280 Enhancing Antibody Agonism

Asset Overview

Product Type	Antibody
Indication	Oncology
Current Stage	Proof of Concept
Target(MoA)	Antibodies containing modified IgG2 domains which elicit agonist or antagonistic properties.
Brief Description	• Monoclonal antibodies (mAbs) that stimulate anticancer immune responses are proving increasingly effective in cancer treatment, with growing evidence that such responses can be harnessed to provide durable eradication of tumours. • This versatile and patented technology provides the exciting opportunity to engineer clinical reagents with defined, tuneable therapeutic activity regardless of FcγR expression levels in the local microenvironment. • Through a combination of in vitro and in vivo approaches, it has been shown that the human IgG2 hinge and CH1 domains impart FcγR-independent agonistic activity to immunostimulatory mAbs that bind to -CD40 and that this might also apply to other specificities. • Activity is provided by a structurally constrained isoform of hIgG2 due to its unique arrangement of disulfide bonds which confers distinct agonistic (or super agonistic) properties to the mAb.
Organization	CRUK

Differentiation

□ **Unmet needs: Influence of immunoglobulin isotype on therapeutic antibody function**

- It was unclear to the optimal isotope which should be used in agonistic mAbs or fusion proteins which are to be used for human therapy.
- There is little understanding as to how antibody isotype may affect the therapeutic properties of therapeutic antibody, i.e., the agonistic or antagonistic properties thereof.
- This technology addresses this need and provides improved agonistic (as well as antagonistic) antibodies and further provides means for the synthesis thereof.

□ **Advantages**

- The observation that IgG2 constant regions also conferred FcγR-independent activity on another anti-hCD40 mAb, SGN40 and also possibly other receptors (data not shown), suggests this may be a general property of this restricted conformation.

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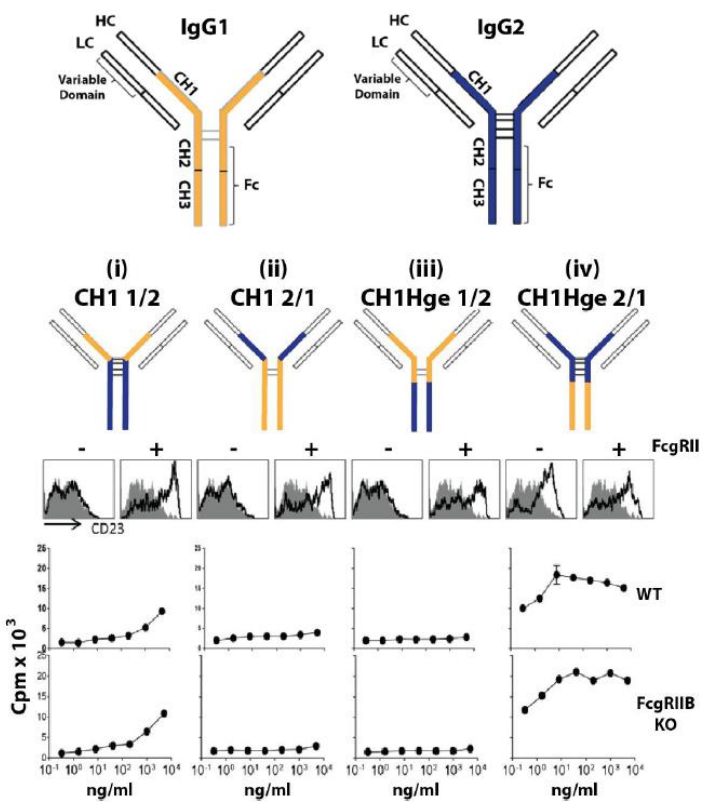
Key Data

Agonistic Activity Depends on Both the Human IgG2 Hinge and CH1 Domains (*in vitro*)



The Hinge and CH1 domains confer activity to ChiLob7/4 h2. Schematics of ChiLob 7/4 h1 (top left, in yellow) and ChiLob 7/4 h2 (top right, in blue) and hybrids (second row) where the CH1 (i, CH1 1/2 and ii, CH1 2/1) or CH1 and hinge regions (iii, CH1Hge 1/2 and iv, CH1Hge2/1) of h1 and h2 were swapped. Third row: **CD23 expression on human B cells in the absence or presence of FcγRIIB expressing crosslinking cells**. Bottom: hCD40 Tg FcγRIIB WT or KO **B cell proliferation** in response to the chimeric mAb (mean and range of duplicates).

Only when both CH1 and the hinge of h1 were replaced with that of h2 (CH1Hge 2/1, iv) robust human B cell activation and proliferation of both FcγRIIB WT and KO hCD40 Tg B cells was observed

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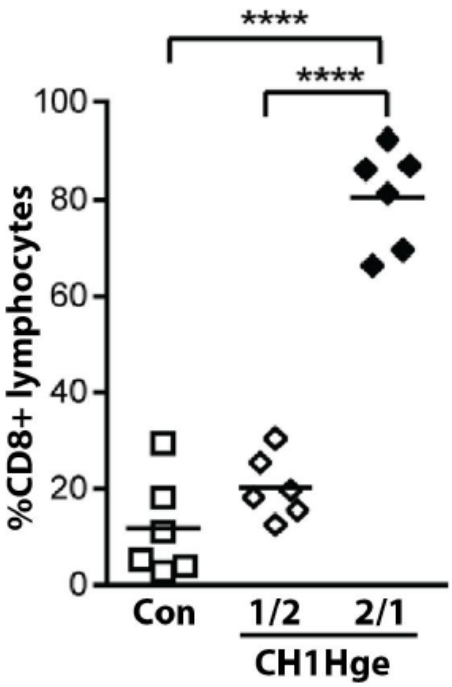
Key Data

Agonistic Activity Depends on Both the Human IgG2 Hinge and CH1 Domains (*in vivo*)

ChiLob 7/4 CH1Hge 2/1 (iv) produced significant increases in OVA-specific CD8+ T cell expansion, whereas ChiLob 7/4 CH1Hge 1/2 (iii) was inactive



OT I CD8+ T cell responses in hCD40 Tg mice treated with the indicated mAb. ****p < 0.0001

OT I CD8+ T cells have a transgenic T cell receptor designed to recognize ovalbumin residues 257-264 (OVA) and they are used to study the response of CD8+ T cells to antigen (OVA-specific response).

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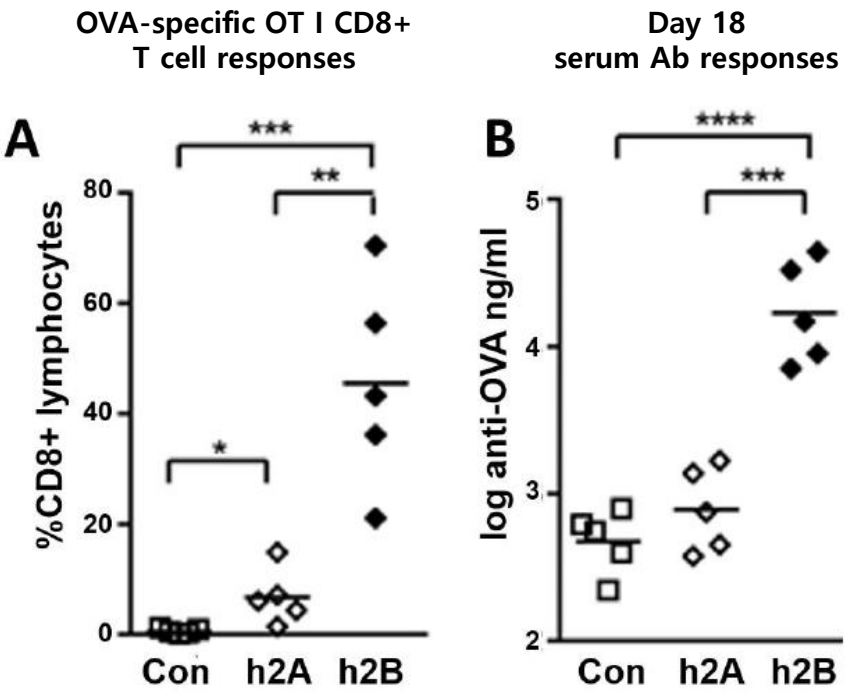
Key Data

Human IgG2 Activity Is Dependent upon Its Disulfide Bond Configuration and Mutagenesis Produces a Range of IgG2 Agonistic Activities



hCD40 Tg FcγRIIB KO mice immunised with OVA peptide plus 100 µg of chemically 'locked' h2A or h2B forms of ChiLob 7/4 hIgG2.

- Differences in ChiLob 7/4 h2A and ChiLob 7/4 h2B activity *in vivo*, where h2B caused significantly greater expansion of OVA-specific CD8+ T cells (Figure A) and production of OVA-specific IgG (Figure B) when compared to h2A
- Data have demonstrated that ChiLob 7/4 h2 could be manipulated in vitro and in vivo to achieve a range of agonistic activities.

IgG2 is unique among human IgG in its ability to ''shuffle'' disulfide bonds in its CH1 and hinge regions resulting in a range of isoforms. The molecule is believed to be synthesized in its ''h2A'' form, which then gradually converts in the blood through a series of intermediates to its ''h2B'' form

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Intellectual Property

Patent No.	PCT/IB2015/052166
Application Date	
Status	Registered
Country	US, EP, JP, CN, GB, CA, AU

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