

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

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ACR, San Francisco, Nov 2015

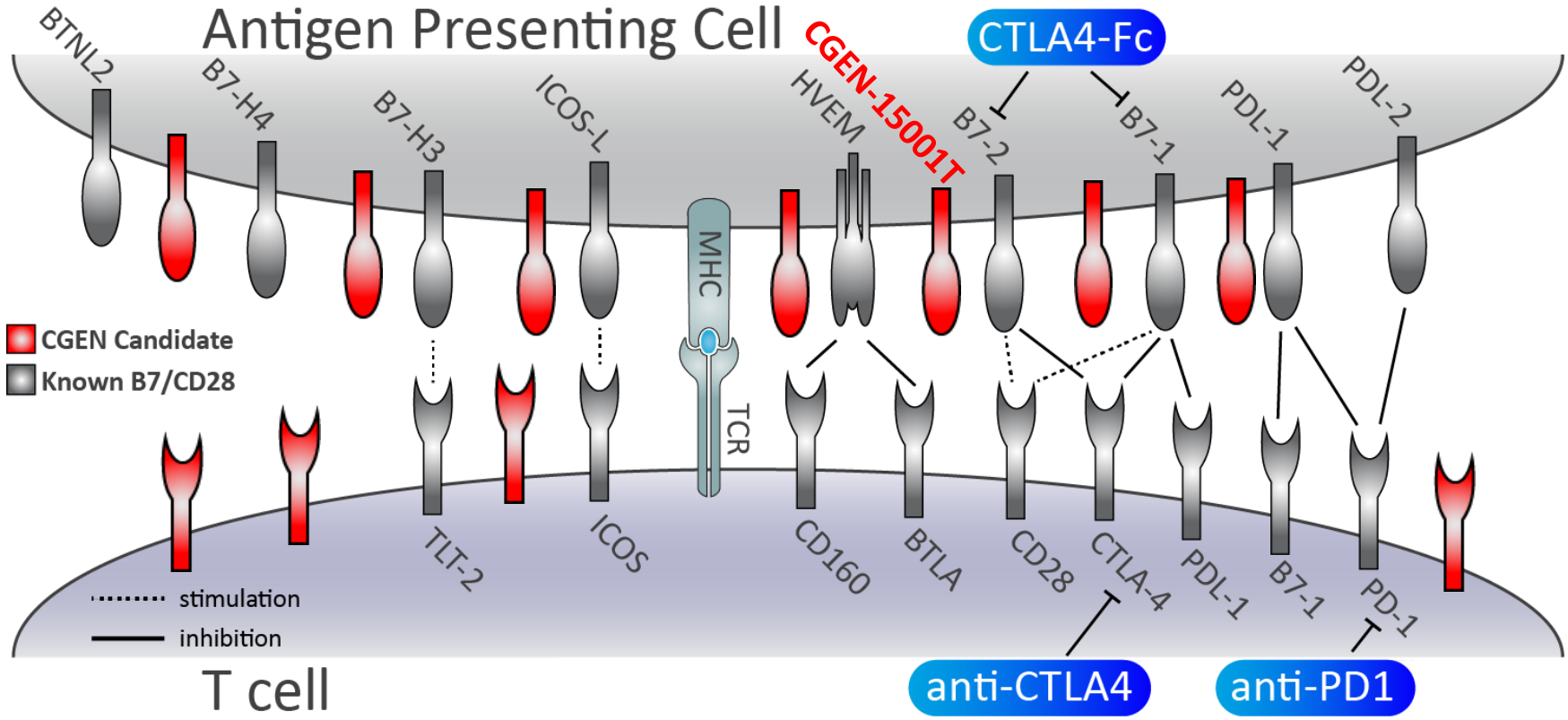
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CGEN-15001T – a novel B7-like Immune Checkpoint protein

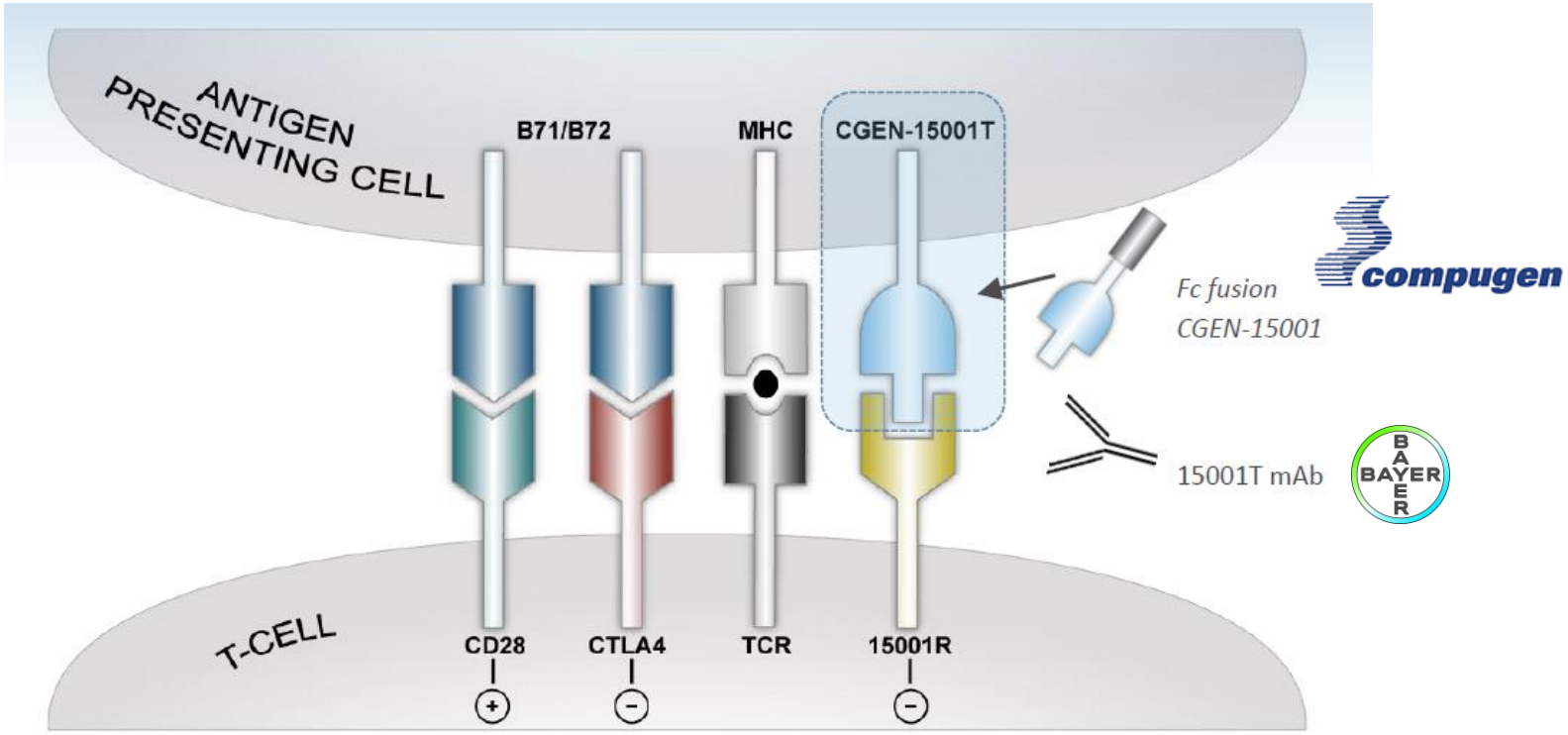
Mission: discovery of novel targets and develop first-in class biologics for key medical needs, focusing on immunoncology and autoimmunity

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

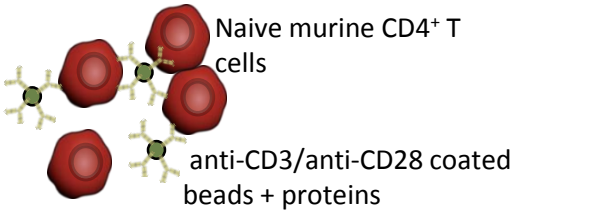


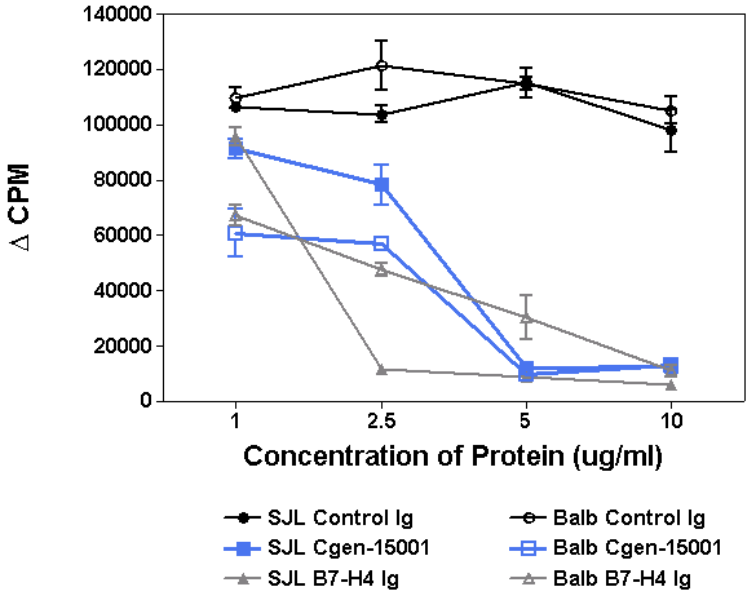
CGEN-15001 is a fusion protein: Fc + ECD of CGEN15001T

Inhibition of T Cell Activation by CGEN-15001 fusion protein

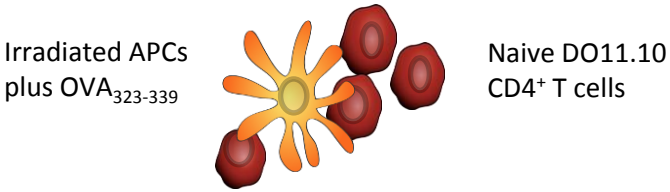
Polyclonal & Ag Specific Proliferation

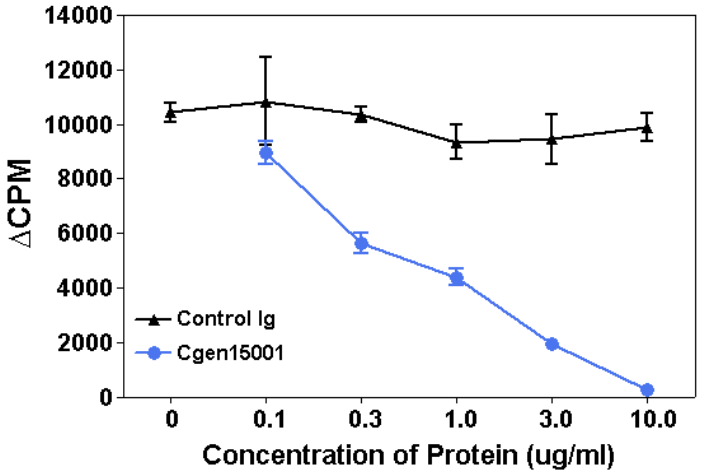
Polyclonal T cell activation





Antigen specific T cell Activation

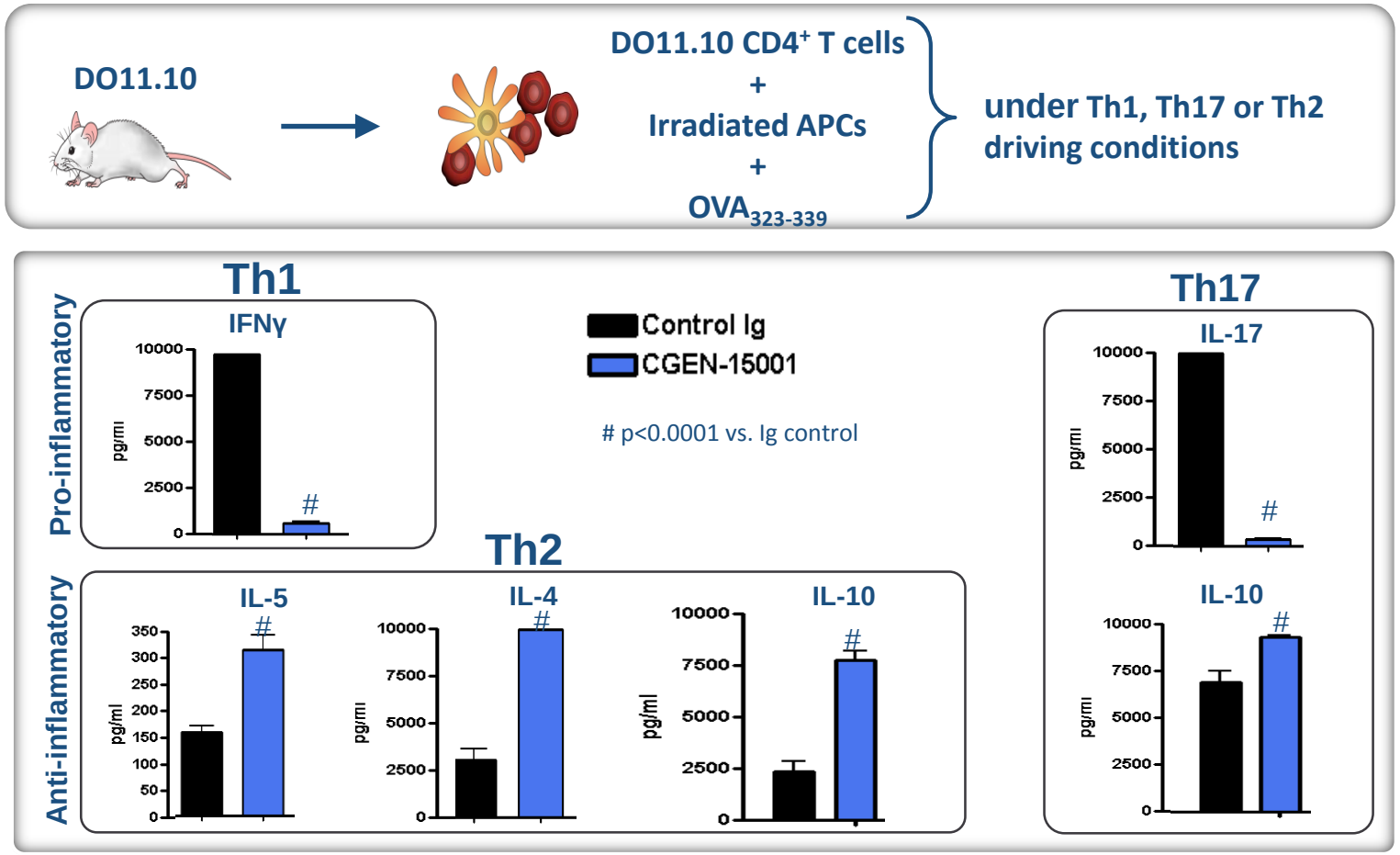




- Robust inhibition of T cell proliferation following polyclonal or Ag specific activation
  - Demonstrated with various additional assays and readouts

Miller and Podojil, Northwestern Univ.

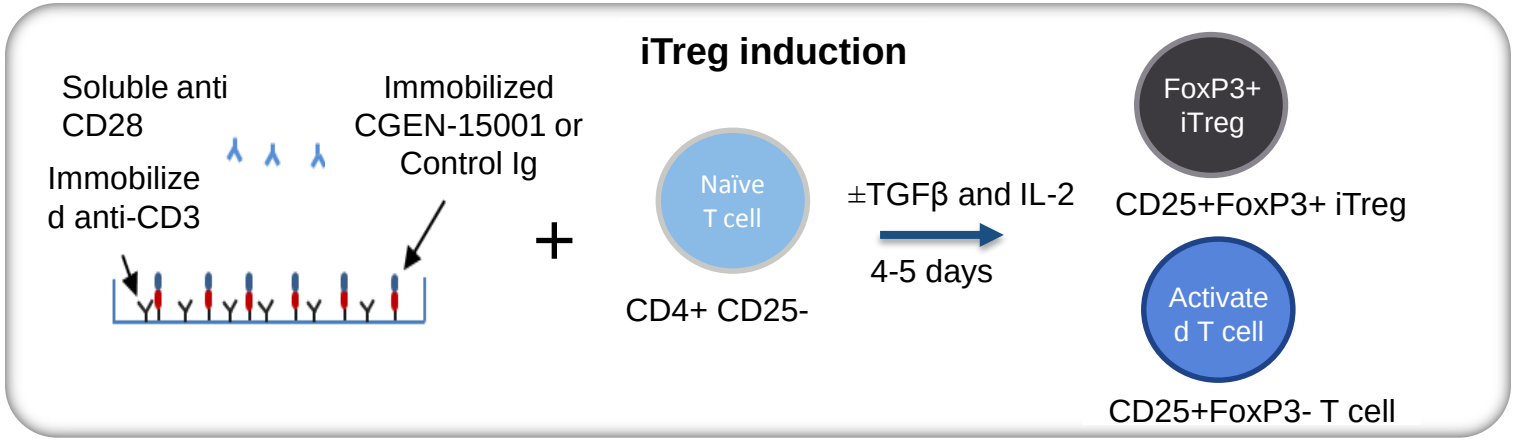
Immune balance restoration: Th1/Th17 to Th2 skew

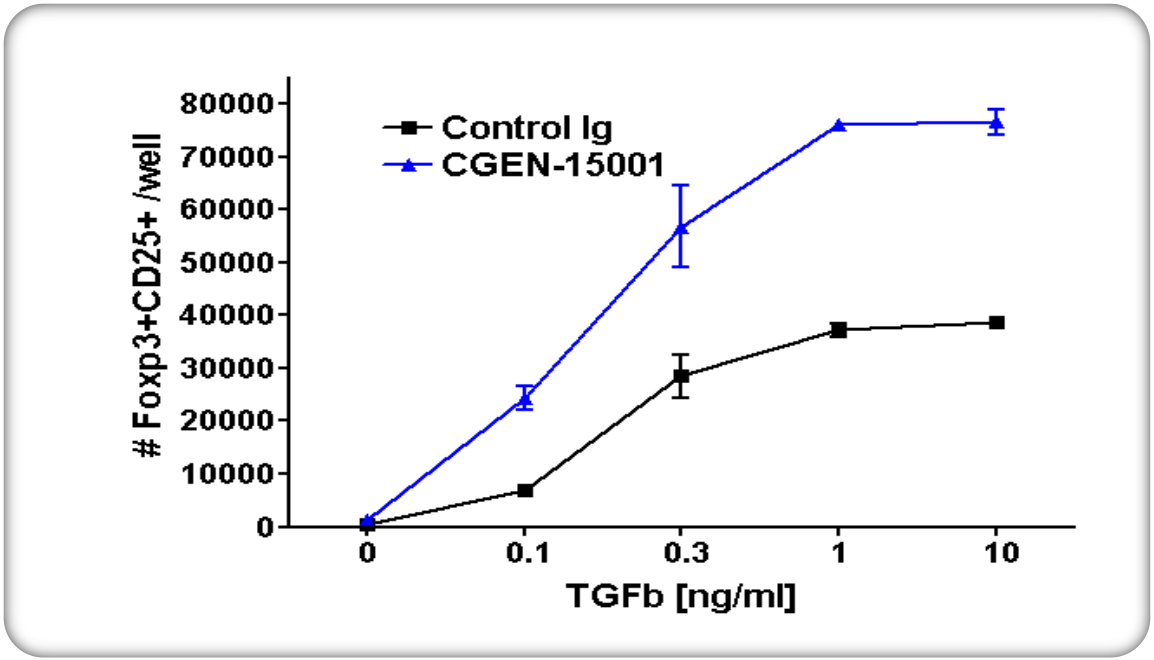


- Reduction of pro-inflammatory Th1 and Th17 responses
- Enhancement of anti-inflammatory cytokines and Th2 responses
- Similar 'Th1/Th2 shift' obtained with human cells and in recall responses obtained from mice with EAE following CGEN-15001 treatment

Miller and Podojil, Northwestern Univ.

Enhancement of inducible regulatory T cells (iTregs) differentiation



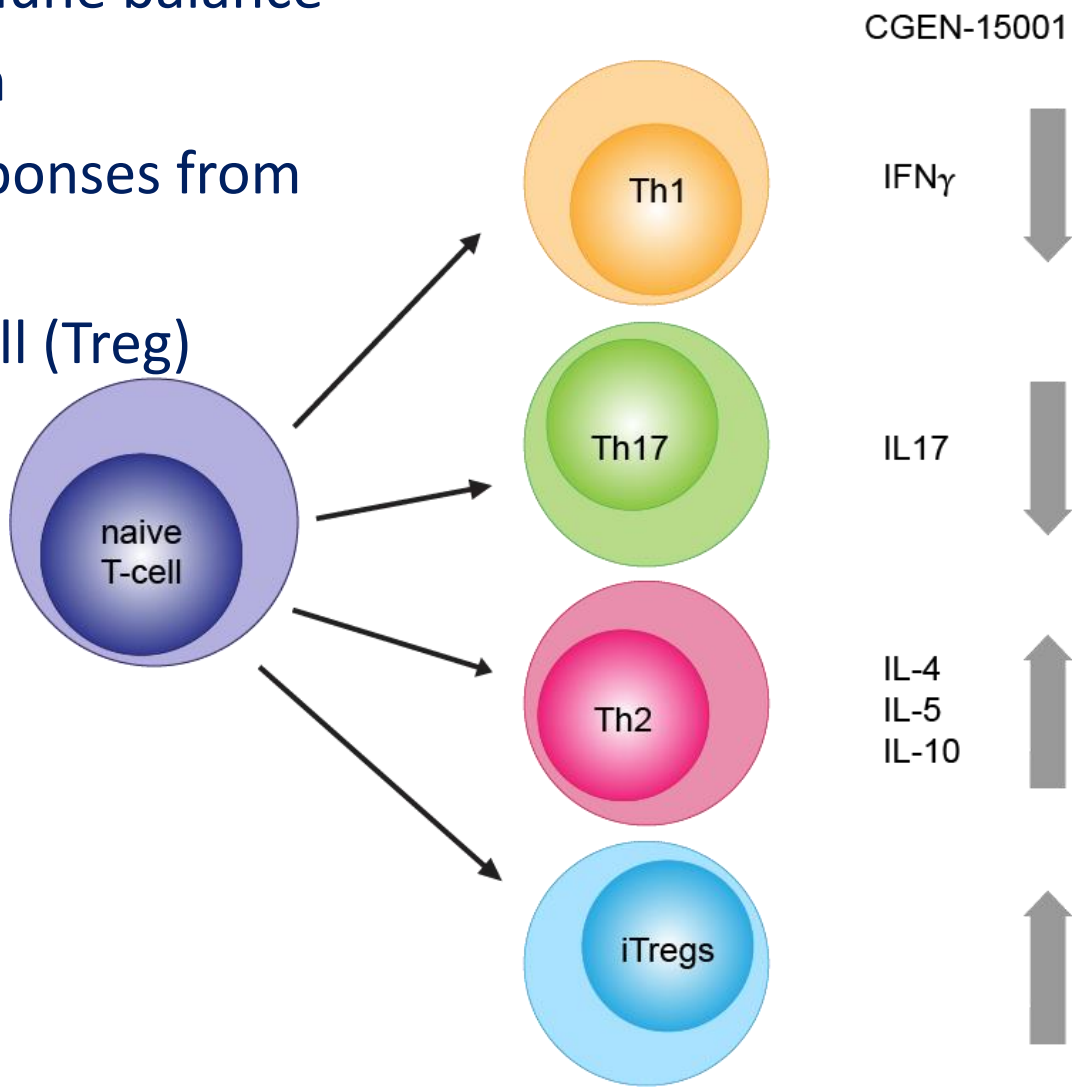


In house, Compugen, Tel Aviv

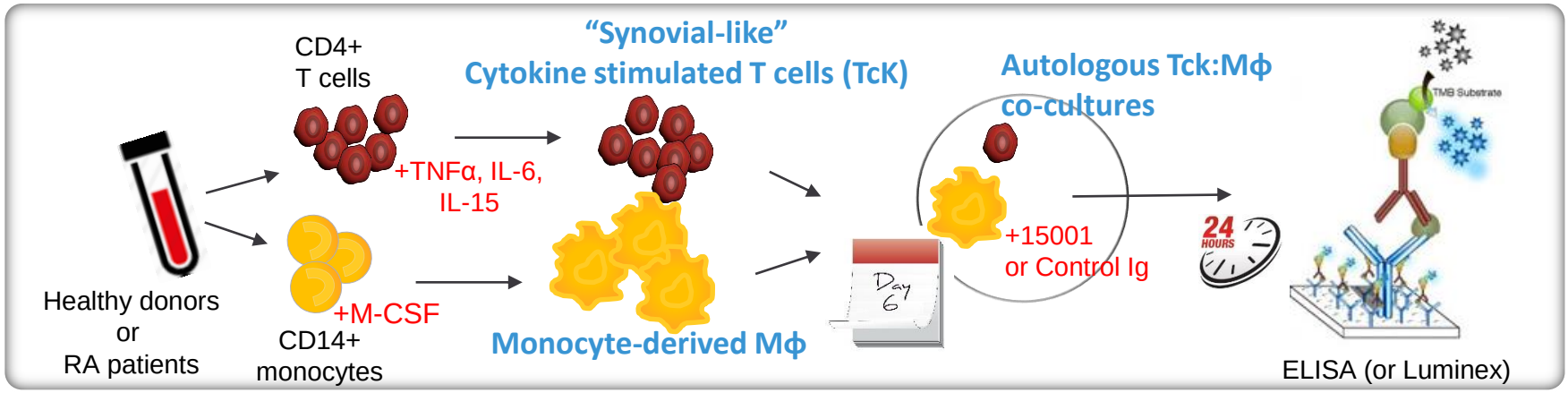
CGEN-15001 mediates immune modulation

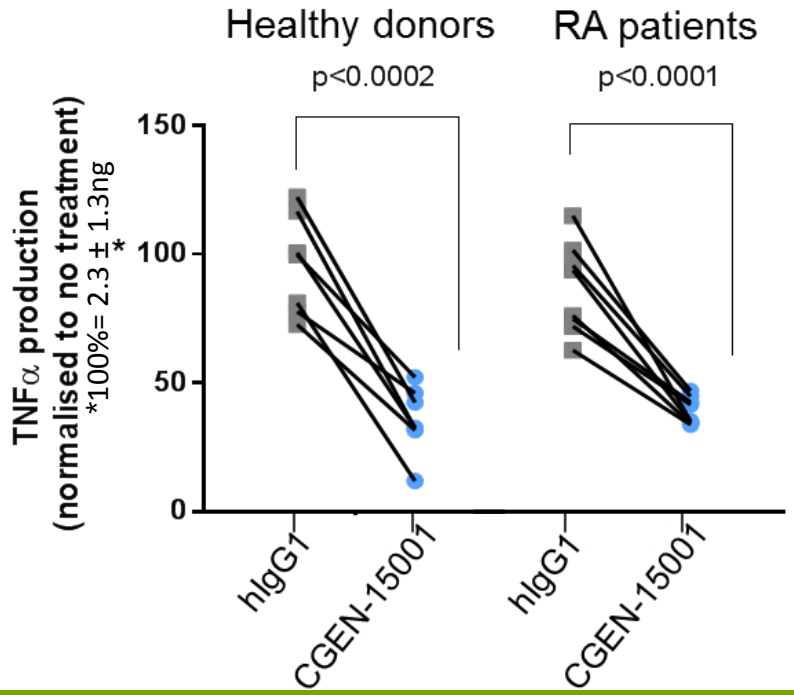
CGEN-15001 restores immune balance

- 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

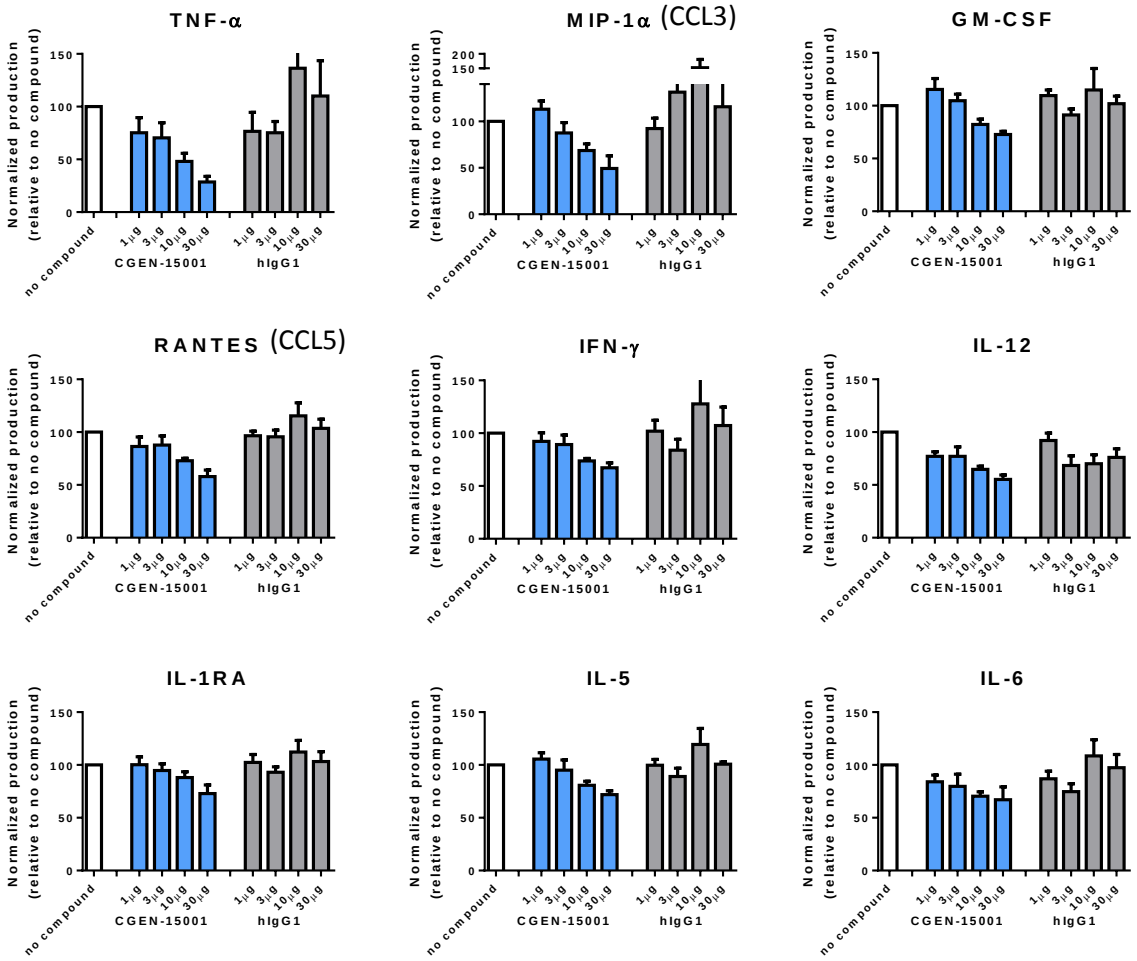




- CGEN-15001 pathway is functional and responsive in RA patients

McInnes, Glasgow Univ.

Inhibition of RA-Related cytokines secretion in TcK:MΦ co-culture
(normalized data, average of 4 donors)

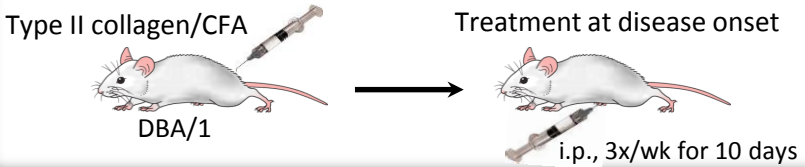


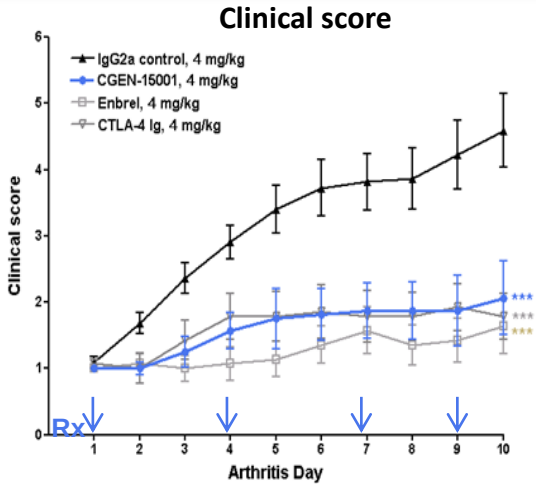
- Luminex results on additional cytokines:
  - Mild inhibition: IL-17, IL-13, IL-2R
  - No effect: IL-10, IL-15, IFNα, IL-7

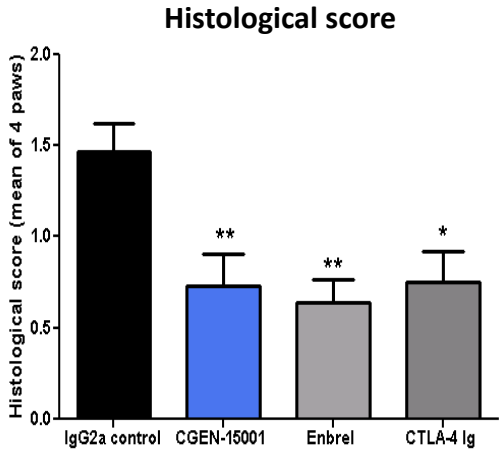
McInnes, Glasgow Univ.

Efficacy in Models of Autoimmune Diseases: Therapeutic Effect in Mouse Model of RA (CIA)

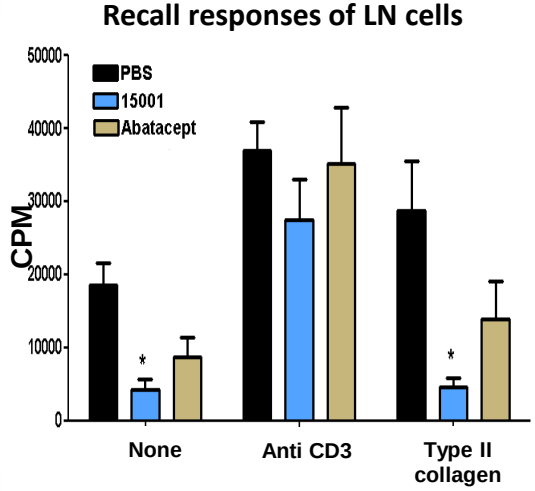
Collagen Induced Arthritis (CIA)







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



* p < 0.05, vs. PBS

- 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

Williams and McNamee, Oxford Univ.

Prevention of Type 1 Diabetes in NOD Model

Sustained Long Term Efficacy

Nonobese Diabetic Mice (NOD)

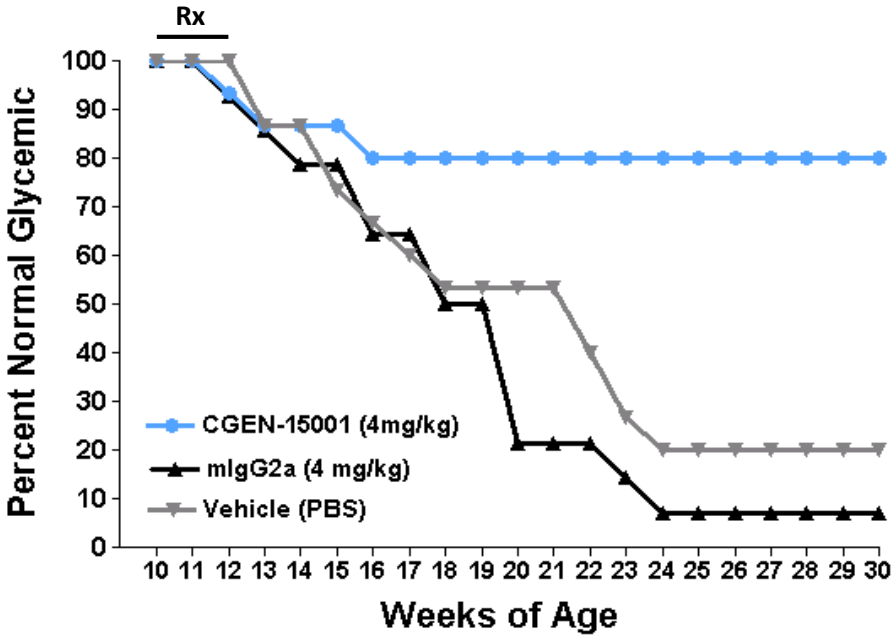
Prediabetic NOD
(10 wks old)





i.p., 3x/wk for 2 wks

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

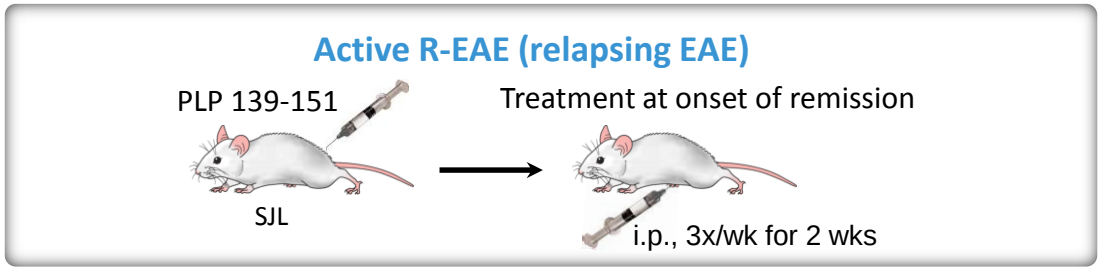


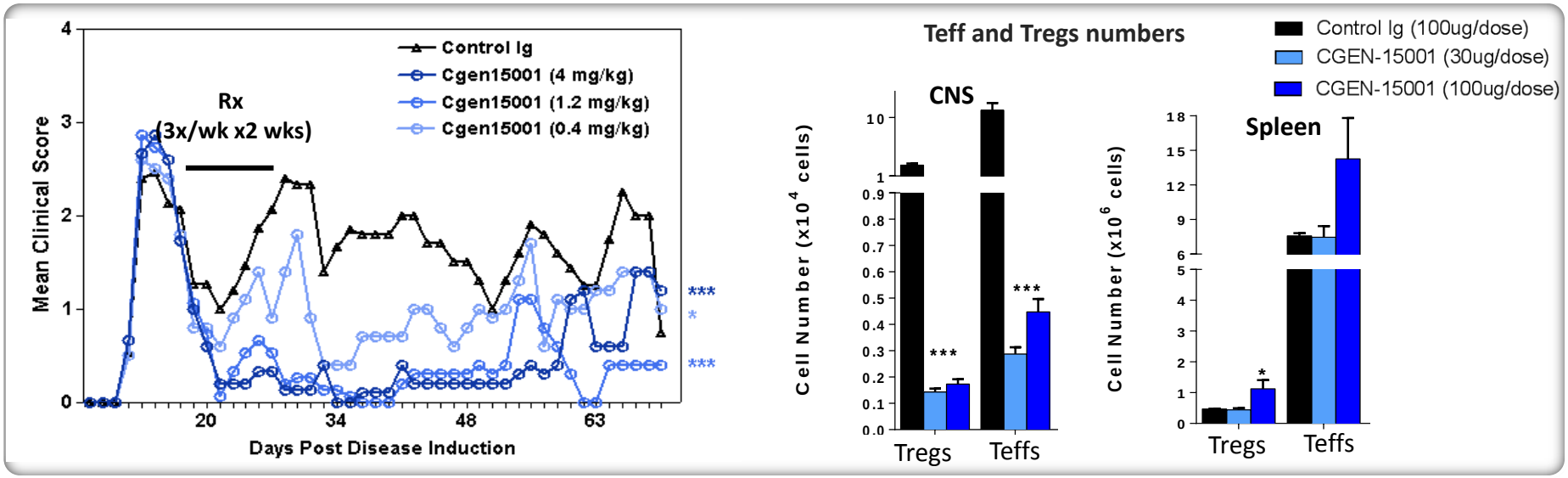
n = 15 mice per group

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

Miller and Podojil, Northwestern Univ.

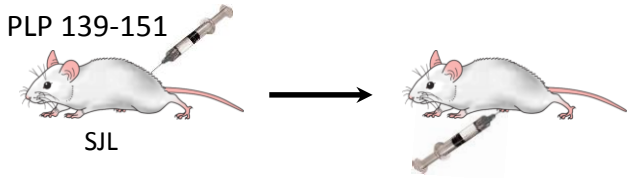
Potential Re-establishment of Immune Tolerance in Models of Autoimmune Diseases and Transplantation





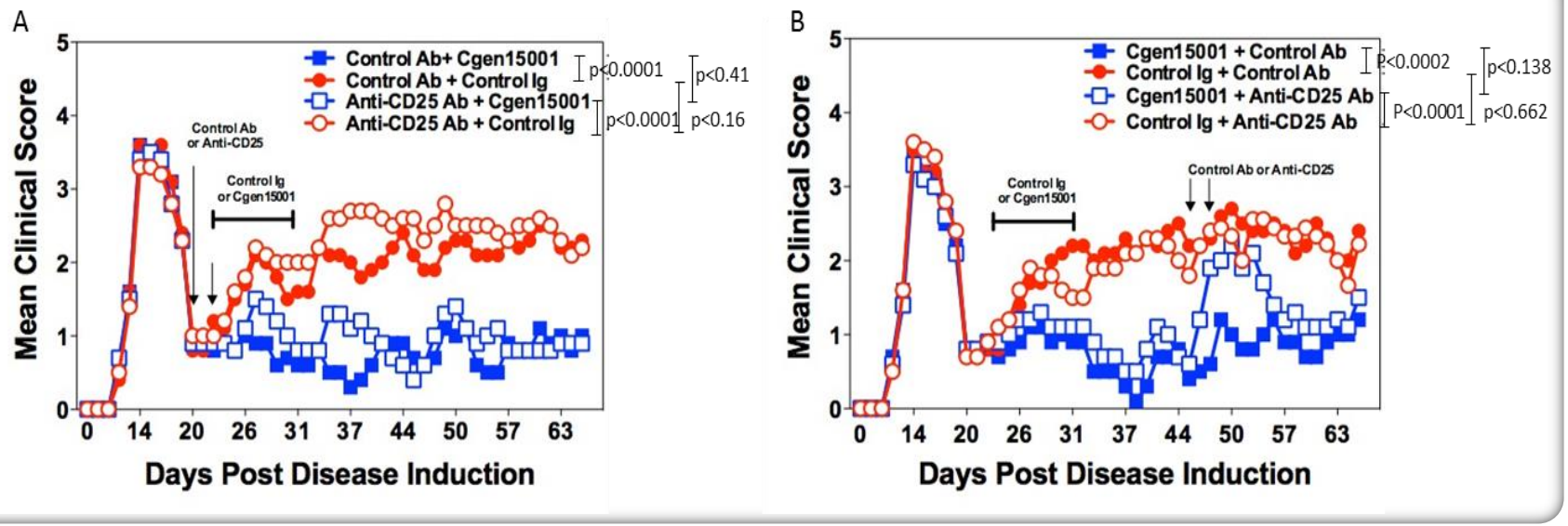
- Long term reduction in disease score and inhibition of disease relapse
- Inhibition of autoreactive T cell infiltration to the CNS and increase in spleen Treg number
- Inhibition of epitope spreading (recall responses and DTH with spread epitopes peptides, not shown)
- Th1/ Th17 to Th2 shift (in ex-vivo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

CGEN-15001 induced long-term remission is mediated by Tregs



Treatment with CGEN-15001 or Isotype control i.p., 3x/wk for 2 wks from onset of remission

A. Concomitant administration of anti-CD25 (7D4) or Control Ab
B. Late administration of anti-CD25 (2wks after the last treatment with CGEN-15001



- 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

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Thank you