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 impaired immune tolerance. A major medical need in autoimmunity is restoration of immune tolerance to self-antigens and immune homostasis. 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 immunologic homostasis
- Regulates immune homostasis – inhibiting Th1/Th17 responses while enhancing Th2 and anti-inflammatory cytokines (IL-4, IL-10) and promoting Treg differentiation
- CGEN-15001 leads to long-term therapeutic effect in models of autoimmunity disease
- The durable therapeutic effect is Treg dependent
- The therapeutic effect is transferable, and mediated by induction of Ag-specific tolerance. Previous knowledge of the antigen is not required
- Promotion of donor-specific tolerance leading to graft survival in bone marrow transplantation model with an HLA 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 translation from immune-oncology to autoimmunity
- Tolerance induction offers safety advantage vs. immune-suppression

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

Adaptive transfer
R-EAE model:
Cytokine secretion following ex-vivo reactivation of splenocytes with PLP139-151/85-99
- Inhibition of pro-inflammatory cytokines (IFNγ, IL-17, GM-CSF) and promotion of anti-inflammatory cytokines (IL-4, IL-10)
- Similar findings were observed in-vivo, following 1h differentiation of mouse or human CD4 cells

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

Non-obese Diabetic Mice (NOD)
- 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 12 weeks after cessation of treatment
- Suggests tolerance induction

TREG & TOLERANCE INDUCTION

CGEN-15001 ENHANCES iTREG DIFFERENTIATION

CGEN-15001 INDUCES iTREGs IN THE R-EAE MODEL

INDUCTION OF ANTIGEN-SPECIFIC TOLERANCE BY CGEN-15000

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

CGEN-15001 INDUCES TOLERANCE IN A BONE MARROW TRANSPLANTATION MODEL

HY (histocompatibility Y chromosome) Minor Ag mismatch bone marrow transplantation
- Graft survival (blood CM5.1 cells)
- Number of Tregs in spleen

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

PBMcs from MS patients activated with MS-related antigen (MBP35-40)
- CGEN-15001 shifts Th2/Th17 responses to Th2 and regulatory profile in a translational assay:
  - Inhibits proliferation and secretion of IFNγ, IL-17 and Th17a
  - Increases anti-inflammatory and regulatory cytokines IL-4 and IL-10

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

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

Active R-EAE (relapsing EAE)
- 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 12 weeks after cessation of treatment
- Suggests tolerance induction

CGEN-15001 PATHWAY IS FUNCTIONAL AND RESPONSIVE IN RA PATIENTS

Healthy donors
- RA patients