ARFYNDLGEORFKGLVLITAF SOMLOEIDS YDS RAELL VOEVIDFARTIC VADESAANODES LETLEGDFLCAIPALE ENMOELADOOL KOEFERNEOFLOUWD DNES LEPEERPEASAMOTSPRENPTIFMOE YLHEVANRHPYFYAGELLYNA SOF NEILTOOCAE ADRESCUTPRLEGVWEKALVSSVRORMEUS SMORFOEFAFKAVA VARLSQLFUNADFAELTKLAIDLTKVNKECOBGULESCAEDRAELAEYMCEN QA TISSVI GTOODEVELKKAHOLSEVERDIMPALLFAIAAUFVEDQEVOKN YAEAK DYFLGTFLITENSKRHPDISVELLERLAFKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELLERLAFKYRAILERGCAEARFAOMGIN ZAEAK PVFLGTFLITENSKRHPDISVELLERLAFKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELLERLAFKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELLERLAFKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELLERLAFKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELERAIDENSKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELERAIDENSKRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELERAIDENSKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISVELERAIDENSKYRAILERGCAEARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISKER DEN DEN DYRCHAERAARFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISKER DEN DYRCHAERAAFFAOMGIN ZAEAK DYFLGTFLITENSKRHPDISKERAFFAR
83	gWiz-LS- mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK138- (Gly4Ser)- His6	ATGUACA EGA GAGEROO EGUTUAGO EGUTUGOOC LIGUTEO EGUTUGOO LIGUT GGUTURAA EGUGAARCA CAUAAGAGUTAGA EGUCUAL OSGUATAAL GAUTUG GGAGAA CARCATTEURAAGGOCTAGEOTGA ETGOCTTU ECC AGCATUUDOAG AAALGO LUATAOGA LUADOA EGUUAAAL EACTUUAGGAAUTAAOAGAUTUL GOA AAARCCHOTOTTGCCCATCACTOTOO COCCAACTATGACAAAL COCODOA DACT OT UTTERGAGATAAGTTGUTGOOAT TUCAAACO LUGGT BRAARCTADGGTGAA CTCCCTCACECOTOTRCRAAACARGACCACCACUTUGAAAACGACAGAUTUCCCHOGAA CACARRGA TGACARCCCCAGOCTACCACUTUGAAAGGUCAGAGGCTGAGGOC ATGLGCAGTGACARCCCCAGOCTACCACUTULA ELGUGACACULATTU GOAL CACARRGA TGACARCCCCAGOCTACCACUTULA ELGUGACACULATTU GOAL CACARRGA TGACARCCCCAGOCTACCACUTULA ELGUGACACULATTU GOAL CACARRGA TGACARCCCCAGOCTACCACCACUTULA ALGUGACACULATTU GOAL CACARRGA TGACARCCCCAGOCTACCAGOCTULA ALGUGACACULATTU GOAL CACARRGA TGACARCAGAL ECTGACOCAGEGTU ELGUGAGGOCILAUTU GOAL COCTORCCCCCGAACTTECTTATTTCTACGACGACGACOACULTUCACACULACTCCCCC CGUCACAGGACACTGUTCCAGCAGACACUTOCCAGACCTTCCCCCCCACACACU CCCTCACCAGGACTGCUTCCAGCACCACULACCACCACULTURACULTUCCCACAC AT CSCCACALAGCUCCCAGCACCACULCACCACCACULTUCCCACULT CACCTGOLIGGAATGCOCCAGCCCCCAGCGACCACULTUCCCACULTUCCCACULT CACCTGOLIGAATGCOCCCCCCCCCGCCCCCCCCCACULTUCCCACULT CACCTGOLIGGAATGCOCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC

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		CCAAACCTTGTCACTAGACCAAAGACCCCTTAGCC <u>GGTGGAGGAGGCTCTGGT</u> <u>GGAGGCGGTAGCGGAGGCGGAGGGTCG</u> GCTATCCAGATGACCCGGTCCCCGAGC TCCCTGTCCGCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAG
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84	gWiz-LS-	ATGCACATCASASIGCOTOCICACOTOCICCOCCOCCUSUCCOTOCUSUCCACOTOCUSUCCOCOCUSUCCOTOCUSUCCOCUSUCCOCUSUCCOCOCUSUCCOCOCUSUCCOCUSUCCOCUSUCCUSUCCOCUSUCCOCUSUCCUSUCCOCUSUCCOCUSUCUSUCCU
04	mouse SA- (Gly4Ser)3-	OCTINUTARATISE GAAGGACA CAARAGUSAGATOOCCURTOROLA HAADRATUHG GGAGAAAAAATUHCAAAGGUCLAG LOUTSAL LOCCAGUALOLOUAG RAATROUCAHAGRAUSAGCATOCCARATTAGUGCARRAASIRAAARACUTDOOA
	$scFv (V_L-V_H) CK157-$	AAGACGTUTUTUGCUATGAGTUTUGCGGCGASUTGTGAGAAATGCCTTUGACACT CTUTUTUGCGAGATAACTTUTUGCCGTUGCAAAGGUUUGAAACUACCGUUGAA CTUUTUGUUUUUACAAAAGAGAGGUUUGAAAGAACGAALUTUTUCUTUGAA
	(Gly4Ser)- His6	CHOSCHENCHOUND IN LARAMENTER COCCERNATIONS OF A LEATENER CROMMENT CACAR DOCCACCOURCE ACCACCHUT CAAR DOCCOURCACCOURCE AND FOR COURCE ACCACCOURCE ACCACCHUT AT SIGNAL ACCAUTE ACCAC SANGET GOURGARGACATOOF EATTTOEREGOURCE GAGACTTOLE LACTAL GOE CROSCACCHACAATGACATTOESE ACCOURCE GAGACAACTTOLE LACTAL GOE COURCE ACCACCAAR OF ECTOR OF GEGENOTORS GAGACTTOLE CAARGAAASC ECCUTGACCCCGAAR OF ECATORS 6 ECAAGGACAAGCAFE GEDUURCE FOISTC

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03	gWiz-LS-	GO JUUTAGA I GUBARGOAGE GARGAG JUBGAI COCUUAL COG LETARL GA JTTS
	mouse SA-	
	(Gly4Ser)3-	GGAGAACEECATTICEEAGGOOLEGICOTGETIGCOTTI FCCCEGIAICUCOEG
	$scFv (V_L-$	AAATGOTUATAOGATGAGOATGOUAAATTAGTGOAGGAAGTAAOAGAUTTJOOA
		ARVACCIDTOTIECCOATVASICTODDVCCAROTVEGACAARICCCUDOADACE
	V <sub>H</sub> ) CK129-	CTUTTICGAGATAACTTCUUTWOOATUUCARACCUUCAU SAAASULAUGUUGAA
	(Gly4Ser)-	CTCCCT/ACTCCTCTACAABACAAGACCCCG/AAACBAACGAATCTCCCCCCAA
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86	gWiz-LS- mouse SA- (Gly4Ser)3-	ATGCACATGACACTACTCOTORATTCOTOPECCICOTACTCOCOTACTCOCOT COTROTAGALCOGAAGCACAAGAGUGACATCGCOCACCGGUATAATGALTTG GGAGAACAACATTTCAAAGGOCTAGTCOTOATTGCOTTTTUCCAGTATUTOCAG
	$scFv (V_L-$	ARAFOCIDARAJGA DOACCA FOCORART FACTODASGAA OTRAJAGA OTDI OCA AAGAGASI STOLIEGIOSA FOSGI O DOCUSCI RACTORAGARAL GUULTOR DAUT
	V <sub>H</sub> ) CK138-	CEDTTP-PRGATAASEFCCOCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
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	$(V_L 100^{Q>C} /$	CACAAAGSTGROAACUUCAGOC LSUCACCA LTTGRAAGGCUAGAGGCLGAGGGC
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		CAGCCAGGGGGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTTCAACCTCTCT
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		GCCCTGGTCACCGTCTCCTCGCGGGGGGGGGGGGGGGGG
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	(Gly4Ser)3-	ARATOCI VATACCATO SCARATTA VICCACCAAVTAACACACTI ICCA
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	V <sub>H</sub> ) CK138-	CVL EFF GGAGAE AAGTTSL GEGCUATLOOKAACULOOG LGAARAO LAUGSL GAA
	,	CT SSCI GAOI SCIGUAGAAACAAGA SCCCGAAASAACGAAU SHUDOOL SCAA
	ds2	CACAAASA EGACAACCCCACUCLACCACUAL EEGAAASSOCIAGASSOL GACGUC
	$(V_L 43^{A>C} /$	ATOTOCASCECCTTTRAGCAAAASCCAACCACCETTATSSCACACTATETOCAT
	$V_{H}105^{Q>C}$ )-	A FORCAUCTUUTTERACUBARAUCCASUBAUCTETRAT-SUAUSULATEEUGAT GAAGTTEUUAGAAGAUATOOTTATTTOTATGUUUCAGAAUTTOOTTAUTATGOT
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		CTCTCTTACTACGGTATGCACTGGGTGCGTCAGGCCCCGGGTAAGGGCCTGGAA
		TGGGTTGCATACATTGCTTCTTACCCTGGCTACACTTCTTATGCCGATAGCGTC
		ARGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
		ATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTACTATTGTGCTCGCTC
		TACAGTTACTCCCGTATTATTCTTGGTTCTCTGCTGGTATGAACTACTGGGGT
		NROGGAGCCCTGGTCACCGTCTCCTCG_ <u>GGAGGGGGGGGGTCC</u> CACCATCACCAC
		CATCACTGATAG
88	gWiz-LS-	ATGEACALGAGESESCE GUTCASE L'OUTRESCE GUTERSE (GUTERSE L'OUT
	mouse SA-	COTOCASATAS COCOSO SA
	(Gly4Ser)3-	GGNGAACEACAPTCEARGAGOLEGUOTEATEGOTTUICCCAGDELUUDOAG
		AAALGO JUARAOGA JUAROA EGUUAAALEAGTEUAOGAAGTAROAGACTULIGOA
	$scFv (V_L-$	ANSACCIMPOTESCORAPSACENCESCORACESESCARAL COLUMNIACE
	V <sub>H</sub> ) CK157-	CELTTTB9AGATAAGEEGIST900AELISUAAACOLISUSE9AAAAUTALG9IIGAA
	ds1	Сторот за сторота са какоажба ороб за за окако бак потопострока
		CACAAAGE ISACAACUCCASSOCIECCASSA DE FISAAAGE CLASGAGE USAGGE
	$(V_L 100^{Q>C}/$	AT VER AGET SCHELAAD VAAAAGGGAACCAGET HATCOGA SACTATTE NAT
	$V_H 44^{E>C}$ )-	CASTINGOAGASASAOATCOTTATTOTATGOOCEASAAOTTOTTTAGTATSOT
	· · · · ·	

(G) His	(27)- CACAGO ACAATCA CRETTCICOLOGICA CONTENTICA CALCULAGA DE L'ECADADE A ACOLOGICA CONTENTICA POLICITO CALCULAGA DE L'ECADADE DE CARGENER DE CARGENER EN CONTENTICA POLICITO DE CARGENER DE CARGENER EN CONTENTICA POLICITO DE CARGENER EN CONTENTICA POLICITO DE CARGENER EN CONTENTICA POLICITO DE CARGENER EN CONTENTI CONTENTICA POLICITA DE CARGENER EN CONTENTI CONTENTICA POLICITA DE CARGENER EN CONTENTI CONTENTICA POLICITA DE CARGENER EN CONTENTI CONTENTI DE CARGENER EN CONTENT DE CARGENER EN CON
89 gW mo	SA- GGUACTAGALGOGAAGCACACAAAGACCGCCCAUCGUATAAUGADTTO
	Ser)3- SGAGAACEAUAL E ECEAAGGOO LEGTOO EGATTGOO E LITUUCAG LATUU DOAG AAATGOTOATACGATGAGGATGOOAAATTAGDOOASGAAGTAACEGAOTOITGUA
V <sub>H</sub> , ds2	K157-       CTUTTTESSAGAPAASTECUTOCCATUCCAACCUTCCC SABAACTAUCCUCAA         CUGSOTSECISCTSUECAAAACA2SASCOCCEAASAAACSAESTUUUUUSCAA         CASC/       CASTAACATOASAACCOCRECCACOTUTATGSGAACSCUACTUSCEA

	V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)- His <sub>6</sub>	CAACITECCIACAACACATECCITATITECTATICCICACAACTECITCACAACACCI CACCACITECCAACATECICACITECTCICACACITECTCICACACITECTACACACCAACCI TOCCICACACITECCICACITECTCICACACITECTCICACACITECTCACACITECTCACACITECTCICACITECCICACICACICACICACICACICACICACICACICACI
		TTCGCAACTTATTACTGTCAGCAACCATCTCATCTGATCACGTTCGGACAGGGT ACCGAGGTGGAGATCAAAGGTACTACTGCCGCTAGTGGGAGTAGTGGTGGCAGGT AGCAGTGGTGCCGAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCA GGGGGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTCCAACCCCTACTACTAC
90	gWiz-LS- mouse SA- (Gly4Ser)-V <sub>L</sub> CK157-His6	ATGCACATERCACTECCTCAECTECTOESCOTOCTCOTECTECCCCOESCUPOT GGL 90 FAGATECCAASGCCTACTCOTECTCOTCCTECTECCCCCCCAE GOAGACAACATTECAASGCCTACTCUTCATCCTTLTTOCCAETACOCCCAE AAATGCL CALACGAL GAGCATGCCCACTTAGEGCAEGAAGEAACAGAC FL LEGA BRCACCTCTCTTCOTCCCCACTCCCCCCACACTCCCCACACACCCCCCCC

		A TOTOCASC FOUTTUA ACCAAAASC CAAODACCE DITAT DECACAODAD TUDOAT CAAOTTUDUACAAGA CATCOTTATITOTATUDUCCCAGAACUTECT CACTALOOT CAAGAC CAGACCAGE CATCOTTATITOTATUDUCCCAGAACUTECT CACTALOOT CAAGAC CAGACCAGE CATTOTER COCCAST GEDOTO CAGACOCTACACCAACCAACC TOCCTS ADDOCCGAGOTTER TEGOTOTER AGGAGAAR SCATTOSUCTOA TOUSTC CGUUAGAGAAU CAAGE SCUULAGE A EQUAGAAG E DEGACAGAGAGAGE SUCTOA TOUSTC CGUUAGAGAAU CAAGE SCUULAGE A EQUAGAAG E DEGACAGAGAGAGAGE SUCTOA TOUSTC CGUUAGAGAAU CAGACOCTGACCAGACATUCCCCAACT SCUTGACCAGAA ATCACCAACTECCTCATCOCAGACOCTGACCAACATUCCCCAACTACACCACUS COCCAUCAU 997 CACTGCTCC RATCOCCAGACOCTGACCAGACOTTGCCCAACTACACCACUS COC CCURGOAUTGCTCCATCACCACGACOCTGCCCAACTACCACCACUS COCC CCURGOAUTGCTGCTCTCC FECCACGACCAGGACOCTGCCCAGGACCTCCTGACCACCACUS COCCACUS COCCACUS COCCACUS COCCACUS CAAGAACUS COCCACUS CAACAACUS CAACCACUS CAACCACUS CAACAACUS CAACCACCACUS COCCACUS CAACAACUS COCCACUS CAACAACUS COCCACUS CAACAACUS COCCACUS CAACAACUS COCCACUS CAACAACUS COCCACUS CAACAACUS COCCACUS COCCACUS CAACAACUS COCCACUS COCCACUS COCCACUS CAACAACUS COCCCACUS COCCACUS CAACAACUS COCCCCUCUS COCCACUS COCCACUS COCCCUCUS COCCACUS COCCCUCUS COCCUCUS COCUCUCUCUCUCUCUCUCUCUCUCUCUCUCUCUCUCUC
		GAGAAGACCCAGTG2GTGAGG2TGTUAGG2GTGGGGGGGGGGGGGGGGGG
		CCCAACHUTACACOHUAGCAACUUAACACUUTCADCCAUUACUUTCUACACUUT CTGRATACAUGTTGCRAGGOTGCUGACACGGCACOTGCUTCUGRACUUAGGAT CURAACCUUTGUCACUEGAUGCACGCOUCUUTABOOC <u>GGTGGAGGAGGCTCTGGT</u> <u>GGAGGCGGTAGCGGAGGCGGAGGGTCG</u> GATATCCAGATGACCCAGTCCCCGAGC
		TCCCTGTCCGCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAG TCTTACGGTGGTGTAGCCTGGTATCAACAGAAACCAGGAAAAGCCCCGAAGCTT CTGATTTACTCTGCATCCTACCTCTGGAGTCCCTTCTCGGCTTCTCGGT AGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGAC TTCGCAACTTATTACTGTCAGCAACCATCTCATCT
91	gWiz-LS- mouse SA- (Gly4Ser)- V <sub>H</sub> CK157- His6	ATGUAGATEACACT-RECTORER TOOTORRECTOOTALTGC TODRECTOOT GUIROTAGATEACACT-RECTORER TOOTORRECTOOTALTGC TODRECTOOT GUIROTAGATEACACACAAGACCTEACTCOCACTUCCAGTATUTORAG ARATOCIDATACCADOACCATOCCAAATTACTCOASGAACTAACAGACTCICCA AAGAGUIGTEETGUCGATGAGTCTEGOUGUCAACTUTGACARA.UUULICAUAUT CTITTT-DIAGATAACTTCICTCOCATCOCAAACCIDOOCCUAAAACCACCICCICAA CTEROTGACTGCTECRCAAACAAGAGCCDOOCCUAAAACCACCICCICCAA
		CACAAAGATGACAACCCCAGCCLACCACTTEGAAGGCCGAGAGGCUGAGGC ATGTSCACCTTEAAGGAAACCCCACACTTETGAAGGCUGAGAGGCUGAGGC ATGTSCCAGAGAGACALCCTTALLECTATGCCCCAGAACLLCCTTACLALGUT GACCTGCCAGAGACALCCTTALLECTATGCCCCAGAACLLCCTTACLALGUT GACCTGACCCGAAGCTTGATGCTGCACACGCTGCAGACGCACGC

		A CACCARA TOCORACE CACOUNT CONCERNENT CONCER
		AA STACAACOASAT DAACAAACAAAC SECTETTO TECACOTO TECAACOA DAAC OODAAGGOTA DE SEGRAGODAAC DAAAGE ET GEOALDEGAT ASOLDEGOACA SETE ET GUATROA I GETEGOAAGGETEO FOACAAGGAACCETEO FICIL OBACILGA SUUT CEAACOUTECTOACE AGGEGGAGGGETEO GGAGGEGGTAGEGGAGGEGGAGGGETEO GGAGGEGGTAGEGGAGGEGGAGGGETEO GGTGGCCTGGTGCAGCCAGGGGGGETEO GGTGGCCTGGTGCAGCCAGGGGGGGETECCCGGTTGTCCTGTGCAGCCCGGGTGGG GGTGGCCTGGTGCAGCCAGGGGGGGETECTACCCGGTTGTCCCGGCGGGGGGGGGG
92	gWiz-LS- mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129- ds1 (V <sub>L</sub> 100 <sup>Q&gt;C</sup> / V <sub>II</sub> 44 <sup>G&gt;C</sup> )- (Gly4Ser)- His6	ATGMACATGMACAGEGORGOTICAGET CONSTRUCTION SUPERITICIES TERMENTISUES GATERIA ATTO-DAACCOCTAGET CONSTRUCTION CONSTRUCTIONS AAATGOTICAT AGGATIGAGEA TERCIDAATTAGTEG AGGAAGEACTIC TOCAC AAATGOTICAT AGGATIGAGEA TERCIDAATTAGTEG AGGAAGEACTIC TOCAC AAATGOTICAT AGGATIGAGEA TERCIDAATTAGTEG AGGAAGEACTIC TOCAC AAATGOTICAT AGGATIGAGEACTICICAAATTAGTEG AGGAAGEACTIC TOCACACT CTUTTTEGAGGATAGET TOUSTGOCAT TOCAAACTTCOVITGAAAGEACTIC CONSTAA CTUTTTEGAGGATAGET TOUSTGOCAT TOCAAACTTCOVITGAAAGEACTIC CONSTAA CTUTTEGAGGATAGET CONSTRUCTION CONSTRUCTION TAGTEG CACAAFGET GAGAACCOC AGOOTE COACCACUTTEGAAGEACGAACTTCOTTIC CONSTA CACAAFGET GAGAACCOC AGOOTE COACCACUTTEGAAGEACGACTIC TUTTGAT CAAFTT COCASTAGEACACTTCITE COACCACUTTET AT SEAC ACCACUTTEGAT CAASTT COCASTAGEACACTTCITE COACCACUTTET AT COCOCACCACUTTET TO TTEGAGEACACUT TOCOTOACCOCCACUTTEGT COTTECT COACCACUTTET TO TOTICACUT COTOACCCCCACUTTECT TO TECT CAACAACCACUTTET TO TO CGTOACGACUCCCCCACUTTECT COACCACUTTET TO TO CGTOACGACUCCCCCACUTTECT COACCACUTTECT COCOCATE TO TO CGTOACGACUCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC

		CCTCATTECTCTCTCTCTCTCTCSCCCTCTCSCCCCCTCTCCCCCCCC
		CTOGARAZCTOCTOCUCTOAAGCUAATOCTCUCCATOCTACCOCACLUTOCTT
		COLVAATOTOASCCIOTTVIAGAACASCASCASCASCTICCIOAAAACCAA ITST
		GATCTEDAOGAGAAGOTEGGAGAATATGGATTOCAAAATGOCADECTAGTECGC
		LACACODAGAAAGCACCECAGALGECAACCOCAACIUECGEGGAGGCLGCAAGA
		AACOTAGGAAGAGTGGGCACCAAGTGTTGTACACTTOCIGAAGATCAGAGACTG
		CULTERGRAGACIAICTETUTSCATOUTSRACCELSISUETCUSUESCAT
		CRYRAGACCCCACHOS OF PACCAPCTOR COACCAS OF SUCCESSION AUCCOC NUTC
		GRARGOGGOCRIGOTTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOTO
		GROTTTARAGOTOR RECEIPOR DETECORDECTOR TATCHOCA CACELUC CACAC
		ANGANGAR GCAGASTIRAGAAACARACGGGT CTTGCEGAR CTGGTGAASCACAAS
		OCCAACCUTACAGCCUAGCAAC JUAAGAC LOTUAL GGA LUACLI I GCAUAG ELC
		CCAAAODEEG JUACI, AGA JUUAAAGACUKUJ, EAGCU <b>GGTGGAGGAGGCTCTGGT</b>
		GGAGGCGGTAGCGGAGGCGGAGGGTCGGATATCCAGATGACCCAGTCCCCGAGC
		CCCCTGTCCGCCTCTGTGGGCCGATAGGGTCACCATCACCTGCCGTGCCAGTCAG
		TACGGTGGTTACGTAGCCTGGTATCAACAGAAACCAGGAAAAGCTCCGAAGCTT
		CTGATTTACGGTGCATCCCTTCTCTCTGGAGTCCCTTCTCGGCT
		GGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGAC
		TTCGCAACTTATTACTGTCAGCGAGGTCATGCTCTGATCACGTTCGGA 7867GGT
		ACCAAGGTGGAGATCGAAGGTACTACTGCCGCTAGTGGTAGTAGTGGTGGCAGT
		AGCAGTGGTGCCGAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCA
		GGGGGGCTCACTCCGTTTATCCTGTGCAGCTTCTGGCTTCAACATCTCTTTAC
		GGTTCTATGCACTGGGTGCGTCAGGCCCCGGGTAAG®GCCTGGAATGGGTTGCA
		GGTTCTATGCACTGGGTGCGTCAGGCCCCGGGTAAG%GCCTGGAATGGGTTGCA TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT
		TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT
		TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
		TCTATTTACCCTTACTCTAGCTCTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
		TCTATTTACCCTTACTCTAGCTCTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
- 93	a Wiz-I S-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	gWiz-LS-	TCTATTTACCCTTACTCTAGCTCTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	mouse SA-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3-	TCTATTTACCCTTACTCTAGCTCTACTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> -	TCTATTTACCCTTACTCTAGCTCTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129-	TCTATTTACCCTTACTCTAGCTCTACTACTATGCCGATAGCGTCAAGGGCCGT         TCCACTATAAGCGCAGACACCTCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2	TCTATTTACCCTTACTCTAGCTCTACTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> /	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3- scFv (VL- VII) CK129- ds2 (VL43 <sup>A&gt;C</sup> / VH105 <sup>Q&gt;C</sup> )-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACTCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly4Ser)3- scFv (VL- VII) CK129- ds2 (VL43 <sup>A&gt;C</sup> / VH105 <sup>Q&gt;C</sup> )-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACACCCAAAAAACAAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACATCCAAAAAACACAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TTCACTATAAGCGCAGACACACCCAAAAAACAAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCAGGCCTACTTACTATGCCGATAGGGCCAAGGGCCGT         TCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCTAGCTCTACTTACTATGCCGATAGCGTCAAGGGCCGT         TCACTATAAGCGCAGACACCATCCAAAAACACAGCCTACCTA
93	mouse SA- (Gly <sub>4</sub> Ser) <sub>3</sub> - scFv (V <sub>L</sub> - V <sub>II</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly <sub>4</sub> Ser)-	TCTATTTACCCTTACTCAGGCCTACTTACTATGCCGATAGGGCCAAGGGCCGT         TCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA

		CACCOCAACCAACTECTTCCTCCCCCACCCTTCCTCTCACAACTATCAACCACACCCCACCCCACCCCCACCCCCC
94	gWiz-LS- mouse SA- (Gly4Ser)3- scFv (V <sub>H</sub> - V <sub>L</sub> ) sm3E-ds (V <sub>H</sub> 44 <sup>R&gt;G</sup> / V <sub>L</sub> 100 <sup>G&gt;C</sup> )- (Gly4Ser)- His6	ATGRACATSAGARTSCCTROTCASCTROTGRSCCTROTROSSCCTROTROSSCCROTROSSCCROTROSSCCROTROSSCCROTROSSCCROTROSSCCROTROSSCCROTROSSCCROTTER GGDPOTASSATROGRAGOSACACAAGAGGGGGAATCOCOCACGGGTATAATGATTE COASAACAAGATTECAAA DECCHACTOCTATTODUTETTOODAGTADOD DCAG AAGACGUGATACGADAAGCATGOCAAATTAGTROSGGAARTAACAGAOTOTIGCA AAGACGUGATACGADAAGCATGOCAAATTAGTROSGGAAATAACAGAOTOTIGCA AAGACGUGATACGADAAGTGOCGATDOCAAACCTOOOTGAAAACTATGGJGAA CTCROTGECTGOTROTECGATDOCAAACCTOOOTGAAAACTATGGJGAA CTCROTGECTGOTROTECGATDOCAAACCTOOOTGAAAACTATGGJGAA CTCROTGECTGOTROTECGATDOCAAACCTOOOTGAAAACTATGGJGAA CTCROTGECTGOTROTECGATDOCAAACCTOOOTGGAAAACTATGGJGAA CTCROTGECTGOTROTECGATCTCOCCCACAACTACCCCCA AAGACTTOCCACAACACACCCACACTTCAAGGGAAAACTATCOCCC ATGTGCACAACACACACCCTATTTECTATCCCCCACAACTTCCTTACTACTATCCCT GACACTACCAACACACTCOCACACTTGTGCAGAGGCTTGGJGACAGGACAACTATCCT COTCAGAGAACGAACACTCCAGTATTGCGACAAGGAGGAGGACGACACTATCCCA GACACTACCAACACTCCCACGACACTTGGGAGAGGAGGAGGACTCTGAAA GCATGGGCAGTAGTCGACCCAGTATGCCGCAAACTAGGGAGAGGACTCTCAAA GCATGGGCAGTAGTGCCCCCAGTATGCCGCGAAACCTCCCCCACACTCCCCCCCC

		CACCERCIAL CONTROLOGICULAR CONTROLOGICA ACTIVE A CAACE ACCARES CONTRAL ALCONDUCTOR OF CONTRALACE CONTROLOGICULAR CAACE ACCARES CONTROLOGICULAR
95	LS-mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK138- (Gly4Ser)- His6	MOMENTAQLIGLILIZIPGARCEAUKSEIAHEYNDLGEONTKGLVLIAVSQTLQ KOSYDEHARIVQEV DEPAKTUVAEESAARODESIHTIECERI DALEN LRENVGE LADOOTKOEREENECPLOHEDDNESLEPPTEREEAESACTS PRENETTPMOHYDE EVARKEETETAEELLITTAEQYNELLIQOOAHADEESULTPALEOVKEKALVESV RORMROSSMOKEGEESTKAPAVAELSOTERESDTAEITELATELTEVNKEOOFO DILEORDBRAELAEYHCENOATISSKLOTOODKPLLARAAROISEVENDTMPADI PATAADEVED QEVOKMYAEAKEVPLOOFIAETSSRLOTOODKPLLARAAROISEVENDTMPADI PATAADEVED QEVOKMYAEAKEVPLOOFIAETSSRLOTOODKPLLARAAROISEVENDTMPADI PATAADEVED QEVOKMYAEAKEVPLOOFIAETSSRLOTOODKPLLARAAROISEVENDTMPADI PATAADEVED QEVOKMYAEAKEVPLOOFIAETSSRLOTOODKPLARAAROISEVENDTMPADI PATAADEVED QEVOKMYAEAKEVPLOOFIAETSSRLOTOODKENTIODIYEKKIAET LEAUGAEAREPAUNGTVLAEVQELVEEPKNIJKINDELYEKKIAETOPROTOILE SKOTEVERNYTKOOSGSIVERREOFSALTVDETYVEKERIAETFOFREDTOILEE KEKQLAEQTALAELVEEKEKAIAEQIKIVEDEVAQELDIOKAADEDIUFSIEG PALIVTKOKDALA <u>GGGGSGGGGGGGGGGGS</u> ASAIQMTRSPSSLSASVGDRVTITCRA SQYHDGSAAWYQQKPGKAPKLLIYGASYLYSGVPSRFSGSRSGTDFTLTISSLQ PEDFATYYCQQSSYSLITFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESDGG LVQPGGSLRLSCAASGFNLSYYGMHWVRQAPGKGLEWVAYIASYPGYTSYADSV KGRFTISADTSKNTAYLQMNSLRAEDTAVYCARSGYSYSPYYSWFSAGMNYWG QGALVTVSS <u>GGGGS</u> BHENDH=-

96	LS-mouse	MEMENPAQUE GULE LALP CANCEAAN SE FARRY REDUCE OR PROLYL FAR SOYEA
90		ICSYDEEARLYCEVIDEAETCVADESAENCDRSLETLEGDRICATPNLRESSIG
	SA-	LADCOT KOEFEENE OF LOFF OONPALLEF FERPEARAMOUSE KENFUUFMORY L
	(Gly4Ser)3-	EV ARREPYEY AREA DY MAROVARE I DTOCORRADKES OF TER KED GVERMALV SSY
	$scFv (V_L-$	RORMOSSIQKSGERAFXAMAVAS LOOISPILADI AS LES LATULS E VIKS OCH
	V <sub>II</sub> ) CK157-	DILECALBRAELAKYNORAQATUS SELQTCOERFLUKKAROLSEVERDTERAD
	(Gly <sub>4</sub> Ser)-	PALAAUSVERQEVCKNTAEASOVSEGEREYETSREETUYSVSLEEREAREYEA
	His <sub>6</sub>	I BROOMESNIPPACYSTYLAEROPUYEEPARUVKTNODLYEKT CEYGRQUAUUV
	11136	YTOKAPOVSTPILVEBARNLORVSTKOCILFEDORLPOVEDYI SAILDRVOLL
		SKLEVSREVTKOOSOS LVERPECEVALE VELTYVEKEE KASTELERSE ULLEP
		EREQIKKQTALSEI VKARPEATAEQIETVEDDEAQFLDUCCHASDKDUCESTE
		PALIVTRUKDALLA <u>GGGGSGGGGGGGGGGGGG</u> AS <b>DIQMTQSPSSLSASVGDRVTITCR</b>
		SQSYGGVAWYQQKPGKAPKLLIYSASYLYSGVPSRFSGSRSGTDFTLTISSLQ
		EDFATYYCQQPSHLITFGQGTEVEIKGTTAASGSSGGSSSGAEVQLVESGGGL
		QPGGSLRLSCAASGSNPYYYGGTHWVRQAPGEELEWVASIGSYPGYTDYADSVI
		GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARHYYWYDATDYWGQGTLVTVS
		GGGGSNNNNN
97	LS-mouse	<u>MMEYPAQLIGUU IMIPGARI</u> EARISEIAHRYNDUSEQRFEGUVIIAFSQXL
	SA-	KCSYOEHAKINGEVIDERKTOVADERAANOOKSIHTLPODKICAIPNLPENYO
	$(Gly_4Ser)_3$ -	IADOCTEQUPERRECFLQERDENE SI PRECE EAEAMOLSZKENPUTEMSEVI.
		SVARPHEYFYAPELLYYAEQIDEILIQOOAEADKESOLLEKEUSVEEKAEVSS
	$scFv(V_L-$	ROBINCSSWORFGERAFEAWAVARLSQTFPNADFAELIKLATELIKVNAECCH
	V <sub>H</sub> ) CK129-	DILLECADDRAE LAKYMOENGAT I SSELIGTOODAPLI LIKAHOL SEVEED I EPAP
	(Gly4Ser)-	PALIAADEVEDQEVCERMAEAADVELGTELYEMSREAPDYSTILLELEKKSEA
	His <sub>6</sub>	I SKOCREBUPPACYGTVI ARSON LVSEPACLYKUPCOLYEKI GEYGFQUALLU.
		XIQKAFQVSTF1VEAARBEEVCTCOC1.FEBQREECVEDYSABRV DEE
		ENTRY SERVICES GELVER RECESSIONER VEREFRAME TRESPICTATION CONTRUCTS CONTRUCTS AND A CONTRUCT AND A CONTRUCTS AND A CONTRUCT AND A CONTRUCTS AN
		ELEQIKKQIALABEVKHEPEATANQLETVRODINQFEUU COLAADKOL OFSTU PMEVIERUSDALAGGGGSGGGGGGGGGGSASDIQMTQSPSPLSASVGDRVTITCR
		SQYGGYVAWYQQKPGKAPKLLIYGASLLYSGVPSRFSGGRSGTDFTLTISSLQ
		EDFATYYCQRGHALITFGQGTKVEIEGTTAASGSSGGSSSGAEVQLVESGGGL
		QPGGSLRLSCAASGFNISSYGSMHWVRQAPGKGLEWVASIYPYSSSTYYADSV
		GRFTISADTSKNTAYLOMNSLRAEDTAVYYCARGYGPWYAYSYFALDYWGQGT
		VTVSS <u>GGGGS</u> HHHHHH—
98	LS-mouse	MDMRVFAQIA.CLUEIWIJPCARCEAHKSBIAHRYNDELCECHEKCEVEI AESCYL
90		KONYDEREKI VOEVIDVAKTOVADES RANODKSI BILESDKI CALENIASEN IS
	SA-	LADOC ENGENERGEON LORKDORF DE PERTERE KARAROLIS (KENPLLIPTISE VE
	(Gly4Ser)3-	EVAP REPYPYAPELLY YAEQYNELLI QCCAEADRESCI UPRIECSVKERALVSS
	scFv (V <sub>L</sub> -	RORMECSSROAFGERAFARAMARLSOTFFEADEAEITKLAEDEIKVERECCE
	V <sub>H</sub> ) CK138-	DILLECADDPARLARYMCENQATI SSKLQTO DKPLLERKAHCI SEVENDTHPAG
	dsl	PAJAAOFVEDGEVCEBYAKAKOVFLGTELTEYSRREPOYSVSI LLELAKKYEA
	$(V_L 100^{Q>C})$	LERCCARANGERCYCTVLAREQELVEREKNLVKTUCHLYEKLYRCQRALIA.
		TTOKAPOVOTOTUVEAADMUGRVOTECCTEDEDODELTOVEDTUSAJILMAVUUL
	$V_H 44^{G>C}$ )-	EELE VSEEVEROUSGSLIVERREONSALLIVONE VVPNLEKANEE INTESDECTER
	( <i>Gly</i> <sub>4</sub> Ser)-	EELEVSERVERGISSEVERSPORSALTVORETVERBEKAREELVESDECTE KEKOERIGTALAELVERKKATAEGEKTVEDDRAGFEDI.COMAADEDIOFSTE

		SQYHDGSAAWYQQKPGKAPKLLIYGASYLYSGVPSRFSGSRSGTDFTLTISSL PEDFATYYCQQSSYSLITFG©GTKVEIKGTTAASGSSGGSSSGAEVQLVESDG LVQPGGSLRLSCAASGFNLSYYGMHWVRQAPGK©LEWVAYIASYPGYTSYADSV KGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSGYSYSPYYSWFSAGMNYWC QGALVTVSS <u>GGGGS</u> HHHHHH
99	LS-mouse SA- $(Gly_4Ser)_3$ - $scFv (V_L-$ $V_H) CK138$ - ds2 $(V_L43^{A>C} /$ $V_H105^{Q>C})$ - $(Gly_4Ser)$ - $His_6$	MDME VPAQLEGEDILMERSECEARS BETABRYNDEGEGRENGEVILTAF SYNT ECSYDDEAAL VGEVIDEAE TOVADESAANGEKSLETEFØDALCA I PNEPENYGE TADOOTEGEFERRECELOBKODDEGIFFEREPEREAMOUSFKERETEMEN VES KORRACSBERKEGERFKAMAVAKES (IEFRADEAELIE EATUELEVERETOMEN VE NORRACSBERKEGERFKAMAVAKES) IEFRADEAELIE EATUELEVERETOME DILECADDRABEAXYMOENGATIS SELGTOODRELEVKAROLEEVERDTMEAD FA LAADE VEDGEVORNYAELSKOVELGIPLYENSEREFOYSVSILLERLAKKYRA TEKOCHEMPPACEGTET AEFOETVEEPRIEVETNODE ZEVIGE OF GEDALEVE YTOKAPOVETELEVERANNER VETKOOTEDEREVENDE ZEVIGE OF GEDALEVE IEFOIFKOTALASIVKREFFATAEGEETVEDDE VEREFKARTETETESETOTEFE IEFOIFKOTALASIVKREFFATAEGEETVEDDE AGSTOTOCEAADKDOOFSTER PNLVTECKDALA <u>GGGGSGGGGGGGGGSAFAIOM</u> TRSPSSLSASVGDRVTITCRA SQYHDGSAAWYQQKPGKOPKLLIYGASYLYSGVPSRFSGSRSGTDFTLTISSLO PEDFATYYCQQSSYSLITFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESDGG LVQPGGSLRESCAASGFNESYYGMHWYQAPGKGLEWVAYIASYPGYTSYADSY KGRFTISADTSKNTAYLQMNSLRAEDTAVYCARSGYSYSPYYSWFSAGMNYW CGALVTVSS <u>CCCCS</u> HNNHNH
100	LS-mouse SA- $(Gly_4Ser)_3$ - $scFv (V_L-$ $V_H) CK157$ - ds1 $(V_L100^{Q>C} /$ $V_H44^{E>C})$ - $(Gly_4Ser)$ - $His_6$	MMRMPNQLLGLUL MLRGARCEARE SETARBITAD LGEGREEG LVIL AE SQYLA         KC SY DERBEKI VOEVUDPAKTOVADUS AANODEST BILLEDDYT CALENDEEN YOJ         LADOOT LGEPERRECE LGERKEDNE SI PPEEPE BAEAMOUS TKENPUTERBEN YOJ         LADOOT LGEPERRECE LGERKED YAARD ARLS OT LOT LEKKAROLSEVERD INFADE         PALAADF VEDCEVCENYABAAR VELOUTEL YEN SKREPPYSNELLELAFKYRAAD         LEKOOABAND PACT GUVLABE OF DE LVEEPKALD VELOUEN STALLNY         YOVAP (VATPT LUVEAAENDGRY OTHOUTT PEOPEEPCVEPTISALLNY         YOVAP (VATPTLOCSGELIVEE ROOF BALLYKEN NODL YE SIGAL NY         KENQI KKOTALASI VKHEPSATAEQI NY VEREFKASTE UPEDITOTIST         KENQI KKOTALASI VKHEPSATAEQI NY VEREFKASTE UPEDITOTIST         KENQI KKOTALASI VKHEPSATAEQI NY         SQSYGGVAWYQQKPGKAPKLLI YSASYLYSGVPSRFSGSSGSSGAEVQLVESGGGLV         QPGGSLRLSCAASGSNPYYYGGTHWVRQAPGE CLEWVAS IGSYPGYTDYADSV         GGGGS       SATANY         GGGSLREN
101	LS-mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK157- ds2	MDMRVFRQIROLLI IMIROARGEAHESBIAHRVHDLOBOHEKOLVEI AESOTU KOSYDEHEKI VQEVIDVAKTOVADESRARODESI HELEGDELOAIPNIKEN YO LADOO EKQEVERECE IQHKDIDEEL YRELKE KARAMOIS EKERELIPHONEN EVAR RHYYFYAPETIIYYABQYNELLIQOOAEADRESCI TRREDSVKERALVIST PQEMKOSSHQAFGERAFRAMAVARLSOTFURADESELTKLA ID UTKVRKEOCO DI LEOADDRAELAIYMCENOATIS SKLOTOODKYLLIKAAHOI SEVEHDIMPAD. FALAADFVEDQEVCENYABAKDVELITELEYSREPISVSI. LLELAKKYEA

	(V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )- (Gly4Ser)- His6	LERCCAEANFFACY TIVLASFQPEVEEF KNUWTINOPI YEKLOBYCEQNA LEW YTOKAPOVSTPTLVEAARNLOEVOTKOOTLPEDQRLPOVEDYLSA LLBRVOLLA EKTPVSERVTKOOSOS LVERPPOPSALTVDETYVPKEEKASTFTEHSETOTIJE KEEQIKKOTALSETVKAEPENTAEQLETVRDPAQFEDTOORAADKLOOPSTEG PALVTNOKDALA <u>GGGGSGGGGSGGGGS</u> AS <b>DIQMTQSPSSLSASVGDRVTITCRA</b> SQSYGGVAWYQQKPGKOPKLLIYSASYLYSGVPSRFSGSRSGTDFTLTISSLQP EDFATYYCQQPSHLITFGQGTEVEIKGTTAASGSSGGSSSGAEVQLVESGGGLV QPGGSLRLSCAASGSNPYYYGGTHWVRQAPGEELEWVASIGSYPGYTDYADSVK GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARHYYWYDATDYWGOGTLVTVSS <u>GGGGS</u> HNNHNH
102	LS-mouse SA- (Gly4Ser)-V <sub>L</sub> CK157-His6	<u>MOMENT AQLIGITI IMIPGARC</u> EARABEIABRYRDIGEOBEIGUVI DAEBOYLQ KOSYDEBAKLYQBYTDEAETOVADESAANODKSIBTLP DKICA I PRIPENYOE LADOTEGEPERRECELORKDONESI PEEEPEEEAMOTSEKENETTEMGRYLE SVARPREYFYADELLYYARQ MELLTQOCAEAUKESOLLE KLDBVEEEALVSSY ROEMYCOS MOREGERABIAWAVARLBOTTENADEAEITKLATELTKVRRECOUG DLIEGADDRAELAKYMOENGATIS DELGTCODRELUKKAROLSEVEHDTMEADI PA LADOEVEDGEVOKHYAEAROVELGTELYENSPREPOYSYLLL REAKYN CAT LEKOCAEANPPACYGTVI AEFOEUVEERARUVKINODLYEVI GEYOFQUATIVE YTQKARQVSTETIJVEAARDESPVOTROOTIPEOQREROVEDYI SAILDRAYDIAL REEVGERVTECCEGS IMPERPORAUVUETYVEREKARTE TEHSEYOTUPE REEQIKKQI ALAGUYKAEAROVELGIGI TVRODEACEUU. OCEAADKU. OESTUG PNLVTROEDALA <u>CCCGSSCCGCSGCCCS</u> AS <b>DIQMTQSPSSLSASVGDRVTITCRA</b> SQSYGGVAWYQQKPGKAPKLLIYSASYLYSGVPSRFSGSRSGTDFTLTISSLQP EDFATYYCQQPSHLITFGQGTEVEIK <u>CGGGS</u> NHNNNH
103	LS-mouse SA- (Gly4Ser)- V <sub>H</sub> CK157- His <sub>6</sub>	MEMRYPAQLIGLILLMUPGARCEAUXSEINHE MEDLGEGEVKGLVLIGESOVLQ KUSYDEBARI VQEVILFAKI OVALESAARCDESI EILECHKLOAIPELKENTGE LROCUTKGEDEENECELGHEDDNEBLDD PERPEREMUTSEEREUTTFMOHYLM EVAB KREYFYAF BILLYTAEGYNEILI I GOUAEADEESULI EKLEGVKEKALVGUV RORMACSSMOKFGEFAFKAMAVAF LGOTEENS DTAEITITLATLITEVEKED OFG UILECADEKAELAEMMUENQAIISVKLQI CCERFILKEABUI SEVEREPTREADI PALAADEVEDGEVCKNYAEAKUVELGTEENEN DTAEITITLATLITEVEKED OFG UILECADEKAELAEMMUENQAIISVKLQI CCERFILKEABUI SEVEREPTREADI PALAADEVEDGEVCKNYAEAKUVELGTEENEN PREUPDYS VOLUERLAARVEAT LEECCAEARFFACYGTVLAEFOOLVEEF KNLYRTNODI YERLGEYGFORATUVR YTGSAFQVSTEELVERARDLCRVUTKCOTI PEDGREFOVEDYLEATEDERSDICTLEE KEKQIERGTALAELVEEKERAIAEGI KIVEDEFAQELDI CUKAADEDIUFSIEG PALVIKCRDALA <u>GGGGGGGGGGGGGGGGGASAEVQIVESGGGLVQPGGSLRLSCAA</u> SGSNPYYGGTHWVRQAPGEELEWASIGSYPGYTDYADSVKGRFTI SADISKN TAYLQMNSLRAEDTAVYYCARHYYWYDATDYWGQGTLVIVSS <u>CCCCS</u> NNNNNN
104	LS-mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129- ds1	MEMOVFAQUICLUL INTEGARCEANS SETANEVED LODONEKCUVETAESON LO KOSYDEREKEVQEVIDUAKEOVADUS AARODESTRELEGDET CATENDREESE LAGOOTEQUEERACE LORKDDE SEERELEE BAAROLS FRERELIPHONESE EVAPREESE VARUUT ABOVNET LOQUAEADEBOITERED SVERALVSJV PORMOS SEQLEGERAFEAMAVARISOTENADE ABITKLATE LIKVRECORG UT LEOADDRAELAEVMCENOATISGELOTODERPLIKRAHOT SEVERDIEPADE PALAADEVEOQEVCENYAKARD VELOLETTERREPYSVST. LIRLAKKYEAT

	(V <sub>L</sub> 100 <sup>Q&gt;C</sup> / V <sub>H</sub> 44 <sup>G&gt;C</sup> )- (Gly4Ser)- His6	LER COMEMPERCY ITVLAR POPLYELE BREVKINGELYEKLORY OF ONATEVR YTORAPOVSTPTLYEAARNLOPYOTKOOTLEBOORLPOVEDYLSATEDRVOLLA ERCEVSERVTKOOSOGEVERPPOPSALTYDETYVPKEEKASTETEHSETOTIE REEQIKKOTALSETVRAEPEATAROLETYREOFAQETOTOGAASDKOOOPSTEG PALVTROKDALA <u>GGGGSGGGGSGGGGS</u> AS <b>DIQMTQSPSPLSASVGDRVTITCRA</b> SQYGGYVAWYQQKPGKAPKLLIYGASLLYSGVPSRFSGGRSGTDFTLTISSLQP EDFATYYCQRGHALITFGOGTKVEIEGTTAASGSSGGSSSGAEVQLVESGGGLV QPGGSLRLSCAASGFNISSYGSMHWVRQAPGKCLEWVASIYPYSSSTYYADSVK GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGYGPWYAYSYFALDYWGQGTL VTVSS <u>GGGGS</u> HHREMM
105	LS-mouse SA- $(Gly_4Ser)_3$ - scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129- ds2 $(V_L43^{A>C} / V_H105^{Q>C})$ - $(Gly_4Ser)$ - His6	MMENT AQLLGETI LYLPGARGEAREBETARRYRDEGEGREEGEVI TAF SQYLQ KOSYO ERAKUVQEVI DEARTOVADESAARODKSURTUP DKI CATPRIPER OG LABOOTEQEPERRECETQRRDORFST PEPEPEREAMOI SYKERETIEMGRYLB EVARERYYY ABELLYYARQ (RETUDOCAEADKESOLTE KUD9VEEKALVSSY EOEMKOSSMOEFGERAFERMAN ARLSOTEPNADERETTKLATDETKVRRECCEG DLIBCADDRAEDAKYMOERQAT DEBELQTCODREDUKKAROLSEVERDTMERDT PA TAADE VEDQEVORKYAEAROVELGITELYENSPREEDYSVST. ELRIAKKY GAT LEKOOREARPERACYCITVI AREOPTIVEEPRREVETRODI YEKT CEYOFQNATUVE YTOKAFQWETPTIVEARREEPVOIR OTTIPEOQREPOVENTI SATLDRAVILE EETEMSERVIECCEGES LVEERPOPRALTYRDETYVEKEFKARTE DEBEDICITEE LEAGTKKOTALAGEOKOCGESCOGGESASDIQMTQSPSPLSASVGDRVTITCRA SQYGGYVAWYQQKPGKOPKLLIYGASLLYSGVPSRFSGGRSGIDFTLITISSLQP EDFATYYCQRGHALITFGQGTKVEIEGTTAASGSSGGSSSGAEVQLVESGGGLV QPGGSLRLSCAASGFNISSYGSMHWVRQAPGKGLEWVASIYPSLDYWGOGIL VTVSS <u>GGGGS</u> HENNENH
106	LS-mouse SA- $(Gly_4Ser)_3$ - $scFv (V_{II}-$ $V_L) sm3E-ds$ $(V_{II}44^{R>C} /$ $V_L100^{G>C})$ - $(Gly_4Ser)$ - His <sub>6</sub>	<u>MMRVPAQLEGELELW_PGANORAHESELAHRTRIDEGEGESEGEUVELANSOVEQ</u> KCSYDERAYLVORVIDVAKTOVADEGAANORGEHTLEGDVICALENERENYGE LADOCIEGEBERECKLORKBERESEPPEREREAKAMOLSSKENTIEREDVICALENEREVGE PADARREYFYAPELLYYARQYNEILTQCCARADRESCUTEREDGYKEKALVSSY RORMUCSSMOEPGERAFIAWAVARLBOTPINADEAEITKERTEETKVNREDCEG BILLECADDPAELANYMCENGATISSKLOTODDKPLENNAHCISEVEHDTHPAGI PATAADFVEDOEVCEDYARANDVPLGTELTEYSKRRPDYSVSILLELZKKYRAT LEKOCARANPACIGTVEARREYFYDTOCTUPEDQEDPOCVEDYISATINR YTOKAPGVSTPTTIVEARRESRYGTNÖCTUPEDQEDPOCVEDYISATINRVÜLDH RELEVSERVERCUSGSLIVESRPOFSALTVURETYPESFKAREFITESDECILLE KENCLINGTALAREVKYRATARGINTVURETYPESFKAREFITESDECILLE KENCLINGTALAREVKYRATARGINTVURETYPESFKAREFITESDECILLE KENCLINGTALAREVKERATARGINTURETYPESFKAREFITESDECILLE KENCLINGTALAREVKERATARGINTDPENGDTEYAPKFORATFTTDTSANTA YLGLSSLRPEDTAVYCNEGTPTGPYYFDYNGQGTLVTVSSGGGGSGGGGSGGG GSENVLTQSPSSMSVSVGDRVTIACSASSSVPYMHWLQQKPGKSPKLLIYLTSN LASGVPSRFSGSGSGTDYSLTISSVQPEDAATYYCQQRSSYPLTFGCGTKLEIK

	hCXCL1 <sup>38-</sup> <sup>107</sup> -G3-c- myc-Aga2	AAGACAGCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
108	pCHA-LS- hCXCL2 <sup>38-</sup> <sup>107</sup> -G <sub>3</sub> -c- myc-Aga2	ATG       ATG         ATG       AGACOGE         AGACOGE       AGACACCCAGAGCCTGAGAGCCAGCAGTCCCCAGCCCAG
109	pCHA-LS- hCXCL3 <sup>38-</sup> <sup>107</sup> -G3-c- myc-Aga2	ATGAAGOTTTCGAT CODE TOTTCOOLATCITCOURSCITTCOURSCITTCOURSCITTCOURSCITCOURSCITCOURSCITCUUS         ATGAAGOTTATTTATACTACOTTOUS         ARCACAGTGACCGAGCTGAGATGCCAGTGCCTCCAGACACTCCAGGGCATCCAC         CTGAAGAACATCCAGAGCGTGAACGTGCGGGAGCCCTGGCCCTCATTGTGCCCAG         ACAGAAGTGATCGCCACCCTGAAGAAGGCCTGGCCTGACCCGCCC         AGCCCTATGGTGCAGAAGATCATCGAGAAGAGCCTGCCTG
110	<i>pCHA-LS-</i> <i>hCXCL4<sup>32-</sup></i> <sup>101</sup> - <i>G</i> <sub>3</sub> - <i>c</i> - <i>myc-Aga</i> 2	ATGAACCTTTCHAT DOTOL HER DOOD A HOT DOD HER DODOLIGACIONO DETA         COLCAACCOOLIAT DOTAL TACOOLOGICATO TOD HER DODOLIGACAACCOOLITE SCAC         AAGAGAGAGGCTGAAGAGGGCGCGATCTCCAGTGCCTGTGCGTGAAAACCACC         AGCCAAGTGCGGCCCAGACACATCACCAGCCTGGAAGTGATCAAGGCCGGACCC         CACTGTCCTACCGCCCAGCCGATCTCCCAGCCTGAAGAACGGCCGGAAGATCTGC         CTGGACCTCCAGGCCCCCCTGTACAAGAAGATCATCAAGAACGGCCGGAAGATCTGC         CTGGACCTCCAGGCCCCCCTGTACAAGAAGATCATCAAGAACGGCCGGAAGATCTGC         GGCGGAGGCGAACAAAGCTTATCTCCGAAGAAGACTTGCACCAACTAACAACT         ATATGOGAGCAAATOOOC JOADOAAC JTTASAATCGACGACTTCTCCAATATTAC         ACCACTATTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT
111	<i>pCHA-LS-</i> <i>hCXCL5</i> <sup>44-</sup> <sup>114</sup> - <i>G</i> <sub>3</sub> - <i>c</i> -	ATGAAGGETELGALIGEOLEGELGGOLATOLTOGOLGGOLTTGODALIGGODELA           OODCAAGOOOTTATTTOTACTACOOTDGGELGGODEGCAGAAGGCCCOCTOLGGAC           AAGAGACTGCGCGAGCTGAGATGCGTGTGCCTGCAGACCACCCAGGGCGTGCAC

	myc-Aga2	CCCAAGATGATCAGCAACCTCCAGGTGTTCGCCATCGGCCCCCAGTGCAGCAAG GTGGAAGTGGTGGCCAGCCTGAAGAAGAGCGCAAAGAGATCTGCCTGGACCCCGAG GCCCCATTCCTGAAGAAAGTGATCCAGAAGATCTGGACGGCGGCAACAAAGAG AAC GGCGGAGCGAACAAAAGCTTATCTCCGAAGAAGACTTGCB SUAACTUBUA AC DATAL SUGAUCAAATCUUTTACCAGAAGAAGACTTGCB SUAACTUBUA AC DATAL SUGAUCAAATCUUTTACCAGAUTLI AGAATUSAOGCUUTACTUTUB TCAAOGACTACTATCTTCGOOAACSGGAAGSCAATGAAGGACGTCUTUBAATAT TACAAASTUBUTAACGTTTGTCGAGTAACTGCGGGTTCTTCGAAGAACTAGC AAAGSCAGOOCCATAAACGACAGTACUSTTUTTT
112	pCHA-LS- hCXCL6 <sup>44-</sup> <sup>114</sup> -G <sub>3</sub> -c- myc-Aga2	ATGAAGGETT, GALLGET, IGLLGGCLAIC, TUSCIGO, TTSCCA, GGUCCIIA OD, CAACUUCI, IAL, TUTACI ACCUTOSCI, CUCCIGCAGAACSC, CUTTOSCA AACACACTGACCGAGCTGCGGGTGCACCTGTCTGAGAGTGACCCTGCGCGCGTGAAC CCCAAGACCATCGGCAAGCTCCAGGTGTTCCCTGCCGGCCCTCAGTGCAGCAAG GTGGAAGTGGTGGCCAGCCTGAAAAACGGAAAACAAGTGTGCCTGGACCCCGAG GCCCCATTCCTGAAGAAAGTGATCCAGAAGATCCTGGACAGCGGCAACAAGAAG AAC <u>GCCGAGCC</u> GAACAAAAGCTTATCTCCCGAAGAAGCTTGCA GGAACUUACA ACCATACTSCGAGCAAATCCCCTCAACAACGCAACCTTGCAGAGCGGCAACAAGAAG TCAACCACTACTATCTCCCCAACACCCCTCAACAACCTTGCAAATT TACAAACCACTACCTTTCTCCCGAACACCCCTCAACAACCTACT AACGCACTACTATCTCCCCAACCCCCTCAACAACCCCCCCC
113	<i>pCHA-LS-</i> <i>hCXCL7<sup>59-</sup></i> <sup>121</sup> -G <sub>3</sub> -c- <i>myc-Aga2</i>	ATGAACGETTELGALLSTALLEGELSGOLATCITUSOTGOLETEGOALLSGOLETEGOALLSGOLETEGOALLSGOLETEGOALLSGOLETEGOALLSGOLETEGOALLSGOLETEGOALLSGOLETEGOAC         SULCAACUGSLEAELTUTACEACUGTOGOLUCUSOTGOAGAAGGOLOUTTISGAC         AAGAGGETTELGALLSGOLATGTGCATCAAGACCACCAGCGGAATCCACCCC         AAGAATATCCAGTCCCTGGAAGTGATTGGCAAGGGCACCCACTGCAACCAGGTG         GAAGTGATTGCCACACTGGAAGGGCCGGAAGATCTGCCTGGACCCTGACGCC         CCCAGAATCAAGAAAATCGTGCAGAAAAAGCTG         GGCGGAGGCGAACGAAAAAGCTTATCTCCGAAGAAGACTTGCOACAACUGAACUTCTTUTCA         ACGACTACEACCACCGCAACUGGAAACUGCAACUTCTTUTCA         ACGACTACEACUTCACCAACUGGAAGGUGAACUCCACUTCTTUTCA         ACGACTACEACUTCACUACUACUCUACUCUTCCACOCUTCAACAACUTAGOAAA         COCACCCUCALAAACGUACUACUCUACUTCTTUEEETAA
114	pCHA-LS- hCXCL8 <sup>29-</sup> <sup>99</sup> -G <sub>3</sub> -c- myc-Aga2	ATG AAGSTITISATISTIC FOTUSSI ATCUTUGO FOOTUGO ACCORDING ON THE SACONA CONTRACTOR ON THE SACONA CONTRACTOR ON THE SACONA CONTRACTOR ON THE SACONA CONTRACTOR OF THE SACONA C
115	<i>pCHA-LS-</i> <i>hCXCL9</i> <sup>23-</sup> <sup>115</sup> - <i>G</i> <sub>3</sub> - <i>c</i> -	ATG

	myc-Aga2	AGCTGCGAGAAGATCGAGATTATCGCCACACTGAAAAACGGGGTGCAGACCTGC CTGAACCCCCGACAGCGCCGACGTGAAAGAACTGATCAAGAAATGGGAGAAACAG
		GTGTCCCAGAAGAAGAAGAAGAAGAAGAACGGAAAGAAGCACCAGAAAAAGAAAGGA
		CTGAAAGTGCGGAAGTCCCAGCGGAGCCGGCAGAAGAAAACCACAGGGGGAGGG
		GAACAAAAGCTTATCTCCGRAGAAGACTTGCACCAAUTCACAACTACATOUAC
		CARATOCCUTORODARCHITAGAATCOROGCUSTROTOLIHGUORACGACIROT
		ATTITOGUCAAOGGAAGGOAATGCAAGGAGTTTTTGAATATTACAAATCAGTA
		ROUTITOTOA-MAAUTCO-MUTEOTOA-DECCUCAR-DRACUACCARAGOCAC DCC
		AFAAAGACACACIAL BEELTIT <b>TAA</b>
116	pCHA-LS-	ATGAAGATTTUSAEURTOLESEURROUSECUTOOSIESCUTTQSSAEURROSEER
	$hCXCL10^{22}$	COLCAACOGOTIAILINOTACIACOGTOGGIIDOOCIGCAGAAGGUICITISGAC
	<sup>98</sup> -G3-C-	AAGAGAGTGCCTCTGAGCAGAACCGTGCGGTGCACCTGTATCAGCATCAGCAAC
	myc-Aga2	CAGCCCGTGAACCCCAGAAGCCTGGAAAAGCTGGAAATCATCCCCCGCCAGCCA
	mye nguz	TGCCTGAACCCCGAGAGCAAGGCCATCAAGAACCTGCTGAAGGCCGTGTCCAAA
		GAGCGGAGCAAGCGGAGCCCAGGCGGAGCGAACAAAAGCTTATCTCCGAAGAA
		GACTTE CARGAACE GACARCEA LA BOOGAG CAAAL COOCH CACOAACLEU AGAA
		TO GACOODSTACTO DE ESDO AROSACITACETA E EL DEGOCIA OS EGAA SISCAATO
		CARGONOTTELIGNATATERCRARTCRGENACUTELIGECONTRAFE.CCCGG. (C)
		CACCCCTCAACAACTAGCAAAGGCAGCCCCATAAACACACAC
117	pCHA-LS-	ATGAACCITICSAFICTOICFGFICCCCTTCCCALICCCIFF
	$hCXCL11^{22-}$	COLCARODOCTEREDICTRCERCOCTOGGEDOCCEECCAGAROCCOCTO XGR
	<sup>94</sup> -G <sub>3</sub> -c-	AAGAGATTCCCCATGTTCAAGCGGGGCAGATGCCTGTGCATCGGCCCTGGCGTG
	_	AAAGCCGTGAAGGTGGCCGATATCGAGAAGGCCAGCATCATGTACCCCAGCAAG
	myc-Aga2	AACTGCGACAAGATCGAAGTGATCATCACCCTGAAAGAGAACAAGGGCCAGAGA
		TGCCTGAATCCCAAGTCCAAGCAGGCCCGGCTGATCATCAAGAAGGTGGAACGG
		AAGAACTTC <u>GGCGGAGGC</u> GAACAAAAGCTTATCTCCGAAGAAGACTTGCABBAA
		CIGAGANCIA LETYOGAGGEAAL COCCTUACCARCTITAGRA LUSACGOOSTAG
		ICOTTOCCAACGACCERCTTOCGGCCAACGGGAAGGGAEGCAACGESUUTTG
		GRATATUS CARATCAUTA ACETUIUT CAGEAA TEGOSCITUT CACCUU VAACA
		ACTAGCAAAGGCAGCOOCATAAAAACACAGGCATGTTTTT <b>TAA</b>
118	pCHA-LS-	ATGAAGGTTTL GAELISTULEGELISKULAECLIKGUEGULTTGUUALLISKUUEEA
	$mCXCL1^{28-}$	COUCAACOCOTHA HITCTACHACCOT DECHICCO DECCACAAD SCUCTUT SCAC
		AAGAGAGCCAACGAGCTGCGGTGCCAGTGCCTGCAGACCATGGCCGGCATCCAG
	<sup>96</sup> -G <sub>3</sub> -c-	CTGAAGAACATCCAGAGCCTGAAGGTGCTGCCCAGCGGCCCTCACTGCACCCA
	myc-Aga2	ACCGAAGTGATCGCCACCCTGAAGAACGGCAGAGAGGCCTGCCT
		GCCCCCCTGGTGCAGAAAATCGTGCAGAAAATGCTGAAGGGCGTGCCCAAGGG
		GGAGGCGAACAAAAGCTTATCTCCGAAGAAGACTTGCAGGAACAAGACAAC
		TRUBAS CAAA UURUCHCA CUAACHTTA BAALICGA CRUCSTACLUHUUGHCAAGA
		ACTA OTA FEFTODO DRACCOCA A WKAS TO DRAGOS OTT FEFTOATA THA CAAR
		TO A 9 TRACGITUT OF CAST RATE GUOGUITOT CACCO O TO AS CAROTA SCARAOOC
		ao de catarajaca casta e cuttu <b>taa</b>
119		ATGAAGGEEEDGA EUGECU POEUSSCUA FOUECRO POU FEROOR DUSSCOPE?
±±/	pCHA-LS-	GUI CAACUSSI, FA FUTUT AC FACUET OBGE JUUSCESCA SAASSO, CUTTU SGA
	-	AACACAGAGCCAGCGAGCTGCGGTGCCAGTGCCTGAAAACCCTGCCCCGGGTGGA
	- CVCI 31-	
	$mCXCL2^{31}$	TTCAAGAACATCCAGAGCCTGAGCGTGACCCCCCCTGGCCCTCACTGTGCCCA

	myc-Aga2	GCCCCCCTGGTGCAGAAGATCATCCAGAAGATCCTGAACAAGGGCAAGGCCAAC
		GGCGGAGGCGAACAAAAGCTTATCTCCGAAGAAGACTTGCAAGAACUGACAAC
		ATAFOCOAODAAATOOODICACGAAODITTAGAAT DIACCOODI ACUOTTI JTCP
		ACGECTACTECTTCGGCCAECCGGCAEGCAEGCAEGAGTTCTTCGAATATTAC
		AAATUASEAACUTTUSECAUTAAEEGCUUTUSECAUGUOECAAGAACLAGGAA
		CCCACCCCCATARACZCACACEA ICTUFFE TAA
120	pCHA-LS-	ATGAAONINI MATERICETETERK DATOCHCCCTOCHICCCACTERCETTA
	$mCXCL3^{31}$	CUDAACCSCITATIICIAOTACCSICAGTICCCCTGCASAAGADICIIIIGGAC
	<sup>100</sup> -G <sub>3</sub> -c-	AAGAAGAGCCCCCGGGTGGAGATGCCAGTGCCTGAACACCCTGCCCCGGGTGGAC
		TTCGAGACAATCCAGAGCCTGACCGTGACCCCCCCTGGCCCTCACTGTACCCAG
	myc-Aga2	ACAGAAGTGATCGCCACCCTGAAGGACGGCCAGGAAGTGTGCCTGAATCCCCAG
		GGCCCCAGACTCCAGATCATCAAGAAGATCCTGAAGTCCGGCAAGAGCAGG
		GCCGCAGCCGAACAAAAGCTTATCTCCGAAGAAGACTTGCAAGAACCUACAACT
		ATRESOGAGORAAECOUL CACCAAULEEAGAATOSAOGOUSLACECITUSECA
		ACCENTATITTCCCCAACCCCAACCCAATCCAACCAATTCTTCAATATTAC
		ARA TCAGTARCUTTURFCA START FOCUST UNFORCESUND FORA CARO PAGOAA
		SGCAGOCCCADAACZCACAGEAISTDITE <b>TAA</b>
121	pCHA-LS-	ATGAASSEEELSAIN GEOLINGIN GGOLAINTE OGORSOLEEGOCALL GGOOTIY
	mCXCL4 <sup>30-</sup>	CC TCAN/DECE TTATENCES OT A DEFECTED CONTROL FAACCOOL DEFECTA
		AAGAAGA GTGACATCTGCCGGCCCTGAGGAAAGCGACGGCGATCTGTCTTGCGT
	$^{105}$ -G <sub>3</sub> -c-	TGCGTGAAAAACCATCAGCAGCGGCATCCACCTGAAGCACATCACCAGCCTGGA
	myc-Aga2	GTGATCAAGGCCGGCAGGCACTGTGCCGTGCCTCAGCTGATTGCCACCCTGAA
		AACGGCCGGAAGATCTGCCTGGACAGACAGGCCCCCCTGTACAAGAAAGTGAT
		AAGAAGATCCTGGAAAGCGGCGGAGGCGAACAAAAGCTTATCTCCCGAAGAAGAC
		TTGOAOGSADL GACASUTREA EGUSASCARATUUCCECACUARCE LISSARECC
		ADDOCC LEUTORACCACTACLA EL ITODOCAACOCCAACCCAA
		998 STUTTERS TATERCARATOR GERECOTTECTARTER SOCIECTOR
		CCCTCARGAACEAC/AARCCCARGACECACECACECACECACECACECACECACECACECACE
122	pCHA-LS-	ATGAAGGE E CATLOEC LTOTLOGO LATULE OGCTGULEEGO CALLOGO CTTZ
	mCXCL5 <sup>48-</sup>	GOLCARDOSSITATI, HORACTADOS FORGTLOOGCINGARAAGROLOL FLORA
	<sup>118</sup> -G <sub>3</sub> -c-	AAGAGA GCCACCGAGCTGAGATGCGTGTGCCTGACCGTGACCCCCAAGATCAA
		CCCAAGCTGATCGCCAACCTGGAAGTGATCCCTGCCGGCCCTCAGTGCCCCAC
	myc-Aga2	GTGGAAGTGATTGCCAAGCTGAAGAACCAGAAAGAAGTGTGCCTGGACCCCGAG
		GCCCCCGTGATCAAGAAGATCATCCAGAAGATCCTGGGCAGCGACAAGAAGAA
		GCC_GGCGGAGGCGAACAAAAGCTTATCTCCGAAGAAGACTTGCAGGAACUGAC
		ACTATATINGAGORAS TOCOCTOS CORACTUTAGRATORS OSCOCIA UTO ETC
		TOAACGAUTADIAI ITTOGOCAACGOGAAGGGGAALGOAAGGAGI. ELIIIGAAAA
		TACABADOAGDBACGTTTGECAGTAADESCGGTTGECACOOCLCABOAAGDBS
		ARAGCCASCCCCATAAACACACASTATCTTTTTT <b>TAA</b>
123	pCHA-LS-	ATGAASSITTUARUSTOLISIIDSSCHERCHTOSCHERCHTOSCHER
	mCXCL7 <sup>48-</sup>	GOLICARDOGGLITATILEO EACTROOGECIGUTLOOGCITSCAGRAGGULOLELIGGA
		AAGAGAATCGAGCTGCGGTGCCGGTGCACCAACACCATCAGCGGCATCCCTTTG
	<sup>113</sup> -G <sub>3</sub> -c-	AACAGCATCAGCCTCGTGAACGTGTACAGACCCGGCGTGCACTGCGCCGACGT
	myc-Aga2	GAAGTGATTGCTACACTGAAGAATGGGCAGAAAACCTGCCTG
		CCTGGCGTGAAGCGGATCGTGATGAAGATTCTGGAAGGCTACGGCGGAGGCGAA

		CARAAGCTTATCTCCGAAGAAGACTTGCAGGSACUGACASCTACACGCGAGGA ALCOCCUGCCAACUTTACAATCUGCCCCCCCUCUTCTTCTCAACGACUGCTACTAC TTOFCCAACCOFAACCCAAFCCAACCACTTTTCTAATATTACAAACCACCTACCATT TTOFCCAAGCOFTAACCCACCACCACAACTAGCAAGGCAGGCCCATS AACSCGCACAGEATCTLEEE <b>TAA</b>
124	<i>pCHA-LS-</i> <i>mCXCL9<sup>22-</sup></i> <sup>126</sup> -G <sub>3</sub> -c- <i>myc-Aga2</i>	ATG
		CTGGACCCCGACAGCGCCAACGTGAAGAAACTGATGAAGGAATGGGAGAAGAAG ATCAGCCAGAAGAAGAAGCAGAAGCGGGGGCAAGAAACACCAGAAAAACATGAAG
		AACCGGAAGCCCAAGACCCCCCAGAGCCGGCGGAGATCCAGAAGACCACA <u>GG</u> <u>GGAGGC</u> GAACAAAGCTTATCTCCGAAGAAGACTTGCACCAACTCACAACTATT TOOSAGCAACTCCCCTCACCCACCTACACTTASSALTOGACSCCCTACTCTTATCAACC ACTACTATTTTCSCCAACGCGGAAGCCAATSCAACGCGGTTTTTCGAATACTACTACAA
		TCAOTAACCEUTOT-DACEAATT-DOCCUTOT-DACCCOTOAACAACTA-MOAAACO/ AGOOOCAEDAAOACACAGASLA EGUTETEL <b>TAA</b>
125	pCHA-LS-	ATGAADSTILL BAT STC. TOT SSC. ATT. LOSCEPC. TLOCOAL SSCOTT
	$mCXCL10^{22}$ -98-G <sub>3</sub> -c-	ATCCCACTGGCCAGAACCGTGCGGTGCAACTGCATCCACATCGACGA GGCCCCGTGCGGATGAGAGCCATCGGCAAGCTGGAAATCATCCCCGCCAGCCT
	myc-Aga2	AGCTGCCCCAGAGTGGAAATTATCGCCACCATGAAGAAGAACGACGAGCAGCG TGCCTGAACCCCGAGAGCAAGACCATCAAGAACCTGATGAAGGCCTTTAGCCA
		AAGCGGAGCAAGAGGGCCCCA GGCGGAGGCGAACAAAAGCTTATCTCCGAAGAJ GACTTGOAGGAACTGAGAAACTADATGOSAGCAAATGOCCCTGAGGAAGATTGASAA
		TOGA GOODEA CHUTTTOTIGAA OBACHA UFNETT I SGUCAR OG SGAR BODAATS
		CAAGGAREEE JEGAARAELAGAAARCAGWAACGELINGTCAGRAATUROOG JEU CACCCC TUAACAAC IEGCAAAGGURGOOCCARAANCACAGAGIARGTIET H <b>TA</b>
126	pCHA-LS- mCXCL11 <sup>22</sup>	CAAGGAGE E E ITGAAE AE LECARAE CASTAROE E ITSTORGEASTIGOOG LTU
126	1	CAAGGAGETTECTGAGETCAAGGAGETTECCAAGGAGETTECCCAGGAGECGAGAGETTECCCGGCGCGCGCGCGCGGCGCG
126	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	CAAUGABEEEETUGAAEAEELAGAAAECAGUAGOELTUTOTOAGEAATUGOOGUTU CAOOOOTUGACAAOTIAGUAAAGGUAGOOCOAETAAOGELTUTOTOAGEAATUGOOGUTU AAGAOOTTUCTGATGUTCAAGCAGGGCCGGTGCCTGTGCATCGGCCCTGGAAT AAGGCCGTGAAGATGGCCGAGATCGAGAAGGCCGGCGGGGCTGTCCACCAGCAGAGGGCAGAGGGCAGAGGCCGGCGGGGCAGAAGGCCAGGGCAGAGGCCAGGGCAGAGGCCAGGGCAGAGGCCAGGGCGGGCGGGCGGC

128	LS- hCXCL2 <sup>38-</sup> <sup>107</sup> -G <sub>3</sub> -c- myc-Aga2	MKVLIVILAIPAALETALAGEVISTIVGSAAEGSIDER <b>ATELRCQCLQTLQGIH</b> LKNIQSVKVKSPGPHCAQTEVIATLKNGQKACLNPASPMVKKIIEKMLKNGKSN <u>GGG</u> EQKLISEEDLQELTTICEQIPSETLESIPYSISTITILANSKAMQGVEEVY SSVTEVSNOGSHPSITSESSPINTQEVF-
129	LS- hCXCL3 <sup>38-</sup> <sup>107</sup> -G <sub>3</sub> -c- myc-Aga2	MEVELVILLA LEXAL PLALAQEVIS TTVÖSAARGBIDKE <b>VTELRCOCLQTLOGIH</b> LKNIQSVNVRSPGPHCAQTEVIATLKNGKKACLNPASPMVQKIIEKILNKGSTN <u>GGG</u> EQKLISEEDIQELTTIDEQIPSPILLBADFASIS TTITLANGRAMQSVPRYY KSVTEVBECGGREBITGKOSEINTQYVE
130	LS- hCXCL4 <sup>32-</sup> <sup>101</sup> -G <sub>3</sub> -c- myc-Aga2	MKVLIVILALFAALFLALAGEVISTUVGSAAEGSIDAR <b>EAEEDGDLQCLCVKTT</b> SQVRPRHITSLEVIKAGPHCPTAQLIATLKNGRKICLDLQAPLYKKIIKKLLES GGGEQKLISEEDLQELTTICEQIFSPTLESTFYSISTTTILANJKAMQCVFEYY SSVTFYSNOGSHPSTTSEGSPINTQYVF-
131	LS- hCXCL5 <sup>44-</sup> <sup>114</sup> -G <sub>3</sub> -c- myc-Aga2	MAYEIVILAIFAAIPLALAQWYISTTVSSAARGSIDYR <b>LRELRCVCLQTTQGVH</b> PKMISNLQVFAIGPQCSKVEVVASLKNGKEICLDPEAPFLKKVIQKILDGGNKE N <u>GGG</u> EQKLISEEDLQEITTICEQIPSPTLESTPYSLSTITTILABORAMQCVPSY YKSVTPYSNCGSAPSTTSKGAPINTQYYP-
132	LS- hCXCL6 <sup>44-</sup> <sup>114</sup> -G <sub>3</sub> -c- myc-Aga2	MEYLIVILA FRAAL PLALACOVISTIYORAAEGS LEAR <b>LTELRCTCLRVTLRVN</b> PKTIGKLQVFPAGPQCSKVEVVASLKNGKQVCLDPEAPFLKKVIQKILDSGNKK NGGGEQKLISEEDLQELTITEECHESPILESTEYSLSTITIE AMGKAMQOVEEY YKSVIEVSBOOSHRSTISKOSRINTQZYE-
133	LS- hCXCL7 <sup>59-</sup> <sup>121</sup> -G3-c- myc-Aga2	<u>KKVLIVILAIFPALPLAIROPVISTTVISAAEOSIDKPAELRCMCIKTTSGIHP</u> KNIQSLEVIGKGTHCNQVEVIATLKDGRKICLDPDAPRIKKIVQKKL <u>GGG</u> EQKLISEEDLQELTTIOSQIPSPILESIPVSISTTITIAASSAMQCVPBYY YSYTPVSNCCSBPSTTSFCSPIRTQYVP-
134	LS- hCXCL8 <sup>29-</sup> <sup>99</sup> -G <sub>3</sub> -c- myc-Aga2	MEYLIVILA FRAAL PLALAGEVISTEVOSAARGOLF RR <b>AKELROQCIKTYSKPF</b> HPKFIKELRVIESGPHCANTEIIVKLSDGRELCLDPKENWVQRVVEKFLKRAEN SGGGEQKLISEEDLQELTITERGIESPILESTEYSLSTITIL ANGKAMQOVEEY YKSVIEVSBOOSHPSTISKOSPINTQYVE -
135	LS- hCXCL9 <sup>23-</sup> <sup>115</sup> -G <sub>3</sub> -c- myc-Aga2	MKVEHVILAIFPALPLAFAQPYIGTTVISAABOSIDKPTPVVRKGRCSCISTNQ GTIHLQSLKDLKQFAPSPSCEKIEIIATLKNGVQTCLNPDSADVKELIKKWEKQ VSQKKKQKNGKKHQKKKVLKVRKSQRSRQKKTTGGGEQKLISBEDLQEHTDIGE QIPGETIBESTPYSESTTEILANDKAMQOVPENVKSVTPVSNCCS6PSITSKCSP INTQIVE-
136	LS- hCXCL10 <sup>22-</sup>	MKVALIVILLALIPAALIPLALAQOVIISITIVOSAABSSIDAEVPLSRTVRCTCISISN QPVNPRSLEKLEIIPASQFCPRVEIIATMKKKGEKRCLNPESKAIKNLLKAVSK

	<sup>98</sup> -G <sub>3</sub> -c-	ERSKRSPGGGRQRLISERDLQRLITHCEQLPSPTLESTPYSLSTTTLLAMARAB
	myc-Aga2	QOVEEYKESVIEVERCOSEPETIEKCEPINIQAVE-
137	LS- hCXCL11 <sup>22-</sup> <sup>94</sup> -G <sub>3</sub> -c- myc-Aga2	MKVLIVILALPAALPLALAGAVISTIVASAAEGSLOKR <b>FPMFKRGRCLCIGPGV</b> KAVKVADIEKASIMYPSNNCDKIEVIITLKENKGQRCLNPKSKQARLIIKKVEI         KNF <u>GGGEQKLISEEDLQ</u> ELTTICEQIPSPTLESTPYSLSTTTILANCSAM)TV3         EYZKSVIFVSNCGSHPSTISKGSPINIQYVP-
138	LS- mCXCL1 <sup>28-</sup> <sup>96</sup> -G <sub>3</sub> -c- myc-Aga2	MEVERYLLAIFAALPLALAQWVISTTVÖSAABOSLDKR <b>ANELRCQCLQTMAGIH LKNIQSLKVLPSGPHCTQTEVIATLKNGREACLDPEAPLVQKIVQKMLKGVPK <u>GGEQKLISEEDLQ</u>KLEELCEQIPSPELLESTPISISTTTLLANGKAMQOVEEYYT SVTFVSNCOSHFSTTSKOBFINTQYVF</b>
139	LS- mCXCL2 <sup>31-</sup> <sup>100</sup> -G <sub>3</sub> -c- myc-Aga2	MKVLIVIJAIPAALPIALAOPVISTIVGSAAEGSIDKE <b>ASELROQOLKTLPRVI</b> FKNIQSLSVTPPGPHCAQTEVIATLKGGQKVOLDPEAPLVQKIIQKILNKGKAN <u>GGG</u> EQKLISEEDLQELTTICEQIFSPILESIFYSISTITILAROKAMQOVEEN SSVIFYSNOGSEPSITSEGSPILTQYVE-
140	LS- mCXCL3 <sup>31-</sup> <sup>100</sup> -G <sub>3</sub> -c- myc-Aga2	REVELVEEA FRALPLALAGEVES FEVOGAARGS EKKR <b>ASELROQOLNTLPRVI</b> FETIQSLTVTPPGPHCTQTEVIATLKDGQEVCLNPQGPRLQIIIIKKILKSGKSS <u>GGGRQKLISEEDIQ</u> EETTIOOOOLESPILESTEMSESTTIIIANGAAMQSVEET KSVIEVSHCGSEPSITEKGSPINTQYVE-
141	LS- mCXCL4 <sup>30-</sup> <sup>105</sup> -G <sub>3</sub> -c- myc-Aga2	MKVLEVILAIPAALPLAERQPVISTTV9SAAEGSIDKP <b>VTSAGPEESDGDLSCV CVKTISSGIHLKHITSLEVIKAGRHCAVPQLIATLKNGRKICLDRQAPLYKKVI KKILES<u>GGGEQKLISEEDLQ</u>SETTECEGIPSPTLESTPYSLSUTTILANGEZER GVEEYYKSVLEVGNO9SHPSTTSK9SPINTQIVE-</b>
142	LS- mCXCL5 <sup>48-</sup> <sup>118</sup> -G <sub>3</sub> -c- myc-Aga2	MEVETVILLA IFZAL PLALAOPVISTIVOSAAEGSIDVE <b>ATELROVCLIVTPKIN PKLIANLEVIPAGPOOPTVEVIAKLKNOKEVOLDPEAPVIKKIIOKILGSDKKI AGGGEORLISEEDLO</b> EITTIGEGIPSPILLESTYYSLETTITIANGLAMOOVPE YKSVIEVSBOGSRESTISKESPILETGYVE-
143	LS- mCXCL7 <sup>48-</sup> <sup>113</sup> -G3-c- myc-Aga2	MXVLIVILAIFAALFLAINOSVISTIVOSAAEGSIDRPIELRCRCTNTISGIPI NSISLVNVYRPGVHCADVEVIATLKNGQKTCLDPNAPGVKRIVMKILEGY <u>GGG</u> QKLISEEDLQELTTICEQIFSPILESTFYSLSTITILANGAAMQGVFETTESV FVSNGGSRPSITSKSSPLNTQXVE-
144	LS- mCXCL9 <sup>22-</sup> <sup>126</sup> -G3-c-	MUVLINILALEMALPLALAGEVISTIVISAAMOSIDKETLVIRNARCSCISTSI GTIHYKSLKDLKQFAPSPNCNKTEIIATLKNGDQTCLDPDSANVKKLMKEWEKI ISQKKKQKRGKKHQKNMKNRKPKTPQSRRRSRKTT <u>GGG</u> EQKLISEEDLQ

	myc-Aga2	CECIESPILESTEX SLSTITILANGKAMQOVEENNS SVIEVSMOOSHPSTIESC SPINTQVVF-
145	LS- mCXCL10 <sup>22</sup> -98-G <sub>3</sub> -c- myc-Aga2	MKVLIVILAIPAALPIALAOPVISTIVOSAAEGSIIAKA <b>IPLARTVRCNCIHIDD</b> GPVRMRAIGKLEIIPASLSCPRVEIIATMKKNDEQRCLNPESKTIKNLMKAFSQ KRSKRAP <u>GGG</u> EQKLISEEDLQEIITIIDEQEPSETIESTEYSESITTIILABIKAM QOVFENYKSVIFYGNOGSHPSTIFROSPINICYVF-
146	LS- mCXCL11 <sup>22</sup> -100-G <sub>3</sub> -c- myc-Aga2	MNVEIVILLAIEMAIPLALAQPVISTIVSSAAEMEIDKE <b>FLMFKQGRCLCIGPGM KAVKMAEIEKASVIYPSNGCDKVEVIVTMKAHKRQRCLDPRSKQARLIMQAIEK KNFLRRQNM<u>GGG</u>EQKLISEEDLQELTIICEQIPSFTLESTEYSLSTTTELANOK AMOGVPEYYKSVTEVSUCGEAESTISKASEIDTONVE-</b>
147	pCHA-LS- hCXCL1- G3-c-myc- Aga2	ATGAAGGTTITGATTGTCTTGTTGGCTACCTTCGGTGCTTTGGCA TTGGCGTTAGCTCAACCGGTTATTTGTAGTACGGTGGGTTGGGT GCAGAAGGCTCTTTGGACAAGAGAGGCCACCGAGGCTGAGATGCCAG TGCCTGCAGACCCTGCAGGGCATCCACCCCAAGAACATCCAGAGC GTGAACGTGAAGTCCCCTGGCCCCCACTGCGCCCAGACCGAAGTG ATCGCCACCCTGAAGAACGGCCGGAAGGCCTGCCTGAACCCCGCC AGCCCCATCGTGAAGAACAGCGGCGGAAGGCCTGCTGAACAGCGAC AAGAGCAAC <u>GGCGGAAGACCGCGAACAAGGCCTGCCTCACCAAGCA</u> TTGCAGGAACTGACAACTATATGCGAGCAAATCCCCTCACCAACT TTAGAATCGACGCCGTACTCTTGTCAACGACTACTATTTCGCC AACGGGAAGSCAATGCAAGGAGTTTTTGAATATTACAAATCAGTA ACGTTTGTCAGTAATTGCGGTTCTCACCCCTCAACAACTAGCAAA GCCAGCCCCATAAACACACAGTATGTTTTTT <b>TAA</b>
148	LS- hCXCL1- G3-c-myc- Aga2	MKVLIVLLATFAALPLALAOPVISTTVGSAAFGSLDKPATELRCQ         CLQTLQGIHPKNIQSVNVKSPGPHCAQTEVIATLKNGRKACLNPA         SPIVKKIIEKMLNSDKSN <u>GGG</u> SQKLISECDLQELTTICEQIFSPT         LESTFYSLSTTTLLANGRAMQGVEEYYKSVTEVSNCGSHPSTTSR         GSPINIQYVF-
149	mouse SA- (Gly4Ser)3- scFv (VL- VH) CK138	ATGSAAGAAAAACCGAAGAGTGAGAACGAAACTACCGAGAGAACAA CAUTTURAAGGCCTAGTCCTGAUTGCCCAUCGGAGATCGACCAGAACAA TACCATGACCATCCCGAACTGUGACAAACACACCTTTCCGAAAGACCTCT GTUGOGGTGAGTCUGCCGCGAACTGUGACAAATCOOTUCACACTCUUTUGGA CALAAGUTGTCIGCCGCGAACTGUGACAAATCOOTUCACACTCUUTUGGA CALAAGUTGTCIGCGCGAACTGUGACAAATCOOTUCACACTCUUTUGGA CALAAGUTGTCIGCGCGAACGACGACGAACTACCACACTCUUTUGGA CALAAGUTGTCIGCGCGAAAGAAACGAATGTTCCCTCAACUUCCUGC TGCTGTAAAAAACCAAGACCCGAAAGAACGAATGTTTCCCTGCAACACAAAAGAT GACAACCCCGACCGAACGACGACGACGACGGCUALGIGCGUG TCCTTTAAGGAAAACCCAACGACCTTCUTTCATCCATCAACUUCCC AGAAGACCCCCACCGCCGAAGAACTTCUTTACTATCCTGAGCGCGCGAGAGTCC AACGACCCCCCCCCC

		CCCARCOTTCATCCTOTCASCCAJAAACCACHCCTCATCTCUCCOTCACACA
		ATCANGLUUTCONGLATUCAGAAUTTICGAUAGAGAGCI TTTAANGUATUCGCA
		CTRECTOTOTORCOACACATICOCORATOCTORCETTICOACEAATORCIAAA
		TTSSCAADAGACCHGADGABGUDAACEBGGAGTSCH9CDATSGHGADDI SCHG
		GAATSUSCAGATSACAGGUGGAACI ISUUAAGIAUATGIGIGAAAACCAGGUG
		actatotecagoahactgoagactigotgogataaaooactgitgaagaaagoo
		CACTETUTIAETEAGUIGAECAIGACCAIGCCTECIGATCIECCIGCCATT
		COLECTION CATTLEGE DOAC FACCACODAN FEODOCANEAAC TAT SCEGACOO DAAG
		GATISTETTYOETISSGENOGTTETTETATISAATATTEXAGAAGAERENCEOTGATTAC
		HOUCTACCCCCCTT DE CACACITUC DA CARA HATCAR DE CACTOD DE AAAC
		TGOTEOSCTGANGOCIATOOTOCOSCATECTIA COGONONSTGOTTOCTISA ATTT
		CASCO ECHTUL AGAAGAGOO EAAGAACE EGGEUAAAACCAACL GEGALULL EAC
		CASKAGOTTOSAGANTATOSANTIODAAKAHOMMATEGEAMTEGGULMMAGSGAG
		AAASUADD ECAGGTGE CAACUDDAAC LUTUGE GGASBOL GCAAGAAADD LAGSA
		AGAGTO DEVACORADISTICTR JANFICOT PAGATOR FAGACIOO UTO DOTO
		GAAGACTE NUTGTOTISCRATOOTISAACOGTGTGTGTGTGTGTGCATGASAAGACO
		CONFIGNOTONSCATOTTACCANOTOCHCHACTOCATCCOTOCUCCAAAC XCCC
		ooa escuroz descuorea casutea usa a acata ese coccasa santicida a
		GC ISAGACCE ISACCE ECCASITO EGA LETUL COACAUTL COAGEGAGGAGEAG
		CAGATTANGANACAARCOGOTOUIGCUGAGCIGGUGRAGCACAAGOCCAAGOOT
		ACAGOGGAGCAACEGAAGACEG ICATEGAEGACHI EGCACAGUI. CO ICGALACA
		TOURCEASOOD COUCACERCECES OF COUTOR DESCUCES OF COERE OT F
		GTCACERGATGUAARGACGUCELAGGU <b>GGTGGAGGGCTCTGGTGGAGGCGGT</b>
		ACCCCACCCCACCCTCCGCTATCCAGATGACCCGGTCCCCGAGCTCCCTGTCC
		GCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
		GGTTCTGCAGCCTGGTATCAACAGAAACCAGGAAAAGCTCCGAAGCTTCTGATT
		TACGGTGCATCCTACCTCTACTCTGGAGTCCCTTCCCGCTTCTCTGGTAGCCGT
		TCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGACTTCGCA
		ACTTATTACTGTCAGCAATCTTCTTATTCTCTGATCACGTTCGGACAGGGTACC
		AAGGTGGAGATCAAAGGTACTACTGCCGCTAGTGGTAGTAGTGGTGGCAGTAGC
		AGTGGTGCCGAGGTTCAGCTGGTGGAGTCTGACGGTGGCCTGGTGCAGCCAGGG
		GGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTTCAACCTCTCTTACTACGGT
		ATGCACTGGGTGCGTCAGGCCCCGGGTAAGGGCCTGGAATGGGTTGCATACATT
		GCTTCTTACCCTGGCTACACTTCTTATGCCGATAGCGTCAAGGGCCGTTTCACT
		ATAAGCGCAGACACATCCAAAAACACAGCCTACCTACAAATGAACAGCTTAAGA
		GCTGAGGACACTGCCGTCTACTATTGTGCTCGCTCTGGTTACAGTTACTCTCCG
		TATTATTCTTGGTTCTCTGCTGGTATGAACTACTGGGGTCAAGGAGCCCTGGTC
		ACCGTCTCCTCGTGATAG
150	mouse SA-	ATGUSARSCACAUARSAG IDAGAS COCUAL COG LATARS GA LITERSSAGASUA
	(Gly4Ser)3-	ACATTE CARACOODIAGECOTOATECCCTTTECCCSCTATCECCACARATCOTO
		AINOSAUJAGOA TECCARATTA SIGCAGSAA SIANOA SA CITUGOA AS SA OSTE
	$scFv (V_L-$	THE FOCUARSASE CREESOCASCHEESACEAAL COLLICACACE CUTTLESS
	<i>V<sub>H</sub></i> ) <i>CK157</i>	AGAHAAGIYOTSIGOOATTOCKAAQOTOOGTQAAASCHAFGOTSASOTSGS
		CEGUISI, ACAABADAAGAGUUGAAAGBAAGBAA INITI, OO EGUAACAAABA
		CADOTIO FACTO ACCOADA ACCOADA ACTURADO ACCOADA COMO TO
		CHOCTTURASGARASOCOACUTUTATESSACACTATHTOCOCCERASUTOC
		CA-MAGAGAR OUTEATT CHAEGOOD CAGAACTT CHTEACTAL WITGAGGAGEA
		CAATSAGATTCESACOOASESTUOTOCESAGOODESECAAGGAASECUROCUSAC
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		CCACAACOTTECCACAATATCCATTCCAAAATCCCATTCTACTTCCCCTACACCCA
		GAAAGCACCECEGELGECCAACCCCCAACCUCCEGEGECEGCAAGAAACCLAEG
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		TTATTACTGTCAGCAACCATCTCATCTGATCACGTTCGGACAGGGTACCGAGGT
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		ACTCCGTTTGTCCTGTGCAGCTTCTGGCTCCAACCCCTACTACTACGGTGGTAC
		GCACTGGGTGCGTCAGGCCCCGGGTGAGGAGCTGGAATGGGTTGCATCTATTGG
		TTCTTACCCTGGCTACACTGACTATGCCGATAGCGTCAAGGGCCGTTTCACTAT
		AAGCGCAGACACATCCAAAAACACAGCCTACCTACAAATGAACAGCTTAAGAGC
		TGAGGACACTGCCGTCTATTATTGTGCTCGCCATTACTACTGGTACGATGCTAC
		TGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGTGATAG
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151	mouse SA-	ATGUAAGOACACAAGAGTUASAUOGOCCATOGGTATAAUGATUUSQGAGAACAA
151	mouse SA- (Gly4Ser)3-	CALTTURARGUUT REFOURELLEGOUTETLECCASTAL CTOURGRATEURUR
151	(Gly4Ser)3-	CALTEURAAGGUUTAGEOURALEGOUETELCOCASEAL CEOLAGAAAEGUIUA ERCOAT-DACCAEGODAAETRACCENACGAA/FERCORAASACOTOT
151	(Gly4Ser)3- scFv (VL-	CALTECAAAGGUUTREEOUEGALTEGOUTETLECCOASTAL CECUASARAEGUEUA TACCAE PAGCAEODAAA TEACEGOAASTAACAGAADEEECGAAAJACCEEC GEDROOSEEGAREOEGOCAASTGDRAGAAAECOREECACAETCEEEEEGA
151	(Gly4Ser)3-	CALIFIC RAAGGUIT REFOUTGAL FEOLITITICOCASTAL CHOLAGARA FEUTUR FACCAT CROCATOD CARA DIACUDO A CORACTAR CACACUTTEC CARACTACOTOT GUIDROOGE FERRITOTISCOROCAEUTECERE ATOROTIC CAC NOTOTITUT LEGA GAL ARG LIGIGE SOCATICOCARA ULTOOGE GAAAROTAL GETERACUTSCL GRO
151	(Gly4Ser)3- scFv (VL-	CALTTURAAGGUUT AGTOUTGALTGOUTTULOOCAGTAL OTOUAGAAATGUTUA TACCAT-SAGCATCO-SAAA DTACUSUACCAACTAACACACATTTECCAAASACOTOT GTUGOOSATGAGTOUSUCGOCAACTGUGACCAAATCOOTUCACACTGUUTULOGGA GALAAG JIIGIIGI GCCATTOOAACUTOOGI GAAAROTALGGUGAACJIGGULGAC TGUTGI ACAAAA CAAGACCCCGAAAGAXACGAATGUTUCOTGCAACACAAAGAT
151	(Gly4Ser)3- scFv (VL-	CALIFIC RAAGGUIT REFOUTGAL FEOLITITICOCASTAL CHOLAGARA FEUTUR FACCAT CROCATOD CARA DIACUDO A CORACTAR CACACUTTEC CARACTACOTOT GUIDROOGE FERRITOTISCOROCAEUTECERE ATOROTIC CAC NOTOTITUT LEGA GAL ARG LIGIGE SOCATICOCARA ULTOOGE GAAAROTAL GETERACUTSCL GRO
151	(Gly4Ser)3- scFv (VL-	CALTTURAAGGUUT AGTOUTGALTGOUTTULOOCAGTAL OTOUAGAAATGUTUA TACCAT-SAGCATCO-SAAA DTACUSUACCAACTAACACACATTTECCAAASACOTOT GTUGOOSATGAGTOUSUCGOCAACTGUGACCAAATCOOTUCACACTGUUTULOGGA GALAAG JIIGIIGI GCCATTOOAACUTOOGI GAAAROTALGGUGAACJIGGULGAC TGUTGI ACAAAA CAAGACCCCGAAAGAXACGAATGUTUCOTGCAACACAAAGAT
151	(Gly4Ser)3- scFv (VL-	CALTTURAAGGUUTAGTOUTGALTGOUTTULOOCASTALOTOUAGAAATGUTUA TACCAT-SAGGATOOSAAGTACCESCACCAGTAACACACETTECCAAASACOTOT GTUGOOSATGAGTOUGUCGOONACTGUGACAAATOOOTUGACAOTOUTTUUGGA GALAAGITETTGUGCCATUOGAAGUUTOOGUGAAAAOTALGETGAACIISGUGACA TGUTGTAOAAAGCAAGAGCCCGAAAGARACGAATGTTTUCOTGCAACAOAAAGAT GACAADOOCAGUUTAOCACCATUUGAAGGOCAGAGGULGAGGUUALGUGCAC
151	(Gly4Ser)3- scFv (VL-	CALTTURAAGGUUTAGTOUTGALTGOUTTURCCAGTAL CTOUAGAAATGUTUA TACCAT-SACCATOUGAATTACUSCACCAAUTAACACACUTTUCCAAAGACOTOT GTURCOGATGAGTOUGUCGOOAAUTGUGACAAATCOOTUGUCACAOTOUTTURGA GALAAGIITGTGE GOCATTOOAAAUUTOOGE GAAAACEA IGGTGAACIIGGUI GAC TGUTGTACAAAAGCUGGAAAGAAACGAATGTTECCOTGUAACAAAAGAT GACGAGOOCAGUUTAOCACCATLE GAAGGGOOAGAGGUI GAGGUUAL GEGGAUC TCOTTTAACCAAAAGCCCAACACUTUCATOGUACAOTACUTUCCATCAACUTICOO

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		GAGAAGCTIGGAGAATATGGAL JUUARAALGUUAL LOLASTITOGOLAGAGOGAG
		AMAGGACOTCAGGECTOMACCCCANCECCTCOCOGGCECOMAGAAAOOEAGGA
		AGAGTGGGGACCAAGEGELIGTACACELICUTGAAGATCAGAGCTGCCLEGIGTG
		GRAGACTA HOTOTOTOWA A TOOTGAA COOT SHEHOTOT STEGGATOA GAGO
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		TSLEGCAAGGEECINACAAGGAUACCEGCUTUTCGACUSAGGECCAAACCEE
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		AGCGGAGGCGGAGGGTCGGCTATCCAGATGACCCGGTCCCCGAGCTCCCTGTCC
		GCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
		GGTTCTGCAGCCTGGTATCAACAGAAACCAGGAAAAGCTCCGAAGCTTCTGATT
		TACGGTGCATCCTACCTCTGCGAGTCCCTTCCCGCTTCTCTGGTAGCCGT
		TCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGACTTCGCA
		ACTTATTACTGTCAGCAATCTTCTTATTCTCTGATCACGTTCGGA %%CCGGTACC
		AAGGTGGAGATCAAAGGTACTACTGCCGCTAGTGGTAGTAGTGGTGGCAGTAGC
		AGTGGTGCCGAGGTTCAGCTGGTGGAGTCTGACGGTGGCCTGGTGCAGCCAGGG
		GGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTTCAACCTCTCTTACTACGGT
		ATGCACTGGGTGCGTCAGGCCCCGGGTAAG®GCCTGGAATGGGTTGCATACATT
		GCTTCTTACCCTGGCTACACTTCTTATGCCGATAGCGTCAAGGGCCGTTTCACT
		ATAAGCGCAGACACATCCAAAAACACAGCCTACCTACAAATGAACAGCTTAAGA
		GCTGAGGACACTGCCGTCTACTATTGTGCTCGCTCTGGTTACAGTTACTCTCCG
		TATTATTCTTGGTTCTCTGCTGGTATGAACTACTGGGGTCAAGGAGCCCTGGTC
		ACCGTCTCCTCGTGATAG
		ACCOLOCICATAC
1.50		λ. Δ.
153	mouse SA-	ATGGAAGGACACAGAGTGAGATGAGCCCATCGGTATAAUGATUUGGAGAACAA
	(Gly <sub>4</sub> Ser) <sub>3</sub> -	OA UTITURAAGGUUT REPOUTERIL PECCITITU COCA STAL OTOLA SARA TOUTUR
	$scFv (V_L-$	TACCAT/JACCATCO/JAAN/JTACU/CACCAA/JTAACACA/JTTTCCAAA/JACCTCT
		GELBOOGA IGAATOLISCOGODAACTGUBADAAA EODATLOACADTOLIELEBBA
	<i>V<sub>H</sub></i> ) <i>CK138</i> -	GALAAG LEGTGE GOOSTTOOAAG CUTOOGE GAAARO EA LIGTTGAAO LIGOL GAO
	ds2	TOCTUT MOADAS CRAGAGOCCCGARAGASACGARTSTTTCOTOCSACAOADAGAT
	$(V_L 43^{A>C} /$	GACAADDOCAGUUTACCACUATU EGAAAGGOCAGAGGUU GAGGUUAL GEGCADD
		TCOTTTAP COARAA SCOR ACCA SCTUTATO SCAC ACTACI UTCO ATCAA SUITCOO
	$V_H 105^{Q>C}$ )	AGAAGACE EUCTTATETUTATGUTUN AGAACEEUTTAGEATGOTGAGUAGTAC
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		UTACCTOUTUTCACCUAURCATIUCUCAATOUTUACTTI UURCAARTURUCAAR
		TT FROAAGACACCEGS CCAAAGTCAA CAAGGS OT REEGC GAT DE GS COT REEG
		GAATSCONGATSROAGGSCSGAACTISCCAAGTACATGTGTGAARACCASGSCG
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		CALIFIC TROCT SUCCESSION TO TATISAA LA TETA AGA CA SA COTOAL FAC
		TO INTROCOUNT SOTOR MAUTORIAN CARTA TRANSCOR DE COLONI, PRO
		FOOTOD FOTGAADD FRAHOOTD DOGCATCOLROGCCADASHOC TTO FUGRATIT
		CARCOTOTIONARASARCOTAASAACTIOSTCAAAACCAACTIOTRANCIUMTAC
		GAGAAGCHTGGAGAATAHGGALLUUAAAALGUUALLOLAUTTOSOLAUACIOAG
		AAAOCAODDAGUTOPAACCCOAACTUTCOTOCAGCUTODAAGAAADDIAGGA
		AGAGTOGGGACCAAGEGELCTACACELCUTGAAGATUAGAGACTOCOLEGICTG
		GRAGACUA FOUCIDUMRA ICOLUAACOCU DEGECICU DEGECICAGACACOC
		CCASTGAUNGAGCAUNTACCAAUNGCTGTAUNGCATCCUNGSDGGAAAGGCGG
		OCAFOCUTOT DEOCUCTORCAGUTORCGARAGAGTATOTOCOCCARAGAGTCURRA
		OCTUAGAOCTTUACOTTUACUTORAUA ECTROAUAUETOCA GAGAAGAA GAAGA
		CAGETTAAGAASEGAAACGCUTULI GO LUADOI GO LUAAQQACAAGOOQAAGGUT
		acagogsagcaadigsagronducategraigs chutegsagroupgessanaa
		TSLEGGAAGSCEGCISACAAGGACACCEGCITUTCGACLGASSGECCAAACCEE
		CTEDACTACAR DOAAACAC CONTENACE COCCOGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
		AGCGGAGGCGGAGGGTCGGCTAGCGCTATCCAGATGACCCGGTCCCCGAGCTCC
		CTGTCCGCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
		CACGACGGTTCTGCAGCCTGGTATCAACAGAAACCAGGAAAA
		CTGATTTACGGTGCATCCTACCTCTACTCTGGAGTCCCTTCCCGCTTCTCTGGT
		AGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGAC
		TTCGCAACTTATTACTGTCAGCAATCTTCTTATTCTCTGATCACGTTCGGACAG
		GGTACCAAGGTGGAGATCAAAGGTACTACTGCCGCTAGTGGTAGTAGTGGTGGC
		AGTAGCAGTGGTGCCGAGGTTCAGCTGGTGGAGTCTGACGGTGGCCTGGTGCAG
		CCAGGGGGGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTTCAACCTCTTAC
		TACGGTATGCACTGGGTGCGTCAGGCCCCGGGTAAGGGCCTGGAATGGGTTGCA
		TACATTGCTTCTTACCCTGGCTACACTTCTTATGCCGATAGCGTCAAGGGCCGT
		TTCACTATAAGCGCAGACACATCCAAAAACACAGCCTACCTA
		TTAAGAGCTGAGGACACTGCCGTCTACTATTGTGCTCGCTC
		TCTCCGTATTATTCTTGGTTCTCTGCTGGTATGAACTACTGGGGT M%CGGAGCC
		CTGGTCACCGTCTCCTCGTGATAG
154	mouse SA-	ATGSAAGAAA SAAGASTSA SATOSOCCATOSSTATAATISATI TSGGASAACAA
1.04		ATGODAY PERSONAL APPOCATOR PERSONAL APPOCAT
	(Gly4Ser)3-	
	$scFv (V_L-$	FROCATOR CONTROL CARACTERCE CORRESPONDENCES CARACTER CONTROL CONTRO
	V <sub>H</sub> ) CK157-	GETGOOSATGAGTOTISCOGODAACEGTAGAAAECOOFTICACAOTOTITETEGGA
1		GALAAG ITETEE GOCATTOOAAADUPOOG EGAAAO EA LEETGAAO IEGOL GAO
	dal	
	ds1	TOCTSTROAMASCANGAGCCCGRAAGASACGAATSTTTCOTOCSACAGAAASAT
	$(V_L 100^{Q>C} /$	GACAADDOCAGUUTACCACCAITLEGAAAGDOCAGAGGUL GAGGUUAL GEGCAUD
		GACABODDCAGCUTADCACCATLEGAABGODAGAGGULGAGGULLGEGCAUD TCCTTTAACGAAABOCCARCCACCATTATCOGACACTATTFCCATCAACUTCCC
	$(V_L 100^{Q>C} /$	GACAADDOCAGUUTACCACUAIL EGAAAGGOCAGAGGUL GAGGUUAL GEGCAUD TCCTTTAPCGAAAADOCRADQADOTTTATOSPACAQTACTTCCATCAPCUINCOC RIGRAGACATCCTTATTTCCATGCUCCAGAACTTCCTTACTATGCTGAGCAGTAC
	$(V_L 100^{Q>C} /$	GACABODDCAGCUTADCACCATLEGAABGODAGAGGULGAGGULLGEGCAUD TCCTTTAACGAAABOCCARCCACCATTATCOGACACTATTFCCATCAACUTCCC

		TTOPCAACACACCEC&OCARACCCAACTACC&CTOUTCCCATOUTCACCCOCCCTC CAATSCGCAGATSACCGGGGGGGGGGGGGGGGGGGGGGGG
		GUIGOT GATTET DET EGAGGACCA SGARGTGESCARGAN TATGOT GASSOCAAG CREDTCUDOCUSCOS COLECTED TATGAA DATTETA GAA CA-DACCODORETAC
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		CAGATTRAGAAAURRACGGUTUL EGUISAGOLGGUIGARGCACAAGUUT ACAGOGSEGCAACTGEAGAOTOTUSTGGATGEUTUTGGACAGUIOOCUGGADAOA TGLEGCAAGOLEGCUGADAAGGACADDEGCUTUTCGACUGAGGEGECCAAADDEE
		CTOTACTACATONAAACAD DOCTIDACDO <u>GGTGGAGGAGGCTCTGGTGGAGGCGGT</u>
		AGCGGAGGCGGAGGGTCGGATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCC
		GCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
		GGTGTAGCCTGGTATCAACAGAAACCAGGAAAAGCCCCGAAGCTTCTGATTTAC TCTGCATCCTACCTCTACTCTGGAGTCCCTTCTCGCTTCTCTGGTAGCCGTTCC
		GGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGACTTCGCAACT
		TATTACTGTCAGCAACCATCTCATCTGATCACGTTCGGA
		GAGATCAAAGGTACTACTGCCGCTAGTGGTAGTAGTGGTGGCAGTAGCAGTGGT
		GCCGAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGGCTCA CTCCGTTTGTCCTGTGCAGCTTCTGGCTCCAACCCCTACTACTACGGTGGTACG
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		AGCGCAGACACATCCAAAAAACACAGCCTACCTACAAATGAACAGCTTAAGAGCT GAGGACACTGCCGTCTATTATTGTGCTCGCCATTACTACTGGTACGATGCTACT GACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGTGATAG
155	mouse SA-	ATGRAAGUAGAGAAGAGTRAGA JUGODOA EOGUTAERA LUAIT. LIGGAGAACAA
	(Gly4Ser)3-	CACHTCAAACARCEACTOCHEACTCCCHTECCCCRFFACCTCCACAAATCCFCA
	$scFv (V_L-$	TACSATGAGGATGJGAAALTAGJGGAGGAAGTAAGAGACTTEGGAAAGAGJTGT Aunggguts in natoriji nagogga natiriji na gana taggats in nagogutu ngga
	V <sub>H</sub> ) CK157-	GERCOODEAEGACEDERCCOCCAASEGECACAAAECCOCEEGACACECEEEEECCA GARAACEEGECACECCAAAACECECAAAAACECCOCEEGAAACEACEGACEGACE
	$ds^2$	TGCESEACAARACAASASOOOGAAAGAAACGAATGEEECCTSCAACACAARGAE
	$(V_L 43^{A>C} /$	GACAACCOCASCCEACCASCTEGAAAGGCCAAGAGGCCACGTGCACC
	$(V_H 105^{Q>C})$	ECCTTTAAGGAAAACCCAACUACCEELATSGGACACTALEEGCATGAAGLEGUC AGAAGASAFCCTTATTFCTATCSSCCAGAASTFCTTTASTATCGTCASCAGTAG
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		ACUMPCIDOAGCAARATGCAGAATTGCTGCGATAAACCAATGIIIGAAGAAAGCC
		CACINICI FACTURES EGGEGUALGACEUCALGOCIGULGA ECISCOL SOCATI
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		TOCISCOTOASGCCATCOTOCOGCATGOTACOSCACASTOCITSCOSAATIT
		CACCCT DETCUBCRA-FACCOTRA-FACCTTO DECAGAGO DESCUCTORUCULTRA
		GAGAAGCIIIGGAGAATAIIGGAMACCAAAAIGCCAIIIMIAGUICGANACACOOAG
		AAAGCACUTCAGGIGTCAACCCCCAACLCTCCTUUAGGACUURGGA
		ACAGEGCACACCCATEGEACACTECECAACAECACACAECECCETEEG
		GAAGACLA EC IGTOL SCAATUCL GAACOGTGE GEGTUTSCEGCATSAGAAGACO
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		TETTECAS GEORGEUGACAAGOACA COTGETTETERA OLGAGESTECIAA COTT
		CTCACEAUAUSCAAAUACSCCELLAUCC <u>GGTGGAGGAGGCTCTGGTGGAGGCGGT</u>
		<u>AGCGGAGGCGGAGGGTCG</u> GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCC
		GCCTCTGTGGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
		GGTGTAGCCTGGTATCAACAGAAACCAGGAAAA ???CCCGAAGCTTCTGATTTAC
		TCTGCATCCTACCTCTACTCTGGAGTCCCTTCTCGCTTCTCTGGTAGCCGTTCC
		GGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGACTTCGCAACT
		TATTACTGTCAGCAACCATCTCATCTGATCACGTTCGGACAGGGTACCGAGGTG
		GAGATCAAAGGTACTACTGCCGCTAGTGGTAGTAGTGGTGGCAGTAGCAGTGGT
		GCCGAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCA
		CTCCGTTTGTCCTGTGCAGCTTCTGGCTCCAACCCCTACTACGGCGGTACG
		CACTGGGTGCGTCAGGCCCCGGGTGAGGAGCTGGAATGGGTTGCATCTATTGGT
		TCTTACCCTGGCTACACTGACTATGCCGATAGCGTCAAGGGCCGTTTCACTATA
		AGCGCAGACACATCCAAAAACACAGCCTACCTACAAATGAACAGCTTAAGAGCT
		GAGGACACTGCCGTCTATTATTGTGCTCGCCATTACTACTGGTACGATGCTACT
		GACTACTGGGGT XXXCGGAACCCTGGTCACCGTCTCCTCGTGATAG
156	mouse SA-	ATGGAAGUAGACAAGAGIGAGAUUSUCCAICSGIAFAAUSAIUOGGGAUAACAA
	$(Gly_4Ser)-V_L$	CAUTTCARAGEOGTA SICCIER DISCOTTI DOCUMENTI CIUCAGRARISOTOR
		TA-DIATCCCATCCCCAACTACTCCA/DIAACDAA/JACACTTT-DIAAACAC TTU
	CK157	GENERAL SECTOR CARCES AND ANTER CRAATER CHILDEN TO THE SEA
		CA DAACT FOF CECC DA FECCAAACC FOODT CAAAS CTAT COFCAACT COC DOAC
		TSOTETA CAARACAA SAGOOOBAA3 GRAROSAATETTTE CTSO ARCA CAARACAT
		SACAACCUUASCO LACUACCA E ITSARAGCUASAGGO I SAGOCCA ISTS CACC
		TOSTEE AAGGAAAACOONACCACOTTEE EGGGACACEAE FEGGATAAGTEGCC
		AGAAGADA FOOTTALE FOLATOOOCAGAADE FOLTTACEA FOOTGAGGAGTAC
		ARTICACATECTICACIOCECECECACACIOCECECACAACICACICACICACIC
		COGAAGUTIGATGGUJIGAAGGAJAAAGCAUIGGTOTGAIOTGCOGULAGAGA
		AR-PACTOOT COACES TO CACAGACITY COACECS TAGOET TTAAACCETC SOCA
		GTASCHORTOUSAGONGACAHUGOOCAAHGOTGACHHURONSAAAHONOCAAA
L	1	1

		THOOCAACACCOT PACCASACT CAACABO PACTODO ATCOTCACCTOOTC
		CARFOCCIACATORCECCOCOCAECTTOCCAECTACETCTCCAEBACUACOCO
		ACTATOROGA DIAAACTO DEFACTTO FECCATRARCCA CTC: FEAACAARCCC
		CACESIOTAGISAGATOGASCATOACACOATOCISCIOATCISCOCOCAET
		CONSUMPLY FIRST GAGGECCARGAACINE FOASBACEA FOUTGARSCOLAAG
		GADGTOTECCTGGGCACGTTOTEGTADGAACZTTOARGAZGACAOCCTGALTAC
		TUTETA TUCUTETEGUTOAGACTIGUTAAGAAATAPEAAGUCACTCIGGARAAG
		TO TECCTORRECORD STCCCCCRETCE CONCRETCE TO TECTORATTE
		CAGCUTCTTGUEGEAGAGCUTEANGARCUTUGETCAALAUCARCUSTGACCUUTTAU
		GROBAC STTCCBCBARTATCCATTCCBABBT SCCRTTCTBSTTCCCCTBCBCCBC
		AAAGAACCECKGGESECAADDOCAACIIDEDGEGGGGGGGGGAAGAAACCIIAGGA
		AGAGEGGGGACCAAGTUTLGEACSUTLCCEGSAGAECAGSGACLGCCTTGLGEG
		CAAGACTATCTCTCCCCAAACCCCCCAACCCCCCCCCCC
		CCASTGAGEGASUAL GE LACUAAGEGCTGTAGEGGATOOCEGGUGGAAAGSUGG
		CCATCCTFCTCTCTCTCACACCFCATCBRA/AFATCTCTCTCTCACACACFTTBRA
		SUTGAGADOTTCACCTTCCACTCTGADATCTUCACACTLCCAGAGAAGUSAGAAG
		CA-VATTEACAAACAAACO-NTCUTCOUFACCICUTAACCACAACCCCAA NCCT
		ADAGOGGAGDAACEGAAGACEGTOAEGSAEGADETEGCADAGOTOCTAGATACA
		EGUTECRAGGOTECL GACAS GERCACOTECL E CECSACL GAGGETCORANCOTT
		GTOACTAGALGOAAAGACGOOTUAGCO <mark>GGTGGAGGAGGCTCTGGTGGAGGCGGT</mark>
		<u>AGCGGAGGCGGAGGGTCG</u> GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCC
		GCCTCTGTGGGCGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
		GGTGTAGCCTGGTATCAACAGAAACCAGGAAAAGCCCCGAAGCTTCTGATTTAC
		TCTGCATCCTACCTCTACTCTGGAGTCCCTTCTCGCTTCTCTGGTAGCCGTTCC
		GGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCGGAAGACTTCGCAACT
		TATTACTGTCAGCAACCATCTCATCTGATCACGTTCGGACAGGGTACCGAGGTG
		GAGATCAAATGATAG
157	mouse SA-	ATGUARCORDAGARCECTURARTOOD DUATCOCTATARTOETU UGGGGGRAGAR
	(Gly <sub>4</sub> Ser)-	CATHERARCCCTRATECTCRTTCCCTTTTCCCRTATCCCCCRARTCCTCR
		TROUGTER COARA CTREUE CREEKE CREEKE FTTE CARAGE CITYT
	<i>V<sub>H</sub> CK157</i>	GTUCCOMPERSONCECCCCRACTCUCBCARATCCCTUCACACTCUUTULCCR
		GATARGUEST GEGOCS TECCARA COECCEGE GARACTAL SUEGARCESS CEGAC
		TO DEGRAGAGE CACEGORAGE CART STITE OF CRACE CARCER
		GACEACCOCAGECTACCACCTETERARSGCCAGAGECTGAGECCACETGCACC
		LOUTTERAGGASARCOCASCURCE L'ATUGGACACTAL ELICATURAS L'IGUC
		BGAAGACSTCOTTAUTECTATGCCCCAGAACTTCUTTACEATGCTGAGCAGTAC
		AATGAGATTUTGACCCAGTGTTGTGCAGAGGCTGACAAGGGAAAGCCGCUTGACC
		COSTAGOTTCATOCICICAACCAACAACACTCOCCTCATOTCICCCCCA SAGA
		ATGAAN SCEUUARI ATGUAGARGEELUGAGAGAGAGAGUU ETEAAAQCATGUGUA
		CTACCT DITCUCAC DIAGACATUCCCAAT DITCACTTUCCACAAAUCACCAAA
		GTACCTOSTONCACOCACACTOSCCCATOCTCACTCOCCCACCACACTOCCCACACTOCCCACACTOCCCACCCCACACTOCCCCCCCC
		TIGROADAGAGOOTGACCAAAGTCAACAAGAGIGOTGCCATGATGACCTGOTG
		TTOGORACEGROOTSECCARACTORECERSTOOTSCORTGROOTSCOTO GARLOCGUEGREGROOGGACTEGCCAGTRONECTGERARCUREGOG
		TTOGONA CAGAOOTSACCAAAGUUAACAAGGASTOOTGCCATOOTGACUUAGOO GAALGOGUAGALGACGGOOGGAACIT, GOCAAGTACALGTGTGAAAAGUAGGOO ACCATCITOORGCARAOTGCAGAOTTGCTGCOATAASCCAOTGUUGAGAAAGCC

GAUGTOTTECTOGGES COTTOTTETATORACISTICA AGASGACACCUTEATTAC TOTTATOOODUTTECTOASACITOCTA AGAAATATCA A COOACTCTOOA AA AG TOTTSCOOTGAS SCONATECTCOOGGATSCTA OOGGACA AGTGCTESOTGAATTE

		CACCOTTITUCACAATACCCTAAJAACTTO FICAAAAO DAACTOTATCTITUCACACTICUTAC CACAACCTTUCACAATATCOATTICCAAAATCCCATTOTAUTTO SOTA CACCOCA AAAACCCTCAAGTOTUCTAACACTTCCTCAAACATCAGAAACCTACCAA AGASTGGGCACCAAGTOTUCTCAACACTTCCTGAAGATCAGAAACCTTCTGTG GAAGACTATCTGTGCTGACACTTCCTGAAGATCAGAAACCTTCTGTG GAAGACTATCTCTGCTCTG
158	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129- ds1 (V <sub>L</sub> 100 <sup>Q&gt;C</sup> / V <sub>H</sub> 44 <sup>G&gt;C</sup> )	ATGUAACCACAGAACAC ( GACAC COC CUBTOUG LATAAL CALL DO CACAACAA CAUTTORA SGROMA STOOTEAUTSCOTT TUCCO AGTACUTCO AGAA TACTA TACGAT CAGCATECUCCOCCCCACTCUCCCACTACUCCCACAGACUTTE CAGAA TACTAC CTUDEC CATORITICUCCOCCCCAACTCUCACAGACUTTE CAGACUTEC DUTCUCCA GAUXAAACAAACAACACCCCCCAACACUTCACAGACUTT DUTCCAACACUGAACACU GACAACUUAGOOTACUCACOATUTGAAAGGCUGGAGAGGU GAGGCOATGTCOACCACAAACAT GACAACUUAGOOTACUCACOATUTGAAAGGCUGGAGAGGU GAGGCOATGTCOACCACAACAACA TOOLI LAAGGAAAACUUARPONCUUTTA LIGGGAGAGGU GAGGCOATGTCOACCACAACACU ACAACUUAGOOTACUCACOATUTGAAAGGCUGGAGAGGU TAT COTOACTACCAACAUAGACU GACAACUUAGOOTACUCACOATUTGAAAGGCUGGCOACGAGGCACUTCOCOTUCACACACACU ACAAGUCOCCCCCCCCCCCCCCCCACAGGCUTGCTCCCCCCCCCCCCC

		CCTDADACTIDADDITICCACITIEA DATODOCACACITICCACACAACACACAAC CACATTAACAAACAACCOCTOTICCTORCTGCTGAACCACACAACCACAAC ACATCACACACACACITCTCCACACITCCCCCCACACCITCCCCCACACCITCCCCCACACCITCCACAACCIT ACATCACAACCACACITCCCATACACITCTCCACACITCCCCCCACACCITCCACAACCIT GICACTACAIGUAAACACCUUT.ACCC <u>GGTGGAGGAGGCTCTGGTGGAGGCCGGT</u> <u>ACCCCACCCCCACGCTCC</u> GATATCCAGATGACCCAGTCCCGAGCCCCCTGTCC GCCTCTGTGGGCGGATAGGGTCACCATCACCTGCCGTGCCAGTCAGT
159	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )	ATGUAA SCACAGAA SAGE CAGACIOG CUATIONG EXTANLIGA ELEUCO PAGAAGAA CAUTTO ANA AGGAO TA STOOT ON TIGO OTTOUCCIONTAICUTCIONA AA AGAO TA TA CUTCIONA AA AGAO TA AA CUTCIONA AU CUTCIONA AA AGAO TA AA CUTCIONA AA CAAD TA AA GAACTA CUTCIONA AA AGAACIAA AGAO TA AA AGAACIAA AGAACIA AA A

		CC COACACCE COACACE CECCE CECCE COACACE CECCE CECE CE
160	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK138	EARNSELARRYNDLGEORFEGIVLLAFSOYLOKOSYDERAKLYOSYLDFAETUW NDESAANODKSLATIFGOKLOAIDUT RENYSELALOOTEOGEPERNEUFLORROO NPSLPFFERPEARAKUTSFKENFTTFMORTLHEVARREYYYN PELLMYAEOYN EI LTOCCARADKESOLTPKIEDGYSERALYSSYRORMKOSOMORFCERAFRAWAY ARLSOTFPRADFAETTRLATULTKYNEEGORODLLECAUDRAELAKYMOENQAT ISSELOTCODEFLEIKKAHOLSEVEHDIMPADEPALAAGEVEDGEVOKNYAEASO VFLOTPWENSREPDYSYSELEEDAKKYRATUKKOAPPADEPAOYSTYTAREO FLYKEMENLYKINODEYEKLGEYGPONALLYKYTOKAFOVSTELIVEAARNIGE VOTFOCTLEEDQREPOVERYLSAILNEVOTIRERTPYSERVTECCSOFLVEEEP OFSALTVDETYYPKEFRAETETFRODICTIPEREEQIKKOTALASIYRAAPAKAT AEQLSTYMDDEAOFIDTOCEAADKDTOFSTEUPNUVTROKDALA <u>GGGGSGGGGS</u> GGGGSASAIOMTRSPSSLSASVGDRVTITCRASOYHDGSAAWYOOKPGKAPKLL IYGASYLYSGVPSRFSGSRSGTDFTLTISSLOPEDFATYYCOOSSYSLITFGOG TKVEIKGTTAASGSSGGSSSGAEVOLVESDGGLVOPGGSLRLSCAASGFNLSYY GMHWVROAPGKGLEWVAYIASYPGYTSYADSVKGRFTISADTSKNTAYLOMNSL RAEDTAVYYCARSGYSYSPYYSWFSAGMNYWGOGALVTVSS
161	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK157	EARNEELARPENDI GEQRENGI VILLAFSQYLQKOSYDEBAKI VQEVLDEARTUV ADES AANODKSLATIEFGUKLOA IPNI RENYSELADOOTEQEPERRECFIQHSOO NE SLEPPERPEARAMUTSEKENETTEMER TIREVAR REPYTYAPELLYYAEQTR EI DEQCOAGADKENOLTEKEDUVSERALVSGVRQRMKOSOMQKECERAFRAWAV ARDSQTFPRADEASI TRIATUVITKVNEEOCHODI.DECADDRAELAKYMOENQAT ESSELQTOODKE DEKKAHOLSEVEHDIMERADI.PAILAGEVEDQEVOKNYAEASO VELQTEDVEN SRREPDYSYSLEDEDAKKYEATDENOOAESUPPAOFSTVELAREQ ELVEEPENEVKI NODLYEKLGENGEQALLVSYTQKAPQVSTELLVEARREGE VOTROODLEEDQEI POVEDYDSAILINEVOLDRETTPYSERVTECOSOFLVEEEP OF SALTVDETYVEKEFRAETETERSDI.CTI PEREEQIKKOTALAEI VRAEP VAT AEQURTVEDDEAQEDVEDYDSARDKDEOFSTEDEDEDVER OKDALLAEGO

		<u>GGGGS</u> AGDIQMTQSPSSLSASVGDRVTITCRASQSYGGVAWYQQKPGKAPKLLI YSASYLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQPSHLITFGQGTE VEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGSNPYYYGG THWVRQAPGEELEWVASIGSYPGYTDYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCARHYYWYDATDYWGQGTLVTVSS
162	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129	EABY GE LARY WELGEORF KET VLIAF SQYLONOSY DEBANL VQEV DEFAUTOV ADESAANODES DET LEGDA DOAL PRIPENY GELADOUT KOMPENNESELOR KEU NESLEFFERPEARAMOTSEKENETTEMMAY DEEVANAREY YN AFELDYY AE OF EILH OOCHEADKESCUTEKLOOVEEKALVESVRORMACS SHOKFEEFAFKAWAY AKLSQIFF NADE AFLIKLAFDLIE VEKALVESVRORMACS SHOKFEEFAFKAWAY AKLSQIFF NADE AFLIKLAFDLIE VEKALVESVRORMACS SHOKFEEFAFKAWAY AKLSQIFF NADE AFLIKLAFDLIE VEKALVESVRORMACS SHOKFEEFAFKAWAY VELOTEDNEY SERBEDY SYSTELE DELAKS Y CATLERCOAF ARE PAOLY TVLASEO PINEEPENDEVKTNOD DYEKLOF ZEFONALL VEYTOKAROV STEDIEVESARNIGE VGLKOOLDUEDOVEELOEZEFERDICTIPEKEROIKKOTALSEI VRAAFKAT AEQUVTVMODFROEDYEKLOFZERDICTIPEKEROIKKOTALSEI VRAAFKAT AEQUVTVMODFROEDYEKLOFZERDICTIPEKEROIKKOTALSEI VRAAFKAT AEQUVTVMODFROEDTOCHAADKETOFSTEOREN VROALS <u>GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG</u>
163	mouse SA- (Gly4Ser)3- scFv (VL- V <sub>H</sub> ) CK138- ds1 (VL100 <sup>Q&gt;C</sup> / VH44 <sup>G&gt;C</sup> )	EARKSE LARRYEDT GEORFIGT VLIAF SOMLOROSYDERARLYOEV DEPARTOV ADESAANODES DETLEODE LOAL PRIFENYSELADOUT KORPENEOFLORKEU ELLTOOCAEADKESCUTPKLOOVEEKALVSSVRORMROSENOKFEEPAFKAWAY AKLSOIFFENEVERSCUTPKLOOVEEKALVSSVRORMROSENOKFEEPAFKAWAY AKLSOIFFENEVERSCUTPKLOOVEEKALVSSVRORMROSENOKFEEPAFKAWAY AKLSOIFFENEVERSCUTPKLOOVEEKALVSSVRORMROSENOKFEEPAFKAWAY AKLSOIFFENEVERSCUTPKLOOVEEKALVSSVRORMROSENOKFEEPAFKAWAY VELSTELTETSEREDTSVSLILERIAREYEAFLEECUAFARPFAUYSLVLAEVO VELSTELTETSEREDTSVSLILERIAREYEAFLEECUAFARPFAUYSLVLAEVO VELSTENEVERTRODINEKLORVSTONALLVEYTOKAROVSTPOLVESARNIOR VGLKOOILUEDORLFOVEDTISAIENRVOLLBERTPVSREVTROOSOBEVERPP OPSALTVDETYVPKEPARETETPRISSICTIPERENDIKKOTALSEIVKRORFAT AEOLKTVMDDFSQFLDTOCEAADRDTOFSTEOPRILVIRGKARIAGEGGGGGGGG GGGGSASAIQMTRSPSSLSASVGDRVTITCRASQYHDGSAAWYQQKPGKAPKLL IYGASYLYSGVPSRFSGSRSGTDFTLTISSLOPEDFATYYCQQSSYSLITFGOG TKVEIKGTTAASGSSGGSSSGAEVQLVESDGGLVQPGGSLRLSCAASGFNLSYY GMHWVRQAPGKOLEWVAYIASYPGYTSYADSVKGRFTISADTSKNTAYLQMNSL RAEDTAVYYCARSGYSYSPYSWFSAGMNYWGQGALVTVSS
164	<i>mouse SA-</i> ( <i>Gly4Ser</i> )3- <i>scFv</i> ( <i>V</i> <sub>L</sub> - <i>V<sub>H</sub></i> ) <i>CK138-</i> <i>ds2</i> ( <i>V</i> <sub>L</sub> 43 <sup>A&gt;C</sup> / <i>V<sub>H</sub>105<sup>Q&gt;C</sup></i> )	EARKGELARKNOLGEORFKGLVLLAFSONLONGSYGERANLVOEVUDFAETUV ADEGAANODES LETLEGDE LUAL PREPENYGELADOUTKOEPERNEOFLORKOU MPS LYFEEPPERSAMUTSPESENPUTYMORYLEEVAR NEPYTYAFGLUTVAEOXN EILTOOCSEADKESCUTPREDOVEEKALVSSVRORMOSSMORFGEPERVAWAV ARLSQIFFENADEAELTNEATDLUSVNRECCHOULLECADENAELAENMUSNOAT ISSKLQUOODEFULKKAROLSEVERDUMPADEPALEADEVEDOEVURNYBEAKU VFLUUTESSREPDTSVSLELERIAREYEATEECUAFANFFAUYGLVLAEVO PLVEEFENDVKTNODUVERLOEVUNDATEVENTONAPPAUYGLVLAEVO VGLKOOTEUGOLPUNEDTERATUSPONATEVENTRAPPAUYGLVERARNEGE

		CFSALTVDETEVPREEKAETETEHSDIGTLPEKERQIRKQTALAGIVKHXPRA ABQLATVMOUPAQELDTCCKAADEUTCEDTEOPHLVTELKUALA <u>CCCGSCCCCC</u> <u>GGGGS</u> ASAIQMTRSPSSLSASVGDRVTITCRASQYHDGSAAWYQQKPGK <pkli IYGASYLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQSSYSLITFGQC TKVEIKGTTAASGSSGGSSSGAEVQLVESDGGLVQPGGSLRLSCAASGFNLSYS GMHWVRQAPGKGLEWVAYIASYPGYTSYADSVKGRFTISADTSKNTAYLQMNSI RAEDTAVYYCARSGYSYSPYYSWFSAGMNYWG©GALVTVSS</pkli 
165	mouse SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK157- ds1 (V <sub>L</sub> 100 <sup>Q&gt;C</sup> / V <sub>H</sub> 44 <sup>E&gt;C</sup> )	EARKSELA URYNOL GEQUFROL VELAFS QYLQKOSYDERA KI VOEVUDFARTON ADES AANOEKSLAT LEGEKLOA DE MERENT GELADOO LEGEPERRECHUGHAM DE SLEPFERY EALAMOUSE KEMPTTYMER LEEVARRERY SYAPELLYYAEQT ETUTQOOAENDEES OLTPEDESVREMA DYSSYRODMACSSMOEFGERAFEAWAN APLS QTFPHADPAELTKLATOL UKYNEBOOREDLLECA DEPAELARYMCENGAT ESSKLOUCCURPLLEKARCLER VEUUMPADEPALAADF VEUGEVOENYAEAAN VFLGTELYEYSRRHPEYSYSILLE LAKKTEAT LEKOOAEANPAONGUVLAEAN VFLGTELYEYSRRHPEYSYSILLE LAKKTEAT LEKOOAEANPAONGUVLAEAN VGUVOULPEDGRIP OVEDYLS ALLAPVOL LREATE VSERVTECOSGELVERAN CFSALTVETNOCHLYENEGEN GEONS II VRYTEKAPOVATETI VEAARNES VOUFOCULPEDGRIP OVEDYLS ALLAPVOL LREATE VSERVTECOSGELVERAN AEQLAT VNEDETNOCHLSEKAETETERSE LOTE DEKLINGIKATALASI VKHEFKAT AEQLAT VNEDETNOCHSEKAETETERSE LOTE DEKLINGIKATALASI VKHEFKAT AEQLAT VNEDETNOCHSELSASVGDRVTITCRASQSYGGVAWYQQKPGKAPKLLI YSASYLYSGVPSRFSGSRSGTETITISSLOPEDFATYYCQQPSHLITFGOGTE VEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGSNPYYGG THWVRQAPGECLEWVASIGSYPGYTETADSVKGRFTISADTSKNTAYLQMNSLI AEDTAVYYCARHYWYDATDYWGQGTLVTVSS
166	mouse SA- (Gly4Ser)3- scFv (VL- VH) CK157- ds2 (VL43 <sup>A&gt;C</sup> / VH105 <sup>Q&gt;C</sup> )	EARKSELS BRYNDL GEQRPKOL VLI APPOYLQKC SYDERS YL VORVUDPAKTON ADESARNODKSLATIEGOKLOAIE DI RERYGELADOOTEQEPERRECFLORKOM BESLEPERPERAROUSE KEMPTYMORYLEEVARREY FYRPELLYXAEQOT ETLIQOOAERDEESOLTEEDGOVREEA DVSSVROEMKOSSMOEPOERAFEAWAN APLSQTEERARDEASI.IKLATULLKVAE EOCHODILLEUA DDRAE LAKYMOERQAT ISSKLOUCOURPILLEEAROLSE VERUUMPADEPAITARDEVEDGEVOERYREASE VFLGIELYEYERRREPYSVELLLE LAKKTEATLEKOOAERBEPAOTGUVIAES PLVEUPKNLVETUODLEEREGENGEOGRAFIIVRYTOKAPOVATETUVEAARNDG VOTFOCULPEDGRIEDOVEDYLGATLEREVOTERESTEVSERVTEICOSGELVERGEN GFSALTVDETYVEREEKRETFTERSDICTIERESTEVSERVTEICOSGELVERGA ASQLKTVMODEAGELDTOCKAADEUTOESTEGENUVTECHUALA <u>GGGGSGGGG GGGGS</u> AODIQMTQSPSSLSASVGDRVTITCRASQSYGGVAWYQQKPGKCPKLLI YSASYLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQPSHLITFGQGTF VEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGSNPYYGG THWVRQAPGEELEWVASIGSYPGYTDYADSVKGRFTISADTSKNTAYLQMNSLF
167	mouse SA- (Gly4Ser)-VL CK157	EARS SELARSTOL JEQRES OF VERAFSQX LOKOSYOERAKI VOSVUDEAKTOT ADESAARODKSLAT LEGEKLOA IE NERENTGELADOOTEQEPERRECELQHAM NE SLEFFERFEALAMOTSE KERETTYMDRY LEEVARREEY FYARELLY XAEQ M ET LTQUOAEADESOL TEELDOVKERA LVSSVROPEKOSSMOEFOERAFEAWA ARLSQTEPRAPEASI, EKLATOL I KVRKEOJEDOLLEUADDRAE LAKYMOERQAT ISSKLOTOODRELLEEAROLSE VERDIMPADDRATAADE VEDGEVOERYAEASE VELGEELYEY SRREEYSVSILLE LAKK TEATLEKOOAEAREDAOTGIVE AEES

		PINEEPKHINKINCOLNERLCENTEONAILVENTORAPOVŠTPTLVEAARNLOR VOTKOOTEPEDORIPOVEDVLEAILNERVOLLBEKTEVSEEVTKOOSOSEVERRP OPSALTVPETYVPHEPRAETETEPESOTOTEPEREKOIKKOATA AELNEERPKAT AEQLKIVMODEROFLETOCEAALKOTOPGTEAPRILVIKOKALA <u>GGGGSGGGGS</u> <u>GGGGS</u> AS <b>DIQMTQSPSSLSASVGDRVTITCRASQSYGGVAWYQQKPGKAPKLLI</b> <b>YSASYLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQPSHLITFGQGTE</b> VEIK
168	mouse SA- (Gly4Ser)- V <sub>II</sub> CK157	EARKSELAWRONDLGEGHENGLVLIAPFOYLQKCSYDEHAKIVQEVIDEAKTOV ADESAANOBKSLATIEFGOKLGATENERENTGELADOOLAGEPERRECELGEROP NESLEFFEREREAAMOTSEKAAPTTEMURTLEEVARGEEYYAPELLYYARQTN EILTQOOARADHESOLTPETDGOVRERALVSSOVROPMYCSSMQEFGERAFEAWAW APLSQTEENADPAETTKLATDETKVNEBOOHEDILLBOADDPAELARYMCENQAT ISSKLQTCCURPLLEKAHOLSEVEWUTHEADDPATAADEVEUGEVOENYAEARD VELGTELYEYSREHPEYSOSILLBLAKKTLATLEKOOALANDPAOLGUVLAREQ ELVEEPKNLVNTNCDLYERDGEYGEONATIVRYTOKAPOVSTETTVEAARNLSR VOTROCTLPEDGELPOVEDYLSATLNEVCELREETEVSERVTETCOSGSLVEREP CESALTVDETNVEREEKAETETEHSDICTLEEKTEQINKQTALASEVKHEPRAT AEQLKTVMUDEAOFLDTCOKAADKUTCEDTEOPHINTELKDALA <u>GOGGSCOCGOS GGGGS</u> ASAEVQLVESGGGLVQPGGSLRLSCAASGSNPYYGGTHWVRQAPGEEL EWVASIGSYPGYTDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARH
169	mouse SA- (Gly4Ser)3- scFv (VL- VH) CK129- ds1 (VL100 <sup>Q&gt;C</sup> / VH44 <sup>G&gt;C</sup> )	EAHVGE LAAR YNDI GEOAFNGI VLIAFGONLOROS YDEHAAL VOEV DEFATTUV ADESAANODES LETIEGDE LUAL DALPENYGELADUUT KOEPEENBUCKION KOU NESLEPFERPEARAKUTSEKENETTEMOAY DHEVARREEYEYAPELUMYAEOYR ENLTOCCEERDESCUTEKLOOVKEKALVES VRORMAUSBOKKEGEEREKAWAV AKUSQIFE NADE AB ITKLAIDLIEVIKKECCHODI DECADE KAELAENMUENQAI IBBELQUOODEF DI KKAHOLSEVERDUMPADLER DAADEVEDOBVOKNYAEAKD YELUTEDTEN SEKEPDYSYS DI DENERVERDUMPADLER DAADEVEDOBVOKNYAEAKD YELUTEDTEN SEKEPDYSYS DI DENERVERDUMPADLER DAADEVEDOBVOKNYAEAKD YELUTEDTEN SEKEPDYSYS DI DENERVERDUMPADLER DAAREEAUNGI VLAEVO PIVEREENDVKINODUVEKLOEZGEONAILVENTOKAEOV SIDELVERARMIDE VGI KOUIDEDORLEUVESTERIEN DENERVIKUP SEEVIKUUSGEDVERE CESALTVEREENDVKINODUSIDISAIENNYOLDERKI. EVSERVIKUUSGEDVERE CESALTVEREENDES OF DISCHARKET DESTERENDVIKUTADEN KARDEVAT AEQUKTVEDER OF DISCEARDEDICTIERSENDVIKOTALDEIVKREEVAT AEQUKTVEDER OF DISCEARDENT FRODICTIERSENDVIKOTALDEIVKREEVAT AEQUKTVEDER OF DISCEARDENT FRODICTIERSENDVIKOTALDEIVKREEVAT AEQUKTVEDER OF DISCEARDENT OF STERENDVIKOTALDEIVKREEVALI YGASLLYSGVESEFSGGRSGIDETLIISSLOPEDFATYYCORGHALIIFGOGIK VEIEGTTAASGSSGGSSSGAEVOLVESGGGLVOPGGSLRLSCAASGFNISSYGS MHWVROAPGKULEWVASIYPYSSTYYADSVKGRFTISADTSKNTAYLOMNSLR AEDTAVYYCARGYGPWYAYSYFALDYWGQGTLVIVSS
170	<i>mouse</i> SA- (Gly4Ser)3- scFv (V <sub>L</sub> - V <sub>H</sub> ) CK129- ds2 (V <sub>L</sub> 43 <sup>A&gt;C</sup> / V <sub>H</sub> 105 <sup>Q&gt;C</sup> )	EARKSEJARE KROLGEORFEGI VLIAFSQULONOS YDERANI VQEVIDFARTOV ADESAANODES LET LEGDE LOAL DALPENYGELADOUT KOEPEENSOELQEKOU NPS LEFFEEPPEARAMOT SPECIDE TEMOO XILEEVAERE PEYYAF SLIJYYAEQEN EILTQOCZEADKESCETPKLOG VKEKALVSSVEQRMADSSMQKFGEPAPKAWAV AKLSQIFF NADE AS LTNE ALDLID VNKECCEODI LECALL KAS LASIMOUSNQA I ISSELQUOODEF DI KKAROLSSVERDIMPADLPAILEADEVEDQEVOKNYAEAKD VELSTELYET SEREPDTSVS LELEELAENYEALEECOAFARPFAOYG. VLAEVQ PI VEEPENIVETNODIVEKLOEKSPONALL VENTOKAPOVSTPOLVEARNIOS VGI KOO LEEDQELFOVEDIENE LENRVOLLEEKLEVSENVKOOSOSIVEPPE

		CF SALTVDETTYVFREFKAETFTFHSDICTI PEKEKQI RKQTALAGI VKHKP KAT AEQLAT VMDDFAQFIDTCCRAADBUTCFSTECPBINTECEDAL A <u>CCCCSCCCCS</u> <u>GGGGS</u> ACDIQMTQSPSPLSASVGDRVTITCRASQYGGYVAWYQQKPGKCPKLLI YGASLLYSGVPSRFSGGRSGTDFTLTISSLQPEDFATYYCQRGHALITFGQGTK VEIEGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGFNISSYGS MHWVRQAPGKGLEWVASIYPYSSSTYYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCARGYGPWYAYSYFALDYWGCGTLVTVSS
171	Human serum	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCV ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDD
	albumin (mature) (HSA)	NPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYK AAFTECCQAADKAACL_PKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAV ARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDS ISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKD
		VFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGK VGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRP CFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKAT KEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL
172	Human	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
172	IgG1	NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
	constant	NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
	region	LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
	(amino acid	EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
	sequence)	KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
		SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
173	Mouse	EAHKSEIAHRYNDLGEQHFKGLVLIAFSQYLQKCSYDEHAKLVQEVTDFAKTCV ADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPERNECFLQHKDD
	serum albumin	ADESAANCDKSLHILFGDKLCAIPNLKENYGELADCCIKQEPERNECFLQHKDD NPSLPPFERPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYN
	arbumin	EILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFKAWAV
		ARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCENQAT
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		VGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVERRP CFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKAT
		AEQLKTVMDDFAQFLDTCCKAADKDTCFSTEGPNLVTRCKDALA
174	Human	EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
	IgG1 Fc	VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
	domain	STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
	(amino acid	AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
	sequence)	WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
	sequence)	NVFSCSVMHEALHNHYTQKSLSLSPGK
175	HSA domain	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCV
175	I	ADESAENCDKSLHT_FGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDD
		NPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYK
		AAFTECCQAADKAACLIPKLDELRDEGKASSAKQR
176	HSA domain	GKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVH
		TECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCLAEVEND EMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLA
		BER HEBT SEARCH VESKEVCKWI KEAKDVE LGME LIEIAKKHEDISVVELEKLA

	KTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQ
HSA domain	NLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCK
III	HPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEV
	DETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAV
	MDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL
(Gly∠Ser) <sub>3</sub>	GGGGSGGGGGGGGS
linker	
domain	
Secretory	MDMRVPAQLLGLILWLPGARC
leader	
sequence	
FLAG tag	DYKDDDDK
Polyhistid	ННННН
ine (6-	
His)	
Hemaggluti	YPYDVPDYA
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Arg	Leu	Ser	Gln	Thr 325	Phe	Pro	Asn	Ala	Asp 330	Phe	Ala	Glu	Ile	Thr 335	Lys
Leu	Ala	Thr	Asp 340	Leu	Thr	LYa	Val	Asn 345	ГЛа	Glu	Сүз	Сүз	His 350	Gly	Asp
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Pro 385	Leu	Leu	Lys	Гла	Ala 390	His	Суз	Leu	Ser	Glu 395	Val	Glu	His	Asp	Thr 400
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Arg Ser Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu 50 55 60
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Lys Ile Ile Glu Lys Ile Leu Asn Lys Gly Ser Thr Asn Gly Gly Gly 85 90 95
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Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys 165 170 175
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Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys 260 265 270
Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val 275 280 285
Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser 290 295 300
Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala 305 310 315 320
Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys 325 330 335
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp 340 345 350
Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys 355 360 365

Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu 435 440 445 Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe 470 475 Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser His His His His His His <210> SEQ ID NO 66 <211> LENGTH: 695 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL432-101-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEQUENCE: 66

Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro

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Val	Lys	Thr 35	Thr	Ser	Gln	Val	Arg 40	Pro	Arg	His	Ile	Thr 45	Ser	Leu	Glu
Val	Ile 50	Lys	Ala	Gly	Pro	His 55	Cys	Pro	Thr	Ala	Gln 60	Leu	Ile	Ala	Thr
Leu 65	Lys	Asn	Gly	Arg	Lys 70	Ile	Суз	Leu	Asp	Leu 75	Gln	Ala	Pro	Leu	Tyr 80
ГЛа	Lys	Ile	Ile	Lys 85	Гла	Leu	Leu	Glu	Ser 90	Gly	Gly	Gly	Gly	Ser 95	Gly
Gly	Gly	Gly	Ser 100	Glu	Ala	His	Lys	Ser 105	Glu	Ile	Ala	His	Arg 110	Tyr	Asn
Asp	Leu	Gly 115	Glu	Gln	His	Phe	Lys 120	Gly	Leu	Val	Leu	Ile 125	Ala	Phe	Ser
Gln	Tyr 130	Leu	Gln	Lys	Суз	Ser 135	Tyr	Asp	Glu	His	Ala 140	Lys	Leu	Val	Gln
Glu 145	Val	Thr	Asp	Phe	Ala 150	ГÀа	Thr	Сүз	Val	Ala 155	Asp	Glu	Ser	Ala	Ala 160
Asn	Cys	Asp	Lys	Ser 165	Leu	His	Thr	Leu	Phe 170	Gly	Asp	ГЛа	Leu	Cys 175	Ala
Ile	Pro	Asn	Leu 180	Arg	Glu	Asn	Tyr	Gly 185	Glu	Leu	Ala	Asp	Cys 190	Сув	Thr
Lys	Gln	Glu 195	Pro	Glu	Arg	Asn	Glu 200	Сүз	Phe	Leu	Gln	His 205	Lys	Asp	Aap
Asn	Pro 210	Ser	Leu	Pro	Pro	Phe 215	Glu	Arg	Pro	Glu	Ala 220	Glu	Ala	Met	Сүз
Thr 225	Ser	Phe	Lys	Glu	Asn 230	Pro	Thr	Thr	Phe	Met 235	Gly	His	Tyr	Leu	His 240
Glu	Val	Ala	Arg	Arg 245	His	Pro	Tyr	Phe	Tyr 250	Ala	Pro	Glu	Leu	Leu 255	Tyr
Tyr	Ala	Glu	Gln 260	Tyr	Asn	Glu	Ile	Leu 265	Thr	Gln	Сүз	Суз	Ala 270	Glu	Ala
Asp	Lys	Glu 275	Ser	Суз	Leu	Thr	Pro 280	Lys	Leu	Asp	Gly	Val 285	Lys	Glu	Lys
Ala	Leu 290	Val	Ser	Ser	Val	Arg 295	Gln	Arg	Met	Lys	Сүв 300	Ser	Ser	Met	Gln
Lуя 305	Phe	Gly	Glu	Arg	Ala 310	Phe	Lys	Ala	Trp	Ala 315	Val	Ala	Arg	Leu	Ser 320
Gln	Thr	Phe	Pro	Asn 325	Ala	Asp	Phe	Ala	Glu 330	Ile	Thr	ГЛа	Leu	Ala 335	Thr
Asp	Leu	Thr	Lys 340	Val	Asn	Гла	Glu	Сув 345	Сув	His	Gly	Asp	Leu 350	Leu	Glu
СЛа	Ala	Asp 355	Asp	Arg	Ala	Glu	Leu 360	Ala	Lys	Tyr	Met	Сув 365	Glu	Asn	Gln
Ala	Thr 370	Ile	Ser	Ser	ГЛа	Leu 375	Gln	Thr	Суз	Суз	Asp 380	ГЛа	Pro	Leu	Leu
Lys 385	Lys	Ala	His	Суз	Leu 390	Ser	Glu	Val	Glu	His 395	Asp	Thr	Met	Pro	Ala 400
Asp	Leu	Pro	Ala	Ile 405	Ala	Ala	Asp	Phe	Val 410	Glu	Asp	Gln	Glu	Val 415	Суз

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Lys	Asn	Tyr	Ala 420	Glu	Ala	Lys	Asp	Val 425	Phe	Leu	Gly	Thr	Phe 430	Leu	Tyr
Glu	Tyr	Ser 435	Arg	Arg	His	Pro	Asp 440	Tyr	Ser	Val	Ser	Leu 445	Leu	Leu	Arg
Leu	Ala 450	Lys	Lys	Tyr	Glu	Ala 455	Thr	Leu	Glu	Lys	Cys 460	Сүз	Ala	Glu	Ala
Asn 465	Pro	Pro	Ala	СЛа	Tyr 470	Gly	Thr	Val	Leu	Ala 475	Glu	Phe	Gln	Pro	Leu 480
Val	Glu	Glu	Pro	Lys 485	Asn	Leu	Val	Lys	Thr 490	Asn	СЛа	Asp	Leu	Tyr 495	Glu
Lys	Leu	Gly	Glu 500	Tyr	Gly	Phe	Gln	Asn 505	Ala	Ile	Leu	Val	Arg 510	Tyr	Thr
Gln	Lys	Ala 515	Pro	Gln	Val	Ser	Thr 520	Pro	Thr	Leu	Val	Glu 525	Ala	Ala	Arg
Asn	Leu 530	Gly	Arg	Val	Gly	Thr 535	Lys	Сүз	Суз	Thr	Leu 540	Pro	Glu	Asp	Gln
Arg 545	Leu	Pro	Суз	Val	Glu 550	Asp	Tyr	Leu	Ser	Ala 555	Ile	Leu	Asn	Arg	Val 560
САа	Leu	Leu	His	Glu 565	ГЛа	Thr	Pro	Val	Ser 570	Glu	His	Val	Thr	Lys 575	Сүз
Сүв	Ser	Gly	Ser 580	Leu	Val	Glu	Arg	Arg 585	Pro	Суз	Phe	Ser	Ala 590	Leu	Thr
Val	Asp	Glu 595	Thr	Tyr	Val	Pro	Lys 600	Glu	Phe	Lys	Ala	Glu 605	Thr	Phe	Thr
Phe	His 610	Ser	Asp	Ile	Сүз	Thr 615	Leu	Pro	Glu	Lys	Glu 620	LÀa	Gln	Ile	Lys
Lys 625	Gln	Thr	Ala	Leu	Ala 630	Glu	Leu	Val	Lys	His 635	Lys	Pro	Lys	Ala	Thr 640
Ala	Glu	Gln	Leu	Lys 645	Thr	Val	Met	Asp	Asp 650	Phe	Ala	Gln	Phe	Leu 655	Asp
Thr	Суз	Суз	Lys 660	Ala	Ala	Asp	Lys	Asp 665	Thr	Суз	Phe	Ser	Thr 670	Glu	Gly
Pro	Asn	Leu 675	Val	Thr	Arg	Сүз	Lys 680	Asp	Ala	Leu	Ala	Gly 685	Gly	Gly	Gly
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Gln	Gly	Val 35	His	Pro	Lys	Met	Ile 40	Ser	Asn	Leu	Gln	Val 45	Phe	Ala	Ile
Gly	Pro	Gln	Суз	Ser	ГЛа	Val	Glu	Val	Val	Ala	Ser	Leu	Lys	Asn	Gly

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	50					55					60				
Lys 65	Glu	Ile	Суз	Leu	Asp 70	Pro	Glu	Ala	Pro	Phe 75	Leu	Lys	Lys	Val	Ile 80
Gln	Lys	Ile	Leu	Asp 85	Gly	Gly	Asn	Гла	Glu 90	Asn	Gly	Gly	Gly	Gly 95	Ser
Gly	Gly	Gly	Gly 100	Ser	Glu	Ala	His	Lys 105	Ser	Glu	Ile	Ala	His 110	Arg	Tyr
Asn	Aab	Leu 115	Gly	Glu	Gln	His	Phe 120	Lys	Gly	Leu	Val	Leu 125	Ile	Ala	Phe
Ser	Gln 130	Tyr	Leu	Gln	Lys	Cys 135	Ser	Tyr	Asp	Glu	His 140	Ala	Lys	Leu	Val
Gln 145	Glu	Val	Thr	Asp	Phe 150	Ala	Lys	Thr	Cys	Val 155	Ala	Asp	Glu	Ser	Ala 160
Ala	Asn	Cys	Asp	Lys 165	Ser	Leu	His	Thr	Leu 170	Phe	Gly	Asp	Lys	Leu 175	СЛа
Ala	Ile	Pro	Asn 180	Leu	Arg	Glu	Asn	Tyr 185	Gly	Glu	Leu	Ala	Asp 190	Суз	СЛа
Thr	Lys	Gln 195	Glu	Pro	Glu	Arg	Asn 200	Glu	Суз	Phe	Leu	Gln 205	His	Lys	Asp
Asp	Asn 210	Pro	Ser	Leu	Pro	Pro 215	Phe	Glu	Arg	Pro	Glu 220	Ala	Glu	Ala	Met
Cys 225	Thr	Ser	Phe	Lys	Glu 230	Asn	Pro	Thr	Thr	Phe 235	Met	Gly	His	Tyr	Leu 240
His	Glu	Val	Ala	Arg 245	Arg	His	Pro	Tyr	Phe 250	Tyr	Ala	Pro	Glu	Leu 255	Leu
Tyr	Tyr	Ala	Glu 260	Gln	Tyr	Asn	Glu	Ile 265	Leu	Thr	Gln	Суз	Cys 270	Ala	Glu
Ala	Asp	Lys 275	Glu	Ser	Суз	Leu	Thr 280	Pro	Lys	Leu	Asp	Gly 285	Val	Lys	Glu
ГЛа	Ala 290	Leu	Val	Ser	Ser	Val 295	Arg	Gln	Arg	Met	Lys 300	Суз	Ser	Ser	Met
Gln 305	Lys	Phe	Gly	Glu	Arg 310	Ala	Phe	Lys	Ala	Trp 315	Ala	Val	Ala	Arg	Leu 320
Ser	Gln	Thr	Phe	Pro 325	Asn	Ala	Asp	Phe	Ala 330	Glu	Ile	Thr	Lys	Leu 335	Ala
Thr	Aab	Leu	Thr 340	Lys	Val	Asn	Lys	Glu 345	Cys	Cys	His	Gly	Asp 350	Leu	Leu
Glu	Суз	Ala 355	Asp	Asp	Arg	Ala	Glu 360	Leu	Ala	Lys	Tyr	Met 365	Cys	Glu	Asn
Gln	Ala 370	Thr	Ile	Ser	Ser	Lys 375	Leu	Gln	Thr	Суз	Суз 380	Asp	Lys	Pro	Leu
Leu 385	Lys	Lys	Ala	His	Сув 390	Leu	Ser	Glu	Val	Glu 395	His	Asp	Thr	Met	Pro 400
Ala	Asp	Leu	Pro	Ala 405	Ile	Ala	Ala	Asp	Phe 410	Val	Glu	Asp	Gln	Glu 415	Val
Cys	Lys	Asn	Tyr 420	Ala	Glu	Ala	Lys	Asp 425	Val	Phe	Leu	Gly	Thr 430	Phe	Leu
Tyr	Glu	Tyr 435	Ser	Arg	Arg	His	Pro 440	Asp	Tyr	Ser	Val	Ser 445	Leu	Leu	Leu
Arg	Leu 450	Ala	Гла	Гла	Tyr	Glu 455	Ala	Thr	Leu	Glu	Lys 460	Суз	Суз	Ala	Glu

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Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys 565 570 Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser His His His His His His <210> SEQ ID NO 68 <211> LENGTH: 697 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL643-114-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEQUENCE: 68 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Val Leu Thr Glu Leu Arg Cys Thr Cys Leu Arg Val Thr Leu Arg Val Asn Pro Lys Thr Ile Gly Lys Leu Gln Val Phe Pro Ala Gly Pro Gln Cys Ser Lys Val Glu Val Val Ala Ser Leu Lys Asn Gly Lys Gln Val Cys Leu Asp Pro Glu Ala Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Ser Gly Asn Lys Lys Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala His Lys Ser Glu Ile Ala His Arg

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Val 145	Gln	Glu	Val	Thr	Asp 150	Phe	Ala	ГЛЗ	Thr	Сув 155	Val	Ala	Asp	Glu	Ser 160
Ala	Ala	Asn	Суз	Asp 165	Lys	Ser	Leu	His	Thr 170	Leu	Phe	Gly	Asp	Lys 175	Leu
Суз	Ala	Ile	Pro 180	Asn	Leu	Arg	Glu	Asn 185	Tyr	Gly	Glu	Leu	Ala 190	Asp	Суз
Суз	Thr	Lys 195	Gln	Glu	Pro	Glu	Arg 200	Asn	Glu	Суз	Phe	Leu 205	Gln	His	Lys
Asp	Asp 210	Asn	Pro	Ser	Leu	Pro 215	Pro	Phe	Glu	Arg	Pro 220	Glu	Ala	Glu	Ala
Met 225	Суз	Thr	Ser	Phe	Lys 230	Glu	Asn	Pro	Thr	Thr 235	Phe	Met	Gly	His	Tyr 240
Leu	His	Glu	Val	Ala 245	Arg	Arg	His	Pro	Tyr 250	Phe	Tyr	Ala	Pro	Glu 255	Leu
Leu	Tyr	Tyr	Ala 260	Glu	Gln	Tyr	Asn	Glu 265	Ile	Leu	Thr	Gln	Cys 270	Суз	Ala
Glu	Ala	Asp 275	Lys	Glu	Ser	Суз	Leu 280	Thr	Pro	Lys	Leu	Asp 285	Gly	Val	Lys
Glu	Lys 290	Ala	Leu	Val	Ser	Ser 295	Val	Arg	Gln	Arg	Met 300	ГЛа	Сув	Ser	Ser
Met 305	Gln	Lys	Phe	Gly	Glu 310	Arg	Ala	Phe	Lys	Ala 315	Trp	Ala	Val	Ala	Arg 320
Leu	Ser	Gln	Thr	Phe 325	Pro	Asn	Ala	Asp	Phe 330	Ala	Glu	Ile	Thr	Lys 335	Leu
Ala	Thr	Asp	Leu 340	Thr	Lys	Val	Asn	Lys 345	Glu	Cys	Суз	His	Gly 350	Asp	Leu
Leu	Glu	Cys 355	Ala	Asp	Asp	Arg	Ala 360	Glu	Leu	Ala	Lys	Tyr 365	Met	Cys	Glu
Asn	Gln 370	Ala	Thr	Ile	Ser	Ser 375	Lys	Leu	Gln	Thr	Сув 380	Суз	Aab	Lys	Pro
Leu 385	Leu	Lys	LÀa	Ala	His 390	САа	Leu	Ser	Glu	Val 395	Glu	His	Aab	Thr	Met 400
Pro	Ala	Aab	Leu	Pro 405	Ala	Ile	Ala	Ala	Asp 410	Phe	Val	Glu	Aab	Gln 415	Glu
Val	Суз	Lys	Asn 420	Tyr	Ala	Glu	Ala	Lys 425	Asb	Val	Phe	Leu	Gly 430	Thr	Phe
Leu	Tyr	Glu 435	Tyr	Ser	Arg	Arg	His 440	Pro	Asp	Tyr	Ser	Val 445	Ser	Leu	Leu
Leu	Arg 450	Leu	Ala	ГЛа	ГЛа	Tyr 455	Glu	Ala	Thr	Leu	Glu 460	ГЛа	Сув	Сув	Ala
Glu 465	Ala	Asn	Pro	Pro	Ala 470	Суз	Tyr	Gly	Thr	Val 475	Leu	Ala	Glu	Phe	Gln 480
Pro	Leu	Val	Glu	Glu 485	Pro	Lys	Asn	Leu	Val 490	Lys	Thr	Asn	Cys	Asp 495	Leu
Tyr	Glu	Lys	Leu 500	Gly	Glu	Tyr	Gly	Phe 505	Gln	Asn	Ala	Ile	Leu 510	Val	Arg

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Ala	Arg 530	Asn	Leu	Gly	Arg	Val 535	Gly	Thr	Lys	Суз	Cys 540	Thr	Leu	Pro	Glu
Asp 545	Gln	Arg	Leu	Pro	Cys 550	Val	Glu	Asp	Tyr	Leu 555	Ser	Ala	Ile	Leu	Asn 560
Arg	Val	Cys	Leu	Leu 565	His	Glu	Lys	Thr	Pro 570	Val	Ser	Glu	His	Val 575	Thr
ГЛЗ	Cys	Суз	Ser 580	Gly	Ser	Leu	Val	Glu 585	Arg	Arg	Pro	Сүз	Phe 590	Ser	Ala
Leu	Thr	Val 595	Asp	Glu	Thr	Tyr	Val 600	Pro	Гла	Glu	Phe	Lys 605	Ala	Glu	Thr
Phe	Thr 610	Phe	His	Ser	Asp	Ile 615	Суз	Thr	Leu	Pro	Glu 620	Гла	Glu	Lys	Gln
Ile 625	Lys	Lys	Gln	Thr	Ala 630	Leu	Ala	Glu	Leu	Val 635	Lys	His	Lys	Pro	Lys 640
Ala	Thr	Ala	Glu	Gln 645	Leu	Lys	Thr	Val	Met 650	Asp	Asp	Phe	Ala	Gln 655	Phe
Leu	Asp	Thr	Cys 660	Сүз	Lys	Ala	Ala	Asp 665	Lys	Asp	Thr	Сүз	Phe 670	Ser	Thr
Glu	Gly	Pro 675	Asn	Leu	Val	Thr	Arg 680	Сув	Lys	Asp	Ala	Leu 685	Ala	Gly	Gly
Gly	Gly 690	Ser	His	His	His	His 695	His	His							
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	3 > 01	THER Gly49	INF( Ser)·	-His	FION		-		LS-ł	ıCXCI	1759 ·	-121	- (Gl <u>3</u>	y4Se:	r)2-mouse SA-
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145					150					155					160
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Tyr	Gly	Glu	Leu 180	Ala	Asp	Сүз	Сүз	Thr 185	Lys	Gln	Glu	Pro	Glu 190	Arg	Asn
Glu	Cys	Phe 195	Leu	Gln	His	ГЛЗ	Asp 200	Asp	Asn	Pro	Ser	Leu 205	Pro	Pro	Phe
Glu	Arg 210	Pro	Glu	Ala	Glu	Ala 215	Met	Суз	Thr	Ser	Phe 220	ГЛа	Glu	Asn	Pro
Thr 225	Thr	Phe	Met	Gly	His 230	Tyr	Leu	His	Glu	Val 235	Ala	Arg	Arg	His	Pro 240
Tyr	Phe	Tyr	Ala	Pro 245	Glu	Leu	Leu	Tyr	Tyr 250	Ala	Glu	Gln	Tyr	Asn 255	Glu
Ile	Leu	Thr	Gln 260	СЛа	Суа	Ala	Glu	Ala 265	Asp	Lys	Glu	Ser	Cys 270	Leu	Thr
Pro	Lys	Leu 275	Asp	Gly	Val	Lys	Glu 280	Lys	Ala	Leu	Val	Ser 285	Ser	Val	Arg
Gln	Arg 290	Met	Lys	Сүв	Ser	Ser 295	Met	Gln	Lys	Phe	Gly 300	Glu	Arg	Ala	Phe
Lys 305	Ala	Trp	Ala	Val	Ala 310	Arg	Leu	Ser	Gln	Thr 315	Phe	Pro	Asn	Ala	Asp 320
Phe	Ala	Glu	Ile	Thr 325	Lya	Leu	Ala	Thr	Asp 330	Leu	Thr	ГЛа	Val	Asn 335	Lys
Glu	Сув	Сув	His 340	Gly	Asp	Leu	Leu	Glu 345	Суз	Ala	Asp	Asp	Arg 350	Ala	Glu
Leu	Ala	Lys 355	Tyr	Met	Суз	Glu	Asn 360	Gln	Ala	Thr	Ile	Ser 365	Ser	Lys	Leu
Gln	Thr 370	Cys	Суз	Asp	Lys	Pro 375	Leu	Leu	Lys	Lys	Ala 380	His	Суз	Leu	Ser
Glu 385	Val	Glu	His	Asp	Thr 390	Met	Pro	Ala	Asp	Leu 395	Pro	Ala	Ile	Ala	Ala 400
Asp	Phe	Val	Glu	Asp 405	Gln	Glu	Val	Суз	Lys 410	Asn	Tyr	Ala	Glu	Ala 415	Lys
Asp	Val	Phe	Leu 420	Gly	Thr	Phe	Leu	Tyr 425	Glu	Tyr	Ser	Arg	Arg 430	His	Pro
Asp	Tyr	Ser 435	Val	Ser	Leu	Leu	Leu 440	Arg	Leu	Ala	ГЛа	Lys 445	Tyr	Glu	Ala
Thr	Leu 450	Glu	Lys	СЛа	Суа	Ala 455	Glu	Ala	Asn	Pro	Pro 460	Ala	Суз	Tyr	Gly
Thr 465	Val	Leu	Ala	Glu	Phe 470	Gln	Pro	Leu	Val	Glu 475	Glu	Pro	Lys	Asn	Leu 480
Val	Lys	Thr	Asn	Cys 485	Aap	Leu	Tyr	Glu	Lys 490	Leu	Gly	Glu	Tyr	Gly 495	Phe
Gln	Asn	Ala	Ile 500	Leu	Val	Arg	Tyr	Thr 505	Gln	Lys	Ala	Pro	Gln 510	Val	Ser
Thr	Pro	Thr 515	Leu	Val	Glu	Ala	Ala 520	Arg	Asn	Leu	Gly	Arg 525	Val	Gly	Thr
Lys	Суз 530	Суз	Thr	Leu	Pro	Glu 535	Asp	Gln	Arg	Leu	Pro 540	СЛа	Val	Glu	Asp
Tyr 545	Leu	Ser	Ala	Ile	Leu 550	Asn	Arg	Val	Суз	Leu 555	Leu	His	Glu	Lys	Thr 560
					550					555					500

Pr	o Val	Ser	Glu	His 565	Val	Thr	Lys	СЛа	Суз 570	Ser	Gly	Ser	Leu	Val 575	Glu
Ar	g Arg	Pro	Cys 580	Phe	Ser	Ala	Leu	Thr 585	Val	Asp	Glu	Thr	Tyr 590	Val	Pro
Γλ	s Glu	Phe 595	Lys	Ala	Glu	Thr	Phe 600	Thr	Phe	His	Ser	Asp 605	Ile	Сүз	Thr
Le	u Pro 610	Glu	Lys	Glu	Гла	Gln 615	Ile	ГÀа	Lys	Gln	Thr 620	Ala	Leu	Ala	Glu
Le 62	u Val 5	Lys	His	Lys	Pro 630	Lys	Ala	Thr	Ala	Glu 635	Gln	Leu	Lys	Thr	Val 640
Me	t Asp	Asp	Phe	Ala 645	Gln	Phe	Leu	Asp	Thr 650	Суз	СЛа	ГЛа	Ala	Ala 655	Asp
Lу	a Yab	Thr	Cys 660	Phe	Ser	Thr	Glu	Gly 665	Pro	Asn	Leu	Val	Thr 670	Arg	Cys
Lу	a yab	Ala 675	Leu	Ala	Gly	Gly	Gly 680	Gly	Ser	His	His	His 685	His	His	His
<2 <2 <2 <2		ENGT YPE : RGAN EATU THER	H: 6 PRT ISM: RE:	97 Art: ORMA	TION		-		LS-]	hCXCI	L828	-99-	(Gly4	1Ser)	2-mouse SA-
< 4	00> SI	EQUE	NCE :	70											
Me 1	t Arg	Val	Pro	Ala 5	Gln	Leu	Leu	Gly	Leu 10	Leu	Leu	Leu	Trp	Leu 15	Pro
Gl	y Ala	Arg	Суз 20	Ser	Ala	Lys	Glu	Leu 25	Arg	Сүз	Gln	Сүз	Ile 30	Lys	Thr
Ту	r Ser	Lys 35	Pro	Phe	His	Pro	Lys 40	Phe	Ile	Lys	Glu	Leu 45	Arg	Val	Ile
Gl	u Ser 50	Gly	Pro	His	Cys	Ala 55	Asn	Thr	Glu	Ile	Ile 60	Val	Lys	Leu	Ser
As 65	p Gly	Arg	Glu	Leu	Cys 70	Leu	Asp	Pro	Lys	Glu 75	Asn	Trp	Val	Gln	Arg 80
Va	l Val	Glu	Lys	Phe 85	Leu	Lys	Arg	Ala	Glu 90	Asn	Ser	Gly	Gly	Gly 95	Gly
Se	r Gly	Gly	Gly 100	Gly	Ser	Glu	Ala	His 105	Lys	Ser	Glu	Ile	Ala 110	His	Arg
ту	r Asn	Asp 115	Leu	Gly	Glu	Gln	His 120	Phe	Lys	Gly	Leu	Val 125	Leu	Ile	Ala
Ph	e Ser 130	Gln	Tyr	Leu	Gln	Lys 135	Сүз	Ser	Tyr	Asp	Glu 140	His	Ala	Lys	Leu
Va 14	l Gln 5	Glu	Val	Thr	Asp 150	Phe	Ala	Lys	Thr	Cys 155	Val	Ala	Asp	Glu	Ser 160
Al	a Ala	Asn	Суз	Asp 165	Lys	Ser	Leu	His	Thr 170	Leu	Phe	Gly	Asp	Lys 175	Leu
Су	s Ala	Ile	Pro 180	Asn	Leu	Arg	Glu	Asn 185	Tyr	Gly	Glu	Leu	Ala 190	Asp	Cys
су	s Thr	Lys 195	Gln	Glu	Pro	Glu	Arg 200	Asn	Glu	Суз	Phe	Leu 205	Gln	His	Lys
As	p Asp	Asn	Pro	Ser	Leu	Pro	Pro	Phe	Glu	Arg	Pro	Glu	Ala	Glu	Ala

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	210					215					220				
Met 225	Cys	Thr	Ser	Phe	Lys 230	Glu	Asn	Pro	Thr	Thr 235	Phe	Met	Gly	His	Tyr 240
Leu	His	Glu	Val	Ala 245	Arg	Arg	His	Pro	Tyr 250	Phe	Tyr	Ala	Pro	Glu 255	Leu
Leu	Tyr	Tyr	Ala 260	Glu	Gln	Tyr	Asn	Glu 265	Ile	Leu	Thr	Gln	Cys 270	Cys	Ala
Glu	Ala	Asp 275	Lys	Glu	Ser	Суз	Leu 280	Thr	Pro	Lys	Leu	Asp 285	Gly	Val	Lys
Glu	Lys 290	Ala	Leu	Val	Ser	Ser 295	Val	Arg	Gln	Arg	Met 300	Lys	Cys	Ser	Ser
Met 305	Gln	Lys	Phe	Gly	Glu 310	Arg	Ala	Phe	Lys	Ala 315	Trp	Ala	Val	Ala	Arg 320
Leu	Ser	Gln	Thr	Phe 325	Pro	Asn	Ala	Asp	Phe 330	Ala	Glu	Ile	Thr	Lys 335	Leu
Ala	Thr	Aab	Leu 340	Thr	Lys	Val	Asn	Lys 345	Glu	Сув	Сүз	His	Gly 350	Aab	Leu
Leu	Glu	Сув 355	Ala	Asp	Asp	Arg	Ala 360	Glu	Leu	Ala	Гла	Tyr 365	Met	Сув	Glu
Asn	Gln 370	Ala	Thr	Ile	Ser	Ser 375	Lys	Leu	Gln	Thr	Сув 380	СЛа	Asp	Lys	Pro
Leu 385	Leu	Lys	Lys	Ala	His 390	Сүз	Leu	Ser	Glu	Val 395	Glu	His	Asp	Thr	Met 400
Pro	Ala	Aap	Leu	Pro 405	Ala	Ile	Ala	Ala	Asp 410	Phe	Val	Glu	Asp	Gln 415	Glu
Val	Cys	Lys	Asn 420	Tyr	Ala	Glu	Ala	Lys 425	Asp	Val	Phe	Leu	Gly 430	Thr	Phe
Leu	Tyr	Glu 435	Tyr	Ser	Arg	Arg	His 440	Pro	Asp	Tyr	Ser	Val 445	Ser	Leu	Leu
Leu	Arg 450	Leu	Ala	Lys	Lys	Tyr 455	Glu	Ala	Thr	Leu	Glu 460	ГЛЗ	Суз	Суз	Ala
Glu 465	Ala	Asn	Pro	Pro	Ala 470	Суз	Tyr	Gly	Thr	Val 475	Leu	Ala	Glu	Phe	Gln 480
Pro	Leu	Val	Glu	Glu 485	Pro	Lys	Asn	Leu	Val 490	Lys	Thr	Asn	Суз	Asp 495	Leu
Tyr	Glu	Lys	Leu 500	Gly	Glu	Tyr	Gly	Phe 505	Gln	Asn	Ala	Ile	Leu 510	Val	Arg
Tyr	Thr	Gln 515	Lys	Ala	Pro	Gln	Val 520	Ser	Thr	Pro	Thr	Leu 525	Val	Glu	Ala
Ala	Arg 530	Asn	Leu	Gly	Arg	Val 535	Gly	Thr	Lys	Cys	Cys 540	Thr	Leu	Pro	Glu
Asp 545	Gln	Arg	Leu	Pro	Cys 550	Val	Glu	Asp	Tyr	Leu 555	Ser	Ala	Ile	Leu	Asn 560
Arg	Val	Cys	Leu	Leu 565	His	Glu	Lys	Thr	Pro 570	Val	Ser	Glu	His	Val 575	Thr
Lys	Cys	Cys	Ser 580	Gly	Ser	Leu	Val	Glu 585	Arg	Arg	Pro	Cys	Phe 590	Ser	Ala
Leu	Thr	Val 595	Asp	Glu	Thr	Tyr	Val 600	Pro	Lys	Glu	Phe	Lys 605	Ala	Glu	Thr
Phe	Thr 610	Phe	His	Ser	Asp	Ile 615	Сүз	Thr	Leu	Pro	Glu 620	Lys	Glu	Lys	Gln

Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser His His His His His His 690 695 <210> SEQ ID NO 71 <211> LENGTH: 728 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL923-115-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEQUENCE: 71 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Thr Pro Val Val Arg Lys Gly Arg Cys Ser Cys Ile 2.0 Ser Thr Asn Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp Leu Lys Gln Phe Ala Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile Ala Thr Leu Lys Asn Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala Asp Val Lys Glu Leu Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys Lys Gln Lys Asn Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys Val Arg Lys Ser Gln Arg Ser Arg Gln Lys Lys Thr Thr Gly Gly Gly Ser Gly Gly Gly Ser Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe 145 150 155 160 Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu

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			260					265					270		
His	Glu	Val 275	Ala	Arg	Arg	His	Pro 280	Tyr	Phe	Tyr	Ala	Pro 285	Glu	Leu	Leu
Tyr	Tyr 290	Ala	Glu	Gln	Tyr	Asn 295	Glu	Ile	Leu	Thr	Gln 300	СЛа	Суз	Ala	Glu
Ala 305	Asp	Lys	Glu	Ser	Cys 310	Leu	Thr	Pro	Lys	Leu 315	Asp	Gly	Val	Lys	Glu 320
Гла	Ala	Leu	Val	Ser 325	Ser	Val	Arg	Gln	Arg 330	Met	ГЛЗ	Суз	Ser	Ser 335	Met
Gln	Lys	Phe	Gly 340	Glu	Arg	Ala	Phe	Lys 345	Ala	Trp	Ala	Val	Ala 350	Arg	Leu
Ser	Gln	Thr 355	Phe	Pro	Asn	Ala	Asp 360	Phe	Ala	Glu	Ile	Thr 365	ГÀа	Leu	Ala
Thr	Asp 370	Leu	Thr	ГÀа	Val	Asn 375	ГЛа	Glu	Суз	Сүз	His 380	Gly	Asp	Leu	Leu
Glu 385	Суз	Ala	Asp	Asp	Arg 390	Ala	Glu	Leu	Ala	Lys 395	Tyr	Met	САа	Glu	Asn 400
Gln	Ala	Thr	Ile	Ser 405	Ser	ГЛа	Leu	Gln	Thr 410	Сув	Сүз	Asp	LÀa	Pro 415	Leu
Leu	Lys	Lys	Ala 420	His	САа	Leu	Ser	Glu 425	Val	Glu	His	Asp	Thr 430	Met	Pro
Ala	Asp	Leu 435	Pro	Ala	Ile	Ala	Ala 440	Asp	Phe	Val	Glu	Asp 445	Gln	Glu	Val
Суз	Lys 450	Asn	Tyr	Ala	Glu	Ala 455	Lys	Asp	Val	Phe	Leu 460	Gly	Thr	Phe	Leu
Tyr 465	Glu	Tyr	Ser	Arg	Arg 470	His	Pro	Asp	Tyr	Ser 475	Val	Ser	Leu	Leu	Leu 480
Arg	Leu	Ala	Lys	Lys 485	Tyr	Glu	Ala	Thr	Leu 490	Glu	Lys	САа	Суз	Ala 495	Glu
Ala	Asn	Pro	Pro 500	Ala	Сүз	Tyr	Gly	Thr 505	Val	Leu	Ala	Glu	Phe 510	Gln	Pro
Leu	Val	Glu 515	Glu	Pro	Гла	Asn	Leu 520	Val	LÀ2	Thr	Asn	Сув 525	Asp	Leu	Tyr
Glu	Lys 530	Leu	Gly	Glu	Tyr	Gly 535	Phe	Gln	Asn	Ala	Ile 540	Leu	Val	Arg	Tyr
Thr 545	Gln	Lys	Ala	Pro	Gln 550	Val	Ser	Thr	Pro	Thr 555	Leu	Val	Glu	Ala	Ala 560
Arg	Asn	Leu	Gly	Arg 565	Val	Gly	Thr	ГЛЗ	Cys 570	Суз	Thr	Leu	Pro	Glu 575	Asp
Gln	Arg	Leu	Pro 580	СЛа	Val	Glu	Asp	Tyr 585	Leu	Ser	Ala	Ile	Leu 590	Asn	Arg
Val	Сув	Leu 595	Leu	His	Glu	Lys	Thr 600	Pro	Val	Ser	Glu	His 605	Val	Thr	Lys
Сув	Cys 610	Ser	Gly	Ser	Leu	Val 615	Glu	Arg	Arg	Pro	Суз 620	Phe	Ser	Ala	Leu
Thr 625	Val	Asp	Glu	Thr	Tyr 630	Val	Pro	Lys	Glu	Phe 635	ГЛа	Ala	Glu	Thr	Phe 640
Thr	Phe	His	Ser	Asp 645	Ile	Cys	Thr	Leu	Pro 650	Glu	Lys	Glu	Lys	Gln 655	Ile
Lys	Lys	Gln	Thr 660	Ala	Leu	Ala	Glu	Leu 665	Val	Lys	His	ГЛа	Pro 670	Lys	Ala

Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly 705 710 Gly Ser His His His His His <210> SEQ ID NO 72 <211> LENGTH: 702 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL1022-98-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEQUENCE: 72 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys Ile 20 25 30 Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala Thr Met Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Arg Ser Lys Arg Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys

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		275					280					285			
Leu	Asp 290	Gly	Val	Lys	Glu	Lys 295	Ala	Leu	Val	Ser	Ser 300	Val	Arg	Gln	Arg
Met 305	Lys	Cys	Ser	Ser	Met 310	Gln	Lys	Phe	Gly	Glu 315	Arg	Ala	Phe	Lys	Ala 320
Trp	Ala	Val	Ala	Arg 325	Leu	Ser	Gln	Thr	Phe 330	Pro	Asn	Ala	Asp	Phe 335	Ala
Glu	Ile	Thr	Lys 340	Leu	Ala	Thr	Asp	Leu 345	Thr	Lys	Val	Asn	Lys 350	Glu	Суз
Суа	His	Gly 355	Asp	Leu	Leu	Glu	Суз 360	Ala	Asp	Asp	Arg	Ala 365	Glu	Leu	Ala
Lys	Tyr 370	Met	Суз	Glu	Asn	Gln 375	Ala	Thr	Ile	Ser	Ser 380	ГЛа	Leu	Gln	Thr
Суя 385	Cys	Asp	Lys	Pro	Leu 390	Leu	Lys	Lys	Ala	His 395	Суз	Leu	Ser	Glu	Val 400
Glu	His	Asp	Thr	Met 405	Pro	Ala	Asp	Leu	Pro 410	Ala	Ile	Ala	Ala	Asp 415	Phe
Val	Glu	Asp	Gln 420	Glu	Val	Суз	Lys	Asn 425	Tyr	Ala	Glu	Ala	Lys 430	Asp	Val
Phe	Leu	Gly 435	Thr	Phe	Leu	Tyr	Glu 440	Tyr	Ser	Arg	Arg	His 445	Pro	Asp	Tyr
Ser	Val 450	Ser	Leu	Leu	Leu	Arg 455	Leu	Ala	Lys	Lys	Tyr 460	Glu	Ala	Thr	Leu
Glu 465	Lys	Cys	Сүз	Ala	Glu 470	Ala	Asn	Pro	Pro	Ala 475	Суз	Tyr	Gly	Thr	Val 480
Leu	Ala	Glu	Phe	Gln 485	Pro	Leu	Val	Glu	Glu 490	Pro	ГЛЗ	Asn	Leu	Val 495	Lys
Thr	Asn	Суз	Asp 500	Leu	Tyr	Glu	Lys	Leu 505	Gly	Glu	Tyr	Gly	Phe 510	Gln	Asn
Ala	Ile	Leu 515	Val	Arg	Tyr	Thr	Gln 520	Lys	Ala	Pro	Gln	Val 525	Ser	Thr	Pro
Thr	Leu 530	Val	Glu	Ala	Ala	Arg 535	Asn	Leu	Gly	Arg	Val 540	Gly	Thr	Lys	Суз
Суз 545	Thr	Leu	Pro	Glu	Asp 550	Gln	Arg	Leu	Pro	Суз 555	Val	Glu	Asp	Tyr	Leu 560
Ser	Ala	Ile	Leu	Asn 565	Arg	Val	Сүз	Leu	Leu 570	His	Glu	ГЛа	Thr	Pro 575	Val
Ser	Glu	His	Val 580	Thr	ГÀа	САа	Сүз	Ser 585	Gly	Ser	Leu	Val	Glu 590	Arg	Arg
Pro	Cys	Phe 595	Ser	Ala	Leu	Thr	Val 600	Asp	Glu	Thr	Tyr	Val 605	Pro	Lys	Glu
Phe	Lys 610	Ala	Glu	Thr	Phe	Thr 615	Phe	His	Ser	Asp	Ile 620	Сүз	Thr	Leu	Pro
Glu 625	Lys	Glu	Lys	Gln	Ile 630	Lys	Lys	Gln	Thr	Ala 635	Leu	Ala	Glu	Leu	Val 640
Lys	His	Lys	Pro	Lys 645	Ala	Thr	Ala	Glu	Gln 650	Leu	ГЛа	Thr	Val	Met 655	Asp
Asp	Phe	Ala	Gln 660	Phe	Leu	Asp	Thr	Cys 665	Cys	Lys	Ala	Ala	Asp 670	Lys	Asp
Thr	Сув	Phe 675	Ser	Thr	Glu	Gly	Pro 680	Asn	Leu	Val	Thr	Arg 685	Суз	Lys	Asp

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Ala Leu Ala Gly Gly Gly Gly Ser His His His His His His <210> SEQ ID NO 73 <211> LENGTH: 698 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL1122-94-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEQUENCE: 73 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Phe Pro Met Phe Lys Arg Gly Arg Cys Leu Cys Ile 20 \$25\$ 30 Gly Pro Gly Val Lys Ala Val Lys Val Ala Asp Ile Glu Lys Ala Ser 35 40 45 Ile Met Tyr Pro Ser Asn Asn Cys Asp Lys Ile Glu Val Ile Ile Thr Leu Lys Glu Asn Lys Gly Gln Arg Cys Leu Asn Pro Lys Ser Lys Gln 65 70 75 80 Ala Arg Leu Ile Ile Lys Lys Val Glu Arg Lys Asn Phe Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys 130 135 Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys

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				325					330					335	
Leu	Ala	Thr	Asp 340	Leu	Thr	Гла	Val	Asn 345	Lys	Glu	Сүз	Сүз	His 350	Gly	Asp
Leu	Leu	Glu 355	Суз	Ala	Asp	Asp	Arg 360	Ala	Glu	Leu	Ala	Lys 365	Tyr	Met	Суз
Glu	Asn 370	Gln	Ala	Thr	Ile	Ser 375	Ser	Lys	Leu	Gln	Thr 380	Суз	Суз	Asp	Lys
Pro 385	Leu	Leu	Lys	Гла	Ala 390	His	Суз	Leu	Ser	Glu 395	Val	Glu	His	Asp	Thr 400
Met	Pro	Ala	Asp	Leu 405	Pro	Ala	Ile	Ala	Ala 410	Asp	Phe	Val	Glu	Asp 415	Gln
Glu	Val	Cys	Lys 420	Asn	Tyr	Ala	Glu	Ala 425	Lys	Asp	Val	Phe	Leu 430	Gly	Thr
Phe	Leu	Tyr 435	Glu	Tyr	Ser	Arg	Arg 440	His	Pro	Asp	Tyr	Ser 445	Val	Ser	Leu
Leu	Leu 450	Arg	Leu	Ala	Lys	Lys 455	Tyr	Glu	Ala	Thr	Leu 460	Glu	Lys	Сүз	Cys
Ala 465	Glu	Ala	Asn	Pro	Pro 470	Ala	Сүз	Tyr	Gly	Thr 475	Val	Leu	Ala	Glu	Phe 480
Gln	Pro	Leu	Val	Glu 485	Glu	Pro	Lys	Asn	Leu 490	Val	Lys	Thr	Asn	Cys 495	Asp
Leu	Tyr	Glu	Lys 500	Leu	Gly	Glu	Tyr	Gly 505	Phe	Gln	Asn	Ala	Ile 510	Leu	Val
Arg	Tyr	Thr 515	Gln	Гла	Ala	Pro	Gln 520	Val	Ser	Thr	Pro	Thr 525	Leu	Val	Glu
Ala	Ala 530	Arg	Asn	Leu	Gly	Arg 535	Val	Gly	Thr	Lys	Cys 540	Суз	Thr	Leu	Pro
Glu 545	Asp	Gln	Arg	Leu	Pro 550	Суз	Val	Glu	Asp	Tyr 555	Leu	Ser	Ala	Ile	Leu 560
Asn	Arg	Val	Суз	Leu 565	Leu	His	Glu	Lys	Thr 570	Pro	Val	Ser	Glu	His 575	Val
Thr	Lys	Суз	Cys 580	Ser	Gly	Ser	Leu	Val 585	Glu	Arg	Arg	Pro	Cys 590	Phe	Ser
Ala	Leu	Thr 595	Val	Asp	Glu	Thr	Tyr 600	Val	Pro	Lys	Glu	Phe 605	Lys	Ala	Glu
Thr	Phe 610	Thr	Phe	His	Ser	Asp 615	Ile	Суз	Thr	Leu	Pro 620	Glu	Lys	Glu	Lys
Gln 625	Ile	Lys	Lys	Gln	Thr 630	Ala	Leu	Ala	Glu	Leu 635	Val	ГЛа	His	Lys	Pro 640
Lys	Ala	Thr	Ala	Glu 645	Gln	Leu	Lys	Thr	Val 650	Met	Asp	Asp	Phe	Ala 655	Gln
Phe	Leu	Asp	Thr 660	Сув	Суз	Lys	Ala	Ala 665	Asp	Lys	Asp	Thr	Cys 670	Phe	Ser
Thr	Glu	Gly 675	Pro	Asn	Leu	Val	Thr 680	Arg	Суз	Lys	Aap	Ala 685	Leu	Ala	Gly
Gly	Gly 690	Gly	Ser	His	His	His 695	His	His	His						

<210> SEQ ID NO 74 <211> LENGTH: 697 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence

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Gln T		let 5	Ala	Gly	Ile	His	Leu 40	Lys	Asn	Ile	Gln	Ser 45	Leu	Lys	Val
Leu P: 5		er	Gly	Pro	His	Суз 55	Thr	Gln	Thr	Glu	Val 60	Ile	Ala	Thr	Leu
Lys A: 65	sn G	ly	Arg	Glu	Ala 70	Суз	Leu	Asp	Pro	Glu 75	Ala	Pro	Leu	Val	Gln 80
Lys I	le V	al	Gln	Lys 85	Met	Leu	Lys	Gly	Val 90	Pro	Lys	Gly	Gly	Gly 95	Gly
Ser G	ly G		Gly 100	Gly	Ser	Glu	Ala	His 105	Lys	Ser	Glu	Ile	Ala 110	His	Arg
Tyr A		ap 15	Leu	Gly	Glu	Gln	His 120	Phe	Lys	Gly	Leu	Val 125	Leu	Ile	Ala
Phe Se 1	er G 30	ln	Tyr	Leu	Gln	Lys 135	Сүз	Ser	Tyr	Asp	Glu 140	His	Ala	Lys	Leu
Val G 145	ln G	lu	Val	Thr	Asp 150	Phe	Ala	Lys	Thr	Сув 155	Val	Ala	Asp	Glu	Ser 160
Ala A	la A	sn	Суз	Asp 165	Lys	Ser	Leu	His	Thr 170	Leu	Phe	Gly	Asp	Lys 175	Leu
Сув А	la I		Pro 180	Asn	Leu	Arg	Glu	Asn 185	Tyr	Gly	Glu	Leu	Ala 190	Asp	Сув
Cys Tl		ys 95	Gln	Glu	Pro	Glu	Arg 200	Asn	Glu	Суз	Phe	Leu 205	Gln	His	Lys
Asp As 2	sp A 10	sn	Pro	Ser	Leu	Pro 215	Pro	Phe	Glu	Arg	Pro 220	Glu	Ala	Glu	Ala
Met C 225	ys T	'hr	Ser	Phe	Lys 230	Glu	Asn	Pro	Thr	Thr 235	Phe	Met	Gly	His	Tyr 240
Leu H	is G	lu	Val	Ala 245	Arg	Arg	His	Pro	Tyr 250	Phe	Tyr	Ala	Pro	Glu 255	Leu
Leu T	yr T	-	Ala 260	Glu	Gln	Tyr	Asn	Glu 265	Ile	Leu	Thr	Gln	Cys 270	Суз	Ala
Glu A		sp 75	rÀa	Glu	Ser	СЛа	Leu 280	Thr	Pro	Lys	Leu	Asp 285	Gly	Val	Гла
Glu Ly 2	ув А 90	la	Leu	Val	Ser	Ser 295	Val	Arg	Gln	Arg	Met 300	ГÀа	Сув	Ser	Ser
Met G 305	ln L	ys	Phe	Gly	Glu 310	Arg	Ala	Phe	Lys	Ala 315	Trp	Ala	Val	Ala	Arg 320
Leu S	er G	ln	Thr	Phe 325	Pro	Asn	Ala	Asp	Phe 330	Ala	Glu	Ile	Thr	Lys 335	Leu
Ala T	hr A	-	Leu 340	Thr	Lys	Val	Asn	Lys 345	Glu	Сув	Сүз	His	Gly 350	Asp	Leu
Leu G		уя 55	Ala	Asp	Asp	Arg	Ala 360	Glu	Leu	Ala	Lys	Tyr 365	Met	Суз	Glu
Asn G	ln A	la	Thr	Ile	Ser	Ser	Lys	Leu	Gln	Thr	Сүз	Сүз	Asp	Lys	Pro

	370					375					380				
Leu 385	Leu	Lys	Lys	Ala	His 390	Сүз	Leu	Ser	Glu	Val 395	Glu	His	Asp	Thr	Met 400
Pro	Ala	Asp	Leu	Pro 405	Ala	Ile	Ala	Ala	Asp 410	Phe	Val	Glu	Asp	Gln 415	Glu
Val	Cys	Lys	Asn 420	Tyr	Ala	Glu	Ala	Lys 425	Asp	Val	Phe	Leu	Gly 430	Thr	Phe
Leu	Tyr	Glu 435	Tyr	Ser	Arg	Arg	His 440	Pro	Asp	Tyr	Ser	Val 445	Ser	Leu	Leu
Leu	Arg 450	Leu	Ala	ГÀа	ГЛа	Tyr 455	Glu	Ala	Thr	Leu	Glu 460	ГЛа	Суз	Суз	Ala
Glu 465	Ala	Asn	Pro	Pro	Ala 470	Суз	Tyr	Gly	Thr	Val 475	Leu	Ala	Glu	Phe	Gln 480
Pro	Leu	Val	Glu	Glu 485	Pro	Lys	Asn	Leu	Val 490	Lys	Thr	Asn	Cys	Asp 495	Leu
Tyr	Glu	Lys	Leu 500	Gly	Glu	Tyr	Gly	Phe 505	Gln	Asn	Ala	Ile	Leu 510	Val	Arg
Tyr	Thr	Gln 515	Lys	Ala	Pro	Gln	Val 520	Ser	Thr	Pro	Thr	Leu 525	Val	Glu	Ala
Ala	Arg 530	Asn	Leu	Gly	Arg	Val 535	Gly	Thr	Lys	Сув	Cys 540	Thr	Leu	Pro	Glu
Asp 545	Gln	Arg	Leu	Pro	Cys 550	Val	Glu	Asp	Tyr	Leu 555	Ser	Ala	Ile	Leu	Asn 560
Arg	Val	Сув	Leu	Leu 565	His	Glu	Lys	Thr	Pro 570	Val	Ser	Glu	His	Val 575	Thr
Lys	Суз	Суз	Ser 580	Gly	Ser	Leu	Val	Glu 585	Arg	Arg	Pro	Суз	Phe 590	Ser	Ala
Leu	Thr	Val 595	Asp	Glu	Thr	Tyr	Val 600	Pro	Lys	Glu	Phe	Lys 605	Ala	Glu	Thr
Phe	Thr 610	Phe	His	Ser	Asp	Ile 615	Суз	Thr	Leu	Pro	Glu 620	Lys	Glu	Lys	Gln
Ile 625	Lys	Lys	Gln	Thr	Ala 630	Leu	Ala	Glu	Leu	Val 635	ГЛЗ	His	Lys	Pro	Lys 640
Ala	Thr	Ala	Glu	Gln 645	Leu	Lys	Thr	Val	Met 650	Asp	Asp	Phe	Ala	Gln 655	Phe
Leu	Aab	Thr	Cys 660	Сүз	Lys	Ala	Ala	Asp 665	Lys	Asp	Thr	Сүз	Phe 670	Ser	Thr
Glu	Gly	Pro 675	Asn	Leu	Val	Thr	Arg 680	Сув	Lys	Asp	Ala	Leu 685	Ala	Gly	Gly
Gly	Gly 690	Ser	His	His	His	His 695	His	His							
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Gly	Ala	Arg	Cys 20	Ala	Val	Val	Ala	Ser 25	Glu	Leu	Arg	Сув	Gln 30	Сув	Leu
Lys	Thr	Leu 35	Pro	Arg	Val	Asp	Phe 40	Lys	Asn	Ile	Gln	Ser 45	Leu	Ser	Val
Thr	Pro 50	Pro	Gly	Pro	His	Суз 55	Ala	Gln	Thr	Glu	Val 60	Ile	Ala	Thr	Leu
Lys 65	Gly	Gly	Gln	ГЛа	Val 70	Суз	Leu	Asp	Pro	Glu 75	Ala	Pro	Leu	Val	Gln 80
ГЛа	Ile	Ile	Gln	Lys 85	Ile	Leu	Asn	Lys	Gly 90	Lys	Ala	Asn	Gly	Gly 95	Gly
Gly	Ser	Gly	Gly 100	Gly	Gly	Ser	Glu	Ala 105	His	Lys	Ser	Glu	Ile 110	Ala	His
Arg	Tyr	Asn 115	Aap	Leu	Gly	Glu	Gln 120	His	Phe	Lys	Gly	Leu 125	Val	Leu	Ile
Ala	Phe 130		Gln	Tyr	Leu	Gln 135	Lys	Суз	Ser	Tyr	Asp 140		His	Ala	Lys
Leu 145		Gln	Glu	Val	Thr 150	Asp	Phe	Ala	Lys	Thr 155		Val	Ala	Asp	Glu 160
	Ala	Ala	Asn				Ser	Leu			Leu	Phe	Gly		
Leu	Суз	Ala		165 Pro	Asn	Leu	Arg		170 Asn	Tyr	Gly	Glu		175 Ala	Asp
Суз	Cys		180 Lys	Gln	Glu	Pro	Glu	185 Arg	Asn	Glu	Суз		190 Leu	Gln	His
Lys		195 Asp	Asn	Pro	Ser	Leu	200 Pro	Pro	Phe	Glu	Arg	205 Pro	Glu	Ala	Glu
Ala	210 Met	Сув	Thr	Ser	Phe	215 Lys	Glu	Asn	Pro	Thr	220 Thr	Phe	Met	Gly	His
225		-			230	-	Arg			235				-	240
-				245		-	-		250	-		-		255	
		-	260				Tyr	265					270	-	-
Ala	Glu	Ala 275	Asp	Lys	Glu	Ser	Cys 280	Leu	Thr	Pro	ГЛЗ	Leu 285	Asp	Gly	Val
ГЛа	Glu 290	Lys	Ala	Leu	Val	Ser 295	Ser	Val	Arg	Gln	Arg 300	Met	Lys	Суз	Ser
Ser 305	Met	Gln	ГЛа	Phe	Gly 310		Arg	Ala	Phe	Lys 315	Ala	Trp	Ala	Val	Ala 320
Arg	Leu	Ser	Gln	Thr 325	Phe	Pro	Asn	Ala	Asp 330	Phe	Ala	Glu	Ile	Thr 335	Lys
Leu	Ala	Thr	Asp 340	Leu	Thr	Lys	Val	Asn 345	Lys	Glu	Суз	Суз	His 350	Gly	Asp
Leu	Leu	Glu 355	Суз	Ala	Asp	Asp	Arg 360	Ala	Glu	Leu	Ala	Lys 365	Tyr	Met	Суз
Glu	Asn 370	Gln	Ala	Thr	Ile	Ser 375	Ser	Lys	Leu	Gln	Thr 380	СЛа	Суз	Asp	Lya
Pro 385		Leu	Lys	Lys	Ala 390	His	Сув	Leu	Ser	Glu 395		Glu	His	Asp	Thr 400
	Pro	Ala	Asp				Ile	Ala			Phe	Val	Glu	-	
Glu	Val	Cys	Lys	405 Asn	Tyr	Ala	Glu	Ala	410 Lys	Asp	Val	Phe	Leu	415 Gly	Thr
		1.0	1.5		1-				1.5	- L				-1	

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	420					425					430		
Phe Leu Ty 43		Tyr	Ser	Arg	Arg 440	His	Pro	Asp	Tyr	Ser 445	Val	Ser	Leu
Leu Leu Ar 450	rg Leu	Ala	Lys	Lys 455	Tyr	Glu	Ala	Thr	Leu 460	Glu	Lys	Сүз	Суз
Ala Glu Al 465	.a Asn	Pro	Pro 470	Ala	Суз	Tyr	Gly	Thr 475	Val	Leu	Ala	Glu	Phe 480
Gln Pro Le	eu Val	Glu 485	Glu	Pro	Lys	Asn	Leu 490	Val	Гла	Thr	Asn	Cys 495	Asp
Leu Tyr Gl	u Lys. 500		Gly	Glu	Tyr	Gly 505	Phe	Gln	Asn	Ala	Ile 510	Leu	Val
Arg Tyr Th 51		Lys	Ala	Pro	Gln 520	Val	Ser	Thr	Pro	Thr 525	Leu	Val	Glu
Ala Ala Ar 530	g Asn	Leu	Gly	Arg 535	Val	Gly	Thr	Lys	Cys 540	Суз	Thr	Leu	Pro
Glu Asp Gl 545	.n Arg	Leu	Pro 550	Суз	Val	Glu	Asp	Tyr 555	Leu	Ser	Ala	Ile	Leu 560
Asn Arg Va	al Cys	Leu 565	Leu	His	Glu	Гла	Thr 570	Pro	Val	Ser	Glu	His 575	Val
Thr Lys Cy	78 Cys 580		Gly	Ser	Leu	Val 585	Glu	Arg	Arg	Pro	Сув 590	Phe	Ser
Ala Leu Th 59	nr Val		Glu	Thr	Tyr 600		Pro	Lys	Glu	Phe 605		Ala	Glu
Thr Phe Tr 610		His	Ser	Asp 615		Суз	Thr	Leu	Pro 620		Lys	Glu	Гла
Gln Ile Ly 625	vs Lys	Gln	Thr 630		Leu	Ala	Glu	Leu 635		Lys	His	Lys	Pro 640
Lys Ala Tr	nr Ala	Glu 645		Leu	Гла	Thr	Val 650		Asp	Asp	Phe	Ala 655	
Phe Leu As		Cys	Cys	Гла	Ala			Lys	Asp	Thr			Ser
Thr Glu Gl	-		Leu	Val		665 Arg	Суз	Lys	Asp		670 Leu	Ala	Gly
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Asn Thr Le 35		Arg	Val	Asp	Phe 40	Glu	Thr	Ile	Gln	Ser 45	Leu	Thr	Val
Thr Pro Pr 50		Pro	His	Суз 55		Gln	Thr	Glu	Val 60		Ala	Thr	Leu
50				55					00				

													CIII	<u>ucu</u>	
Lys 65	Asp	Gly	Gln	Glu	Val 70	Суз	Leu	Asn	Pro	Gln 75	Gly	Pro	Arg	Leu	Gln 80
Ile	Ile	Ile	Гла	Lys 85	Ile	Leu	Lys	Ser	Gly 90	Lys	Ser	Ser	Gly	Gly 95	Gly
Gly	Ser	Gly	Gly 100	Gly	Gly	Ser	Glu	Ala 105	His	Lys	Ser	Glu	Ile 110	Ala	His
Arg	Tyr	Asn 115	Asp	Leu	Gly	Glu	Gln 120	His	Phe	Lys	Gly	Leu 125	Val	Leu	Ile
Ala	Phe 130	Ser	Gln	Tyr	Leu	Gln 135	-	Суз	Ser	Tyr	Asp 140	Glu	His	Ala	Lys
Leu 145	Val	Gln	Glu	Val	Thr 150	Asp	Phe	Ala	Lys	Thr 155	Суз	Val	Ala	Asp	Glu 160
Ser	Ala	Ala	Asn	Cys 165	Asp	LÀa	Ser	Leu	His 170	Thr	Leu	Phe	Gly	Asp 175	Lys
Leu	Cys	Ala	Ile 180	Pro	Asn	Leu	Arg	Glu 185	Asn	Tyr	Gly	Glu	Leu 190	Ala	Asp
Сүз	Cys	Thr 195	Lys	Gln	Glu	Pro	Glu 200	Arg	Asn	Glu	Суз	Phe 205	Leu	Gln	His
Lys	Asp 210	Asp	Asn	Pro	Ser	Leu 215	Pro	Pro	Phe	Glu	Arg 220	Pro	Glu	Ala	Glu
Ala 225	Met	Сув	Thr	Ser	Phe 230	-	Glu	Asn	Pro	Thr 235	Thr	Phe	Met	Gly	His 240
Tyr	Leu	His	Glu	Val 245	Ala	Arg	Arg	His	Pro 250	Tyr	Phe	Tyr	Ala	Pro 255	Glu
Leu	Leu	Tyr	Tyr 260	Ala	Glu	Gln	Tyr	Asn 265	Glu	Ile	Leu	Thr	Gln 270	Сүз	Сув
Ala	Glu	Ala 275	Asp	Lys	Glu	Ser	Cys 280	Leu	Thr	Pro	Lys	Leu 285	Asp	Gly	Val
ГЛа	Glu 290	Lys	Ala	Leu	Val	Ser 295	Ser	Val	Arg	Gln	Arg 300	Met	Lys	Cys	Ser
Ser 305	Met	Gln	Lys	Phe	Gly 310	Glu	Arg	Ala	Phe	Lys 315	Ala	Trp	Ala	Val	Ala 320
Arg	Leu	Ser	Gln	Thr 325	Phe	Pro	Asn	Ala	Asp 330	Phe	Ala	Glu	Ile	Thr 335	Lys
Leu	Ala	Thr	Asp 340		Thr	Lys	Val	Asn 345		Glu	Сүз	Суз	His 350		Asp
Leu	Leu	Glu 355		Ala	Asp	Asp	Arg 360	Ala	Glu	Leu	Ala	Lys 365		Met	Суа
Glu	Asn 370		Ala	Thr	Ile	Ser 375	Ser	Lys	Leu	Gln	Thr 380		Сув	Asp	Lys
Pro 385		Leu	Lys	Lys	Ala 390	His		Leu	Ser	Glu 395		Glu	His	Asp	Thr 400
	Pro	Ala	Asp	Leu 405			Ile	Ala	Ala 410		Phe	Val	Glu	Asp 415	
Glu	Val	Суз	-		Tyr	Ala	Glu	Ala		Asp	Val	Phe			Thr
Phe	Leu	-	420 Glu	Tyr	Ser	Arg	Arg	425 His	Pro	Asp	Tyr		430 Val	Ser	Leu
Leu	Leu	435 Arg	Leu	Ala	Lys	Lys	440 Tyr	Glu	Ala	Thr	Leu	445 Glu	Lys	Cys	Cys
	450	-			-	455	-				460		-	-	-
AIA	GIU	AId	ASI	PI0	PIO	AId	сув	Tyr	σту	1111	val	цец	MIG	GIU	File

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465															
N 7					470					475					480
in	Pro	Leu	Val	Glu 485	Glu	Pro	Lys	Asn	Leu 490	Val	ГЛа	Thr	Asn	Cys 495	Asp
Jeu	Tyr	Glu	Lys 500	Leu	Gly	Glu	Tyr	Gly 505	Phe	Gln	Asn	Ala	Ile 510	Leu	Val
Arg	Tyr	Thr 515	Gln	Lys	Ala	Pro	Gln 520	Val	Ser	Thr	Pro	Thr 525	Leu	Val	Glu
Ala	Ala 530	Arg	Asn	Leu	Gly	Arg 535	Val	Gly	Thr	Lys	Суз 540	СЛа	Thr	Leu	Pro
Glu 545	Asp	Gln	Arg	Leu	Pro 550	Суа	Val	Glu	Asp	Tyr 555	Leu	Ser	Ala	Ile	Leu 560
Asn	Arg	Val	Cys	Leu 565	Leu	His	Glu	Lys	Thr 570	Pro	Val	Ser	Glu	His 575	Val
Γhr	Lys	Cys	Cys 580	Ser	Gly	Ser	Leu	Val 585	Glu	Arg	Arg	Pro	Суз 590	Phe	Ser
Ala	Leu	Thr 595	Val	Asp	Glu	Thr	Tyr 600	Val	Pro	Lys	Glu	Phe 605	Lys	Ala	Glu
Γhr	Phe 610	Thr	Phe	His	Ser	Asp 615	Ile	Cys	Thr	Leu	Pro 620	Glu	Lys	Glu	Lys
Gln 625	Ile	Lys	Lys	Gln	Thr 630	Ala	Leu	Ala	Glu	Leu 635	Val	Lya	His	Lys	Pro 640
lys	Ala	Thr	Ala	Glu 645	Gln	Leu	Lys	Thr	Val 650	Met	Asp	Asp	Phe	Ala 655	Gln
Phe	Leu	Asp	Thr 660	Суз	Сүз	Гла	Ala	Ala 665	Asp	Lys	Asp	Thr	Cys 670	Phe	Ser
Γhr	Glu	Gly 675	Pro	Asn	Leu	Val	Thr 680	Arg	Cys	Lys	Asp	Ala 685	Leu	Ala	Gly
Jly	Gly 690		Ser	His	His	His 695	His	His	His						
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<211 <212 <213 <220 <223 <400 Met 1 Gly	L> LH 2> TY 3> OF 0> FH 3> OT (( 0)> SH Arg Ala	ENGTH (PE: RGANI EATUR THER Sly45 EQUEN Val Arg	H: 70 PRT ISM: RE: INFO Ser)- NCE: Pro Cys 20	D1 Art: DRMAT -Hise 77 Ala 5 Val	FION 6 Gln	: Syn Leu Ser	Leu Ala	Gly Gly 25	Leu 10 Pro	Leu Glu	Leu Glu	Leu Ser	Trp Asp 30	Leu 15 Gly	Pro Asp
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Ile	Ala	His 115	Arg	Tyr	Asn	Asp	Leu 120	Gly	Glu	Gln	His	Phe 125	Lys	Gly	Leu
Val	Leu 130	Ile	Ala	Phe	Ser	Gln 135	Tyr	Leu	Gln	Lys	Cys 140	Ser	Tyr	Asp	Glu
His 145	Ala	Lys	Leu	Val	Gln 150	Glu	Val	Thr	Asp	Phe 155	Ala	ГÀЗ	Thr	Суз	Val 160
Ala	Asp	Glu	Ser	Ala 165	Ala	Asn	Суз	Asp	Lys 170	Ser	Leu	His	Thr	Leu 175	Phe
Gly	Asp	Lys	Leu 180	Суз	Ala	Ile	Pro	Asn 185	Leu	Arg	Glu	Asn	Tyr 190	Gly	Glu
Leu	Ala	Asp 195	Cys	Сув	Thr	Lys	Gln 200	Glu	Pro	Glu	Arg	Asn 205	Glu	Cys	Phe
Leu	Gln 210	His	Lys	Asp	Asp	Asn 215	Pro	Ser	Leu	Pro	Pro 220	Phe	Glu	Arg	Pro
Glu 225	Ala	Glu	Ala	Met	Сув 230	Thr	Ser	Phe	Lys	Glu 235	Asn	Pro	Thr	Thr	Phe 240
Met	Gly	His	Tyr	Leu 245	His	Glu	Val	Ala	Arg 250		His	Pro	Tyr	Phe 255	Tyr
Ala	Pro	Glu	Leu 260	Leu	Tyr	Tyr	Ala	Glu 265	Gln	Tyr	Asn	Glu	Ile 270	Leu	Thr
Gln	Сув	Cys 275	Ala	Glu	Ala	Asp	Lys 280	Glu	Ser	Суз	Leu	Thr 285	Pro	Lys	Leu
Asp	Gly 290	Val	Lys	Glu	Lys	Ala 295	Leu	Val	Ser	Ser	Val 300	Arg	Gln	Arg	Met
Lys 305	Сув	Ser	Ser	Met	Gln 310	Lys	Phe	Gly	Glu	Arg 315	Ala	Phe	Lys	Ala	Trp 320
Ala	Val	Ala	Arg	Leu 325	Ser	Gln	Thr	Phe	Pro 330	Asn	Ala	Asp	Phe	Ala 335	Glu
Ile	Thr	Lys	Leu 340	Ala	Thr	Asp	Leu	Thr 345	ГЛа	Val	Asn	ГЛа	Glu 350	Суз	Суз
His	Gly	Asp 355	Leu	Leu	Glu	Суз	Ala 360	Asp	Asp	Arg	Ala	Glu 365	Leu	Ala	ГЛЗ
Tyr	Met 370	Сув	Glu	Asn	Gln	Ala 375	Thr	Ile	Ser	Ser	Lуз 380	Leu	Gln	Thr	Суз
Суз 385	Asp	Lys	Pro	Leu	Leu 390	Lys	Lys	Ala	His	Суз 395	Leu	Ser	Glu	Val	Glu 400
His	Asp	Thr	Met	Pro 405	Ala	Asp	Leu	Pro	Ala 410		Ala	Ala	Asp	Phe 415	Val
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Val	Ser 450	Leu	Leu	Leu	Arg	Leu 455	Ala	Гла	ГЛа	Tyr	Glu 460	Ala	Thr	Leu	Glu
Lys 465	Сув	Сув	Ala	Glu	Ala 470	Asn	Pro	Pro	Ala	Cys 475	Tyr	Gly	Thr	Val	Leu 480
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Ala 1	Ile	Leu	Asn	Arg 565	Val	Суз	Leu	Leu	His 570	Glu	Lys	Thr	Pro	Val 575	Ser
Glu H	His	Val	Thr 580	Lys	Суз	Суа	Ser	Gly 585	Ser	Leu	Val	Glu	Arg 590	Arg	Pro
CÀa 1	Phe	Ser 595		Leu	Thr	Val	Asp 600		Thr	Tyr	Val	Pro 605		Glu	Phe
Lys A	Ala 610		Thr	Phe	Thr	Phe 615		Ser	Asp	Ile	Суз 620		Leu	Pro	Glu
Lys C		Lys	Gln	Ile			Gln	Thr	Ala			Glu	Leu	Val	
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Phe A	Ala	Gln		645 Leu	Asp	Thr	Сув	-	650 Lys	Ala	Ala	Asp	-	655 Asp	Thr
Cys I	Phe		660 Thr	Glu	Gly	Pro		665 Leu	Val	Thr	Arg	-	670 Lys	Asp	Ala
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Pro I	Lya	Ile 35	Asn	Pro	ГЛа	Leu	Ile 40	Ala	Asn	Leu	Glu	Val 45	Ile	Pro	Ala
Gly E	Pro 50	Gln	Cys	Pro	Thr	Val 55	Glu	Val	Ile	Ala	Lys 60	Leu	Lys	Asn	Gln
Lys ( 65	Glu	Val	Cys	Leu	Asp 70	Pro	Glu	Ala	Pro	Val 75	Ile	ГЛа	Lys	Ile	Ile 80
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Gly C	Gly	Gly	-		Glu	Ala	His	-		Glu	Ile	Ala	His 110		Tyr
			100					105							
Asn A	Asp			Glu	Gln	His		Lys	Gly	Leu	Val			Ala	Phe
Asn A		115	Gly				120					125	Ile		
Ser C	Gln 130	115 Tyr	Gly Leu	Gln	Lys	Cys 135	120 Ser	Tyr	Asp	Glu	His 140	125 Ala	Ile Lys	Leu	Val

											-	con	tin	ued	
Ala	Asn	Сув	Asp	Lys 165	Ser	Leu	His	Thr	Leu 170	Phe	Gly	Aap	Lys	Leu 175	Сув
Ala	Ile	Pro	Asn 180	Leu	Arg	Glu	Asn	Tyr 185	Gly	Glu	Leu	Ala	Asp 190	Суз	Сүз
Thr	Lys	Gln 195	Glu	Pro	Glu	Arg	Asn 200	Glu	Cys	Phe	Leu	Gln 205	His	Lys	Asp
Asp	Asn 210	Pro	Ser	Leu	Pro	Pro 215	Phe	Glu	Arg	Pro	Glu 220	Ala	Glu	Ala	Met
Cys 225	Thr	Ser	Phe	Lys	Glu 230	Asn	Pro	Thr	Thr	Phe 235	Met	Gly	His	Tyr	Leu 240
His	Glu	Val	Ala	Arg 245	Arg	His	Pro	Tyr	Phe 250	Tyr	Ala	Pro	Glu	Leu 255	Leu
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Ala	Aab	Lys 275	Glu	Ser	Суа	Leu	Thr 280	Pro	Lys	Leu	Asp	Gly 285	Val	Lys	Glu
Lys	Ala 290	Leu	Val	Ser	Ser	Val 295	Arg	Gln	Arg	Met	Lys 300	Cys	Ser	Ser	Met
Gln 305	Lys	Phe	Gly	Glu	Arg 310	Ala	Phe	Lys	Ala	Trp 315	Ala	Val	Ala	Arg	Leu 320
Ser	Gln	Thr	Phe	Pro 325	Asn	Ala	Asp	Phe	Ala 330	Glu	Ile	Thr	Lys	Leu 335	Ala
Thr	Asp	Leu	Thr 340	Гла	Val	Asn	Lys	Glu 345	Суз	Сув	His	Gly	Asp 350	Leu	Leu
Glu	Cys	Ala 355	Asp	Asp	Arg	Ala	Glu 360	Leu	Ala	Lys	Tyr	Met 365	Суз	Glu	Asn
Gln	Ala 370	Thr	Ile	Ser	Ser	Lys 375	Leu	Gln	Thr	Сув	Cys 380	Asp	Lys	Pro	Leu
Leu 385	Lys	Lys	Ala	His	Сув 390	Leu	Ser	Glu	Val	Glu 395	His	Asp	Thr	Met	Pro 400
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Cys	Lys	Asn	Tyr 420	Ala	Glu	Ala	Lys	Asp 425	Val	Phe	Leu	Gly	Thr 430	Phe	Leu
Tyr	Glu	Tyr 435	Ser	Arg	Arg	His	Pro 440	Asp	Tyr	Ser	Val	Ser 445	Leu	Leu	Leu
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Glu	Lys	Leu	Gly 500	Glu	Tyr	Gly	Phe	Gln 505	Asn	Ala	Ile	Leu	Val 510	Arg	Tyr
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580       585       590         Thr Val App Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe       605         Thr Phe His Ser Asp 11e       Cys Thr Leu Pro Glu Lys Glu Lys Glu Lys Gln 11e         c10       610       Thr Ala Glu Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala         c25       Glu Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala       640         c35       Glu Glu Che Lys Thr Val Met App App Ala Clu Phe Ala Glu The Leu       640         c40       Glu Glu Che Lys Thr Val Met App App Ala Leu Ala Gly Gly Gly Gly Gly Gly Gly Cross Fire       650         Gly Pro Asn Leu Val Thr Arg Cys Lys App Ala Leu Ala Gly Gly Gly Gly Gly Gly Gross Fire       650         c210 - SEO ID NO 79       650       650         c212 - YEP PET       700       70         c410 - Hei Glu Leu Arg Cys Lys App Ala Leu Leu Leu Trp Leu Pro       15         c210 - SEO ID NO 79       71         c211 - SEQUENCE: 79       71         wet Arg Val Pro Ala Glu Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro       15         Gly Ala Arg Cys Ile Glu Leu Arg Cys Arg Cys Thr Asn Thr Ile Ser       70         Gly Ile Pro Phe Asn Ser Ile Ser Leu Val Asn Val Trp Arg Pro Gly       45         Gly Thr Cys Leu App Pro Asn Ala Pro Gly Val Lys Arg Ile Val Net       80         Gly Ile Pro Phe Asn Ser Ile Ser Clu Val Asn Val Trp Arg Pro Gly       10					565					570					575		
595600605The Phe His Ser Amp IIe Cya Thr Leu Pro Glu Lya Glu Lya Glu Lya Gln IIe 615Lya Lya Glu Thr Ala Leu Ala Glu Leu Val Lya His Lya Pro Lya Ala 630Gin Thr Ala Leu Ala Glu Leu Val Lya His Lya Pro Lya Ala 640Cya Lya Glu Thr Ala Clu Glu Leu Va Thr Val Met Amp Amp Amp Phe Ala Glu Phe See 660Gin Phe See 670Gin Glu Glu Clua Uya Clua Clua Clua Clua Clua Clua Clua Clu	САа	Cys	Ser	-	Ser	Leu	Val	Glu	-	Arg	Pro	Суз	Phe		Ala	Leu	
610615620Lye Lye Gin Thr Ala Leu Ala Glu Leu Val Lye His Lye Pro Lye Ala 630GasCastGasGasThr Ala Glu Gin Leu Lye Thr Val Met App App Phe Ala Gin Phe Leu 645GasAmp Thr Cye Cye Lye Ala Ala Asp Lye Asp Thr Cye Phe Ser Thr Glu 660Gis Fir Cye Pro Asi Leu Val Thr Arg Cye Lye Asp Ala Leu Ala Gly Gly Gly Gly 685Gly Pro Asi Leu Val Thr Arg Cye Lye Asp Ala Leu Ala Gly Gly Gly Gly 675Gis Fir Sin His His His His His 695Callo SEQ ID NO 79 Callo CRAHIGM: 691Callo SEQ UDN CFI PRT Callo SCQUENCE: 79Met Arg Val Pro Ala Glin Leu Leu Gly Leu Leu Leu Trp Leu Pro 10Gly Ala Arg Cye Ile Glu Leu Arg Cye Arg Cye Thr Am Thr Ile Ser 20Gly Ala Arg Cye Ile Glu Leu Arg Cye Arg Cye Thr Am Thr Ile Ser 20Gly Ja Pro Asi Asp Val Glu Val Ile Ala Thr Leu Lye Asp Gly Gli 40Val Hie Cye Ala Asp Val Glu Val Ile Ala Thr Leu Lye Asp Gly Gli 40So Cos Cye Cye Lye Asp Pro Asi Ala Pro Gly Val Lye Arg Ile Val Met 60So Cye Ser Tyr Ang Glu Ile Ala His Arg Tyr Asi Asp Leu Gly Glu 100Glin His Phe Lye Gly Leu Val Leu Ile Ala Phe Ser Glin Tyr Leu Gli 115Glin His Phe Lye Gly Cal Leu Asp Glu Ser 90Glu Asi Tyr Cye Val Ala Asp Glu Ser Ala Asp Cye Asp Asp Asp Asp Leu Gli Glu Val Thr Asp 116Glu Asi Tyr Arg Glu His Ala Asp Glu Ser Ala Asp Cye Asp Tyr Leu Glin 115Glu Ala His Lyes Cer Glu Ile Ala His Tyr Eu Glin Uli Thr Asp 1120Glu Ala His Lyes Cer Glu Ile Ala Asp Glu Ser Ala Asp Cye Asp Asp 150Glu Ala His Lyes Cer Tyr Asp Glu His Ala Asp Glu Ser Ala Ala Asp Cye Asp Lye 150Glu Ala His Lyes Cer Tyr Asp Glu His Al	Thr	Val	-	Glu	Thr	Tyr	Val		Lys	Glu	Phe	Гла		Glu	Thr	Phe	
625 630 630 635 640 Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu 650 660 660 660 660 660 660 660 660 660	Thr		His	Ser	Asp	Ile	-	Thr	Leu	Pro	Glu	-	Glu	Lys	Gln	Ile	
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$\begin{array}{c} 660 \\ 665 \\ 670 \\ 670 \\ 670 \\ 671 \\ 680 \\ 685 \\ 680 \\ 685 \\$	Thr	Ala	Glu	Gln		ГЛЗ	Thr	Val	Met	_	Asp	Phe	Ala	Gln		Leu	
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1       5       10       15         Gly       Ala       Arg       Cys       Ile       Gu       Leu       Arg       Cys       Th       Asn       Th       Asn       Th       Son       Ile       Ser         Gly       Ile       Pro       Phe       Asn       Son       Val       Son       Ile       Son       Gly       Asn       Th       Asn       Th       Ile       Ser       Gly         Val       Pro       Pro       Pro       Pro       Pro       Pro       Gly       Asn       Val       Typ       Arg       Pro       Gly         Val       Pro	<40	)> SH	EQUEN	ICE :	79												
20       25       30         G1       11e       See       Val       See       Val       See       Val       See       See       G1y         Val       Sin       Val       See       Val       See       Val       See       Val       See       G1y       See       G1y         Val       Sin       Val       See       Val       See       Val       See       Val       See       See </td <td></td> <td>Arg</td> <td>Val</td> <td>Pro</td> <td></td> <td>Gln</td> <td>Leu</td> <td>Leu</td> <td>Gly</td> <td></td> <td>Leu</td> <td>Leu</td> <td>Leu</td> <td>Trp</td> <td></td> <td>Pro</td> <td></td>		Arg	Val	Pro		Gln	Leu	Leu	Gly		Leu	Leu	Leu	Trp		Pro	
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65 $70$ $75$ $80$ Lys       Ile       Leu       Gly	Val		Суз	Ala	Asp	Val		Val	Ile	Ala	Thr		Lys	Asn	Gly	Gln	
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130       135       140         Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys       150       155         145       150       155       160         Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu       175       175         Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro       180       185       190         Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asp Asn Pro Ser Leu       115       140	Gln	His		Lys	Gly	Leu	Val		Ile	Ala	Phe	Ser		Tyr	Leu	Gln	
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	Arg	Glu	Asn		Gly	Glu	Leu	Ala		Cys	Сүз	Thr	Lys		Glu	Pro	
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Glu 225	Asn	Pro	Thr	Thr	Phe 230	Met	Gly	His	Tyr	Leu 235	His	Glu	Val	Ala	Arg 240
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Сув 385	Leu	Ser	Glu	Val	Glu 390	His	Asp	Thr	Met	Pro 395	Ala	Asp	Leu	Pro	Ala 400
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Arg	His	Pro 435		Tyr	Ser	Val	Ser 440		Leu	Leu	Arg	Leu 445		Lys	Lys
Tyr	Glu 450		Thr	Leu	Glu	Lys 455		Суз	Ala	Glu	Ala 460		Pro	Pro	Ala
Cys 465		Gly	Thr	Val	Leu 470		Glu	Phe	Gln	Pro 475		Val	Glu	Glu	Pro 480
	Asn	Leu	Val		Thr	Asn	Суз	Asp			Glu	ГЛа	Leu		
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Gln	Val		500 Thr	Pro	Thr	Leu		505 Glu	Ala	Ala	Arg		510 Leu	Gly	Arg
Val		515 Thr	Lys	Суа	Сув		520 Leu	Pro	Glu	Asp		525 Arg	Leu	Pro	Суз
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	-			565	Ser				570	-	-	-		575	
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Tyr	Val	Pro 595	Lys	Glu	Phe	Lys	Ala 600	Glu	Thr	Phe	Thr	Phe 605	His	Ser	Asp
Ile	Суз	Thr	Leu	Pro	Glu	ГЛа	Glu	ГЛа	Gln	Ile	ГЛа	ГЛа	Gln	Thr	Ala

-	cor	ıti	nu	ed

Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser His His His His His His <210> SEQ ID NO 80 <211> LENGTH: 730 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-mCXCL922-126-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEOUENCE: 80 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Thr Leu Val Ile Arg Asn Ala Arg Cys Ser Cys Ile Ser Thr Ser Arg Gly Thr Ile His Tyr Lys Ser Leu Lys Asp Leu Lys Gln Phe Ala Pro Ser Pro Asn Cys Asn Lys Thr Glu Ile Ile Ala Thr Leu Lys Asn Gly Asp Gln Thr Cys Leu Asp Pro Asp Ser Ala Asn Val Lys Lys Leu Met Lys Glu Trp Glu Lys Lys Ile Ser Gln Lys Lys Lys Gln Lys Arg Gly Lys Lys His Gln Lys Asn Met Lys Asn Arg Lys Pro Lys Thr Pro Gln Ser Arg Arg Arg Ser Arg Lys Thr Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu 

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Leu	Leu 290	Tyr	Tyr	Ala	Glu	Gln 295	Tyr	Asn	Glu	Ile	Leu 300	Thr	Gln	Суз	Суз
Ala 305	Glu	Ala	Asp	Lys	Glu 310	Ser	Суз	Leu	Thr	Pro 315	Lys	Leu	Asp	Gly	Val 320
Lys	Glu	Lys	Ala	Leu 325	Val	Ser	Ser	Val	Arg 330	Gln	Arg	Met	Lys	Cys 335	Ser
Ser	Met	Gln	Lys 340	Phe	Gly	Glu	Arg	Ala 345	Phe	Lys	Ala	Trp	Ala 350	Val	Ala
Arg	Leu	Ser 355		Thr	Phe	Pro	Asn 360		Asp	Phe	Ala	Glu 365		Thr	Lys
Leu	Ala 370		Aap	Leu	Thr	Lys 375		Asn	Lys	Glu	Суа 380		His	Gly	Asp
		Glu	Суз	Ala	_	Asp	Arg	Ala	Glu			Lys	Tyr	Met	-
385 Glu	Asn	Gln	Ala		390 Ile	Ser	Ser	Lys		395 Gln	Thr	Cys	Cys		400 Lys
Pro	Leu	Leu	-	405 Lys	Ala	His	Сүз		410 Ser	Glu	Val	Glu		415 Asp	Thr
Met	Pro	Ala	420 Asp	Leu	Pro	Ala	Ile	425 Ala	Ala	Asp	Phe	Val	430 Glu	Asp	Gln
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	450	-	-		-	455			-	-	460			-	
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Leu	Leu	Arg	Leu	Ala 485	Lys	Lys	Tyr	Glu	Ala 490	Thr	Leu	Glu	Lys	Cys 495	Сүз
Ala	Glu	Ala	Asn 500	Pro	Pro	Ala	Сүз	Tyr 505		Thr	Val	Leu	Ala 510	Glu	Phe
Gln	Pro	Leu 515	Val	Glu	Glu	Pro	Lys 520	Asn	Leu	Val	ГЛЗ	Thr 525	Asn	Суз	Asp
Leu	Tyr 530	Glu	Lys	Leu	Gly	Glu 535	Tyr	Gly	Phe	Gln	Asn 540	Ala	Ile	Leu	Val
Arg 545	Tyr	Thr	Gln	Lys	Ala 550	Pro	Gln	Val	Ser	Thr 555	Pro	Thr	Leu	Val	Glu 560
Ala	Ala	Arg	Asn	Leu 565	Gly	Arg	Val	Gly	Thr 570	Lys	Суа	Суа	Thr	Leu 575	Pro
Glu	Asp	Gln	Arg 580	Leu	Pro	Суа	Val	Glu 585	Asp	Tyr	Leu	Ser	Ala 590	Ile	Leu
Asn	Arg	Val 595	Сүз	Leu	Leu	His	Glu 600	Lys	Thr	Pro	Val	Ser 605	Glu	His	Val
Thr			Суз	Ser	Gly	Ser		Val	Glu	Arg			Суз	Phe	Ser
Ala	610 Leu	Thr	Val	Aap	Glu	615 Thr	Tyr	Val	Pro	Lys	620 Glu	Phe	Lys	Ala	Glu
625 Thr	Phe	Thr	Phe	Ніе	630 Ser	Asp	T10	Cve	Thr	635 Leu	Pro	Glu	Ive	Glu	640 Lvs
				645		-		-	650				-	655	-
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Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly 705 710 Gly Gly Gly Ser His His His His His <210> SEQ ID NO 81 <211> LENGTH: 702 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-mCXCL1022-98-(Gly4Ser)2-mouse SA-(Gly4Ser)-His6 <400> SEOUENCE: 81 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Ile Pro Leu Ala Arg Thr Val Arg Cys Asn Cys Ile His Ile Asp Asp Gly Pro Val Arg Met Arg Ala Ile Gly Lys Leu Glu Ile Ile Pro Ala Ser Leu Ser Cys Pro Arg Val Glu Ile Ile Ala Thr Met Lys Lys Asn Asp Glu Gln Arg Cys Leu Asn Pro Glu Ser Lys Thr Ile Lys Asn Leu Met Lys Ala Phe Ser Gln Lys Arg Ser Lys Arg Ala Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly 180 185 190 Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu 

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Leu	Asp 290	Gly	Val	ГÀа	Glu	Lys 295	Ala	Leu	Val	Ser	Ser 300	Val	Arg	Gln	Arg
Met 305	Lys	Суз	Ser	Ser	Met 310	Gln	Lys	Phe	Gly	Glu 315	Arg	Ala	Phe	Lys	Ala 320
Trp	Ala	Val	Ala	Arg 325		Ser	Gln	Thr	Phe 330	Pro	Asn	Ala	Asp	Phe 335	Ala
Glu	Ile	Thr	Lys 340	Leu	Ala	Thr	Asp	Leu 345	Thr	Lys	Val	Asn	Lys 350	Glu	СЛа
Сүз	His	Gly 355	Asp	Leu	Leu	Glu	Сув 360	Ala	Asp	Asp	Arg	Ala 365	Glu	Leu	Ala
ГЛа	Tyr 370	Met	Суз	Glu	Asn	Gln 375	Ala	Thr	Ile	Ser	Ser 380	Lys	Leu	Gln	Thr
Cys 385	Cys	Asp	Lys	Pro	Leu 390	Leu	Lys	Lys	Ala	His 395	Суз	Leu	Ser	Glu	Val 400
	His	Aab	Thr	Met 405		Ala	Asp	Leu	Pro 410		Ile	Ala	Ala	Asp 415	
Val	Glu	Asp	Gln 420		Val	Суз	Lys	Asn 425		Ala	Glu	Ala	Lys 430		Val
Phe	Leu	Gly 435		Phe	Leu	Tyr	Glu 440		Ser	Arg	Arg	His 445		Asp	Tyr
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	450 Lys	Сув	Суз	Ala		455 Ala	Asn	Pro	Pro		460 Cys	Tyr	Gly	Thr	
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Thr	Asn	Суз	_	485 Leu	Tyr	Glu	Lys		490 Gly	Glu	Tyr	Gly	Phe	495 Gln	Asn
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545					550		Arg			555			-	-	560
				565			Сүз		570					575	
Ser	Glu	His	Val 580	Thr	Lys	Суз	Сүз	Ser 585		Ser	Leu	Val	Glu 590	Arg	Arg
Pro	Сув	Phe 595	Ser	Ala	Leu	Thr	Val 600	Asp	Glu	Thr	Tyr	Val 605	Pro	Lys	Glu
Phe	Lys 610	Ala	Glu	Thr	Phe	Thr 615	Phe	His	Ser	Asp	Ile 620	Cys	Thr	Leu	Pro
Glu 625	Lys	Glu	Lys	Gln	Ile 630	Lys	Lys	Gln	Thr	Ala 635	Leu	Ala	Glu	Leu	Val 640
Lys	His	Lys	Pro	Lys 645	Ala	Thr	Ala	Glu	Gln 650	Leu	Lys	Thr	Val	Met 655	Asp
Asp	Phe	Ala	Gln 660		Leu	Asp	Thr	Cys 665		Lys	Ala	Ala	Asp 670		Asp
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Lys	Ala	Trp	Ala	Val 325	Ala	Arg	Leu	Ser	Gln 330	Thr	Phe	Pro	Asn	Ala 335	Asp
Phe	Ala	Glu	Ile 340	Thr	Lys	Leu	Ala	Thr 345	Asp	Leu	Thr	Lys	Val 350	Asn	Lys
Glu	Cys	Суз 355	His	Gly	Asp	Leu	Leu 360	Glu	Суз	Ala	Asp	Asp 365	Arg	Ala	Glu
Leu	Ala 370	Lys	Tyr	Met	Сүз	Glu 375	Asn	Gln	Ala	Thr	Ile 380	Ser	Ser	Lys	Leu
Gln 385	Thr	Суз	Суз	Asp	Lys 390	Pro	Leu	Leu	Lys	Lys 395	Ala	His	Суз	Leu	Ser 400
Glu	Val	Glu	His	Asp 405	Thr	Met	Pro	Ala	Asp 410	Leu	Pro	Ala	Ile	Ala 415	Ala
Asp	Phe	Val	Glu 420	Asp	Gln	Glu	Val	Cys 425	Lys	Asn	Tyr	Ala	Glu 430	Ala	Lys
Asp	Val	Phe 435	Leu	Gly	Thr	Phe	Leu 440	Tyr	Glu	Tyr	Ser	Arg 445	Arg	His	Pro
Asp	Tyr 450	Ser	Val	Ser	Leu	Leu 455	Leu	Arg	Leu	Ala	Lys 460	ГЛа	Tyr	Glu	Ala
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Lys 545	Cys	Суз	Thr	Leu	Pro 550	Glu	Asp	Gln	Arg	Leu 555	Pro	Суз	Val	Glu	Asp 560
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Lys	Glu 610			Ala	Glu	Thr 615	Phe	Thr	Phe	His	Ser 620		Ile	Суз	Thr
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	Val	Lys	His	Lys 645	Pro		Ala	Thr	Ala 650		Gln	Leu	Lys	Thr 655	
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Lys	Asp	Thr	660 Cys	Phe	Ser	Thr	Glu	665 Gly	Pro	Asn	Leu	Val	670 Thr	Arg	Суз
Lys	Asp	675 Ala	Leu	Ala	Glv	Glv	680 Gly	Glv	Ser	His	His	685 His	His	His	His
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10       15       10       15         eu       Pro       Gly       Ala       Arg       Cys       Glu       Ala       His       Lys       Ser       Glu       Ila       Ala       His       Arg         yr       Asn       Asp       Leu       Gly       Glu       Glu       His       Pro       Gly       Leu       Gly       His       Arg       Ys       Ser       Glu       His       Pho       Gly       Leu       Gly       Leu       Ila       Ala $50$ Gln       Tyr       Leu       Gly       Leu       Ila       Ala       Lys       Leu       Ila       Ala $50$ Gln       Tyr       Leu       Gly       Kap       Gly       Ser       Gly       Nr       Cys       Val       Ila       Lys       Leu       His       Mr $50$ Gln       Tyr       Leu       Gly       Kap       Kap <td></td> <td></td> <td></td> <td></td> <td>Pro</td> <td>∆la</td> <td>Gln</td> <td>I.e11</td> <td>I.011</td> <td>Clu</td> <td>T</td> <td>_</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>					Pro	∆la	Gln	I.e11	I.011	Clu	T	_							
20       25       30         yr       Asn       Asp       Leu       Gly       Gly       Leu       Val       Leu       Ile       Ala         as       So       Gly       Val       Val       Leu       Ile       Ala         as       Gln       Tyr       Leu       Gln       Lys       Cys       Ser       Tyr       Asp       Glu       His       Ala       Lys       Leu       Ile       Ala         al       Gln       Val       Thr       Asp       Phe       Ala       Lys       Thr       Ser       So         al       Gln       Val       Thr       Asp       Phe       Ala       Asp       Glu       Ser       So         al       Asn       Cys       Asp       Phe       Ala       Asp       Glu       Ser       So         yr       Ala       Asn       Cys       Asp       Leu       So       Ser       So	1 1	, nee	111.9		110	111Ca						1.011	Len	Len	Trn				
35       40       45         he       Ser       Gln       Tyr       Leu       Gln       Lys       Cys       Ser       Tyr       Asp       Glu       His       Ala       Lys       Leu         al       Glu       Val       Thr       Asp       Phe       Ala       Lys       Val       Ala       Asp       Glu       Ser         al       Glu       Val       Thr       Asp       Phe       Ala       Lys       Thr       Cys       Val       Ala       Asp       Glu       Ser         al       Ala       Asn       Cys       Asp       Lus       Thr       Cys       Val       Ala       Asp       Glu       Ser         ys       Ala       Asn       Cys       Asp       Lus       Thr       Leu       Phe       Glu       Asp       Lus       Asp       Sup       Lus       Sup       Sup       Lus       Asp       Lus       Asp       Lus       Asp       Lus       Asp       Lus       Asp       Lus       Sup				5						Gry	Leu	Leu	Leu		Trp				
50       55       60         a1       Glu       Val       Thr       Asp       Fhe       Ala       Lys       Thr       Cys       Val       Ala       Asp       Glu       Ser         a       Ala       Asn       Cys       Asp       Lys       Thr       Cys       Val       Ala       Asp       Glu       Ser         1a       Ala       Asn       Cys       Asp       Lys       Ser       Leu       His       Thr       Cys       Val       Ala       Asp       Glu       Ser       80         ys       Ala       Ile       Pro       Asp       Lys       Ser       Leu       His       Thr       Lys       Pro       Lys       Leu       Pro	Leu Prc	Gly			Сүз	Glu	Ala	His	10	-			Ala	15	-				
5       70       75       80         1a       Ala       Asn       Cys       Asp       Lys       Ser       Leu       His       Thr       Leu       Phe       Gly       Asp       Lys       Leu         ys       Ala       Ile       Pro       Asn       Leu       Arg       Glu       Asn       Tyr       Gly       Glu       Leu       Ala       Asp       Cys         ys       Ala       Ile       Pro       Asn       Leu       Arg       Glu       Cys       Glu       Leu       Ala       Asp       Cys         ys       Thr       Lys       Gln       Glu       Arg       Ala       Tyr       Glu       Glu       Asp       Cys         ys       Thr       Lys       Gln       Glu       Arg       Ang       Glu       Cys       Phe       Leu       Glu       Ala       Lys         ys       Thr       Lys       Gln       Glu       Pro       Glu       Ang       Pro       Glu       Ala       Glu       Ala         ys       Thr       Ser       Fro       Pro       Pro       Thr       Pro       Glu       Ala       Pro		1 Asp	20	Arg	-		His	His 25	10 Lys	Ser	Glu	Ile Val	Ala 30	15 His	Arg				
ys       Ala       Ile       Pro       Asn       Leu       Arg       Glu       Asn       Tyr       Gly       Glu       Leu       Ala       Asp       Cys         ys       Thr       Lys       Gln       Glu       Pro       Glu       Arg       Asn       Glu       Cys       Phe       Leu       Gln       His       Lys         ys       Thr       Lys       Gln       Glu       Pro       Glu       Arg       Asn       Glu       Cys       Phe       Leu       Gln       His       Lys         sp       Asp       Asn       Pro       Pho       Glu       Arg       Pro       Glu       Arg       Pro       Glu       Arg       Pro       Glu       Arg       Pro       Glu       Ala       Fit       Fit </td <td>Tyr Asn Phe Ser</td> <td>n Asp 35</td> <td>20 Leu</td> <td>Arg Gly</td> <td>Glu</td> <td>Gln Lys</td> <td>His 40</td> <td>His 25 Phe</td> <td>10 Lys Lys</td> <td>Ser Gly</td> <td>Glu Leu Glu</td> <td>Ile Val 45</td> <td>Ala 30 Leu</td> <td>15 His Ile</td> <td>Arg Ala</td> <td></td> <td></td> <td></td> <td></td>	Tyr Asn Phe Ser	n Asp 35	20 Leu	Arg Gly	Glu	Gln Lys	His 40	His 25 Phe	10 Lys Lys	Ser Gly	Glu Leu Glu	Ile Val 45	Ala 30 Leu	15 His Ile	Arg Ala				
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115       120       125         sp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala 130       135       Pro Phe Glu Arg Pro Glu Ala Glu Ala 140         et Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr 150       150       Pro Tyr 155         eu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu 165       160       Pro Tyr Phe Tyr Ala Pro Glu Leu 175         eu Tyr Tyr Ala Glu Gln Tyr Asn Glu 11e       Leu Thr Gln Cys Cys Ala 190       Pro Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys	Tyr Asn Phe Ser 50 Val Gln 65	n Asp 35 : Gln n Glu	20 Leu Tyr Val	Arg Gly Leu Thr Asp	Glu Gln Asp 70	Gln Lys 55 Phe	His 40 Cys Ala	His 25 Phe Ser Lys	10 Lys Lys Tyr Thr	Ser Gly Asp Cys 75	Glu Leu Glu 60 Val	Ile Val 45 His Ala	Ala 30 Leu Ala Asp	15 His Ile Lys Glu Lys	Arg Ala Leu Ser 80				
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	Tyr Asn Phe Ser 50 Val Gln 65 Ala Ala Cys Ala Cys Ala Cys Thr Asp Asp 130 Met Cys 145 Leu His	35 Gln Asp Glu Asn Ile Lys 115 Asn Thr Glu Glu	20 Leu Tyr Val Cys Pro 100 Gln Pro Ser Val Ala	Arg Gly Leu Thr Asp 85 Asn Glu Ser Phe Ala	Glu Gln Asp 70 Lys Leu Pro Leu Lys 150 Arg	Gln Lys 55 Phe Ser Arg Glu Pro 135 Glu Arg	His 40 Cys Ala Leu Glu Arg 120 Pro Asn His	His 25 Phe Ser Lys His Asn 105 Asn Phe Pro Pro Glu	10 Lys Tyr Thr Thr Glu Glu Thr Tyr Tyr Tyr	Ser Gly Asp Cys 75 Leu Gly Cys Arg Thr 155 Phe	Glu Leu Glu Oval Phe Glu Phe Pho 140 Phe Tyr	Ile Val 45 Ala Gly Leu Leu 125 Glu Met Ala	Ala 30 Leu Ala Asp Ala 110 Gln Ala Gly Pro Cys	15 His Lys Glu Lys Asp His Glu His Glu	Arg Ala Leu Ser 80 Leu Cys Lys Ala Tyr 160 Leu				

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													CIII	<u></u>	
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Ala	Arg	435 Asn	- Leu	Glv	Arq	Val	440 Glv	Thr	Lvs	Cvs	Cvs	445 Thr	Leu	Pro	Glu
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-		-		485		Glu	-		490					495	
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Ile 545	Lys	Lys	Gln	Thr	Ala 550	Leu	Ala	Glu	Leu	Val 555	Lys	His	Lys	Pro	Lys 560
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Gly	Gly		Gly	Gly	Gly	Gly			Gly	Gly	Gly		Ala	Ser	Ala

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Leu Pro Gly Ala Arg Cys Glu Ala His Lys Ser Glu Ile Ala His Arg 20 25 30
Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala 35 40 45
Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu 50 55 60
Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser

65					70					75					80
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Суз	Ala	Ile	Pro 100	Asn	Leu	Arg	Glu	Asn 105	Tyr	Gly	Glu	Leu	Ala 110	Asp	Сув
Суз	Thr	Lys 115	Gln	Glu	Pro	Glu	Arg 120	Asn	Glu	Сув	Phe	Leu 125	Gln	His	Lys
Asp	Asp 130	Asn	Pro	Ser	Leu	Pro 135	Pro	Phe	Glu	Arg	Pro 140	Glu	Ala	Glu	Ala
Met 145	Cys	Thr	Ser	Phe	Lys 150	Glu	Asn	Pro	Thr	Thr 155	Phe	Met	Gly	His	Tyr 160
Leu	His	Glu	Val	Ala 165	Arg	Arg	His	Pro	Tyr 170	Phe	Tyr	Ala	Pro	Glu 175	Leu
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Glu	Ala	Asp 195	Гла	Glu	Ser	Суз	Leu 200	Thr	Pro	Lys	Leu	Asp 205	Gly	Val	Lys
Glu	Lys 210	Ala	Leu	Val	Ser	Ser 215	Val	Arg	Gln	Arg	Met 220	Lys	Сув	Ser	Ser
Met 225	Gln	Lys	Phe	Gly	Glu 230	Arg	Ala	Phe	Lys	Ala 235	Trp	Ala	Val	Ala	Arg 240
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Ala	Thr	Asp	Leu 260	Thr	Lys	Val	Asn	Lys 265	Glu	Сүз	СЛа	His	Gly 270	Asp	Leu
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Asn	Gln 290	Ala	Thr	Ile	Ser	Ser 295	Lys	Leu	Gln	Thr	Суз 300	Сүз	Asp	Lys	Pro
Leu 305	Leu	Lys	Lys	Ala	His 310	Суз	Leu	Ser	Glu	Val 315	Glu	His	Asp	Thr	Met 320
Pro	Ala	Asp	Leu	Pro 325	Ala	Ile	Ala	Ala	Asp 330	Phe	Val	Glu	Asp	Gln 335	Glu
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Tyr	Glu	Lys	Leu 420		Glu	Tyr	Gly	Phe 425		Asn	Ala	Ile	Leu 430		Arg
Tyr	Thr			Ala	Pro	Gln		ser	Thr	Pro	Thr			Glu	Ala
Ala		435 Asn	Leu	Gly	Arg		440 Gly	Thr	Гла	Cys		445 Thr	Leu	Pro	Glu
Asp	450 Gln	Arg	Leu	Pro	Cys	455 Val	Glu	Asp	Tyr	Leu	460 Ser	Ala	Ile	Leu	Asn
465		5			470			T		475					480

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Arg	Val	Суз	Leu	Leu 485	His	Glu	Lys	Thr	Pro 490	Val	Ser	Glu	His	Val 495	Thr
Lya	Сув	Суз	Ser 500	Gly	Ser	Leu	Val	Glu 505	Arg	Arg	Pro	Суз	Phe 510	Ser	Ala
Leu	Thr	Val 515	Asp	Glu	Thr	Tyr	Val 520	Pro	Lys	Glu	Phe	Lys 525	Ala	Glu	Thr
Phe	Thr 530	Phe	His	Ser	Asp	Ile 535	Суз	Thr	Leu	Pro	Glu 540	Lys	Glu	Lys	Gln
Ile 545	Lys	ГЛа	Gln	Thr	Ala 550	Leu	Ala	Glu	Leu	Val 555	ГЛа	His	ГЛа	Pro	Lys 560
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Leu	Asp	Thr	Суз 580	СЛа	ГЛа	Ala	Ala	Asp 585	ГÀа	Asp	Thr	СЛа	Phe 590	Ser	Thr
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Gly	Gly 610	Ser	Gly	Gly	Gly	Gly 615	Ser	Gly	Gly	Gly	Gly 620	Ser	Ala	Ser	Asp
Ile 625	Gln	Met	Thr	Gln	Ser 630	Pro	Ser	Ser	Leu	Ser 635	Ala	Ser	Val	Gly	Asp 640
Arg	Val	Thr	Ile	Thr 645	Сүз	Arg	Ala	Ser	Gln 650	Ser	Tyr	Gly	Gly	Val 655	Ala
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Ser	Gly 690	Thr	Asp	Phe	Thr	Leu 695	Thr	Ile	Ser	Ser	Leu 700	Gln	Pro	Glu	Asp
705			-	-	710					715					720
	Gly			725			-	-	730					735	
	Gly	-	740			-		745					750		-
-	Gly	755				-	760			-		765	-		
Ser	770					775		Gly			780				
785					790					795					800
-	Tyr		-	805		-			810	-				815	
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Ala	Glu	Asp 835	Thr	Ala	Val	Tyr	Tyr 840	Суз	Ala	Arg	His	Tyr 845	Tyr	Trp	Tyr
Asp	Ala 850	Thr	Asp	Tyr	Trp	Gly 855	Gln	Gly	Thr	Leu	Val 860	Thr	Val	Ser	Ser
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Leu	Tyr	Glu 355	Tyr	Ser	Arg	Arg	His 360	Pro	Asp	Tyr	Ser	Val 365	Ser	Leu	Leu
Leu	Arg 370	Leu	Ala	Lys	Lys	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	Lys	Cys	Cys	Ala
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Сүз	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400
Pro	Leu	Val	Glu	Glu 405	Pro	Lys	Asn	Leu	Val 410	Lys	Thr	Asn	Суз	Asp 415	Leu
Tyr	Glu	Lys	Leu 420	Gly	Glu	Tyr	Gly	Phe 425	Gln	Asn	Ala	Ile	Leu 430	Val	Arg
Tyr	Thr	Gln 435	Lys	Ala	Pro	Gln	Val 440	Ser	Thr	Pro	Thr	Leu 445	Val	Glu	Ala
Ala	Arg 450	Asn	Leu	Gly	Arg	Val 455	Gly	Thr	ГЛа	Сув	Сув 460	Thr	Leu	Pro	Glu
Asp 465	Gln	Arg	Leu	Pro	Cys 470	Val	Glu	Asp	Tyr	Leu 475	Ser	Ala	Ile	Leu	Asn 480
Arg	Val	Сув	Leu	Leu 485	His	Glu	Lys	Thr	Pro 490	Val	Ser	Glu	His	Val 495	Thr
Lys	Суз	Сув	Ser 500	Gly	Ser	Leu	Val	Glu 505	Arg	Arg	Pro	Сув	Phe 510	Ser	Ala
Leu	Thr	Val 515	Asp	Glu	Thr	Tyr	Val 520	Pro	Lys	Glu	Phe	Lys 525	Ala	Glu	Thr
Phe	Thr 530	Phe	His	Ser	Asp	Ile 535	Суз	Thr	Leu	Pro	Glu 540	Lys	Glu	Lys	Gln
Ile 545	Lys	Lys	Gln	Thr	Ala 550	Leu	Ala	Glu	Leu	Val 555	ГÀа	His	Lys	Pro	Lys 560
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Leu	Asp	Thr	Суз 580	Суз	Lys	Ala	Ala	Asp 585	ГÀЗ	Asp	Thr	Суз	Phe 590	Ser	Thr
Glu	Gly	Pro 595	Asn	Leu	Val	Thr	Arg 600	Суз	Lys	Asp	Ala	Leu 605	Ala	Gly	Gly
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625	Gln				630					635				-	640
Arg	Val	Thr	Ile	Thr 645	Суз	Arg	Ala	Ser	Gln 650	Tyr	Gly	Gly	Tyr	Val 655	Ala
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Phe 705	Ala	Thr	Tyr	Tyr	Cys 710	Gln	Arg	Gly	His	Ala 715	Leu	Ile	Thr	Phe	Gly 720
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Ser	Gly	Gly	Ser 740	Ser	Ser	Gly	Ala	Glu 745	Val	Gln	Leu	Val	Glu 750	Ser	Gly

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Ser	Gly 770	Phe	Asn	Ile	Ser	Ser 775	Tyr	Gly	Ser	Met	His 780	Trp	Val	Arg	Gln
Ala 785	Pro	Gly	Lys	Gly	Leu 790	Glu	Trp	Val	Ala	Ser 795	Ile	Tyr	Pro	Tyr	Ser 800
Ser	Ser	Thr	Tyr	Tyr 805	Ala	Asp	Ser	Val	Lys 810	Gly	Arg	Phe	Thr	Ile 815	Ser
Ala	Aab	Thr	Ser 820	Lys	Asn	Thr	Ala	Tyr 825	Leu	Gln	Met	Asn	Ser 830	Leu	Arg
Ala	Glu	Asp 835	Thr	Ala	Val	Tyr	Tyr 840	Суз	Ala	Arg	Gly	Tyr 845	Gly	Pro	Trp
Tyr	Ala 850	Tyr	Ser	Tyr	Phe	Ala 855	Leu	Asp	Tyr	Trp	Gly 860	Gln	Gly	Thr	Leu
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1 Leu	Pro	Gly		5 Arg	Суз	Glu	Ala		10 Lys	Ser	Glu	Ile		15 His	Arg
Tyr	Asn		20 Leu	Gly	Glu	Gln	His 40	25 Phe	Lys	Gly	Leu	Val 45	30 Leu	Ile	Ala
Phe	Ser 50	35 Gln	Tyr	Leu	Gln	Lys 55		Ser	Tyr	Asp	Glu 60		Ala	Lys	Leu
Val 65		Glu	Val	Thr	Asp 70		Ala	Lys	Thr	Суз 75		Ala	Asp	Glu	Ser 80
	Ala	Asn	Суз	Asp 85	Lys	Ser	Leu	His	Thr 90		Phe	Gly	Asp	Lys 95	
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Суз	Thr	Lys 115	Gln	Glu	Pro	Glu	Arg 120	Asn	Glu	Cys	Phe	Leu 125	Gln	His	Lys
Asp	Asp 130	Asn	Pro	Ser	Leu	Pro 135	Pro	Phe	Glu	Arg	Pro 140	Glu	Ala	Glu	Ala
Met 145	Сув	Thr	Ser	Phe	Lys 150	Glu	Asn	Pro	Thr	Thr 155	Phe	Met	Gly	His	Tyr 160
Leu	His	Glu	Val	Ala 165	Arg	Arg	His	Pro	Tyr 170	Phe	Tyr	Ala	Pro	Glu 175	Leu
Leu	Tyr	Tyr	Ala 180	Glu	Gln	Tyr	Asn	Glu 185	Ile	Leu	Thr	Gln	Cys 190	СЛа	Ala
Glu	Ala	Asp 195	Lys	Glu	Ser	Суз	Leu 200	Thr	Pro	Lys	Leu	Asp 205	Gly	Val	Lys
Glu	Lys 210	Ala	Leu	Val	Ser	Ser 215	Val	Arg	Gln	Arg	Met 220	Lys	Суз	Ser	Ser

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Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu 325 330 Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly 595 600 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Ala 

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I1 62		Gln	Met	Thr	Arg	Ser 630	Pro	Ser	Ser	Leu	Ser 635	Ala	Ser	Val	Gly	Asp 640			
Ar	g	Val	Thr	Ile	Thr 645	Суз	Arg	Ala	Ser	Gln 650	Tyr	His	Asp	Gly	Ser 655	Ala			
Al	.a	Trp	Tyr	Gln 660	Gln	Lys	Pro	Gly	Lys 665	Ala	Pro	ГЛа	Leu	Leu 670	Ile	Tyr			
Gl	y .	Ala	Ser 675	Tyr	Leu	Tyr	Ser	Gly 680	Val	Pro	Ser	Arg	Phe 685	Ser	Gly	Ser			
Ar		Ser 690	Gly	Thr	Asp	Phe	Thr 695	Leu	Thr	Ile	Ser	Ser 700	Leu	Gln	Pro	Glu			
As 70	_	Phe	Ala	Thr	Tyr	Tyr 710	Суз	Gln	Gln	Ser	Ser 715	Tyr	Ser	Leu	Ile	Thr 720			
Ph	ne	Gly	Cys	Gly	Thr 725	Lys	Val	Glu	Ile	Lys 730	Gly	Thr	Thr	Ala	Ala 735	Ser			
Gl	·У	Ser	Ser	Gly 740		Ser	Ser	Ser	Gly 745	Ala	Glu	Val	Gln	Leu 750	Val	Glu			
Se	er.	Asp	Gly 755		Leu	Val	Gln	Pro 760	Gly	Gly	Ser	Leu	Arg 765	Leu	Ser	Суз			
Al		Ala 770			Phe	Asn	Leu 775	Ser	Tyr	Tyr	Gly	Met 780		Trp	Val	Arg			
G1 78	.n		Pro	Gly	Lys	Cys 790		Glu	Trp	Val	Ala 795		Ile	Ala	Ser	Tyr 800			
		Gly	Tyr	Thr	Ser 805	Tyr	Ala	Asp	Ser	Val 810		Gly	Arg	Phe	Thr 815				
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Ar	g	Ala	Glu 835		Thr	Ala	Val	Tyr 840		Сув	Ala	Arg	Ser 845		Tyr	Ser			
Ту				Tyr	Tyr	Ser	Trp 855		Ser	Ala	Gly			Tyr	Trp	Gly			
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				NCE :															
M∈ 1	et .	Asp	Met	Arg	Val 5	Pro	Ala	Gln	Leu	Leu 10	Gly	Leu	Leu	Leu	Leu 15	Trp			
Le	eu	Pro	Gly	Ala 20	Arg	Сүз	Glu	Ala	His 25	Lys	Ser	Glu	Ile	Ala 30	His	Arg			
Ту	r.	Asn	Asp 35	Leu	Gly	Glu	Gln	His 40	Phe	Lys	Gly	Leu	Val 45	Leu	Ile	Ala			
Ph		Ser 50	Gln	Tyr	Leu	Gln	Lys 55	Суз	Ser	Tyr	Asp	Glu 60	His	Ala	Lys	Leu			
Va 65		Gln	Glu	Val	Thr	Asp 70	Phe	Ala	Lys	Thr	Сув 75	Val	Ala	Asp	Glu	Ser 80			

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Суз	Ala	Ile	Pro 100	Asn	Leu	Arg	Glu	Asn 105	Tyr	Gly	Glu	Leu	Ala 110	Asp	Суз
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Leu	Tyr	Glu 355	Tyr	Ser	Arg	Arg	His 360	Pro	Asp	Tyr	Ser	Val 365	Ser	Leu	Leu
Leu	Arg 370	Leu	Ala	Lys	Lys	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	Lys	Суз	Сүз	Ala
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Суз	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400
Pro	Leu	Val	Glu	Glu 405	Pro	Lys	Asn	Leu	Val 410	Lys	Thr	Asn	Суа	Asp 415	Leu
Tyr	Glu	Lys	Leu 420	Gly	Glu	Tyr	Gly	Phe 425	Gln	Asn	Ala	Ile	Leu 430	Val	Arg
Tyr	Thr	Gln 435	Lys	Ala	Pro	Gln	Val 440	Ser	Thr	Pro	Thr	Leu 445	Val	Glu	Ala
Ala	Arg 450	Asn	Leu	Gly	Arg	Val 455	Gly	Thr	Lys	Сув	Сув 460	Thr	Leu	Pro	Glu
Asp 465		Arg	Leu	Pro	Cys 470	Val	Glu	Asp	Tyr	Leu 475	Ser	Ala	Ile	Leu	Asn 480
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Ile 545	Lys	Lys	Gln	Thr	Ala 550	Leu	Ala	Glu	Leu	Val 555	Lys	His	Lys	Pro	Lys 560
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Glγ	Ala	Ser 675	Tyr	Leu	Tyr	Ser	Gly 680	Val	Pro	Ser	Arg	Phe 685	Ser	Gly	Ser
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As <u>r</u> 705	Phe	Ala	Thr	Tyr	Tyr 710	Суз	Gln	Gln	Ser	Ser 715	Tyr	Ser	Leu	Ile	Thr 720
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Glγ	Ser	Ser	Gly 740	Gly	Ser	Ser	Ser	Gly 745	Ala	Glu	Val	Gln	Leu 750	Val	Glu
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Leu	Tyr	Glu 355	Tyr	Ser	Arg	Arg	His 360	Pro	Asp	Tyr	Ser	Val 365	Ser	Leu	Leu
Leu	Arg 370	Leu	Ala	Lys	Lys	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	Lys	Cys	Суз	Ala
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Сүз	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400
Pro	Leu	Val	Glu	Glu 405	Pro	Lys	Asn	Leu	Val 410	Lys	Thr	Asn	Cys	Asp 415	Leu
Tyr	Glu	Lys	Leu 420	Gly	Glu	Tyr	Gly	Phe 425	Gln	Asn	Ala	Ile	Leu 430	Val	Arg
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Arg	Val	Thr	Ile	Thr 645	Сүз	Arg	Ala	Ser	Gln 650	Ser	Tyr	Gly	Gly	Val 655	Ala
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	Val	Сув	Leu	Leu 485		Glu	Lys	Thr	Pro 490		Ser	Glu	His	Val 495	
Lys	Сув	Сув	Ser		Ser	Leu	Val	Glu		Arg	Pro	Суз	Phe		Ala

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-	CO	LL.	ι.	1	11	u	e	CI.

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His	His	His													
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Leu	Tyr	Glu 355	Tyr	Ser	Arg	Arg	His 360	Pro	Asp	Tyr	Ser	Val 365	Ser	Leu	Leu
Leu	Arg 370	Leu	Ala	Lys	Lys	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	Lys	Суз	Суз	Ala
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Сүз	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400
Pro	Leu	Val	Glu	Glu 405	Pro	ГЛЗ	Asn	Leu	Val 410	Гла	Thr	Asn	Суз	Asp 415	Leu
Tyr	Glu	Lys	Leu 420	Gly	Glu	Tyr	Gly	Phe 425	Gln	Asn	Ala	Ile	Leu 430	Val	Arg
Tyr	Thr	Gln 435	Lys	Ala	Pro	Gln	Val 440	Ser	Thr	Pro	Thr	Leu 445	Val	Glu	Ala
Ala	Arg 450	Asn	Leu	Gly	Arg	Val 455	Gly	Thr	Lys	Суз	Cys 460	Thr	Leu	Pro	Glu
Asp 465	Gln	Arg	Leu	Pro	Cys 470	Val	Glu	Asp	Tyr	Leu 475	Ser	Ala	Ile	Leu	Asn 480
Arg	Val	Суз	Leu	Leu 485	His	Glu	Lys	Thr	Pro 490	Val	Ser	Glu	His	Val 495	Thr
Lys	Суз	Суз	Ser 500	Gly	Ser	Leu	Val	Glu 505	Arg	Arg	Pro	Суз	Phe 510	Ser	Ala

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Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr 515 520 525	
Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln 530 535 540	
Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys 545 550 555 560	
Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe 565 570 575	
Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr 580 585 590	
Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly 595 600 605	
Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Ala 610 615 620	
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 625 630 635 640	
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Asn Pro Tyr Tyr Tyr 645 650 655	
Gly Gly Thr His Trp Val Arg Gln Ala Pro Gly Glu Glu Leu Glu Trp 660 665 670	
Val Ala Ser Ile Gly Ser Tyr Pro Gly Tyr Thr Asp Tyr Ala Asp Ser 675 680 685	
Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala 690 695 700	
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr 705 710 715 720	
Cys Ala Arg His Tyr Tyr Trp Tyr Asp Ala Thr Asp Tyr Trp Gly Gln 725 730 735	
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser His His His 740 745 750	
His His	
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Leu Pro Gly Ala Arg Cys Glu Ala His Lys Ser Glu Ile Ala His Arg 20 25 30	
Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala 35 40 45	
Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu 50 55 60	
Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser	
65 70 75 80 Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu	
85 90 95	

Cys	Ala	Ile	Pro 100	Asn	Leu	Arg	Glu	Asn 105	Tyr	Gly	Glu	Leu	Ala 110	Asp	Сув	
Cys	Thr	Lys 115	Gln	Glu	Pro	Glu	Arg 120	Asn	Glu	Cys	Phe	Leu 125	Gln	His	Lys	
Asp	Asp 130	Asn	Pro	Ser	Leu	Pro 135	Pro	Phe	Glu	Arg	Pro 140	Glu	Ala	Glu	Ala	
Met 145	Cys	Thr	Ser	Phe	Lys 150	Glu	Asn	Pro	Thr	Thr 155	Phe	Met	Gly	His	Tyr 160	
Leu	His	Glu	Val	Ala 165	Arg	Arg	His	Pro	Tyr 170	Phe	Tyr	Ala	Pro	Glu 175	Leu	
Leu	Tyr	Tyr	Ala 180	Glu	Gln	Tyr	Asn	Glu 185	Ile	Leu	Thr	Gln	Cys 190	Суз	Ala	
Glu	Ala	Asp 195	Lys	Glu	Ser	Суз	Leu 200	Thr	Pro	Lys	Leu	Asp 205	Gly	Val	Lys	
Glu	Lys 210	Ala	Leu	Val	Ser	Ser 215	Val	Arg	Gln	Arg	Met 220	Lys	Cys	Ser	Ser	
Met 225	Gln	Lys	Phe	Gly	Glu 230	Arg	Ala	Phe	Lys	Ala 235	Trp	Ala	Val	Ala	Arg 240	
Leu	Ser	Gln	Thr	Phe 245	Pro	Asn	Ala	Asp	Phe 250	Ala	Glu	Ile	Thr	Lys 255	Leu	
Ala	Thr	Asp	Leu 260	Thr	Lys	Val	Asn	Lys 265	Glu	Cys	Cys	His	Gly 270	Asp	Leu	
Leu	Glu	Cys 275	Ala	Asp	Asp	Arg	Ala 280	Glu	Leu	Ala	Lys	Tyr 285	Met	Суз	Glu	
Asn	Gln 290	Ala	Thr	Ile	Ser	Ser 295	Lys	Leu	Gln	Thr	Суз 300	Сүз	Aab	Lys	Pro	
Leu 305	Leu	Lys	Lys	Ala	His 310	Суз	Leu	Ser	Glu	Val 315	Glu	His	Aab	Thr	Met 320	
Pro	Ala	Asp	Leu	Pro 325	Ala	Ile	Ala	Ala	Asp 330	Phe	Val	Glu	Asp	Gln 335	Glu	
Val	Суа	Lys	Asn 340	Tyr	Ala	Glu	Ala	Lys 345	Asp	Val	Phe	Leu	Gly 350	Thr	Phe	
Leu	Tyr	Glu 355	Tyr	Ser	Arg	Arg	His 360	Pro	Asp	Tyr	Ser	Val 365	Ser	Leu	Leu	
Leu	Arg 370	Leu	Ala	ГЛа	ГЛа	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	ГЛа	Суз	Суз	Ala	
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Сүз	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400	
Pro	Leu	Val	Glu	Glu 405	Pro	Lys	Asn	Leu	Val 410	Lys	Thr	Asn	Cys	Asp 415	Leu	
Tyr	Glu	Γλa	Leu 420	Gly	Glu	Tyr	Gly	Phe 425	Gln	Asn	Ala	Ile	Leu 430	Val	Arg	
Tyr	Thr	Gln 435	Lys	Ala	Pro	Gln	Val 440	Ser	Thr	Pro	Thr	Leu 445	Val	Glu	Ala	
Ala	Arg 450	Asn	Leu	Gly	Arg	Val 455	Gly	Thr	Lys	Cys	Cys 460	Thr	Leu	Pro	Glu	
Asp 465	Gln	Arg	Leu	Pro	Cys 470	Val	Glu	Asp	Tyr	Leu 475	Ser	Ala	Ile	Leu	Asn 480	
Arg	Val	Суз	Leu	Leu 485	His	Glu	Lys	Thr	Pro 490	Val	Ser	Glu	His	Val 495	Thr	

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Lys	Cys	Сув	Ser 500	Gly	Ser	Leu	Val	Glu 505	Arg	Arg	Pro	СЛа	Phe 510	Ser	Ala
Leu	Thr	Val 515	Asp	Glu	Thr	Tyr	Val 520	Pro	Lys	Glu	Phe	Lys 525	Ala	Glu	Thr
Phe	Thr 530	Phe	His	Ser	Asp	Ile 535	-	Thr	Leu	Pro	Glu 540	ГЛа	Glu	Lys	Gln
Ile 545	Lys	Lys	Gln	Thr	Ala 550	Leu	Ala	Glu	Leu	Val 555	ГÀз	His	Lys	Pro	Lys 560
Ala	Thr	Ala	Glu	Gln 565	Leu	Lys	Thr	Val	Met 570	Asp	Asp	Phe	Ala	Gln 575	Phe
Leu	Asp	Thr	Cys 580	Суа	ГЛа	Ala	Ala	Asp 585	ГЛа	Asp	Thr	Суз	Phe 590	Ser	Thr
Glu	Gly	Pro 595	Asn	Leu	Val	Thr	Arg 600		ГЛа	Asp	Ala	Leu 605	Ala	Gly	Gly
Gly	Gly 610	Ser	Gly	Gly	Gly	Gly 615		Gly	Gly	Gly	Gly 620	Ser	Ala	Ser	Asp
Ile 625	Gln	Met	Thr	Gln	Ser 630	Pro	Ser	Pro	Leu	Ser 635	Ala	Ser	Val	Gly	Asp 640
Arg	Val	Thr	Ile	Thr 645	Суа	Arg	Ala	Ser	Gln 650	Tyr	Gly	Gly	Tyr	Val 655	Ala
Trp	Tyr	Gln	Gln 660	Lys	Pro	Gly	Lys	Ala 665	Pro	Lys	Leu	Leu	Ile 670	Tyr	Gly
Ala	Ser	Leu 675	Leu	Tyr	Ser	Gly	Val 680	Pro	Ser	Arg	Phe	Ser 685	Gly	Gly	Arg
Ser	Gly 690	Thr	Asp	Phe	Thr	Leu 695	Thr	Ile	Ser	Ser	Leu 700	Gln	Pro	Glu	Asp
Phe 705	Ala	Thr	Tyr	Tyr	Cys 710	Gln	Arg	Gly	His	Ala 715	Leu	Ile	Thr	Phe	Gly 720
СЛа	Gly	Thr	Lys	Val 725	Glu	Ile	Glu	Gly	Thr 730	Thr	Ala	Ala	Ser	Gly 735	Ser
Ser	Gly	Gly	Ser 740	Ser	Ser	Gly	Ala	Glu 745	Val	Gln	Leu	Val	Glu 750	Ser	Gly
Gly	Gly	Leu 755	Val	Gln	Pro	Gly	Gly 760		Leu	Arg	Leu	Ser 765	Суз	Ala	Ala
Ser	Gly 770	Phe	Asn	Ile	Ser	Ser 775	Tyr	Gly	Ser	Met	His 780	Trp	Val	Arg	Gln
Ala 785	Pro	Gly	Lys	Суз	Leu 790	Glu	Trp	Val	Ala	Ser 795	Ile	Tyr	Pro	Tyr	Ser 800
	Ser	Thr	Tyr	Tyr 805	Ala	Asp	Ser	Val	Lys 810	Gly	Arg	Phe	Thr	Ile 815	
Ala	Asp	Thr	Ser 820	Гла	Asn	Thr	Ala	Tyr 825	Leu	Gln	Met	Asn	Ser 830	Leu	Arg
Ala	Glu	Asp 835		Ala	Val	Tyr	Tyr 840	-	Ala	Arg	Gly	Tyr 845	Gly	Pro	Trp
Tyr			Ser	Tyr	Phe		Leu		Tyr	Trp			Gly	Thr	Leu
	850 Thr	Val	Ser	Ser	-	-		Gly	Ser		860 His	His	His	His	
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<211> LENGTH: 880 <212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-mouse SA-(Gly4Ser)3-scFv (VL-VH) CK129-ds2 (VL43A>C / VH105Q>C)-(Gly4Ser)-His6 <400> SEQUENCE: 105 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser 65 70 75 80 Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu 275 280 285 Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu 

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Leu	Arg 370	Leu	Ala	Lys	Lys	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	Lys	Сув	Суз	Ala
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Сүз	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400
Pro	Leu	Val	Glu	Glu 405	Pro	Lys	Asn	Leu	Val 410	Lys	Thr	Asn	Cys	Asp 415	Leu
Tyr	Glu	Lys	Leu 420	Gly	Glu	Tyr	Gly	Phe 425	Gln	Asn	Ala	Ile	Leu 430	Val	Arg
Tyr	Thr	Gln 435	Lys	Ala	Pro	Gln	Val 440	Ser	Thr	Pro	Thr	Leu 445	Val	Glu	Ala
Ala	Arg 450	Asn	Leu	Gly	Arg	Val 455	Gly	Thr	Lys	Сув	Cys 460	Thr	Leu	Pro	Glu
Asp 465	Gln	Arg	Leu	Pro	Cys 470	Val	Glu	Asp	Tyr	Leu 475	Ser	Ala	Ile	Leu	Asn 480
Arg	Val	Cys	Leu	Leu 485	His	Glu	Lys	Thr	Pro 490	Val	Ser	Glu	His	Val 495	Thr
ГЛа	Cys	Cys	Ser 500	Gly	Ser	Leu	Val	Glu 505	Arg	Arg	Pro	Суз	Phe 510	Ser	Ala
Leu	Thr	Val 515	Asp	Glu	Thr	Tyr	Val 520	Pro	Lys	Glu	Phe	Lys 525	Ala	Glu	Thr
Phe	Thr 530	Phe	His	Ser	Asp	Ile 535	Сүз	Thr	Leu	Pro	Glu 540	Lys	Glu	Lys	Gln
Ile 545	Lys	Lys	Gln	Thr	Ala 550	Leu	Ala	Glu	Leu	Val 555	Lys	His	Lys	Pro	Lys 560
Ala	Thr	Ala	Glu	Gln 565	Leu	Lys	Thr	Val	Met 570	Asp	Asp	Phe	Ala	Gln 575	Phe
Leu	Asp	Thr	Cys 580	Сув	Lys	Ala	Ala	Asp 585	Lys	Asp	Thr	Суз	Phe 590	Ser	Thr
Glu	Gly	Pro 595	Asn	Leu	Val	Thr	Arg 600	Суз	Lys	Asp	Ala	Leu 605	Ala	Gly	Gly
Gly	Gly 610	Ser	Gly	Gly	Gly	Gly 615	Ser	Gly	Gly	Gly	Gly 620	Ser	Ala	Ser	Asp
Ile 625	Gln	Met	Thr	Gln	Ser 630	Pro	Ser	Pro	Leu	Ser 635	Ala	Ser	Val	Gly	Asp 640
Arg	Val	Thr	Ile	Thr 645	Суз	Arg	Ala	Ser	Gln 650	Tyr	Gly	Gly	Tyr	Val 655	Ala
Trp	Tyr	Gln	Gln 660	Гла	Pro	Gly	ГЛа	Суз 665	Pro	ГЛа	Leu	Leu	Ile 670	Tyr	Gly
Ala	Ser	Leu 675	Leu	Tyr	Ser	Gly	Val 680	Pro	Ser	Arg	Phe	Ser 685	Gly	Gly	Arg
Ser	Gly 690	Thr	Asp	Phe	Thr	Leu 695	Thr	Ile	Ser	Ser	Leu 700	Gln	Pro	Glu	Asp
Phe 705	Ala	Thr	Tyr	Tyr	Cys 710	Gln	Arg	Gly	His	Ala 715	Leu	Ile	Thr	Phe	Gly 720
Gln	Gly	Thr	Lys	Val 725	Glu	Ile	Glu	Gly	Thr 730	Thr	Ala	Ala	Ser	Gly 735	Ser
Ser	Gly	Gly	Ser 740		Ser	Gly	Ala	Glu 745		Gln	Leu	Val	Glu 750	Ser	Gly
Gly	Gly			Gln	Pro	Gly	-		Leu	Arg	Leu			Ala	Ala
Ser	Gly	755 Phe	Asn	Ile	Ser	Ser	760 Tyr	Gly	Ser	Met	His	765 Trp	Val	Arg	Gln

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770     775     780       Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Ser Ile Tyr Pro Tyr Ser	
785 790 795 800	
Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser 805 810 815	
Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg 820 825 830	
Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Tyr Gly Pro Trp 835 840 845	
Tyr Ala Tyr Ser Tyr Phe Ala Leu Asp Tyr Trp Gly Cys Gly Thr Leu 850 855 860	
Val Thr Val Ser Ser Gly Gly Gly Gly Ser His His His His His His 865 870 875 880	
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Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala 35 40 45	
Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu 50 55 60	
Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser 65 70 75 80	
Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu 85 90 95	
Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys 100 105 110	
Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys 115 120 125	
Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala 130 135 140	
Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr 145 150 155 160	
Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu 165 170 175	
Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala 180 185 190	
Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys 195 200 205	
Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser 210 215 220	
Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg 225 230 235 240	

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Leu	Ser	Gln	Thr	Phe 245	Pro	Asn	Ala	Asp	Phe 250	Ala	Glu	Ile	Thr	Lys 255	Leu
Ala	Thr	Asp	Leu 260	Thr	Lys	Val	Asn	Lys 265		Суз	СЛа	His	Gly 270	Asp	Leu
Leu	Glu	Cys 275	Ala	Asp	Asp	Arg	Ala 280	Glu	Leu	Ala	Lys	Tyr 285	Met	Суз	Glu
Asn	Gln 290	Ala	Thr	Ile	Ser	Ser 295	Lys	Leu	Gln	Thr	Суз 300	Суз	Asp	Lys	Pro
Leu 305	Leu	Lys	Lys	Ala	His 310	Суз	Leu	Ser	Glu	Val 315	Glu	His	Asp	Thr	Met 320
Pro	Ala	Asp	Leu	Pro 325	Ala	Ile	Ala	Ala	Asp 330	Phe	Val	Glu	Asp	Gln 335	Glu
Val	Cys	Lys	Asn 340		Ala	Glu	Ala	Lys 345		Val	Phe	Leu	Gly 350	Thr	Phe
Leu	Tyr	Glu 355	Tyr	Ser	Arg	Arg	His 360		Asp	Tyr	Ser	Val 365	Ser	Leu	Leu
Leu	Arg 370	Leu	Ala	ГЛа	Lya	Tyr 375	Glu	Ala	Thr	Leu	Glu 380	ГЛа	Суз	Суз	Ala
Glu 385	Ala	Asn	Pro	Pro	Ala 390	Суа	Tyr	Gly	Thr	Val 395	Leu	Ala	Glu	Phe	Gln 400
Pro	Leu	Val	Glu	Glu 405	Pro	Lys	Asn	Leu	Val 410	Lys	Thr	Asn	Суз	Asp 415	Leu
Tyr	Glu	Lys	Leu 420		Glu	Tyr	Gly	Phe 425		Asn	Ala	Ile	Leu 430		Arg
Tyr	Thr	Gln 435		Ala	Pro	Gln	Val 440	Ser	Thr	Pro	Thr	Leu 445	Val	Glu	Ala
Ala	Arg 450		Leu	Gly	Arg	Val 455		Thr	Lys	Суз	Cys 460		Leu	Pro	Glu
Asp 465		Arg	Leu	Pro	Cys 470	Val	Glu	Asp	Tyr	Leu 475		Ala	Ile	Leu	Asn 480
	Val	Cys	Leu	Leu 485		Glu	Lys	Thr	Pro 490		Ser	Glu	His	Val 495	
Lys	Суз	Суз	Ser 500		Ser	Leu	Val	Glu 505		Arg	Pro	Суз	Phe 510		Ala
Leu	Thr			Glu	Thr	Tyr			Lys	Glu	Phe	-		Glu	Thr
Phe		515 Phe	His	Ser	Asp	Ile	520 Cys	Thr	Leu	Pro		525 Lys	Glu	Lys	Gln
	530 Lys	Lys	Gln	Thr		535 Leu	Ala	Glu	Leu		540 Lys	His	Lys	Pro	-
545 Ala	Thr	Ala	Glu		550 Leu	Lys	Thr	Val		555 Asp	Aap	Phe	Ala	Gln	560 Phe
Leu	Asp	Thr	Cys	565 Cys	Lys	Ala	Ala	Asp	570 Lys	Asp	Thr	Cys	Phe	575 Ser	Thr
	-		580	-	-			585	-	-		-	590		
	-	595				Thr	600	-	-	-		605		-	-
Gly	Gly 610	Ser	Gly	Gly	Gly	Gly 615	Ser	Gly	Gly	Gly	Gly 620	Ser	Ala	Ser	Gln
Val 625	Lys	Leu	Glu	Gln	Ser 630	Gly	Ala	Glu	Val	Val 635	ГЛа	Pro	Gly	Ala	Ser 640
Val	Lys	Leu	Ser	Сув	LYa	Ala	Ser	Gly	Phe	Asn	Ile	ГЛа	Asp	Ser	Tyr

645 650 655	
Met His Trp Leu Arg Gln Gly Pro Gly Gln Cys Leu Glu Trp Ile Gly	
660 665 670	
Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe Gln675680685	
Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Ala Asn Thr Ala Tyr Leu 690 695 700	
Gly Leu Ser Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn 705 710 715 720	
Glu Gly Thr Pro Thr Gly Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly 725 730 735	
Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly 740 745 750	
Ser Gly Gly Gly Gly Ser Glu Asn Val Leu Thr Gln Ser Pro Ser Ser 755 760 765	
Met Ser Val Ser Val Gly Asp Arg Val Thr Ile Ala Cys Ser Ala Ser 770 775 780	
Ser Ser Val Pro Tyr Met His Trp Leu Gln Gln Lys Pro Gly Lys Ser	
785         790         795         800           Pro Leg Leg Leg Leg Thr Cor Am Leg Als Cor Cly Vol Pro         Pro         Pro	
Pro Lys Leu Leu Ile Tyr Leu Thr Ser Asn Leu Ala Ser Gly Val Pro 805 810 815	
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile 820 825 830	
Ser Ser Val Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg 835 840 845	
Ser Ser Tyr Pro Leu Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys 850 855 860	
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gagetgagat gecagtgeet geagaceetg cagggeatee acceeaagaa cateeagage	180
gtgaacgtga agtcccctgg cccccactgc gcccagaccg aagtgatcgc caccctgaag	240
aacggccgga aggcctgcct gaaccccgcc agccccatcg tgaagaaaat catcgagaag	300
atgetgaaca gegacaagag caaeggegga ggegaacaaa agettatete egaagaagae	360
ttgcaggaac tgacaactat atgcgagcaa atcccctcac caactttaga atcgacgccg	420
tactctttgt caacgactac tattttggcc aacgggaagg caatgcaagg agtttttgaa	480
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	Gln Lys Le	u Ile Ser (	3lu Glu As	p Leu Gln Glu	ı Leu Thr T	hr Ile Cys		

Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser 130 135 140 Thr Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser 165 170 Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr Gln Tyr Val Phe <210> SEQ ID NO 128 <211> LENGTH: 190 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL238-107-G3-c-myc-Aga2 <400> SEQUENCE: 128 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu Gly Ser Leu Asp Lys Arg Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr Leu Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Lys Val Lys Ser Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn Gly Gln Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Lys Lys Ile Ile Glu Lys Met Leu Lys Asn Gly Lys Ser Asn Gly Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln Glu Leu Thr Thr Ile Cys Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr Gln Tyr Val Phe <210> SEQ ID NO 129 <211> LENGTH: 190 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL338-107-G3-c-myc-Aga2 <400> SEQUENCE: 129 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu 

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Thr	Leu 50	Gln	Gly	Ile	His	Leu 55	Lys	Asn	Ile	Gln	Ser 60	Val	Asn	Val	Arg
Ser 65	Pro	Gly	Pro	His	Cys 70	Ala	Gln	Thr	Glu	Val 75	Ile	Ala	Thr	Leu	Lys 80
Asn	Gly	Lys	Lys	Ala 85	Суз	Leu	Asn	Pro	Ala 90	Ser	Pro	Met	Val	Gln 95	Lys
Ile	Ile	Glu	Lys 100	Ile	Leu	Asn	Lys	Gly 105	Ser	Thr	Asn	Gly	Gly 110	Gly	Glu
Gln	ГЛа	Leu 115	Ile	Ser	Glu	Glu	Asp 120	Leu	Gln	Glu	Leu	Thr 125	Thr	Ile	Суз
Glu	Gln 130	Ile	Pro	Ser	Pro	Thr 135	Leu	Glu	Ser	Thr	Pro 140	Tyr	Ser	Leu	Ser
Thr 145	Thr	Thr	Ile	Leu	Ala 150	Asn	Gly	Lys	Ala	Met 155	Gln	Gly	Val	Phe	Glu 160
Tyr	Tyr	Lys	Ser	Val 165	Thr	Phe	Val	Ser	Asn 170	Cys	Gly	Ser	His	Pro 175	Ser
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						_	_						_	_	_
Met 1	Lys	Val	Leu	Ile 5	Val	Leu	Leu	Ala	Ile 10	Phe	Ala	Ala	Leu	Pro 15	Leu
Ala	Leu	Ala	Gln 20	Pro	Val	Ile	Ser	Thr 25	Thr	Val	Gly	Ser	Ala 30	Ala	Glu
Gly	Ser	Leu 35	Aab	Lys	Arg	Glu	Ala 40	Glu	Glu	Asp	Gly	Asp 45	Leu	Gln	Суа
Leu	Сув 50	Val	ГЛа	Thr	Thr	Ser 55	Gln	Val	Arg	Pro	Arg 60	His	Ile	Thr	Ser
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					70					75					80
Ala	Thr	Leu	Lys	Asn 85	70 Gly	Arg	Lys	Ile	Суз 90	75 Leu	Thr	Leu	Gln	Ala 95	80 Pro
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Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln Glu Leu Thr Thr Ile Cys Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr Gln Tyr Val Phe <210> SEQ ID NO 133 <211> LENGTH: 183 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL759-121-G3-c-myc-Aga2 <400> SEQUENCE: 133 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu Gly Ser Leu Asp Lys Arg Ala Glu Leu Arg Cys Met Cys Ile Lys Thr Thr Ser Gly Ile His Pro Lys Asn Ile Gln Ser Leu Glu Val Ile Gly Lys Gly Thr His Cys Asn Gln Val Glu Val Ile Ala Thr Leu Lys Asp Gly Arg Lys Ile Cys Leu Asp Pro Asp Ala Pro Arg Ile Lys Lys Ile Val Gln Lys Lys Leu Gly Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln Glu Leu Thr Thr Ile Cys Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser Thr Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr Gln Tyr Val Phe <210> SEQ ID NO 134 <211> LENGTH: 191 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-hCXCL829-99-G3-c-myc-Aga2 <400> SEQUENCE: 134 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu 1 5 Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu

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			20					25					30		
Gly	Ser	Leu 35	Asp	Lys	Arg	Ala	Lys 40	Glu	Leu	Arg	Суз	Gln 45	Cys	Ile	Lys
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Glu	Gln	Lys 115	Leu	Ile	Ser	Glu	Glu 120	Asp	Leu	Gln	Glu	Leu 125	Thr	Thr	Ile
Сув	Glu 130	Gln	Ile	Pro	Ser	Pro 135	Thr	Leu	Glu	Ser	Thr 140	Pro	Tyr	Ser	Leu
Ser 145	Thr	Thr	Thr	Ile	Leu 150	Ala	Asn	Gly	Lys	Ala 155	Met	Gln	Gly	Val	Phe 160
Glu	Tyr	Tyr	Lys	Ser 165	Val	Thr	Phe	Val	Ser 170	Asn	Сув	Gly	Ser	His 175	Pro
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Gly	Ser	T						25	1111	Val	Gly	Ser	30	AIA	Glu
Cys		цец 35	Asp	ГЛа	Arg	Thr	Pro 40								
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Leu 65	50	35	Thr	Asn	Gln	Gly 55	40 Thr	Val Ile	Val His	Arg Leu	Lys Gln 60	Gly 45 Ser	30 Arg Leu	Cys Lys	Ser Asp
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Ala 65	Ser	Ile	Met	Tyr	Pro 70	Ser	Asn	Asn	Cys	Asp 75	Lys	Ile	Glu	Val	Ile 80
Ile	Thr	Leu	Lys	Glu 85	Asn	Lys	Gly	Gln	Arg 90	Суз	Leu	Asn	Pro	Lys 95	Ser
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Val	Phe	Glu	Tyr	Tyr 165	Lys	Ser	Val	Thr	Phe 170	Val	Ser	Asn	Суз	Gly 175	Ser
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Phe															
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Ile	Val	Gln	Lys 100		Leu	ГЛа	Gly	Val 105		Lys	Gly	Gly	Gly 110	Glu	Gln
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Gln	Ile 130	Pro	Ser	Pro	Thr	Leu 135	Glu	Ser	Thr	Pro	Tyr 140	Ser	Leu	Ser	Thr
Thr 145	Thr	Ile	Leu	Ala	Asn 150	Gly	Lys	Ala	Met	Gln 155	Gly	Val	Phe	Glu	Tyr 160
Tyr	Lys	Ser	Val	Thr 165	Phe	Val	Ser	Asn	Cys 170	Gly	Ser	His	Pro	Ser 175	Thr
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Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln Glu Leu Thr Thr Ile Cys 115 120 125 Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser 135 140 130 Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu 145 150 155 160 Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser 170 165 175 Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr Gln Tyr Val Phe 180 185 <210> SEQ ID NO 141 <211> LENGTH: 196 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-mCXCL430-105-G3-c-myc-Aga2 <400> SEOUENCE: 141 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu 1 5 10 15 Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu 20 25 30 Gly Ser Leu Asp Lys Arg Val Thr Ser Ala Gly Pro Glu Glu Ser Asp 35 40 45 Gly Asp Leu Ser Cys Val Cys Val Lys Thr Ile Ser Ser Gly Ile His 50 55 60 Leu Lys His Ile Thr Ser Leu Glu Val Ile Lys Ala Gly Arg His Cys 65 70 80 Ala Val Pro Gln Leu Ile Ala Thr Leu Lys Asn Gly Arg Lys Ile Cys 85 90 95 Leu Asp Arg Gln Ala Pro Leu Tyr Lys Lys Val Ile Lys Lys Ile Leu 100 105 110 Glu Ser Gly Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln 120 115 125 Glu Leu Thr Thr Ile Cys Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser 135 130 140 Thr Pro Tyr Ser Leu Ser Thr Thr Thr Ile Leu Ala Asn Gly Lys Ala 145 150 155 160 Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn 165 170 175 Cys Gly Ser His Pro Ser Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr 180 185 190 Gln Tyr Val Phe 195 <210> SEQ ID NO 142 <211> LENGTH: 191 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-mCXCL548-118-G3-c-myc-Aga2 <400> SEQUENCE: 142 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu 1 5 10 15

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Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu Gly Ser Leu Asp Lys Arg Ala Thr Glu Leu Arg Cys Val Cys Leu Thr Val Thr Pro Lys Ile Asn Pro Lys Leu Ile Ala Asn Leu Glu Val Ile Pro Ala Gly Pro Gln Cys Pro Thr Val Glu Val Ile Ala Lys Leu Lys Asn Gln Lys Glu Val Cys Leu Asp Pro Glu Ala Pro Val Ile Lys Lys Ile Ile Gln Lys Ile Leu Gly Ser Asp Lys Lys Lys Ala Gly Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln Glu Leu Thr Thr Ile 115 120 Cys Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser Thr Thr Ser Lys Gly Ser Pro Ile Asn Thr Gln Tyr Val Phe <210> SEQ ID NO 143 <211> LENGTH: 186 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: LS-mCXCL748-113-G3-c-myc-Aga2 <400> SEQUENCE: 143 Met Lys Val Leu Ile Val Leu Leu Ala Ile Phe Ala Ala Leu Pro Leu Ala Leu Ala Gln Pro Val Ile Ser Thr Thr Val Gly Ser Ala Ala Glu Gly Ser Leu Asp Lys Arg Ile Glu Leu Arg Cys Arg Cys Thr Asn Thr Ile Ser Gly Ile Pro Phe Asn Ser Ile Ser Leu Val Asn Val Tyr Arg Pro Gly Val His Cys Ala Asp Val Glu Val Ile Ala Thr Leu Lys Asn Gly Gln Lys Thr Cys Leu Asp Pro Asn Ala Pro Gly Val Lys Arg Ile Val Met Lys Ile Leu Glu Gly Tyr Gly Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gln Glu Leu Thr Thr Ile Cys Glu Gln Ile Pro Ser Pro Thr Leu Glu Ser Thr Pro Tyr Ser Leu Ser Thr Thr Thr Ile Leu Ala Asn Gly Lys Ala Met Gln Gly Val Phe Glu Tyr Tyr Lys Ser Val Thr Phe Val Ser Asn Cys Gly Ser His Pro Ser Thr Thr Ser Lys 

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gccaaattag tgcaggaagt aacagacttt gcaaagacgt gtgttgccga tgagtctg	cc 180
gccaactgtg acaaatccct tcacactctt tttggagata agttgtgtgc cattccaa	ac 240
ctccgtgaaa actatggtga actggctgac tgctgtacaa aacaagagcc cgaaagaa	ac 300
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	ag 600
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ccgaagettg atggtgtgaa ggagaaagea ttggteteat etgteegtea gagaatga tgeteeagta tgeagaagtt tggagagaga gettttaaag eatgggeagt agetegte ageeagaeat teeceaatge tgaetttgea gaaateacea aattggeaae agaeetga aaagteaaca aggagtgetg eeatggtgae etgetggaat gegeagatga eagggegg	ag 600 tg 660 cc 720 aa 780 gc 840

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Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp 35 40 45	

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Glu	Arg	Asn	Glu 100	-	Phe	Leu	Gln	His 105	ГЛа	Asp	Asp	Asn	Pro 110	Ser	Leu		
Pro	Pro	Phe 115	Glu	Arg	Pro	Glu	Ala 120	Glu	Ala	Met	Суз	Thr 125	Ser	Phe	Lys		
Glu	Asn 130	Pro	Thr	Thr	Phe	Met 135	Gly	His	Tyr	Leu	His 140	Glu	Val	Ala	Arg		
Arg 145	His	Pro	Tyr	Phe	Tyr 150	Ala	Pro	Glu	Leu	Leu 155	Tyr	Tyr	Ala	Glu	Gln 160		
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Суз	Суз	Ala 170	Glu	Ala	Asp	Lys	Glu 175	Ser		
Суа	Leu	Thr	Pro 180	ГЛа	Leu	Asp	Gly	Val 185	ГЛа	Glu	ГЛа	Ala	Leu 190	Val	Ser		
Ser	Val	Arg 195	Gln	Arg	Met	ГЛа	Cys 200	Ser	Ser	Met	Gln	Lуя 205	Phe	Gly	Glu		
Arg	Ala 210		Lys	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro		
Asn 225	Ala	Asp	Phe	Ala	Glu 230	Ile	Thr	Lys	Leu	Ala 235	Thr	Asp	Leu	Thr	Lys 240		
Val	Asn	Lys	Glu	Cys 245		His	Gly	Asp	Leu 250	Leu	Glu	Сүз	Ala	Asp 255	Asp		
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Суз	Leu 290		Glu	Val	Glu	His 295		Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala		
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Суз	ГЛа	Asn	Tyr	Ala 320		
Glu	Ala	Lys	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg		
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys		
Tyr	Glu	Ala 355	Thr	Leu	Glu	Lys	Суз 360	Суз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala		
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro		
Lys 385	Asn	Leu	Val	Lys	Thr 390	Asn	Сүз	Asp	Leu	Tyr 395	Glu	Lys	Leu	Gly	Glu 400		
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro		
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg		
Val	Gly	Thr 435	Lys	Суз	Сүз	Thr	Leu 440	Pro	Glu	Asp	Gln	Arg 445	Leu	Pro	Сүз		
Val	Glu	Aab	Tyr	Leu	Ser	Ala	Ile	Leu	Asn	Arg	Val	Сув	Leu	Leu	His		

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Glu 465	Lys	Thr	Pro	Val	Ser 470	Glu	His	Val	Thr	Lys 475	Сүз	Сүз	Ser	Gly	Ser 480
Leu	Val	Glu	Arg	Arg 485	Pro	Суз	Phe	Ser	Ala 490	Leu	Thr	Val	Asp	Glu 495	Thr
Tyr	Val	Pro	Lys 500	Glu	Phe	Lys	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ser	Asp
Ile	Cys	Thr 515	Leu	Pro	Glu	Lys	Glu 520	Lys	Gln	Ile	Lys	Lys 525	Gln	Thr	Ala
Leu	Ala 530	Glu	Leu	Val	Lys	His 535	Lys	Pro	Lys	Ala	Thr 540	Ala	Glu	Gln	Leu
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Cys	Cys	Lys 560
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val
Thr	Arg	Cys	Lys 580	Asp	Ala	Leu	Ala	Gly 585	Gly	Gly	Gly	Ser	Gly 590	Gly	Gly
Gly	Ser	Gly 595	Gly	Gly	Gly	Ser	Ala 600	Ser	Ala	Ile	Gln	Met 605	Thr	Arg	Ser
Pro	Ser 610	Ser	Leu	Ser	Ala	Ser 615	Val	Gly	Asb	Arg	Val 620	Thr	Ile	Thr	Сув
Arg 625	Ala	Ser	Gln	Tyr	His 630	Asp	Gly	Ser	Ala	Ala 635	Trp	Tyr	Gln	Gln	Lys 640
Pro	Gly	Lys	Ala	Pro 645	Lys	Leu	Leu	Ile	Tyr 650	Gly	Ala	Ser	Tyr	Leu 655	Tyr
Ser	Gly	Val	Pro 660	Ser	Arg	Phe	Ser	Gly 665	Ser	Arg	Ser	Gly	Thr 670	Asp	Phe
Thr	Leu	Thr 675	Ile	Ser	Ser	Leu	Gln 680	Pro	Glu	Asp	Phe	Ala 685	Thr	Tyr	Tyr
САа	Gln 690	Gln	Ser	Ser	Tyr	Ser 695	Leu	Ile	Thr	Phe	Gly 700	Gln	Gly	Thr	Lys
Val 705	Glu	Ile	Lys	Gly	Thr 710	Thr	Ala	Ala	Ser	Gly 715	Ser	Ser	Gly	Gly	Ser 720
Ser	Ser	Gly	Ala	Glu 725	Val	Gln	Leu	Val	Glu 730	Ser	Asp	Gly	Gly	Leu 735	Val
Gln	Pro	Gly	Gly 740	Ser	Leu	Arg	Leu	Ser 745	Суз	Ala	Ala	Ser	Gly 750	Phe	Asn
Leu	Ser	Tyr 755	Tyr	Gly	Met	His	Trp 760	Val	Arg	Gln	Ala	Pro 765	Gly	Lys	Gly
Leu	Glu 770	Trp	Val	Ala	Tyr	Ile 775	Ala	Ser	Tyr	Pro	Gly 780	Tyr	Thr	Ser	Tyr
Ala 785	Asp	Ser	Val	Гла	Gly 790	Arg	Phe	Thr	Ile	Ser 795	Ala	Asp	Thr	Ser	Lys 800
Asn	Thr	Ala	Tyr	Leu 805	Gln	Met	Asn	Ser	Leu 810	Arg	Ala	Glu	Asp	Thr 815	Ala
Val	Tyr	Tyr	Cys 820	Ala	Arg	Ser	Gly	Tyr 825	Ser	Tyr	Ser	Pro	Tyr 830	Tyr	Ser
Trp	Phe	Ser 835	Ala	Gly	Met	Asn	Tyr 840	Trp	Gly	Gln	Gly	Ala 845	Leu	Val	Thr
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Lys 385	Asn	Leu	Val	Lys	Thr 390	Asn	Сүз	Asp	Leu	Tyr 395	Glu	Lys	Leu	Gly	Glu 400
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg
Val	Gly	Thr 435	Lys	Суа	Суа	Thr	Leu 440	Pro	Glu	Asp	Gln	Arg 445	Leu	Pro	Сүз
Val	Glu 450	Asp	Tyr	Leu	Ser	Ala 455	Ile	Leu	Asn	Arg	Val 460	САа	Leu	Leu	His
Glu 465	Lys	Thr	Pro	Val	Ser 470	Glu	His	Val	Thr	Lys 475	Суз	Суз	Ser	Gly	Ser 480
Leu	Val	Glu	Arg	Arg 485	Pro	Сүз	Phe	Ser	Ala 490	Leu	Thr	Val	Asp	Glu 495	Thr
Tyr	Val	Pro	Lys 500	Glu	Phe	ГЛа	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ser	Aap
Ile	Суз	Thr 515	Leu	Pro	Glu	ГЛа	Glu 520	ГЛа	Gln	Ile	ГЛа	Lys 525	Gln	Thr	Ala
Leu	Ala 530	Glu	Leu	Val	ГЛа	His 535	Lys	Pro	Lys	Ala	Thr 540	Ala	Glu	Gln	Leu
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Cys	Суз	Lys 560
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Arg 625	Ala	Ser	Gln	Ser	Tyr 630	Gly	Gly	Val	Ala	Trp 635	Tyr	Gln	Gln	Lys	Pro 640
Gly	ГЛЗ	Ala	Pro	Lys 645	Leu	Leu	Ile	Tyr	Ser 650	Ala	Ser	Tyr	Leu	Tyr 655	Ser
Gly	Val	Pro	Ser 660	Arg	Phe	Ser	Gly	Ser 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	СЛа
Gln	Gln 690	Pro	Ser	His	Leu	Ile 695	Thr	Phe	Gly	Gln	Gly 700	Thr	Glu	Val	Glu
Ile 705	Гла	Gly	Thr	Thr	Ala 710	Ala	Ser	Gly	Ser	Ser 715	Gly	Gly	Ser	Ser	Ser 720
Gly	Ala	Glu	Val	Gln 725	Leu	Val	Glu	Ser	Gly 730	Gly	Gly	Leu	Val	Gln 735	Pro
Gly	Gly	Ser	Leu 740	Arg	Leu	Ser	Суз	Ala 745	Ala	Ser	Gly	Ser	Asn 750	Pro	Tyr

Tyr Tyr Gly Gly Thr His Trp Val Arg Gln Ala Pro Gly Glu Glu Leu 755 760 765 Glu Trp Val Ala Ser Ile Gly Ser Tyr Pro Gly Tyr Thr Asp Tyr Ala 770 775 780 Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg His Tyr Tyr Trp Tyr Asp Ala Thr Asp Tyr Trp 820 825 830 Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 162 <211> LENGTH: 847 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: mouse SA-(Gly4Ser)3-scFv (VL-VH) CK129 <400> SEQUENCE: 162 Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu 2.05 Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp

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Ser	Lys	Leu 275	Gln	Thr	Сув	Сүз	Asp 280	Lys	Pro	Leu	Leu	Lys 285	Lys	Ala	His
Суз	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Суз	ГЛа	Asn	Tyr	Ala 320
Glu	Ala	Lys	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	ГЛа	Cys 360	Суз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lys 385	Asn	Leu	Val	Lys	Thr 390	Asn	Сүз	Asp	Leu	Tyr 395	Glu	Lys	Leu	Gly	Glu 400
	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410		Thr	Gln	Lys	Ala 415	
Gln	Val	Ser	Thr 420		Thr	Leu	Val	Glu 425		Ala	Arg	Asn	Leu 430		Arg
Val	Gly			Суз	Сув	Thr			Glu	Asp	Gln			Pro	Суз
Val		435 Asp	Tyr	Leu	Ser		440 Ile	Leu	Asn	Arg		445 Cys	Leu	Leu	His
	450 Lys	Thr	Pro	Val	Ser	455 Glu	His	Val	Thr		460 Cys	Суз	Ser	Gly	
465 Leu	Val	Glu	Arg	Arg	470 Pro	Суз	Phe	Ser	Ala	475 Leu	Thr	Val	Asp	Glu	480 Thr
			-	485	Phe	-			490				-	495	
-			500			-		505					510		-
	-	515			Glu	-	520	-			-	525			
	530				Lys	535	-		-		540				
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Суз	Суз	Lys 560
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val
Thr	Arg	Сув	Lys 580	Asp	Ala	Leu	Ala	Gly 585	Gly	Gly	Gly	Ser	Gly 590	Gly	Gly
Gly	Ser	Gly 595	Gly	Gly	Gly	Ser	Ala 600	Ser	Asp	Ile	Gln	Met 605	Thr	Gln	Ser
Pro	Ser 610	Pro	Leu	Ser	Ala	Ser 615	Val	Gly	Asp	Arg	Val 620	Thr	Ile	Thr	Суз
Arg 625	Ala	Ser	Gln	Tyr	Gly 630	Gly	Tyr	Val	Ala	Trp 635	Tyr	Gln	Gln	Lys	Pro 640
Gly	Lys	Ala	Pro	Lys 645	Leu	Leu	Ile	Tyr	Gly 650	Ala	Ser	Leu	Leu	Tyr 655	Ser
				545					550						

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Gly	Val	Pro	Ser 660	Arg	Phe	Ser	Gly	Gly 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	Суз
Gln	Arg 690		His	Ala	Leu	Ile 695	Thr	Phe	Gly	Gln	Gly 700	Thr	Lys	Val	Glu
Ile 705	Glu	Gly	Thr	Thr	Ala 710	Ala	Ser	Gly	Ser	Ser 715	Gly	Gly	Ser	Ser	Ser 720
Gly	Ala	Glu	Val	Gln 725	Leu	Val	Glu	Ser	Gly 730	Gly	Gly	Leu	Val	Gln 735	Pro
Gly	Gly	Ser	Leu 740	Arg	Leu	Ser	Суз	Ala 745	Ala	Ser	Gly	Phe	Asn 750	Ile	Ser
Ser	Tyr	Gly 755	Ser	Met	His	Trp	Val 760	Arg	Gln	Ala	Pro	Gly 765	Lys	Gly	Leu
Glu	Trp 770	Val	Ala	Ser	Ile	Tyr 775	Pro	Tyr	Ser	Ser	Ser 780	Thr	Tyr	Tyr	Ala
Asp 785	Ser	Val	Lys	Gly	Arg 790	Phe	Thr	Ile	Ser	Ala 795	Asp	Thr	Ser	Lys	Asn 800
Thr	Ala	Tyr	Leu	Gln 805	Met	Asn	Ser	Leu	Arg 810	Ala	Glu	Asp	Thr	Ala 815	Val
Tyr	Tyr	Суз	Ala 820	Arg	Gly	Tyr	Gly	Pro 825	Trp	Tyr	Ala	Tyr	Ser 830	Tyr	Phe
Ala	Leu	Asp 835	Tyr	Trp	Gly	Gln	Gly 840	Thr	Leu	Val	Thr	Val 845	Ser	Ser	
<21 <22		RGAN EATUI FHER	ISM: RE: INF(	ORMA:	FION	: Syr	-								
<40	0> SI			(•==	LOOOS	>C /		1G>C)		e Sl	A- (G	ly4Se	er)3.	-scF	/ (VL-VH)
Glu 1		2Õ0 FI	ICE :		10003	>C /				se Sl	A- (G]	ly4Se	∍r)3·	-scF	/ (VL-VH)
	Ala	-		163			VH44	1G>C)	į			-			
Gln	Ala His	His	Lys	163 Ser 5	Glu	Ile	VH44 Ala	4G>C) His	Arg 10	Tyr	Asn	Asp	Leu	Gly 15	Glu
		His Phe	Lys Lys 20	163 Ser 5 Gly	Glu Leu	Ile Val	VH44 Ala Leu	His His Ile 25	Arg 10 Ala	Tyr Phe	Asn Ser	Asp Gln	Leu Tyr 30	Gly 15 Leu	Glu Gln
Lys	His	His Phe Ser 35	Lys Lys 20 Tyr	163 Ser 5 Gly Asp	Glu Leu Glu	Ile Val His	VH44 Ala Leu Ala 40	His His Ile 25 Lys	Arg 10 Ala Leu	Tyr Phe Val	Asn Ser Gln	Asp Gln Glu 45	Leu Tyr 30 Val	Gly 15 Leu Thr	Glu Gln Asp
Lys Phe	His Cys Ala	His Phe Ser 35 Lys	Lys 20 Tyr Thr	163 Ser 5 Gly Asp Cys	Glu Leu Glu Val	Ile Val His Ala 55	VH44 Ala Leu Ala 40 Asp	4G>C) His Ile 25 Lys Glu	Arg 10 Ala Leu Ser	Tyr Phe Val Ala	Asn Ser Gln Ala 60	Asp Gln Glu 45 Asn	Leu Tyr 30 Val Cys	Gly 15 Leu Thr Asp	Glu Gln Asp Lys
Lys Phe Ser 65	His Cys Ala 50	His Phe Ser 35 Lys His	Lys 20 Tyr Thr Thr	163 Ser 5 Gly Asp Cys Leu	Glu Leu Glu Val Phe 70	Ile Val His Ala 55 Gly	VH44 Ala Leu Ala 40 Asp Asp	4G>C) His Ile 25 Lys Glu Lys	Arg 10 Ala Leu Ser Leu	Tyr Phe Val Ala Cys 75	Asn Ser Gln Ala 60 Ala	Asp Gln Glu 45 Asn Ile	Leu Tyr 30 Val Cys Pro	Gly 15 Leu Thr Asp Asn	Glu Gln Asp Lys Leu 80
Lys Phe Ser 65 Arg	His Cys Ala 50 Leu	His Phe Ser 35 Lys His Asn	Lys 20 Tyr Thr Thr Tyr	163 Ser 5 Gly Asp Cys Leu Gly 85	Glu Leu Glu Val Phe 70 Glu	Ile Val His Ala 55 Gly Leu	VH44 Ala Leu Ala 40 Asp Asp Ala	4G>C) His 11e 25 Lys Glu Lys Asp	Arg 10 Ala Leu Ser Leu Cys 90	Tyr Phe Val Ala Cys 75 Cys	Asn Ser Gln Ala 60 Ala Thr	Asp Gln Glu 45 Asn Ile Lys	Leu Tyr 30 Val Cys Pro Gln	Gly 15 Leu Thr Asp Asn Glu 95	Glu Gln Asp Lys Leu 80 Pro
Lys Phe Ser 65 Arg Glu	His Cys Ala 50 Leu Glu	His Phe Ser 35 Lys His Asn	Lys 20 Tyr Thr Thr Tyr Glu 100	163 Ser 5 Gly Asp Cys Leu Gly 85 Cys	Glu Leu Glu Val Phe 70 Glu Phe	Ile Val His Ala 55 Gly Leu Leu	VH44 Ala Leu Ala 40 Asp Ala Gln	His Ile 25 Lys Glu Lys Asp His 105	Arg 10 Ala Leu Ser Leu Cys 90 Lys	Tyr Phe Val Ala Cys 75 Cys Asp	Asn Ser Gln Ala 60 Ala Thr Asp	Asp Gln Glu 45 Asn Ile Lys Asn	Leu Tyr 30 Val Cys Gln Pro 110	Gly 15 Leu Thr Asp Asn Glu 95 Ser	Glu Gln Asp Lys Leu 80 Pro Leu
Lys Phe Ser 65 Arg Glu Pro	His Cys Ala 50 Leu Glu Arg	His Phe Ser 35 Lys His Asn Asn Phe 115	Lys 20 Tyr Thr Thr Glu 100 Glu	163 Ser 5 Gly Asp Cys Leu Gly 85 Cys Arg	Glu Leu Glu Val Phe 70 Glu Phe Pro	Ile Val His Ala 55 Gly Leu Leu Glu	VH44 Ala Leu Ala 40 Asp Ala Gln Ala 120	His Ile 25 Lys Glu Lys Asp His 105 Glu	Arg 10 Ala Leu Leu Leu Lys Ala	Tyr Phe Val Ala Cys Cys Asp Met	Asn Ser Gln Ala 60 Ala Thr Asp Cys	Asp Gln Glu 45 Asn Ile Lys Asn Thr 125	Leu Tyr 30 Val Cys Gln Pro 110 Ser	Gly 15 Leu Thr Asp Asn Glu 95 Ser Phe	Glu Gln Asp Lys Pro Leu Lys

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145					150					155					160
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Суз	Суз	Ala 170	Glu	Ala	Asp	Lys	Glu 175	Ser
Сүз	Leu	Thr	Pro 180	Lys	Leu	Asp	Gly	Val 185	Lys	Glu	Lys	Ala	Leu 190	Val	Ser
Ser	Val	Arg 195	Gln	Arg	Met	Lys	Cys 200	Ser	Ser	Met	Gln	Lys 205	Phe	Gly	Glu
Arg	Ala 210	Phe	Lys	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro
Asn 225	Ala	Asp	Phe	Ala	Glu 230	Ile	Thr	Lys	Leu	Ala 235	Thr	Asp	Leu	Thr	Lys 240
Val	Asn	Lys	Glu	Cys 245	Сүз	His	Gly	Asp	Leu 250	Leu	Glu	Суа	Ala	Asp 255	Asp
Arg	Ala	Glu	Leu 260	Ala	Lys	Tyr	Met	Cys 265	Glu	Asn	Gln	Ala	Thr 270	Ile	Ser
Ser	Lys	Leu 275	Gln	Thr	Суз	Суз	Asp 280	Lys	Pro	Leu	Leu	Lys 285	Lys	Ala	His
Суз	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Сув	Lys	Asn	Tyr	Ala 320
Glu	Ala	Lys	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	Lys	Суз 360	Суз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lys 385	Asn	Leu	Val	Lys	Thr 390	Asn	Суз	Asp	Leu	Tyr 395	Glu	Lys	Leu	Gly	Glu 400
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg
Val	Gly	Thr 435	Lya	СЛа	САа	Thr	Leu 440		Glu	Asp	Gln	Arg 445	Leu	Pro	Сүз
Val	Glu 450		Tyr	Leu	Ser	Ala 455			Asn	Arg	Val 460		Leu	Leu	His
Glu 465		Thr	Pro	Val	Ser 470		His	Val	Thr	Lys 475	Суз	Суз	Ser	Gly	Ser 480
	Val	Glu	Arg	Arg 485		Суз	Phe	Ser	Ala 490		Thr	Val	Asp	Glu 495	
Tyr	Val	Pro	Lys 500		Phe	Lys	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510		Asp
Ile	Суз			Pro	Glu	Lys			Gln	Ile	Lys	-		Thr	Ala
Leu	Ala	515 Glu	Leu	Val	Lys	His	520 Lys	Pro	Lys	Ala	Thr	525 Ala	Glu	Gln	Leu
Lvs	530 Thr	Val	Met	Asp	Asp	535 Phe	Ala	Gln	Phe	Leu	540 Asp	Thr	Çva	Çvs	Lvs
545		var	nee	mpp	550	I IIC	ma	GIII	i iic	555	пор		сур	сyы	560

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Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Ala Ile Gln Met Thr Arg Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys 610 615 Arg Ala Ser Gln Tyr His Asp Gly Ser Ala Ala Trp Tyr Gln Gln Lys 625 630 635 640 Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser Tyr Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Tyr Ser Leu Ile Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Gly Thr Thr Ala Ala Ser Gly Ser Ser Gly Gly Ser Ser Ser Gly Ala Glu Val Gln Leu Val Glu Ser Asp Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Leu Ser Tyr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val Ala Tyr Ile Ala Ser Tyr Pro Gly Tyr Thr Ser Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Ser Tyr Ser Pro Tyr Tyr Ser Trp Phe Ser Ala Gly Met Asn Tyr Trp Gly Gln Gly Ala Leu Val Thr Val Ser Ser <210> SEQ ID NO 164 <211> LENGTH: 851 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: mouse SA-(Gly4Ser)3-scFv (VL-VH) CK138-ds2 (VL43A>C / VH105Q>C) <400> SEQUENCE: 164 Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp

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Ser 65	Leu	His	Thr	Leu	Phe 70	Gly	Asp	Гла	Leu	Cys 75	Ala	Ile	Pro	Asn	Leu 80
Arg	Glu	Asn	Tyr	Gly 85	Glu	Leu	Ala	Asp	Суз 90	Суз	Thr	ГЛа	Gln	Glu 95	Pro
Glu	Arg	Asn	Glu 100	Суз	Phe	Leu	Gln	His 105	Lys	Asp	Asp	Asn	Pro 110	Ser	Leu
Pro	Pro	Phe 115	Glu	Arg	Pro	Glu	Ala 120	Glu	Ala	Met	Суз	Thr 125	Ser	Phe	Lys
Glu	Asn 130	Pro	Thr	Thr	Phe	Met 135	Gly	His	Tyr	Leu	His 140	Glu	Val	Ala	Arg
Arg 145	His	Pro	Tyr	Phe	Tyr 150	Ala	Pro	Glu	Leu	Leu 155	Tyr	Tyr	Ala	Glu	Gln 160
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Сүз	Сүз	Ala 170	Glu	Ala	Asp	Lys	Glu 175	Ser
Суз	Leu	Thr	Pro 180	ГÀа	Leu	Asp	Gly	Val 185	ГÀа	Glu	LYa	Ala	Leu 190	Val	Ser
Ser	Val	Arg 195	Gln	Arg	Met	Lys	Cys 200	Ser	Ser	Met	Gln	Lys 205	Phe	Gly	Glu
Arg	Ala 210	Phe	ГÀа	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro
Asn 225	Ala	Asp	Phe	Ala	Glu 230	Ile	Thr	ГЛа	Leu	Ala 235	Thr	Asp	Leu	Thr	Lys 240
Val	Asn	Lys	Glu	Cys 245	Суз	His	Gly	Asp	Leu 250	Leu	Glu	Суз	Ala	Asp 255	Asp
Arg	Ala	Glu	Leu 260	Ala	Lys	Tyr	Met	Cys 265	Glu	Asn	Gln	Ala	Thr 270	Ile	Ser
Ser	Lys	Leu 275	Gln	Thr	Сүз	Сүз	Asp 280	Lys	Pro	Leu	Leu	Lys 285	Lys	Ala	His
Суз	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asb	Leu	Pro	Ala
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Сүз	Lys	Asn	Tyr	Ala 320
Glu	Ala	Lys	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	ГЛа	Сув 360	Сүз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lys 385	Asn	Leu	Val	ГÀа	Thr 390	Asn	Суз	Asp	Leu	Tyr 395	Glu	ГÀа	Leu	Gly	Glu 400
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg
Val	Gly	Thr 435	Lys	Сүз	Суз	Thr	Leu 440	Pro	Glu	Asp	Gln	Arg 445	Leu	Pro	Суз

Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Ala Ile Gln Met Thr Arg Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Tyr His Asp Gly Ser Ala Ala Trp Tyr Gln Gln Lys Pro Gly Lys Cys Pro Lys Leu Leu Ile Tyr Gly Ala Ser Tyr Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Tyr Ser Leu Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Thr Thr Ala Ala Ser Gly Ser Ser Gly Gly Ser Ser Ser Gly Ala Glu Val Gln Leu Val Glu Ser Asp Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Leu Ser Tyr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly 755 760 765 Leu Glu Trp Val Ala Tyr Ile Ala Ser Tyr Pro Gly Tyr Thr Ser Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Ser Tyr Ser Pro Tyr Tyr Ser Trp Phe Ser Ala Gly Met Asn Tyr Trp Gly Cys Gly Ala Leu Val Thr 

Val Ser Ser 

<210> SEQ ID NO 165 <211> LENGTH: 842 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: mouse SA-(Gly4Ser)3-scFv (VL-VH) CK157-ds1 (VL100Q>C / VH44E>C) <400> SEQUENCE: 165 Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln 20 25 30 Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu 65 70 75 80 Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro 85 90 95 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg 

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Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	Lys	Cys 360	Суз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lys 385	Asn	Leu	Val	Lys	Thr 390	Asn	Суз	Asp	Leu	Tyr 395	Glu	Гла	Leu	Gly	Glu 400
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg
Val	Gly	Thr 435	Lys	Сув	Сүз	Thr	Leu 440	Pro	Glu	Asp	Gln	Arg 445	Leu	Pro	Сүз
Val	Glu 450	Asp	Tyr	Leu	Ser	Ala 455	Ile	Leu	Asn	Arg	Val 460	Суз	Leu	Leu	His
Glu 465	LÀa	Thr	Pro	Val	Ser 470	Glu	His	Val	Thr	Lys 475	СЛа	СЛа	Ser	Gly	Ser 480
Leu	Val	Glu	Arg	Arg 485	Pro	Сув	Phe	Ser	Ala 490	Leu	Thr	Val	Asp	Glu 495	Thr
Tyr	Val	Pro	Lys 500	Glu	Phe	Lys	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ser	Asp
Ile	Суз	Thr 515	Leu	Pro	Glu	Lys	Glu 520	Гла	Gln	Ile	Lys	Lys 525	Gln	Thr	Ala
Leu	Ala 530	Glu	Leu	Val	Гла	His 535	Lys	Pro	Lys	Ala	Thr 540	Ala	Glu	Gln	Leu
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Суз	Суз	Lys 560
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val
Thr	Arg	Cys	Lys 580	Asp	Ala	Leu	Ala	Gly 585	Gly	Gly	Gly	Ser	Gly 590	Gly	Gly
Gly	Ser	Gly 595	Gly	Gly	Gly	Ser	Ala 600	Ser	Asp	Ile	Gln	Met 605	Thr	Gln	Ser
Pro	Ser 610	Ser	Leu	Ser	Ala	Ser 615	Val	Gly	Asp	Arg	Val 620	Thr	Ile	Thr	Сүз
Arg 625	Ala	Ser	Gln	Ser	Tyr 630	Gly	Gly	Val	Ala	Trp 635	Tyr	Gln	Gln	Lys	Pro 640
Gly	Lys	Ala	Pro	Lys 645	Leu	Leu	Ile	Tyr	Ser 650	Ala	Ser	Tyr	Leu	Tyr 655	Ser
Gly	Val	Pro	Ser 660	Arg	Phe	Ser	Gly	Ser 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	САа
Gln	Gln 690	Pro	Ser	His	Leu	Ile 695	Thr	Phe	Gly	Cys	Gly 700	Thr	Glu	Val	Glu
Ile 705	Lys	Gly	Thr	Thr	Ala 710	Ala	Ser	Gly	Ser	Ser 715	Gly	Gly	Ser	Ser	Ser 720
Gly	Ala	Glu	Val	Gln 725	Leu	Val	Glu	Ser	Gly 730	Gly	Gly	Leu	Val	Gln 735	Pro

											-	con	tın	ued	
Gly	Gly	Ser	Leu 740	Arg	Leu	Ser	Сүз	Ala 745	Ala	Ser	Gly	Ser	Asn 750	Pro	Tyr
Tyr	Tyr	Gly 755	Gly	Thr	His	Trp	Val 760	Arg	Gln	Ala	Pro	Gly 765	Glu	Суз	Leu
Glu	Trp 770	Val	Ala	Ser	Ile	Gly 775	Ser	Tyr	Pro	Gly	Tyr 780	Thr	Asp	Tyr	Ala
Asp 785	Ser	Val	Lys	Gly	Arg 790	Phe	Thr	Ile	Ser	Ala 795	Asp	Thr	Ser	Lys	Asn 800
Thr	Ala	Tyr	Leu	Gln 805	Met	Asn	Ser	Leu	Arg 810	Ala	Glu	Asp	Thr	Ala 815	Val
Tyr	Tyr	Cys	Ala 820	Arg	His	Tyr	Tyr	Trp 825	Tyr	Asp	Ala	Thr	Asp 830	Tyr	Trp
Gly	Gln	Gly 835	Thr	Leu	Val	Thr	Val 840	Ser	Ser						
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Glu		EQUEN His		Ser	Glu	Ile	Ala	His		Tyr	Asn	Asp	Leu	-	Glu
1 Gln	His	Phe	Lys 20	5 Gly	Leu	Val	Leu	Ile 25	10 Ala	Phe	Ser	Gln	Tyr 30	15 Leu	Gln
Lys	Суз	Ser 35		Asp	Glu	His	Ala 40		Leu	Val	Gln	Glu 45		Thr	Asp
Phe	Ala 50		Thr	Суз	Val	Ala 55	Asp	Glu	Ser	Ala	Ala 60		Суз	Asp	Lys
Ser 65	Leu	His	Thr	Leu	Phe 70	Gly	Asp	Lys	Leu	Cys 75	Ala	Ile	Pro	Asn	Leu 80
Arg	Glu	Asn	Tyr	Gly 85	Glu	Leu	Ala	Asp	Cys 90	Суз	Thr	Lys	Gln	Glu 95	Pro
Glu	Arg	Asn	Glu 100	Cys	Phe	Leu	Gln	His 105	Lys	Asp	Asp	Asn	Pro 110	Ser	Leu
Pro	Pro	Phe 115	Glu	Arg	Pro	Glu	Ala 120	Glu	Ala	Met	СЛа	Thr 125	Ser	Phe	Lys
Glu	Asn 130	Pro	Thr	Thr	Phe	Met 135	Gly	His	Tyr	Leu	His 140	Glu	Val	Ala	Arg
Arg 145	His	Pro	Tyr	Phe	Tyr 150	Ala	Pro	Glu	Leu	Leu 155	Tyr	Tyr	Ala	Glu	Gln 160
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Сув	Сув	Ala 170	Glu	Ala	Asp	Lys	Glu 175	Ser
Сүз	Leu	Thr	Pro 180	Lys	Leu	Asp	Gly	Val 185	ГÀа	Glu	Lys	Ala	Leu 190	Val	Ser
Ser	Val	Arg 195	Gln	Arg	Met	ГЛа	Cys 200	Ser	Ser	Met	Gln	Lys 205	Phe	Gly	Glu
Arg	Ala 210	Phe	Lys	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro
Asn 225		Asp	Phe	Ala	Glu 230		Thr	Lys	Leu	Ala 235		Asp	Leu	Thr	Lys 240
223					002					200					210

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Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys 545 550 555 560 Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Tyr Gly Gly Val Ala Trp Tyr Gln Gln Lys Pro 

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													CIII	<u>u</u>	
Gly	Lys	Cys	Pro	Lys 645	Leu	Leu	Ile	Tyr	Ser 650	Ala	Ser	Tyr	Leu	Tyr 655	Ser
Gly	Val	Pro	Ser 660	Arg	Phe	Ser	Gly	Ser 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	Сүз
Gln	Gln 690	Pro	Ser	His	Leu	Ile 695	Thr	Phe	Gly	Gln	Gly 700	Thr	Glu	Val	Glu
Ile 705	Lys	Gly	Thr	Thr	Ala 710	Ala	Ser	Gly	Ser	Ser 715	Gly	Gly	Ser	Ser	Ser 720
Gly	Ala	Glu	Val	Gln 725	Leu	Val	Glu	Ser	Gly 730	Gly	Gly	Leu	Val	Gln 735	Pro
Gly	Gly	Ser	Leu 740	Arg	Leu	Ser	Cys	Ala 745	Ala	Ser	Gly	Ser	Asn 750	Pro	Tyr
Tyr	Tyr	Gly 755	Gly	Thr	His	Trp	Val 760	Arg	Gln	Ala	Pro	Gly 765	Glu	Glu	Leu
Glu	Trp 770		Ala	Ser	Ile	Gly 775	Ser	Tyr	Pro	Gly	Tyr 780		Aab	Tyr	Ala
Asp 785		Val	Lys	Gly	Arg 790			Ile	Ser	Ala 795		Thr	Ser	Lys	Asn 800
Thr	Ala	Tyr	Leu	Gln 805		Asn	Ser	Leu	Arg 810		Glu	Asp	Thr	Ala 815	
Tyr	Tyr	Cys	Ala 820		His	Tyr	Tyr	Trp 825		Asp	Ala	Thr	Asp 830		Trp
Gly	Суз	Gly 835		Leu	Val	Thr	Val 840		Ser				050		
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Glu 1	Ala	His	Lys	Ser 5	Glu	Ile	Ala	His	Arg 10	Tyr	Asn	Asp	Leu	Gly 15	Glu
Gln	His	Phe	Lys 20	Gly	Leu	Val	Leu	Ile 25	Ala	Phe	Ser	Gln	Tyr 30	Leu	Gln
Lys	Суз	Ser 35	Tyr	Asp	Glu	His	Ala 40	Lys	Leu	Val	Gln	Glu 45	Val	Thr	Asp
Phe	Ala 50	ГЛа	Thr	Суз	Val	Ala 55	Asp	Glu	Ser	Ala	Ala 60	Asn	Суз	Asp	Lys
Ser 65	Leu	His	Thr	Leu	Phe 70	Gly	Asp	Lys	Leu	Cys 75	Ala	Ile	Pro	Asn	Leu 80
Arg	Glu	Asn	Tyr	Gly 85	Glu	Leu	Ala	Asp	Суз 90	Суз	Thr	Lys	Gln	Glu 95	Pro
Glu	Arg	Asn	Glu 100		Phe	Leu	Gln	His 105	Lys	Asp	Asp	Asn	Pro 110	Ser	Leu
Pro	Pro	Phe 115	Glu	Arg	Pro	Glu	Ala 120	Glu	Ala	Met	Суз	Thr 125	Ser	Phe	ГЛЗ
Glu	Asn 130		Thr	Thr	Phe	Met 135	Gly	His	Tyr	Leu	His 140	Glu	Val	Ala	Arg

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Arg 145	His	Pro	Tyr	Phe	Tyr 150	Ala	Pro	Glu	Leu	Leu 155	Tyr	Tyr	Ala	Glu	Gln 160
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Суз	Суз	Ala 170	Glu	Ala	Asp	Lys	Glu 175	Ser
Суз	Leu	Thr	Pro 180	Гла	Leu	Asp	Gly	Val 185	Lys	Glu	Lys	Ala	Leu 190	Val	Ser
Ser	Val	Arg 195	Gln	Arg	Met	Lys	Cys 200	Ser	Ser	Met	Gln	Lys 205	Phe	Gly	Glu
Arg	Ala 210	Phe	Lys	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro
Asn 225	Ala	Asp	Phe	Ala	Glu 230	Ile	Thr	Lys	Leu	Ala 235	Thr	Asp	Leu	Thr	Lys 240
Val	Asn	Гла	Glu	Cys 245	Суз	His	Gly	Asp	Leu 250	Leu	Glu	Суз	Ala	Asp 255	Asp
Arg	Ala	Glu	Leu 260	Ala	Lys	Tyr	Met	Cys 265	Glu	Asn	Gln	Ala	Thr 270	Ile	Ser
Ser	Lys	Leu 275	Gln	Thr	Cya	Сүз	Asp 280	Lys	Pro	Leu	Leu	Lys 285	Lys	Ala	His
Суз	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Суз	Lys	Asn	Tyr	Ala 320
Glu	Ala	Гла	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg
Arg	His	Pro	Asp 340	-	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	Lys	Сув 360	Суз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lys 385	Asn	Leu	Val	ГЛа	Thr 390	Asn	Суа	Asp	Leu	Tyr 395	Glu	ГЛа	Leu	Gly	Glu 400
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro
Gln	Val	Ser	Thr 420		Thr	Leu	Val	Glu 425		Ala	Arg	Asn	Leu 430		Arg
Val	Gly	Thr 435		Суз	Суз	Thr	Leu 440		Glu	Asp	Gln	Arg 445		Pro	Суа
Val	Glu 450		Tyr	Leu	Ser	Ala 455	Ile	Leu	Asn	Arg	Val 460		Leu	Leu	His
Glu 465		Thr	Pro	Val	Ser 470	Glu	His	Val	Thr	Lys 475		Суз	Ser	Gly	Ser 480
	Val	Glu	Arg	Arg 485			Phe	Ser	Ala 490		Thr	Val	Asp	Glu 495	
Tyr	Val	Pro	-		Phe	Lys	Ala			Phe	Thr	Phe			Asp
Ile	Cys		500 Leu	Pro	Glu	Lys	Glu	505 Lys	Gln	Ile	Lys	-	510 Gln	Thr	Ala
Leu	Ala	515 Glu	Leu	Val	Гла	His	520 Lys	Pro	Lys	Ala	Thr	525 Ala	Glu	Gln	Leu
	530				-	535	- Ala		-		540				
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545	_	_	_	_	550		_		_	555	_	_	_		560
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val
Thr	Arg	Cys	Lys 580	Asp	Ala	Leu	Ala	Gly 585	Gly	Gly	Gly	Ser	Gly 590	Gly	Gly
Gly	Ser	Gly 595	Gly	Gly	Gly	Ser	Ala 600	Ser	Asp	Ile	Gln	Met 605	Thr	Gln	Ser
Pro	Ser 610	Ser	Leu	Ser	Ala	Ser 615	Val	Gly	Asp	Arg	Val 620	Thr	Ile	Thr	Сүз
Arg 625	Ala	Ser	Gln	Ser	Tyr 630	Gly	Gly	Val	Ala	Trp 635	Tyr	Gln	Gln	Lys	Pro 640
Gly	Lys	Ala	Pro	Lys 645	Leu	Leu	Ile	Tyr	Ser 650	Ala	Ser	Tyr	Leu	Tyr 655	Ser
Gly	Val	Pro	Ser 660	Arg	Phe	Ser	Gly	Ser 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	Cys
Gln	Gln 690	Pro	Ser	His	Leu	Ile 695	Thr	Phe	Gly	Gln	Gly 700	Thr	Glu	Val	Glu
Ile 705	Lys														
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ГЛа	Суз	Ser 35	Tyr	Asp	Glu	His	Ala 40	ГЛа	Leu	Val	Gln	Glu 45	Val	Thr	Asp
Phe	Ala 50	Lys	Thr	Суз	Val	Ala 55	Asp	Glu	Ser	Ala	Ala 60	Asn	Суз	Asp	Lys
Ser 65	Leu	His	Thr	Leu	Phe 70	Gly	Asp	Lys	Leu	Cys 75	Ala	Ile	Pro	Asn	Leu 80
Arg	Glu	Asn	Tyr	Gly 85	Glu	Leu	Ala	Asp	Сув 90	Суз	Thr	ГЛа	Gln	Glu 95	Pro
Glu	Arg	Asn	Glu 100	Сув	Phe	Leu	Gln	His 105	Lys	Asp	Asp	Asn	Pro 110	Ser	Leu
Pro	Pro	Phe 115	Glu	Arg	Pro	Glu	Ala 120	Glu	Ala	Met	СЛа	Thr 125	Ser	Phe	Lys
Glu	Asn 130	Pro	Thr	Thr	Phe	Met 135	Gly	His	Tyr	Leu	His 140	Glu	Val	Ala	Arg
Arg 145	His	Pro	Tyr	Phe	Tyr 150	Ala	Pro	Glu	Leu	Leu 155	Tyr	Tyr	Ala	Glu	Gln 160
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Сүз	Сүз	Ala 170	Glu	Ala	Aap	Lys	Glu 175	Ser
Cys	Leu	Thr	Pro		Leu	Asp	Gly	Val		Glu	Гла	Ala	Leu		Ser
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Arg	Ala 210	Phe	Lys	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro	
Asn 225	Ala	Asp	Phe	Ala	Glu 230	Ile	Thr	Lys	Leu	Ala 235	Thr	Asp	Leu	Thr	Lys 240	
Val	Asn	Lys	Glu	Cys 245	Суз	His	Gly	Asp	Leu 250	Leu	Glu	Сүз	Ala	Asp 255	Asp	
Arg	Ala	Glu	Leu 260	Ala	ГЛа	Tyr	Met	Cys 265	Glu	Asn	Gln	Ala	Thr 270	Ile	Ser	
Ser	Lys	Leu 275	Gln	Thr	САа	САа	Asp 280	Lys	Pro	Leu	Leu	Lys 285	Lys	Ala	His	
Суз	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala	
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Сүз	ГÀа	Asn	Tyr	Ala 320	
Glu	Ala	LÀa	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg	
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys	
Tyr	Glu	Ala 355	Thr	Leu	Glu	ГÀа	Сув 360	Сүз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala	
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro	
Lys 385	Asn	Leu	Val	ГЛЗ	Thr 390	Asn	Суз	Asp	Leu	Tyr 395	Glu	ГЛЗ	Leu	Gly	Glu 400	
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	Lys	Ala 415	Pro	
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg	
Val	Gly	Thr 435	Lys	Суз	Суз	Thr	Leu 440	Pro	Glu	Asp	Gln	Arg 445	Leu	Pro	Суз	
Val	Glu 450	Asp	Tyr	Leu	Ser	Ala 455	Ile	Leu	Asn	Arg	Val 460	Суз	Leu	Leu	His	
Glu 465	Lys	Thr	Pro	Val	Ser 470	Glu	His	Val	Thr	Lys 475	Суз	Суз	Ser	Gly	Ser 480	
Leu	Val	Glu	Arg	Arg 485	Pro	Сүз	Phe	Ser	Ala 490	Leu	Thr	Val	Asp	Glu 495	Thr	
Tyr	Val	Pro	Lys 500	Glu	Phe	Lys	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ser	Asp	
Ile	Сув	Thr 515	Leu	Pro	Glu	ГÀа	Glu 520	Lys	Gln	Ile	LÀa	Lys 525	Gln	Thr	Ala	
Leu	Ala 530	Glu	Leu	Val	ГЛа	His 535	Гла	Pro	Гла	Ala	Thr 540	Ala	Glu	Gln	Leu	
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Cys	Cys	Lys 560	
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val	
Thr	Arg	Суз	Lys 580	Asp	Ala	Leu	Ala	Gly 585	Gly	Gly	Gly	Ser	Gly 590	Gly	Gly	

Gly Ser Gly Gly Gly Gly Ser Ala Ser Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Asn Pro Tyr Tyr Tyr Gly Gly Thr His Trp Val Arg Gln Ala Pro Gly Glu Glu Leu Glu Trp Val Ala Ser Ile Gly Ser Tyr Pro Gly Tyr Thr Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg His Tyr Tyr 690 695 Trp Tyr Asp Ala Thr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val 705 710 715 720 Ser Ser <210> SEO ID NO 169 <211> LENGTH: 847 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: mouse SA-(Gly4Ser)3-scFv (VL-VH) CK129-ds1 (VL100Q>C / VH44G>C) <400> SEQUENCE: 169 Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu \_\_\_\_\_110 Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu 

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Asp Ile Gln Met Thr Gln Ser 

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Gly	Lys	Ala	Pro	Lys 645	Leu	Leu	Ile	Tyr	Gly 650	Ala	Ser	Leu	Leu	Tyr 655	Ser			
Gly	Val	Pro	Ser 660	Arg	Phe	Ser	Gly	Gly 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr			
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	Cys			
Gln	Arg 690	-	His	Ala	Leu	Ile 695	Thr	Phe	Gly	Сүз	Gly 700	Thr	Lys	Val	Glu			
Ile 705	Glu	Gly	Thr	Thr	Ala 710	Ala	Ser	Gly	Ser	Ser 715	Gly	Gly	Ser	Ser	Ser 720			
Gly	Ala	Glu	Val	Gln 725	Leu	Val	Glu	Ser	Gly 730	Gly	Gly	Leu	Val	Gln 735	Pro			
Gly	Gly	Ser	Leu 740	Arg	Leu	Ser	Cys	Ala 745	Ala	Ser	Gly	Phe	Asn 750	Ile	Ser			
Ser	Tyr	Gly 755	Ser	Met	His	Trp	Val 760		Gln	Ala	Pro	Gly 765	Lys	Сув	Leu			
Glu	Trp 770	Val	Ala	Ser	Ile	Tyr 775	Pro	Tyr	Ser	Ser	Ser 780	Thr	Tyr	Tyr	Ala			
Asp 785		Val	Lys	Gly	Arg 790	Phe	Thr	Ile	Ser	Ala 795	Asp	Thr	Ser	Lys	Asn 800			
Thr	Ala	Tyr	Leu	Gln 805	Met	Asn	Ser	Leu	Arg 810	Ala	Glu	Asp	Thr	Ala 815	Val			
Tyr	Tyr	Cys	Ala 820	Arg	Gly	Tyr	Gly	Pro 825	Trp	Tyr	Ala	Tyr	Ser 830	Tyr	Phe			
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		EQUEN																
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Gln	His	Phe	Lys 20	Gly	Leu	Val	Leu	Ile 25	Ala	Phe	Ser	Gln	Tyr 30	Leu	Gln			
Lys	Суз	Ser 35	Tyr	Asp	Glu	His	Ala 40	Гла	Leu	Val	Gln	Glu 45	Val	Thr	Asp			
Phe	Ala 50	Гла	Thr	Суз	Val	Ala 55	Asp	Glu	Ser	Ala	Ala 60	Asn	Сув	Asp	Lys			
Ser 65	Leu	His	Thr	Leu	Phe 70	Gly	Asp	Lys	Leu	Cys 75	Ala	Ile	Pro	Asn	Leu 80			
Arg	Glu	Asn	Tyr	Gly 85	Glu	Leu	Ala	Asp	Суз 90	Суз	Thr	ГЛа	Gln	Glu 95	Pro			
Glu	Arg	Asn	Glu 100	Суз	Phe	Leu	Gln	His 105	Lys	Asp	Asp	Asn	Pro 110	Ser	Leu			

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Pro	Pro	Phe 115	Glu	Arg	Pro	Glu	Ala 120	Glu	Ala	Met	Сув	Thr 125	Ser	Phe	Lys
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Arg 145	His	Pro	Tyr	Phe	Tyr 150	Ala	Pro	Glu	Leu	Leu 155	Tyr	Tyr	Ala	Glu	Gln 160
Tyr	Asn	Glu	Ile	Leu 165	Thr	Gln	Суз	Суз	Ala 170	Glu	Ala	Asp	Lys	Glu 175	Ser
Сүз	Leu	Thr	Pro 180	Lys	Leu	Asp	Gly	Val 185	Lys	Glu	Lys	Ala	Leu 190	Val	Ser
Ser	Val	Arg 195	Gln	Arg	Met	ГЛЗ	Cys 200	Ser	Ser	Met	Gln	Lys 205	Phe	Gly	Glu
Arg	Ala 210	Phe	Lys	Ala	Trp	Ala 215	Val	Ala	Arg	Leu	Ser 220	Gln	Thr	Phe	Pro
Asn 225	Ala	Asp	Phe	Ala	Glu 230	Ile	Thr	Гла	Leu	Ala 235	Thr	Asp	Leu	Thr	Lys 240
Val	Asn	Lys	Glu	Сув 245	Сув	His	Gly	Asp	Leu 250	Leu	Glu	Суа	Ala	Asp 255	Asp
Arg	Ala	Glu	Leu 260	Ala	ГЛа	Tyr	Met	Сув 265	Glu	Asn	Gln	Ala	Thr 270	Ile	Ser
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Сүз	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Суз	Lys	Asn	Tyr	Ala 320
Glu	Ala	Lys	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	Lys	Суз 360	Суз	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Суз	Tyr 370	Gly	Thr	Val	Leu	Ala 375	Glu	Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lуя 385	Asn	Leu	Val	ГЛЗ	Thr 390	Asn	Суз	Asp	Leu	Tyr 395	Glu	ГЛа	Leu	Gly	Glu 400
Tyr	Gly	Phe	Gln	Asn 405	Ala	Ile	Leu	Val	Arg 410	Tyr	Thr	Gln	ГÀа	Ala 415	Pro
Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Ala	Ala	Arg	Asn	Leu 430	Gly	Arg
Val	Gly	Thr 435	Lys	Сув	Сүз	Thr	Leu 440	Pro	Glu	Asp	Gln	Arg 445	Leu	Pro	Cya
Val	Glu 450	Asp	Tyr	Leu	Ser	Ala 455	Ile	Leu	Asn	Arg	Val 460	Cys	Leu	Leu	His
Glu 465	Lys	Thr	Pro	Val	Ser 470	Glu	His	Val	Thr	Lys 475	Cys	Cys	Ser	Gly	Ser 480
Leu	Val	Glu	Arg	Arg 485	Pro	Сүз	Phe	Ser	Ala 490	Leu	Thr	Val	Asp	Glu 495	Thr
Tyr	Val	Pro	Lys 500	Glu	Phe	Lys	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ser	Asp

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Ile	Cys	Thr 515	Leu	Pro	Glu	Lys	Glu 520	Lys	Gln	Ile	Lys	Lys 525	Gln	Thr	Ala
Leu	Ala 530	Glu	Leu	Val	Lys	His 535		Pro	Lys	Ala	Thr 540	Ala	Glu	Gln	Leu
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Суз	Суз	Lys 560
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val
Thr	Arg	Cys	Lys 580		Ala	Leu	Ala	Gly 585		Gly	Gly	Ser	Gly 590	Gly	Gly
Gly	Ser	Gly 595	Gly	Gly	Gly	Ser	Ala 600	Ser	Asp	Ile	Gln	Met 605	Thr	Gln	Ser
Pro	Ser 610	Pro	Leu	Ser	Ala	Ser 615	Val	Gly	Asp	Arg	Val 620	Thr	Ile	Thr	CAa
Arg 625		Ser	Gln	Tyr	Gly 630	Gly	Tyr	Val	Ala	Trp 635	Tyr	Gln	Gln	Lys	Pro 640
Gly	Lys	Cys	Pro	Lys 645	Leu	Leu	Ile	Tyr	Gly 650	Ala	Ser	Leu	Leu	Tyr 655	Ser
Gly	Val	Pro	Ser 660		Phe	Ser	Gly	Gly 665	Arg	Ser	Gly	Thr	Asp 670	Phe	Thr
Leu	Thr	Ile 675	Ser	Ser	Leu	Gln	Pro 680	Glu	Asp	Phe	Ala	Thr 685	Tyr	Tyr	Сув
Gln	Arg 690		His	Ala	Leu	Ile 695	Thr	Phe	Gly	Gln	Gly 700	Thr	Lys	Val	Glu
Ile 705	Glu	Gly	Thr	Thr	Ala 710	Ala	Ser	Gly	Ser	Ser 715	Gly	Gly	Ser	Ser	Ser 720
Gly	Ala	Glu	Val	Gln 725	Leu	Val	Glu	Ser	Gly 730	Gly	Gly	Leu	Val	Gln 735	Pro
Gly	Gly	Ser	Leu 740	Arg	Leu	Ser	Суз	Ala 745	Ala	Ser	Gly	Phe	Asn 750	Ile	Ser
Ser	Tyr	Gly 755	Ser	Met	His	Trp	Val 760	Arg	Gln	Ala	Pro	Gly 765	Lys	Gly	Leu
Glu	Trp 770	Val	Ala	Ser	Ile	Tyr 775	Pro	Tyr	Ser	Ser	Ser 780	Thr	Tyr	Tyr	Ala
Asp 785	Ser	Val	Гла	Gly	Arg 790	Phe	Thr	Ile	Ser	Ala 795	Asp	Thr	Ser	Lys	Asn 800
Thr	Ala	Tyr	Leu	Gln 805	Met	Asn	Ser	Leu	Arg 810	Ala	Glu	Aap	Thr	Ala 815	Val
Tyr	Tyr	Суа	Ala 820	Arg	Gly	Tyr	Gly	Pro 825	Trp	Tyr	Ala	Tyr	Ser 830	Tyr	Phe
Ala	Leu	Asp 835	Tyr	Trp	Gly	САа	Gly 840	Thr	Leu	Val	Thr	Val 845	Ser	Ser	
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Asp 1	Ala	His	Lys	Ser 5	Glu	Val	Ala	His	Arg 10	Phe	Lys	Asp	Leu	Gly 15	Glu
Glu	Asn	Phe	Lys 20	Ala	Leu	Val	Leu	Ile 25	Ala	Phe	Ala	Gln	Tyr 30	Leu	Gln
			10					10							

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr 340 345 350 Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys 

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													CIII	<u>u</u>	
Val	Gly	Ser 435	Lys	Сув	Сув	Lys	His 440	Pro	Glu	Ala	Lys	Arg 445	Met	Pro	Сув
	Glu 450	Asp	Tyr	Leu	Ser	Val 455	Val	Leu	Asn	Gln	Leu 460	Cys	Val	Leu	His
Glu 465	Lys	Thr	Pro	Val	Ser 470		Arg	Val	Thr	Lys 475	Сүз	СЛа	Thr	Glu	Ser 480
Leu	Val	Asn	Arg	Arg 485	Pro	Суз	Phe	Ser	Ala 490	Leu	Glu	Val	Asp	Glu 495	Thr
Tyr	Val	Pro	Lys 500	Glu	Phe	Asn	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ala	Asp
Ile	Cys	Thr 515	Leu	Ser	Glu	Lya	Glu 520	Arg	Gln	Ile	ГÀа	Lys 525	Gln	Thr	Ala
Leu	Val 530	Glu	Leu	Val	Lys	His 535	Lys	Pro	Lys	Ala	Thr 540	Lys	Glu	Gln	Leu
Lys 545	Ala	Val	Met	Aap	Asp 550		Ala	Ala	Phe	Val 555	Glu	ГЛа	Суз	Суз	Lys 560
Ala	Asp	Aab	Lys	Glu 565	Thr	Сүз	Phe	Ala	Glu 570	Glu	Gly	Lys	Lys	Leu 575	Val
Ala	Ala	Ser	Gln 580		Ala	Leu	Gly	Leu 585							
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Ser	Thr	Ser	Gly 20	Gly	Thr	Ala	Ala	Leu 25	Gly	Суз	Leu	Val	Lys 30	Asp	Tyr
Phe	Pro	Glu 35	Pro	Val	Thr	Val	Ser 40	Trp	Asn	Ser	Gly	Ala 45	Leu	Thr	Ser
	Val 50	His	Thr	Phe	Pro	Ala 55	Val	Leu	Gln	Ser	Ser 60	Gly	Leu	Tyr	Ser
Leu 65	Ser	Ser	Val	Val	Thr 70	Val	Pro	Ser	Ser	Ser 75	Leu	Gly	Thr	Gln	Thr 80
Tyr	Ile	Cys	Asn	Val 85	Asn	His	Lys	Pro	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Lys	Val	Glu	Pro 100	ГÀа	Ser	Сүз	Asp	Lys 105	Thr	His	Thr	СЛа	Pro 110	Pro	Cys
Pro	Ala	Pro 115	Glu	Leu	Leu	Gly	Gly 120	Pro	Ser	Val	Phe	Leu 125	Phe	Pro	Pro
Lys	Pro 130	Lys	Asp	Thr	Leu	Met 135	Ile	Ser	Arg	Thr	Pro 140	Glu	Val	Thr	Сув
Val 145	Val	Val	Asp	Val	Ser 150	His	Glu	Asp	Pro	Glu 155	Val	ГЛа	Phe	Asn	Trp 160
Tyr	Val	Asp	Gly	Val 165	Glu	Val	His	Asn	Ala 170	Lys	Thr	Lys	Pro	Arg 175	Glu
Glu	Gln	Tyr	Asn 180	Ser	Thr	Tyr	Arg	Val 185	Val	Ser	Val	Leu	Thr 190	Val	Leu
His	Gln	Asp 195	Trp	Leu	Asn	Gly	Lys 200	Glu	Tyr	Lys	Суз	Lys 205	Val	Ser	Asn

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Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe 275 280 285 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr 305 310 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys <210> SEQ ID NO 173 <211> LENGTH: 584 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEOUENCE: 173 Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys

225					230					235					240
Val	Asn	Lys	Glu	Cys 245	Сүз	His	Gly	Asp	Leu 250	Leu	Glu	Суз	Ala	Asp 255	Asp
Arg	Ala	Glu	Leu 260	Ala	Lys	Tyr	Met	Суз 265	Glu	Asn	Gln	Ala	Thr 270	Ile	Ser
Ser	Lys	Leu 275	Gln	Thr	Суз	Сүз	Asp 280	Lys	Pro	Leu	Leu	Lys 285	Lys	Ala	His
Cys	Leu 290	Ser	Glu	Val	Glu	His 295	Asp	Thr	Met	Pro	Ala 300	Asp	Leu	Pro	Ala
Ile 305	Ala	Ala	Asp	Phe	Val 310	Glu	Asp	Gln	Glu	Val 315	Суз	ГЛа	Asn	Tyr	Ala 320
Glu	Ala	Lys	Asp	Val 325	Phe	Leu	Gly	Thr	Phe 330	Leu	Tyr	Glu	Tyr	Ser 335	Arg
Arg	His	Pro	Asp 340	Tyr	Ser	Val	Ser	Leu 345	Leu	Leu	Arg	Leu	Ala 350	Lys	Lys
Tyr	Glu	Ala 355	Thr	Leu	Glu	Гла	Сув 360	Сув	Ala	Glu	Ala	Asn 365	Pro	Pro	Ala
Сув	Tyr 370	Gly	Thr	Val	Leu	Ala 375		Phe	Gln	Pro	Leu 380	Val	Glu	Glu	Pro
Lys 385		Leu	Val	L'Aa	Thr 390		Суз	Asp	Leu	Tyr 395		ГÀа	Leu	Gly	Glu 400
	Gly	Phe	Gln	Asn 405		Ile	Leu	Val	Arg 410		Thr	Gln	Lys	Ala 415	
Gln	Val	Ser	Thr 420		Thr	Leu	Val			Ala	Arg	Asn	Leu 430		Arg
Val	Gly	Thr		Суз	Суз	Thr		425 Pro	Glu	Asp	Gln	-		Pro	Суз
Val		435 Asp	Tyr	Leu	Ser		440 Ile	Leu	Asn	Arg		445 Cys	Leu	Leu	His
Glu	450 Lys	Thr	Pro	Val	Ser	455 Glu	His	Val	Thr	Lys	460 Cys	Суз	Ser	Gly	Ser
465	-	Glu			470					475	-	-		-	480
			-	485		-			490				-	495	
-		Pro	500			-		505					510		-
Ile	Сув	Thr 515				Гла		-	Gln		-	-		Thr	Ala
Leu	Ala 530	Glu	Leu	Val	LÀa	His 535	Lys	Pro	Lys	Ala	Thr 540	Ala	Glu	Gln	Leu
Lys 545	Thr	Val	Met	Asp	Asp 550	Phe	Ala	Gln	Phe	Leu 555	Asp	Thr	Суз	Суз	Lys 560
Ala	Ala	Asp	Lys	Asp 565	Thr	Суз	Phe	Ser	Thr 570	Glu	Gly	Pro	Asn	Leu 575	Val
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<211> LENGTH: 232 <212> TYPE: PRT <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

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Pr	0 0	Ju	Leu	Leu 20	Gly	Gly	Pro	Ser	Val 25	Phe	Leu	Phe	Pro	Pro 30	Lys	Pro		
Lу	s A		Thr 35	Leu	Met	Ile	Ser	Arg 40	Thr	Pro	Glu	Val	Thr 45	Cys	Val	Val		
Va		ab 20	Val	Ser	His	Glu	Asp 55	Pro	Glu	Val	Lys	Phe 60	Asn	Trp	Tyr	Val		
As 65		ly	Val	Glu	Val	His 70	Asn	Ala	Lys	Thr	Lys 75	Pro	Arg	Glu	Glu	Gln 80		
ту	r Æ	lsn	Ser	Thr	Tyr 85	Arg	Val	Val	Ser	Val 90	Leu	Thr	Val	Leu	His 95	Gln		
As	р٦	rp	Leu	Asn 100	Gly	ГЛа	Glu	Tyr	Lys 105	Cys	Lys	Val	Ser	Asn 110	Lys	Ala		
Le	u F		Ala 115		Ile	Glu	ГЛа	Thr 120	Ile	Ser	Lys	Ala	Lys 125		Gln	Pro		
Ar				Gln	Val	Tyr	Thr 135		Pro	Pro	Ser	Arg 140		Glu	Leu	Thr		
Ly 14	s A		Gln	Val	Ser	Leu 150		Cys	Leu	Val	Lys 155		Phe	Tyr	Pro	Ser 160		
		le	Ala	Val			Glu	Ser	Asn	Gly 170		Pro	Glu	Asn	Asn 175			
Ly	s 1	hr	Thr		165 Pro	Val	Leu	Asp			Gly	Ser	Phe		Leu	Tyr		
Se	r I			180 Thr	Val	Asp	Гла		185 Arg	Trp	Gln	Gln	-	190 Asn	Val	Phe		
Se		ys	195 Ser	Val	Met	His		200 Ala	Leu	His	Asn		205 Tyr	Thr	Gln	Lys		
	r I	210 Jeu	Ser	Leu	Ser		215 Gly	Lys				220						
22	5					230												
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				ICE :														
As 1	p₽	Ala	His	Lys	Ser 5	Glu	Val	Ala	His	Arg 10	Phe	Lys	Asp	Leu	Gly 15	Glu		
Gl	u A	Asn	Phe	Lys 20	Ala	Leu	Val	Leu	Ile 25	Ala	Phe	Ala	Gln	Tyr 30	Leu	Gln		
Gl	n C	Ya	Pro 35	Phe	Glu	Asp	His	Val 40	Гла	Leu	Val	Asn	Glu 45	Val	Thr	Glu		
Ph		Ala 50		Thr	Сүз	Val	Ala 55		Glu	Ser	Ala	Glu 60		Cys	Asp	Гла		
	r L		His	Thr	Leu			Asp	Lys	Leu			Val	Ala	Thr			
65 Ar		Ju	Thr	Tyr	Gly	70 Glu	Met	Ala	Asp	Суз	75 Cys	Ala	Lys	Gln	Glu	80 Pro		
Gl	u A	ra	Asn	Glu	85 Cvs	Phe	Leu	Gln	His	90 Lvs	Asp	Asp	Asn	Pro	95 Asn	Leu		
01	~ ~	9		100	215		204	C 1 11	105	-15	p	P		110		204		

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Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His 115 120 125 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg 135 130 140 Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg 145 150 155 160 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala 170 165 175 Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser 180 185 Ser Ala Lys Gln Arg 195 <210> SEQ ID NO 176 <211> LENGTH: 197 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: HSA domain II <400> SEOUENCE: 176 Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln 1 5 10 15 Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser 30 20 25 Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr 35 40 Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu 50 55 60 Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln 65 70 75 80 65 70 80 Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu 90 85 95 Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala 105 100 110 Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys 120 125 Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr 130 135 140 Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Arg 150 155 145 Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala 170 165 175 Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu 185 180 190 Val Glu Glu Pro Gln 195 <210> SEQ ID NO 177 <211> LENGTH: 200 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: HSA domain III <400> SEQUENCE: 177

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Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr 10 1 5 Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln 20 25 30 Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val 40 35 45 Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala 55 Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu 65 70 75 80 Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu 85 90 95 Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr 100 105 110 Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile 125 115 120 Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu 135 130 140 Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys 150 145 155 160 Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Lys Ala 165 175 170 Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala 180 185 190 Ala Ser Gln Ala Ala Leu Gly Leu 195 200 <210> SEQ ID NO 178 <211> LENGTH: 15 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: linker domain <400> SEQUENCE: 178 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser 5 1 10 15 <210> SEQ ID NO 179 <211> LENGTH: 22 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: Secretory leader sequence <400> SEQUENCE: 179 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp 1 5 10 15 Leu Pro Gly Ala Arg Cys 20 <210> SEQ ID NO 180 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic: FLAG tag

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<221> NAME/KEY: misc\_feature

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**1**. A fusion protein, comprising a multispecific variable region operably coupled to a polymer, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines.

**2**. The fusion protein of claim **2**, wherein the multispecific variable region is operably coupled to the C-terminus of the polymer.

**3**. The fusion protein of claim **2**, wherein the multispecific variable region is operably coupled to the N-terminus of the polymer.

**4**. The fusion protein of any one of claims **1-3**, wherein the multispecific variable region is operably coupled to the polymer via a linker.

**5**. The fusion protein of claim **4**, wherein the linker is a Gly-Ser linker.

6. The fusion protein of any one of claims 1-5, wherein the polymer is a serum albumin moiety.

7. The fusion protein of any one of claims 1-5, wherein the polymer is an Fc domain.

**8**. The fusion protein of any one of claims **1-7**, wherein the multispecific variable region is a scFv.

**9**. The fusion protein of any one of claims **1-8**, wherein the multispecific variable region binds at least four ELR+ CXC chemokines selected from the group consisting of: human CXCL1 (Gro $\alpha$ ), human CXCL2 (Gro $\beta$ ), human CXCL3 (Gro $\gamma$ ), human CXCL5 (ENA-78), human CXCL6 (GCP-2), human CXCL7 (NAP-2), human CXCL8 (IL-8), murine CXCL1 (KC), murine CXCL2 (MIP-2), murine CXCL3 (DCIP-1), murine CXCL5 (LIX), and murine CXCL7 (NAP-2).

**10**. The fusion protein of claim **9**, wherein the at least four ELR+ CXC chemokines are hCXCL1, hCXCL2, hCXCL3 and mCXCL1.

11. The fusion protein of any one of claims 1-9, wherein the multispecific variable region binds to at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or at least twelve ELR+ CXC chemokines.

**12**. The fusion protein of claim **11**, wherein the at least six chemokines are human CXCL1, human CXCL5, human CXCL8, murine CXCL1, murine CXCL2 and murine CXCL5.

**13**. The fusion protein of claim **11**, wherein the at least eleven chemokines are human CXCL8, murine CXCL2, murine CXCL1, murine CXCL3, human CXCL5, human CXCL1, murine CXCL5, human CXCL3, human CXCL2, and human CXCL6.

14. The fusion protein of any one of claims 1-9, wherein the multispecific variable region binds murine or human ELR+ CXC chemokines.

**15**. The fusion protein of any one of claims **1-9**, wherein the multispecific variable region binds murine and human ELR+ CXC chemokines.

**16**. The fusion protein of any one of the preceding claims, wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21.

**17**. The fusion protein of any one of the preceding claims, wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**18**. The fusion protein of any one of the preceding claims, wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21, and wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**19**. A fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+CXC chemokines, and wherein the multispecific variable region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in:

(a) SEQ ID NOs: 1 and 2, respectively;

(b) SEQ ID NOs: 11 and 12, respectively; or

(c) SEQ ID NOs: 21 and 22, respectively.

**20**. A fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+CXC chemokines, and wherein the multispecific variable region comprises a heavy chain variable region and light chain variable region comprising amino acid sequences having 90% identity to the amino acid sequences set forth in:

(a) SEQ ID NOs: 1 and 2, respectively;

(b) SEQ ID NOs: 11 and 12, respectively; or

(c) SEQ ID NOs: 21 and 22, respectively.

**21**. A fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+

CXC chemokines, and wherein the multispecific variable region comprises heavy and light chain CDRs selected from the group consisting of:

- (a) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively;
- (b) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 15, 16 and 17, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 18, 19 and 20, respectively; and
- (c) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**22**. A fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+CXC chemokines, and wherein the multispecific variable region comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 11 and 21; and wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 12 and 22.

**23**. The fusion protein of any one of claims **1-22**, wherein the fusion protein inhibits binding of ELR+ CXC chemokines to their cognate CXCR1 and CXCR2.

**24**. An isolated monoclonal antibody, or binding fragment thereof, that binds to at least four ELR+ CXC chemokines.

**25**. The isolated monoclonal antibody, or binding fragment thereof, of claim **24**, wherein the at least four ELR+ CXC chemokines are selected from the group consisting of: human CXCL1 (Gro $\alpha$ ), human CXCL2 (Gro $\beta$ ), human CXCL3 (Gro $\gamma$ ), human CXCL5 (ENA-78), human CXCL6 (GCP-2), human CXCL7 (NAP-2), human CXCL8 (IL-8), murine CXCL1 (KC), murine CXCL2 (MIP-2), murine CXCL3 (DCIP-1), murine CXCL5 (LIX), and murine CXCL7 (NAP-2).

**26**. The isolated monoclonal antibody, or binding fragment thereof, of claim **25**, wherein the at least four ELR+CXC chemokines are hCXCL1, hCXCL2, hCXCL3 and mCXCL1

27. The isolated monoclonal antibody, or binding fragment thereof, of claim 24 or 25, wherein the antibody or binding fragment thereof binds to at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or at least twelve ELR+ CXC chemokines.

**28**. The isolated monoclonal antibody, or binding fragment thereof, of claim **27**, wherein the at least six chemokines are human CXCL1, human CXCL5, human CXCL8, murine CXCL1, murine CXCL2 and murine CXCL5.

**29**. The isolated monoclonal antibody, or binding fragment thereof, of claim **27**, wherein the at least eleven chemokines are human CXCL8, murine CXCL2, murine CXCL1, murine CXCL3, human CXCL7, human CXCL5, human CXCL1, murine CXCL5, human CXCL3, human CXCL6.

**30**. The isolated monoclonal antibody, or binding fragment thereof, of any one of claims **24-25**, wherein the antibody or binding fragment thereof binds murine or human ELR+ CXC chemokines.

**31**. The isolated monoclonal antibody, or binding fragment thereof, of any one of claims **24-25**, wherein the antibody or binding fragment thereof binds murine and human ELR+ CXC chemokines.

**32**. The isolated monoclonal antibody, or binding fragment thereof, of any one of claims **24-31**, wherein the antibody is a single chain variable fragment (scFv).

**33**. The isolated monoclonal antibody, or binding fragment thereof, of any one of claims **24-32**, wherein the antibody or binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21.

**34**. The isolated monoclonal antibody, or binding fragment thereof, of any one of claims **24-33**, wherein the antibody or binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**35**. The isolated monoclonal antibody, or binding fragment thereof, of any one of claims **24-32**, wherein the antibody or binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 1, 11 or 21, and wherein the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NOs: 2, 12 or 22.

**36**. An isolated monoclonal antibody, or binding fragment thereof, that binds at least four ELR+ CXC chemokines, wherein the antibody or binding fragment comprises a heavy chain variable region and light chain variable region comprising the amino acid sequences set forth in:

(a) SEQ ID NOs: 1 and 2, respectively;

(b) SEQ ID NOs: 11 and 12, respectively; or

(c) SEQ ID NOs: 21 and 22, respectively.

**37**. An isolated monoclonal antibody, or binding fragment thereof, that binds at least four ELR+ CXC chemokines, wherein the antibody or binding fragment comprises a heavy chain variable region and light chain variable region comprising amino acid sequences having 90% identity to the amino acid sequences set forth in:

(a) SEQ ID NOs: 1 and 2, respectively;

(b) SEQ ID NOs: 11 and 12, respectively; or

(c) SEQ ID NOs: 21 and 22, respectively.

**38**. An isolated monoclonal antibody, or binding fragment thereof, that binds at least four ELR+ CXC chemokines, wherein the antibody or binding fragment comprises heavy and light chain CDRs selected from the group consisting of:

- (a) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively;
- (b) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 15, 16 and 17, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 18, 19 and 20, respectively; and
- (c) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**39**. An isolated monoclonal antibody, or binding fragment thereof, that binds at least four ELR+ CXC chemokines, wherein the antibody or binding fragment comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 11 or 21; and

wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 12 or 22.

**40**. A method of treating an autoimmune disorder in a subject in need thereof, the method comprising administering an effective amount of the fusion protein of any one of claims **1-23**, or the isolated monoclonal antibody of any one of claims **24-39**.

**41**. The method of claim **40**, wherein the autoimmune disorder is rheumatoid arthritis.

**42**. A method of blocking neutrophil infiltration in a subject with an autoimmune disorder, the method comprising administering an effective amount of the fusion protein of any one of claims **1-23**, or the isolated monoclonal antibody of any one of claims **24-39**.

**43**. The method of claim **42**, wherein neutrophil infiltration of the synovial fluid of arthritic joints is blocked.

44. A method of preventing establishment of an autoimmune disorder in a subject, the method comprising administering an effective amount of the fusion protein of any one of claims 1-23, or the isolated monoclonal antibody of any one of claims 24-39.

**45**. A method of reversing inflammatory arthritis in a subject in need thereof, the method comprising administering an effective amount of the fusion protein of any one of claims **1-23**, or the isolated monoclonal antibody of any one of claims **24-39**.

**46**. A fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+ CXC chemokines, and wherein the multispecific variable region comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 5, 6 and 7, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 8, 9 and 10, respectively.

**47**. A fusion protein, comprising a multispecific variable region operably coupled to a serum albumin moiety, wherein the multispecific variable region binds to at least four ELR+CXC chemokines, and wherein the multispecific variable region comprises heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 25, 26 and 27, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 28, 29 and 30, respectively.

**48**. A fusion protein comprising an amino acid sequence selected from the group consisting of SEQ ID Nos: 95-105 and 160-170.

**49**. A fusion protein comprising an amino acid sequence having at least 90% identity to an amino acid sequence selected from the group consisting of SEQ ID Nos: 95-105 and 160-170.

\* \* \* \* \*