CGEN-15001 A Novel B7-like protein controls inflammation in a translational RA assay and induces long term remission in autoimmune disease models

ACR, San Francisco, Nov 2015
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CGEN-15001T – a novel B7-like Immune Checkpoint protein

**Mission:** discovery of novel targets and develop first-in class biologics for key medical needs, focusing on immunoncology and autoimmunity

**Aim:** discovery of novel members of the B7/CD28 family

*Adapted from J Clin Invest. 2010; 120(1):76-80*
CGEN-15001- an Fc fusion therapeutic candidate

CGEN-15001 is a fusion protein: Fc + ECD of CGEN15001T
Inhibition of T Cell Activation by CGEN-15001 fusion protein
Polyclonal & Ag Specific Proliferation

Polyclonal T cell activation
- Naive murine CD4+ T cells
- anti-CD3/anti-CD28 coated beads + proteins

Antigen specific T cell Activation
- Irradiated APCs plus OVA\textsubscript{323-339}
- Naive DO11.10 CD4+ T cells

Robust inhibition of T cell proliferation following polyclonal or Ag specific activation
- Demonstrated with various additional assays and readouts

Miller and Podojil, Northwestern Univ.
Immune balance restoration: Th1/Th17 to Th2 skew

- Reduction of pro-inflammatory Th1 and Th17 responses
- Enhancement of anti-inflammatory cytokines and Th2 responses
- Similar ‘Th1/Th2 shift’ obtained with human cells and in recall responses obtained from mice with EAE following CGEN-15001 treatment

DO11.10 CD4+ T cells + Irradiated APCs + OVA_{323-339} under Th1, Th17 or Th2 driving conditions

Th1
- Control Ig
- CGEN-15001

Th17
- IL-17

Anti-inflammatory cytokines
- IL-5
- IL-4
- IL-10

Pro-inflammatory cytokines
- IFNγ

# p<0.0001 vs. Ig control
Enhancement of inducible regulatory T cells (iTregs) differentiation

Soluble anti CD28
Immobilized CGEN-15001 or Control Ig
CD4+ CD25-
Naive T cell

±TGFβ and IL-2
4-5 days

iTreg induction

CD25+FoxP3+ iTreg

Activate d T cell

CD25+FoxP3- T cell

 Activation of T cell

#Foxp3+CD25+/well

Control Ig
CGEN-15001

TGFb [ng/ml]

0 0.1 0.3 1 10

0 10000 20000 30000 40000 50000 60000 70000 80000

In house, Compugen, Tel Aviv
CGEN-15001 mediates immune modulation

CGEN-15001 restores immune balance

- Inhibits T cell activation
- Skews the immune responses from Th1/Th17 to Th2
- Induces regulatory T cell (Treg) differentiation.
Inhibition of TNFα secretion in a translational assay mimicking T-cell:Macrophage interactions in RA synovium

Healthy donors or RA patients

CD4+ T cells

CD14+ monocytes

“Synovial-like”
Cytokine stimulated T cells (TcK)

+M-CSF

+TNFα, IL-6, IL-15

Monocyte-derived Mφ

Autologous TcK:Mφ co-cultures

+15001 or Control Ig

ELISA (or Luminex)

Healthy donors

RA patients

p<0.0002

p<0.0001

CGEN-15001 pathway is functional and responsive in RA patients

Mclnnes, Glasgow Univ.
Inhibition of RA-Related cytokines secretion in TcK:ΜΦ co-culture (normalized data, average of 4 donors)

- Luminex results on additional cytokines:
  - Mild inhibition: IL-17, IL-13, IL-2R
  - No effect: IL-10, IL-15, IFNα, IL-7

McInnes, Glasgow Univ.
Efficacy in Models of Autoimmune Diseases: Therapeutic Effect in Mouse Model of RA (CIA)

**Collagen Induced Arthritis (CIA)**

Type II collagen/CFA

DBA/1

Treatment at disease onset

i.p., 3x/wk for 10 days

- Inhibition of disease progression and reduced joint inflammation (similar to positive controls, i.e. CTLA4-Ig and Enbrel)
- Abolishment of recall response to type II collagen in LN cells

* p < 0.05, ** p < 0.01, *** p < 0.001 vs. IgG2a

**Clinical score**

**Histological score**

**Recall responses of LN cells**

Williams and McNamee, Oxford Univ.
Prevention of Type 1 Diabetes in NOD Model
Sustained Long Term Efficacy

Nonobese Diabetic Mice (NOD)

Prediabetic NOD (10 wks old)

Blood glucose levels measured weekly, diabetes is defined as 2 consecutive measurements of >250 mg/dL.

Long standing reduction in disease incidence following short term administration to pre-diabetic mice

Suggests tolerance induction

n = 15 mice per group
Potential Re-establishment of Immune Tolerance in Models of Autoimmune Diseases and Transplantation

- Long term reduction in disease score and inhibition of disease relapse
- Inhibition of autoreactive T cell infiltration to the CNS and increase in spleen Treg number
- Inhibition of epitope spreading (recall responses and DTH with spread epitopes peptides, not shown)
- Th1/Th17 to Th2 shift (in ex-vivo recall responses, not shown)
CGEN-15001 induced long-term remission is mediated by Tregs

- Transient neutralization of Tregs leads to transient abolishment of the long term remission induced by CGEN-15001
- The effect of CGEN-15001 depends on newly generated Ag specific Tregs rather than existing Tregs
CGEN-15001 - A potential candidate for treatment of RA and other autoimmune disease

- A novel inhibitory immune checkpoint pathway

- Translational data:
  - Inhibition of RA-related cytokines and chemokines secretion in ‘synovial-like’ co-cultures with RA patients’ cells

- Efficacious in multiple models of autoimmune diseases
  - CIA (RA), R-EAE (MS), T1D (in NOD), psoriasis (not shown)
  - Durable in vivo effects upon short term treatment in EAE and T1D

- Unique mechanism of action
  - Restoration of immune balance: **Th1/Th17 to Th2 skew**
  - Potential induction of Treg-dependent peripheral **immune tolerance**
## Acknowledgments

### Glasgow Univ.
Iain B. McInnes  
Mariola Kurowska-Stolarska  
Ashley Gilmour  
Clare Tange  
Donna McIntyre

### Oxford Univ.
Richard Williams  
Kay McNamee

### Northwestern Univ.
Stephen D. Miller  
Joseph R. Podojil

### Compugen
Eyal Neria  
Zurit Levine  
Galit Rotman  
Amir Toporik  
Ilan Vaknin  
Anat Oren  
Elisheva Yonish-Rouach  
Rami Khosravi  
Zohar Tiran  
Inbal Barbiro

Thank you