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CGEN-15001: A NOVEL B7-LIKE REGULATOR OF IMMUNE HOMEOSTASIS AND INDUCER OF ANTIGEN-SPECIFIC TOLERANCE

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INTRODUCTION

B7 proteins play critical immunomodulatory roles and provide attractive targets for development of novel therapies for cancer and autoimmunity, both of which involve improper immune tolerance. A major medical need in autoimmunity is restoration of immune tolerance to self-antigens and immune homeostasis. **CGEN-15001** is a first-in-class Fc-fusion protein consisting of the extracellular domain of a novel B7-like protein, discovered by Compugen based on shared bioinformatic characteristics with known B7 members.

CGEN-15001 Induces Antigen Specific Tolerance in Autoimmune Diseases
Unique MOA: Combining tolerance induction and restoration of immunological homeostasis

- Regulates immune homeostasis: inhibiting Th1/Th17 responses while enhancing Th2 and anti-inflammatory cytokines (e.g., IL-10) and promoting iTreg differentiation
- Induces durable therapeutic effect following short-term treatment in models of autoimmune diseases
- The durable therapeutic effect is Treg dependent
- The therapeutic effect is transferable, and mediated by induction of Ag-specific immune tolerance. Previous knowledge of the antigen is not required
- Promotes donor-specific tolerance leading to graft survival in bone marrow transplantation model with HY-minor Ag mismatch

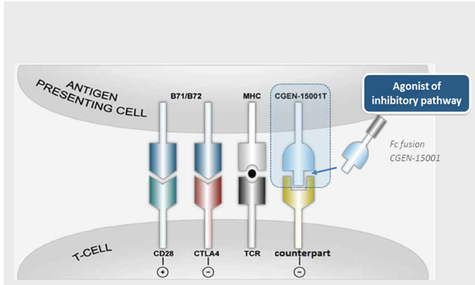
CGEN-15001 provides potential paradigm shift from "standard of care"
Addressing a widely anticipated 'next step' therapeutic in autoimmunity

- Translating the success of checkpoint manipulation from Immuno-Oncology to autoimmunity
- Immune-modulation offers safety advantages vs. immune-suppression

CGEN-15001 IS A LIGAND OF A NOVEL T CELL INHIBITORY PATHWAY

CGEN-15001

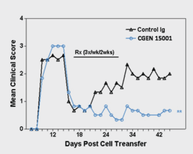
- Fc fusion protein
- Derived from a novel immunomodulatory protein
- Binds to activated T cells
- Activates an inhibitory pathway



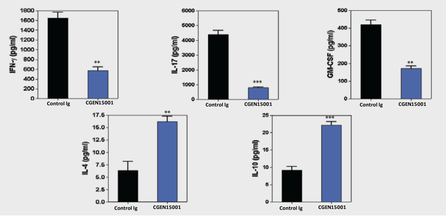
HOMEOSTASIS

CGEN-15001 RESTORES HOMEOSTASIS IN-VIVO BY SHIFTING TH1/TH17 TO TH2

Adoptive transfer R-EAE model:



Cytokine secretion following ex-vivo reactivation of splenocytes with $PLP_{139-151}$-day 45



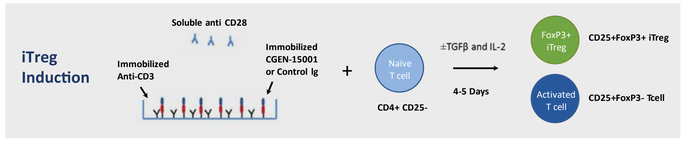
n=6, *p<0.05 ** p<0.01, *** p<0.001 vs. Control Ig

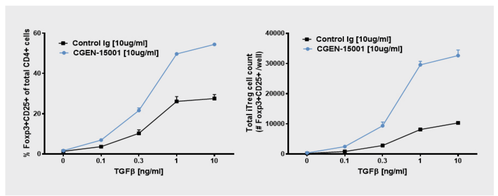
Inhibition of pro-inflammatory cytokines (IFNg, IL-17, GM-CSF) and promotion of anti- inflammatory cytokines (IL-4, IL-10)

- **Similar findings were observed in-vitro, following Th differentiation of mouse or human CD4 cells**

TREG & TOLERANCE INDUCTION

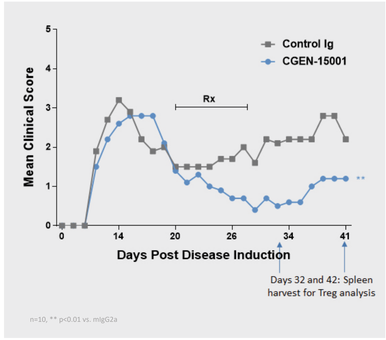
CGEN-15001 ENHANCES iTREG DIFFERENTIATION



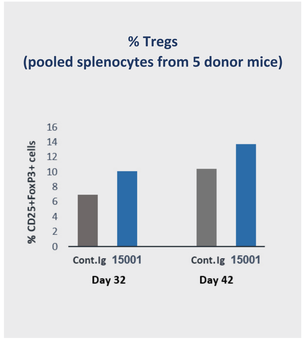


In-vitro enhancement of iTreg differentiation under Treg driving conditions

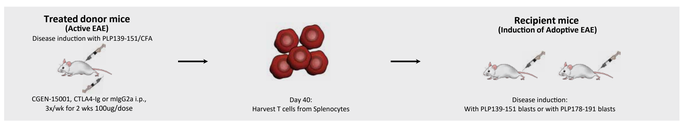
CGEN-15001 INDUCES TREGs IN THE R-EAE MODEL



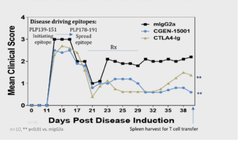
n=10, ** p<0.01 vs. mIgG2a



INDUCTION OF ANTIGEN-SPECIFIC TOLERANCE BY CGEN-15001



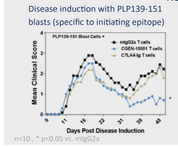
CGEN-15001 Treated Donor mice



n=10, ** p<0.01 vs. mIgG2a

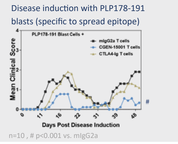
Recipient mice

Disease induction with PLP139-151 blasts (specific to initiating epitope)



n=10 , * p<0.05 vs. mIgG2a

Disease induction with PLP178-191 blasts (specific to spread epitope)

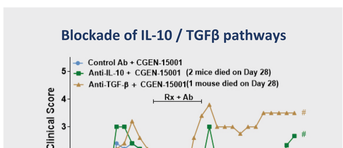


n=10 , # p<0.001 vs. mIgG2a

- **T cells from CGEN-15001-treated mice protect recipients only when disease is driven by the same epitope present during CGEN-15001 treatment of donors (PLP178-191)**
- **CGEN-15001 induces tolerance in treated mice, which can be transferred to recipient mice The immune tolerance induced by CGEN-15001 is Ag-specific (most likely through Ag-specific Tregs)**

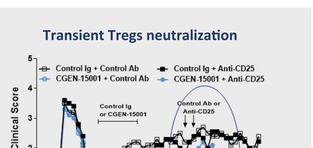
TREGs MEDIATE LONG-TERM REMISSION BY CGEN-15001 IN THE R-EAE MODEL

Blockade of IL-10 / TGFβ pathways



n=10, i.p., 3x/wk for 2 wks, 100ug/dose, #p<0.001 vs. Control Ig+ CGEN-15001

Transient Tregs neutralization

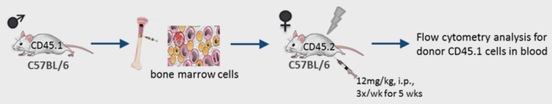


n=10, i.p., 3x/wk for 2 wks, 100ug/dose

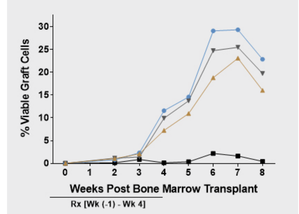
- **Blockade of IL-10 or TGFβ abolishes CGEN-15001 therapeutic effect**
- **Transient neutralization of Tregs (with anti-CD25 Ab) leads to transient abolishment of CGEN-15001 induced long term remission**

CGEN-15001 INDUCES TOLERANCE IN A BONE MARROW TRANSPLANTATION MODEL

HY (histocompatability Y chromosome) Minor Ag mismatch bone marrow transplantation

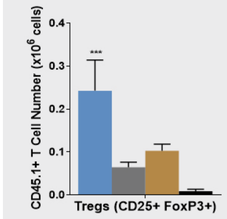


Graft survival (blood CD45.1 cells)



n=6

Number of Tregs in spleen



*** p<0.001 vs. Male donor cells + Control Ig

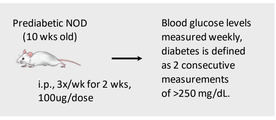
- Male donor cells + CGEN-15001
- Male donor cells + anti-CD40L
- Female donor cells (positive control)
- Male donor cells + Control Ig

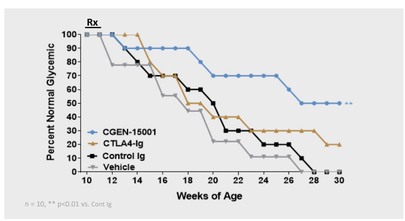
- **CGEN-15001 promotes donor-specific tolerance leading to graft survival**
- **Treatment with CGEN-15001 leads to significant Tregs increase in the spleen**

LONG TERM EFFICACY

LONG TERM EFFICACY IN TYPE 1 DIABETES MODEL PREVENTION OF DISEASE DEVELOPMENT

Non-obese Diabetic Mice (NOD)





n = 10, ** p<0.01 vs. Cont Ig

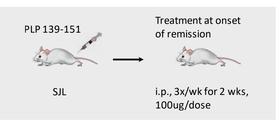
CGEN-15001 administration to pre-diabetic NOD mice prevents disease development

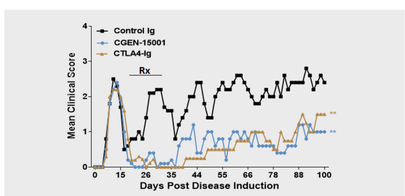
Long duration of response following short term administration (3x/wk for 2wks), lasting at least 18 weeks after cessation of treatment

- Suggests tolerance induction

LONG TERM THERAPEUTIC EFFECT IN MS MODEL FOLLOWING SHORT TREATMENT WITH CGEN-15001 (R-EAE)

Active R-EAE (relapsing EAE)





d1-35 n=10, d36-100 n=5, ** p<0.01 vs. Cont Ig

High efficacy in therapeutic regimen with established disease

Short-term treatment (3x/wk for 2wks) induces long-term remission

- Suggestive of immune tolerance induction

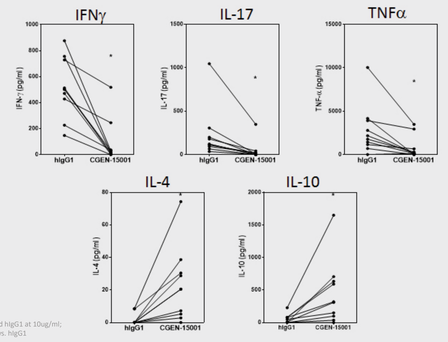
Consistent effect in multiple EAE models

- Dose dependent
- Active PLP/CFA induced
- Passive / adoptive transfer
- Viral (TMEV) induced

TRANSLATIONAL STUDIES

CGEN-15001 PATHWAY IS FUNCTIONAL AND RESPONSIVE IN MS PATIENTS –TH1/TH17 TO TH2 SHIFT

PBMCs from MS patients activated with MS-related antigen (MBP_{84-99})



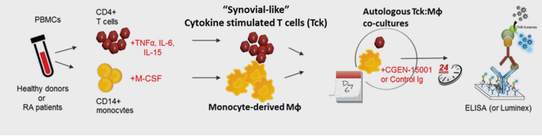
CGEN-15001 and hIgG1 at 10ug/ml; n=10, * p<0.05 vs. hIgG1

CGEN-15001 shifts Th1/Th17 responses to Th2 and regulatory profile in a translational assay:

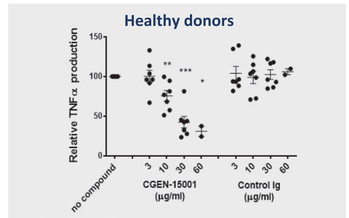
- **Inhibits proliferation and secretion of IFNg, IL-17 and TNFa**
- **Increase anti-inflammatory and regulatory cytokines IL-4 and IL-10**

CGEN-15001 PATHWAY IS FUNCTIONAL AND RESPONSIVE IN RA PATIENTS

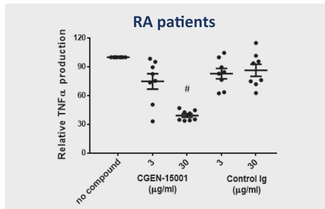
"Synovial-like" co-culture



Healthy donors



RA patients



* p<0.05, **p<0.01, ***p<0.001

# p<0.0001

- **Translational assay mimicking T-cell and macrophage interactions in RA synovium**
- **Inhibition of TNFα secretion**
- **Other pro-inflammatory cytokines and chemokines were also reduced**

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