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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.

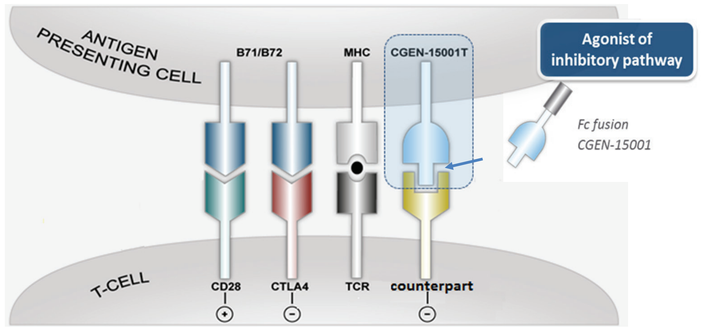
CGEN-15001 Induces Antigen Specific Tolerance in Autoimmune Diseases
Unique MOA: Combining tolerance induction and restoration of immunological homeostasis

- 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

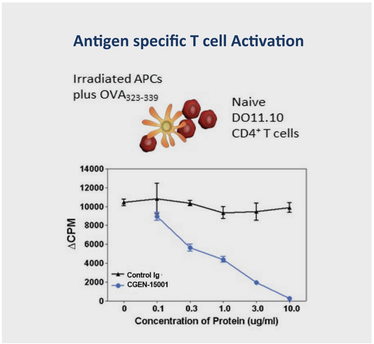
CGEN-15001 provides potential paradigm shift from "standard of care"
Addressing a widely anticipated 'next step' therapeutic in autoimmunity

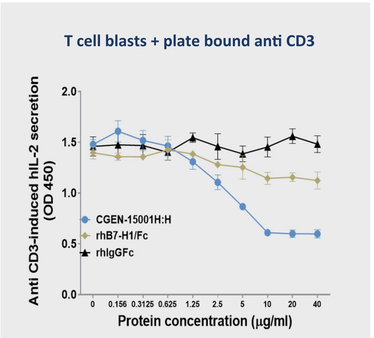
- Translating the success of checkpoint manipulation from Immuno-Oncology to autoimmunity
- Immune-modulation offers safety advantages vs. immune-suppression

CGEN-15001 IS A NOVEL T CELL INHIBITORY LIGAND BINDS TO ACTIVATED T CELLS, ACTIVATES INHIBITORY PATHWAY



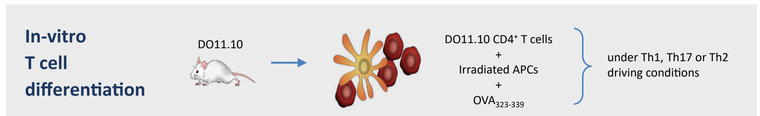
CGEN-15001 INHIBITS MOUSE AND HUMAN T CELL ACTIVATION

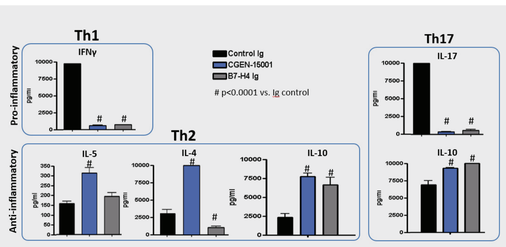




Robust inhibition of T cell proliferation following polyclonal or Ag specific activation

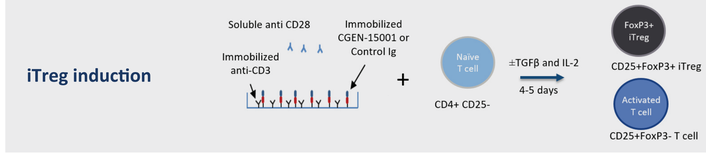
CGEN-15001 IS A POTENT MODULATOR OF T CELLS CYTOKINE PRODUCTION TH1/TH17 TO TH2 SHIFT IN-VITRO

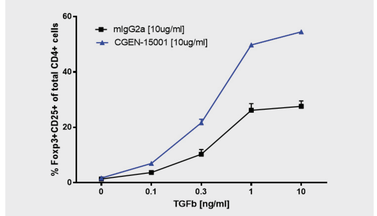


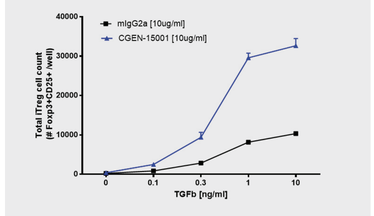


- Reduction of pro-inflammatory Th1 and Th17 responses
- Enhancement of anti-inflammatory cytokines and Th2 responses
- Similar Th1/Th17 to Th2 shift obtained with human cells

CGEN-15001 ENHANCES iTREG DIFFERENTIATION





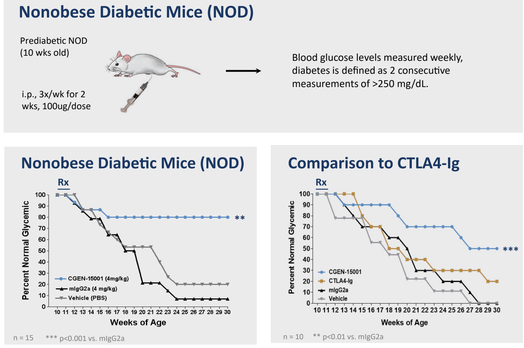


In vitro enhancement of iTreg differentiation under Treg driving conditions

LONG TERM THERAPEUTIC EFFECT FOLLOWING SHORT TREATMENT WITH CGEN-15001 IN MODELS OF AUTOIMMUNE DISEASES

Long term efficacy in NOD model of type 1 diabetes

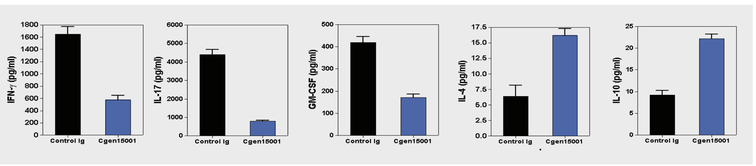
- CGEN-15001 administration to pre-diabetic mice prevents disease development
- Long duration of response following short term administration (3x/wk for 2wks), lasting at least 18 weeks after cessation of treatment
- Suggests tolerance induction and opportunity for drug-free remission

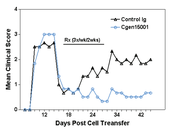


CGEN-15001 MOA COMBINES RESTORATION OF IMMUNE HOMEOSTASIS AND RE-ESTABLISHMENT OF TOLERANCE

CGEN-15001 restores homeostasis in vivo: Th1/Th17 to Th2 shift

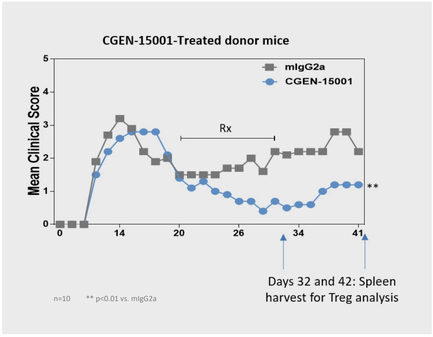
Adoptive transfer RR-EAE model:
Cytokine secretion following in-vitro reactivation of splenocytes with $PLP_{139-151}$- day 45

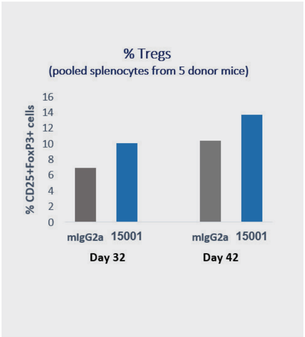




- Inhibition of recall responses to disease inducing (PLP139-151) epitope
- Inhibition of pro-inflammatory cytokines (IFNg, IL-17, GM-CSF) and promotion of anti-inflammatory cytokines (IL-4, IL-10)

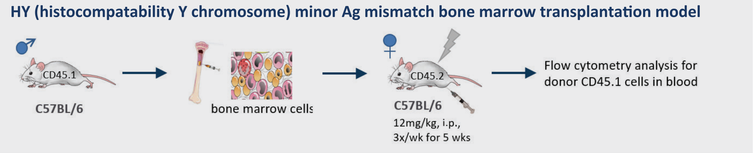
CGEN-15001 induces Tregs in the EAE model

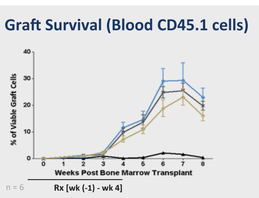


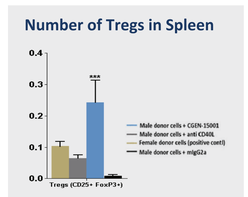


CGEN-15001 induces tolerance in a model of transplantation through induction of Tregs

HY (histocompatability Y chromosome) minor Ag mismatch bone marrow transplantation model

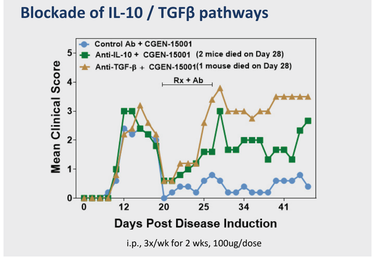


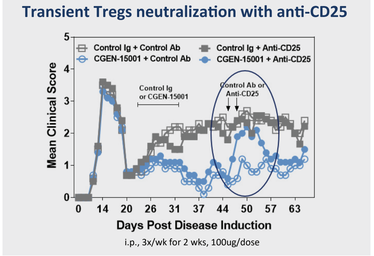




- CGEN-15001 promotes donor-specific tolerance leading to graft survival
- Treatment with CGEN-15001 leads to significant Tregs increase in the spleen
  - Induces higher number of Tregs in Spleen vs. anti-CD40L

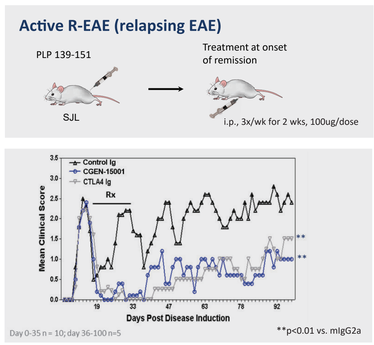
Tregs mediate the CGEN-15001 long-term remission effect R-EAE model





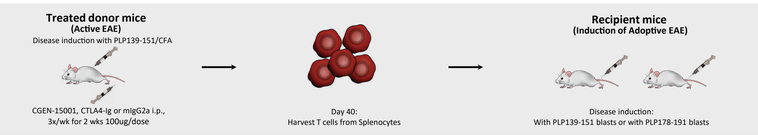
- Blockade of IL-10 or TGFβ abolishes CGEN-15001 therapeutic effect
- Transient neutralization of Tregs (with anti-CD25 Ab) leads to transient reversal of CGEN-15001 effect, manifested in transient abolishment of the long term remission

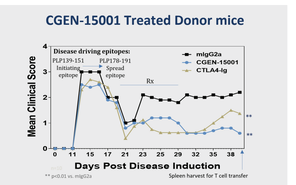
Long term therapeutic effect following short treatment with CGEN-15001 in R-EAE model of multiple sclerosis

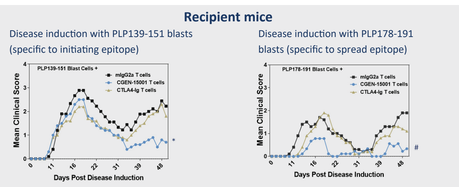


- Short-term treatment (3x/wk for 2wks) induces long-term remission, suggesting induction of immune tolerance
  - Opportunity for drug-free remission
- High efficacy in therapeutic regimen with established disease
- Dose dependent efficacy (in a repeat study)
- Consistent effect in multiple EAE models
  - Active PLP/CFA induced
  - Passive / adoptive transfer
  - Viral (TMEV) induced

CGEN-15001 INDUCED TOLERANCE IS TRANSFERABLE AND ANTIGEN-SPECIFIC







- 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)