Novel Short Peptides for Treating T-cell Mediated Autoimmune Diseases and Inflammation

Yechiel Shai
Department of Molecular Biosciences
The Weizmann Institute of Science, Rehovot, ISRAEL
Currently, there are more than 60 US (FDA)-approved peptide medicines on the market.

Approximately 140 peptide drugs currently in clinical trials.

More than 500 therapeutic peptides in preclinical trials

Peptide therapeutics: current status and future directions. Fosgerau and Hoffmann Drug Discovery Today. 1 January 2015 Zealand Pharma A/S, Denmark
Technologies to be discussed

1: METHODS OF TREATING T-Cell mediated AUTOIMMUNE DISEASES

2: PEPTIDES DERIVED FROM HIV gp41 FOR TREATING T-CELL MEDIATED PATHOLOGIES

3: ANTI-INFLAMMATORY PEPTIDES

4: PEPTIDES BASED ON THE TRANSMEMBRANE DOMAIN OF A TOLL-LIKE RECEPTOR (TLR) FOR TREATMENT OF TLR-MEDIATED DISEASES
Mimicking HIV strategy to reduce T-cell immune response
HIV-1 - CELL FUSION

gp160 = gp120/gp41

HIV-1

CD4 Chemokine Receptor

gp41 trimer

Nucleus
The Immune Synapse

CD3  TCR  CD4  Co-receptor

gp41  Viral Membrane
HIV1 Utilizes Three Domains from gp41 to Suppress the Immune Response
SUBUNIT ORGANIZATION OF HIV-1 gp160

- Loop
- TMD
- Fusion peptide
1
Fusion Peptide Binds T-Cell Receptor (TCR) and Inhibits TCR Activation
Reduction in Autoimmune Response In Mice
(Adjuvant Arthritis)

Implication in Therapy of Autoimmune Diseases
Mechanism of T-Cell Activation

- Anti-CD3
- PMA / Ionomycin

MHC + Antigen → Increase in Intracellular Ca\(^{2+}\) → T cell Activation

Note: Red X indicates an incorrect step.
HIV-1 gp41 Trans-Membrane Domain

Mechanism of T-Cell Activation

- MHC + Antigen
- Increase in Intracellular Ca²⁺
- T cell Activation

- Anti-CD3
- PMA / Ionomycin
The Loop Region

Loop

Ashkenazi A. et al. BLOOD. 2013 121(12):2244-52
ISLAD Inhibits Severity of the EAE Model by Down-Regulation of Pathogenic T Cells \textit{in-vivo} (IP injection of 10 μg/mouse in a single dose)

Day 0: Disease induction with or without ISLAD

Day 10: Onset of the disease

Day 10: Onset of the disease

Clinical score

Day 30: termination

lymph node removal

MOG peptide

Proliferation and cytokine secretion

Mean clinical severity

\( p < 0.01 \)

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Proliferation (cpm)

Day post immunization

PBS

ISLAD

0
1
2
3
4
0
10
20
30
4000
8000
12000
16000

RBS

ISLAD
Experimental autoimmune encephalomyelitis (EAE) was induced in C57BL/6 mice. Two groups of 10 mice each were examined where one group received the HT peptide together with EAE induction. Clinical scoring and weight measurements of the mice were carried out at the points presented in the graphs. Mice treated with the HT showed a reduced progression and severity of the disease as seen by low clinical score and very low weight loss.
EAE-Mice not treated

EAE-Mice treated with peptide
Innate Immunity Regulation with TMDs of TLRs
TLRs are membrane pattern recognition receptors.

TLRs recognize pathogen associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs).
Blocking TLRs signaling by targeting their assembly within the membrane

Immune response

Addition of TMD peptide

Immune response
A mouse model of inflammation

**Graphs:**

- **Graph a:** Survival (%) over time (Days) with 3 conditions: N.T, LTA, LTA + TLR2 TMD.

- **Graph b:** Similar to graph a but with IL-6 levels in N.T, LTA, LTA + TLR2 TMD.

- **Graph c:** Bar graph showing TNF-α levels with conditions: N.T, LTA, LTA + TLR2 TMD.

- **Graph d:** Bar graph showing IL-6 levels with conditions: N.T, LTA, LTA + TLR2 TMD.

**Images:**

- **Image e:** Three images showing Saline, LTA, and LTA + TLR2 TMD peptide treated groups.
Neutralization of pro-inflammatory monocytes by targeting TLR2 dimerization ameliorates Colitis
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