

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

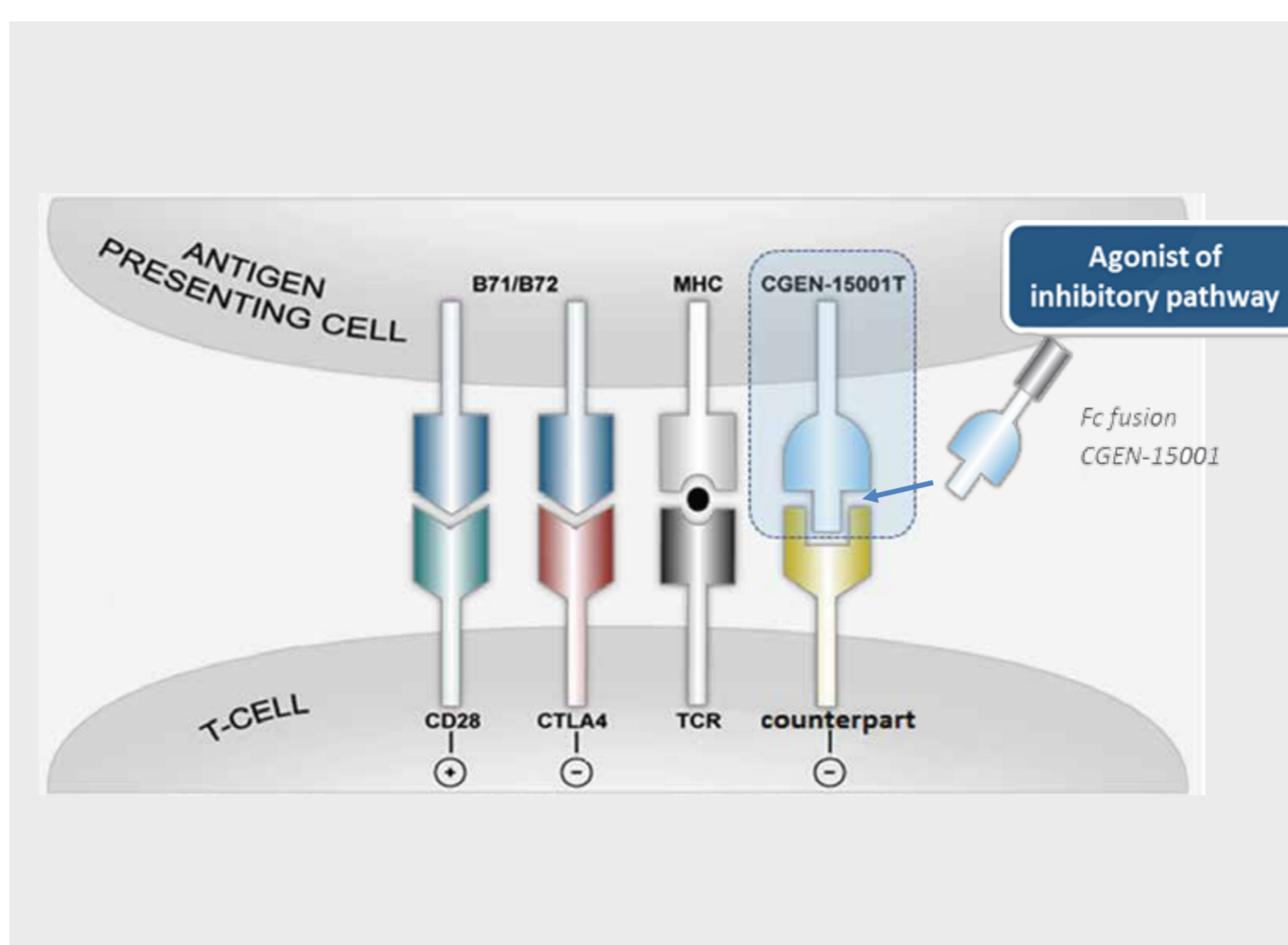
CGEN-15001 provides potential paradigm shift from "standard of care" Addressing a widely anticipated 'next step' therapeutic in autoimmunity

- 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

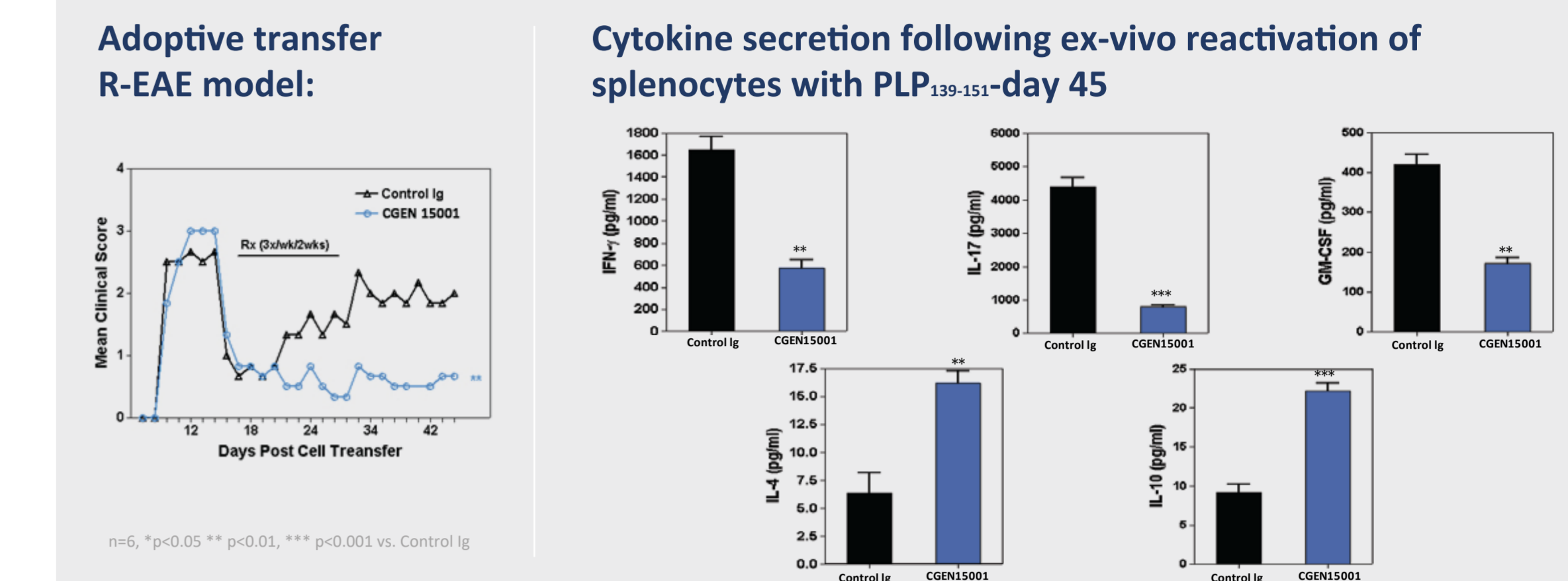
CGEN-15001

- 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

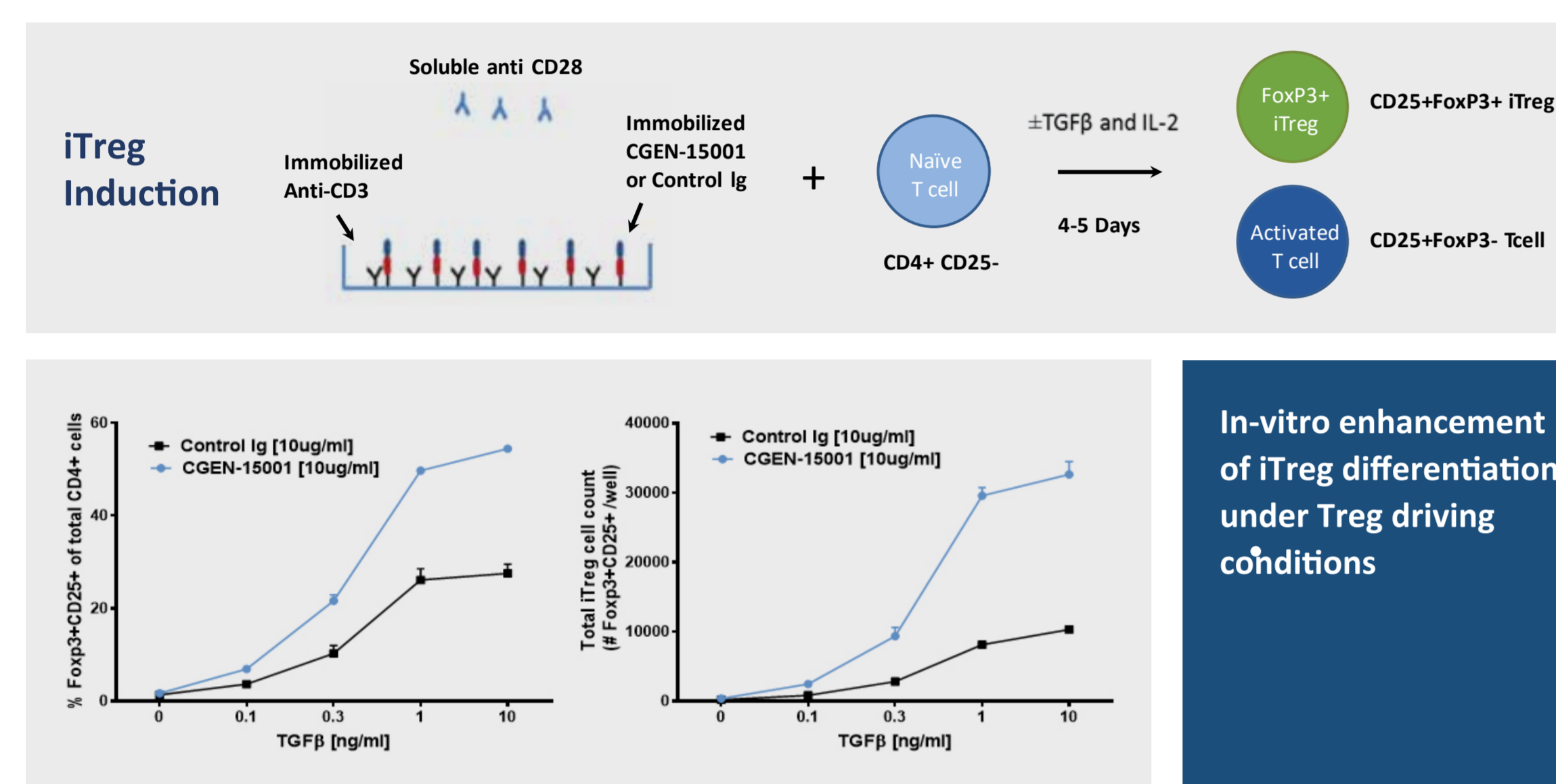


Inhibition of pro-inflammatory cytokines (IFN γ , IL-17, GM-CSF) and promotion of anti-inflammatory cytokines (IL-4, IL-10)

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

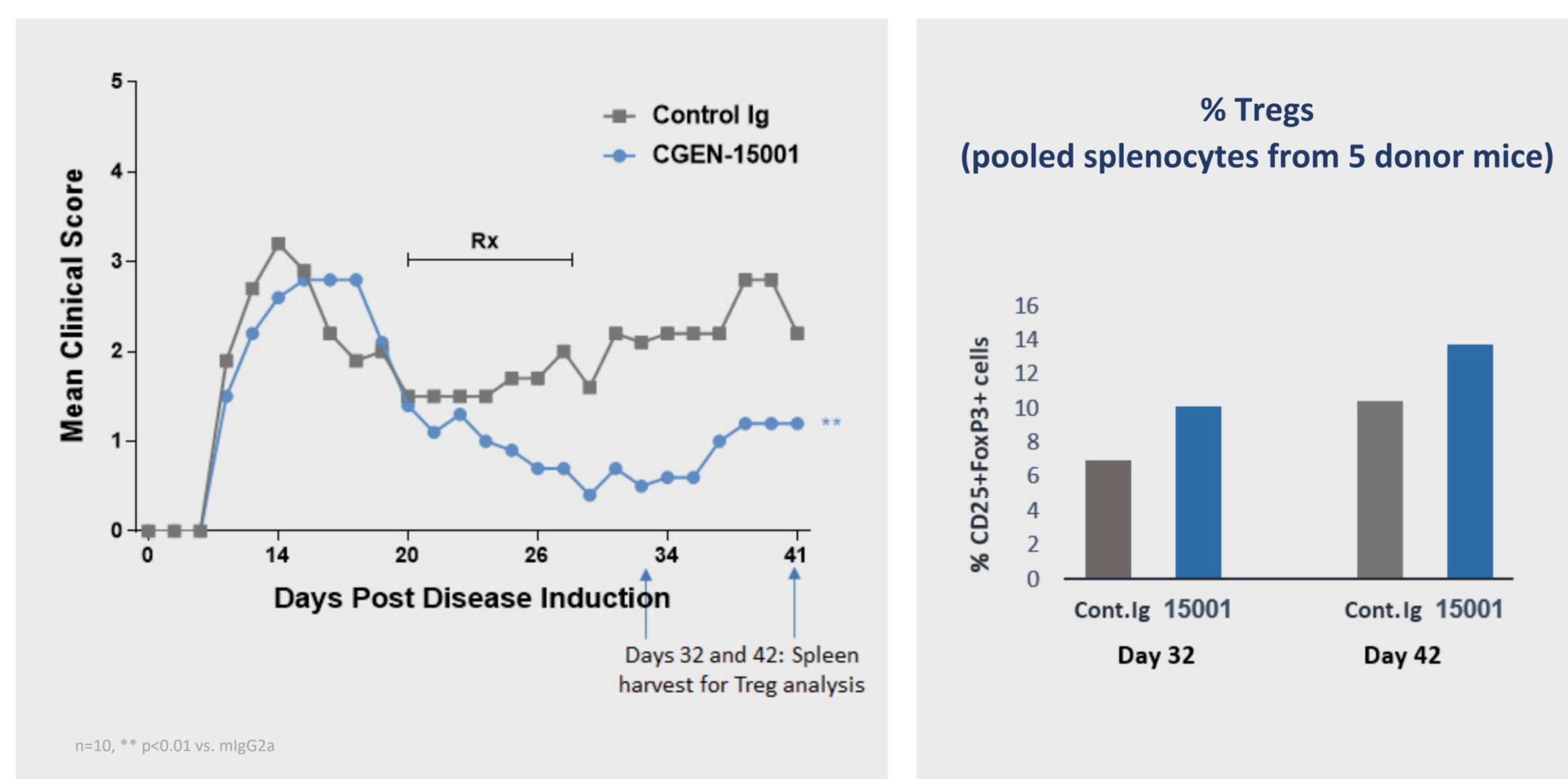
TREG & TOLERANCE INDUCTION

CGEN-15001 ENHANCES iTREG DIFFERENTIATION



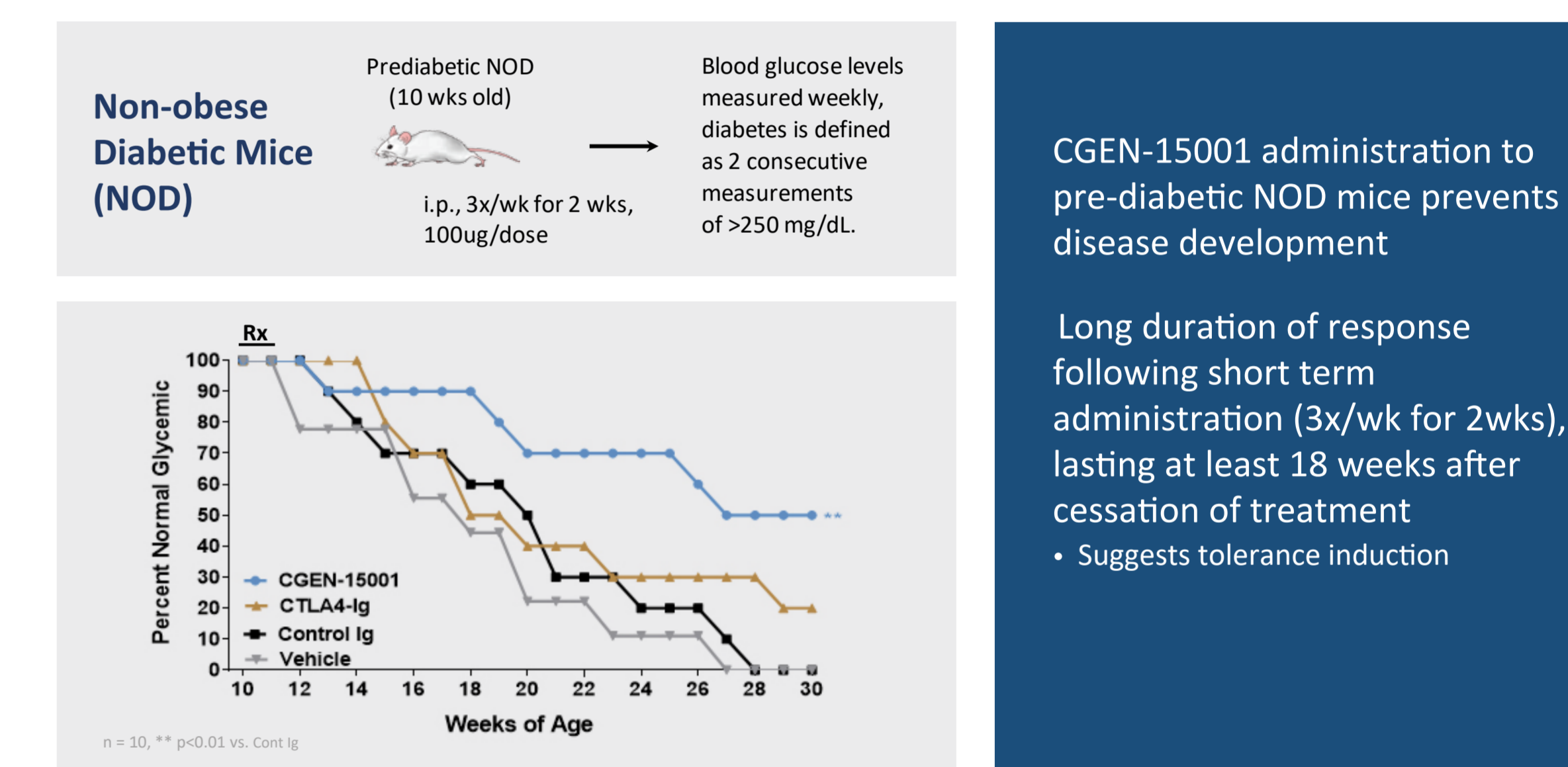
In-vitro enhancement of iTreg differentiation under Treg driving conditions

CGEN-15001 INDUCES TREGs IN THE R-EAE MODEL



LONG TERM EFFICACY

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

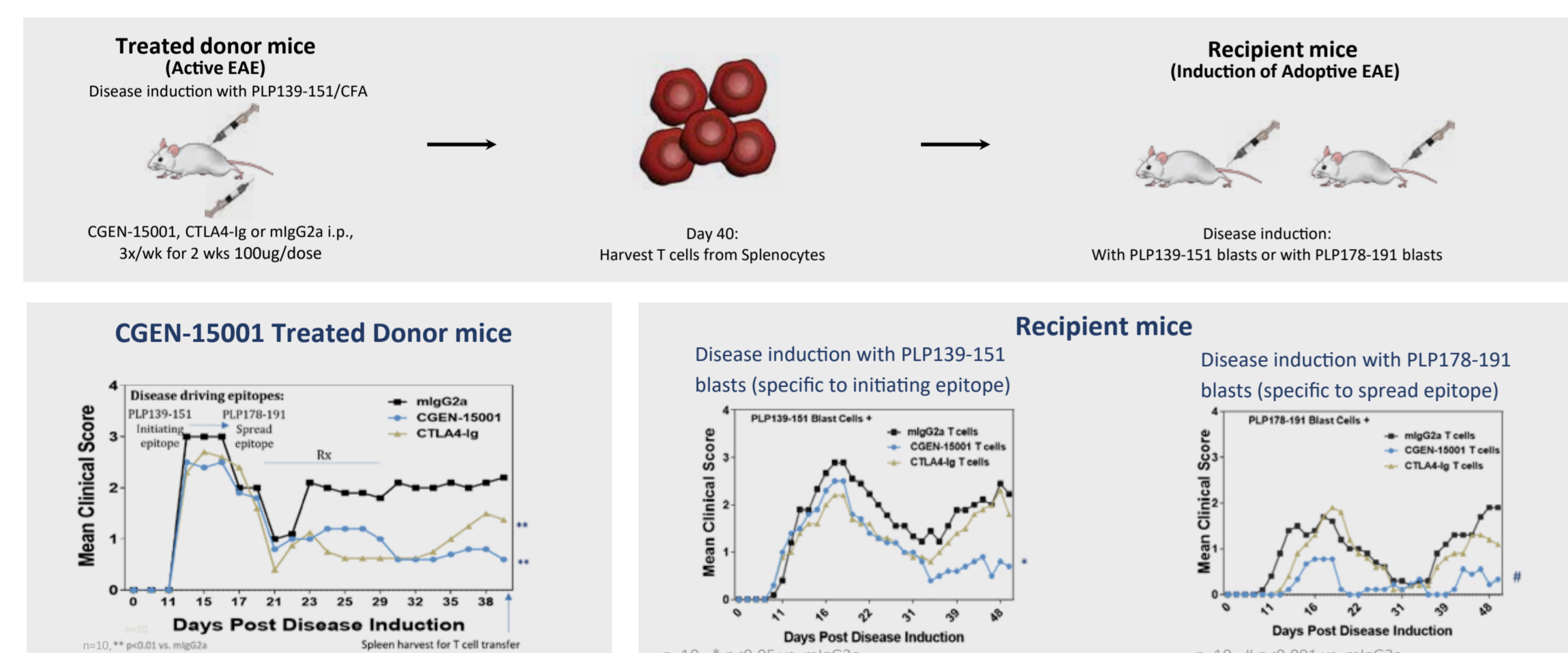


CGEN-15001 administration to pre-diabetic NOD mice prevents disease development

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

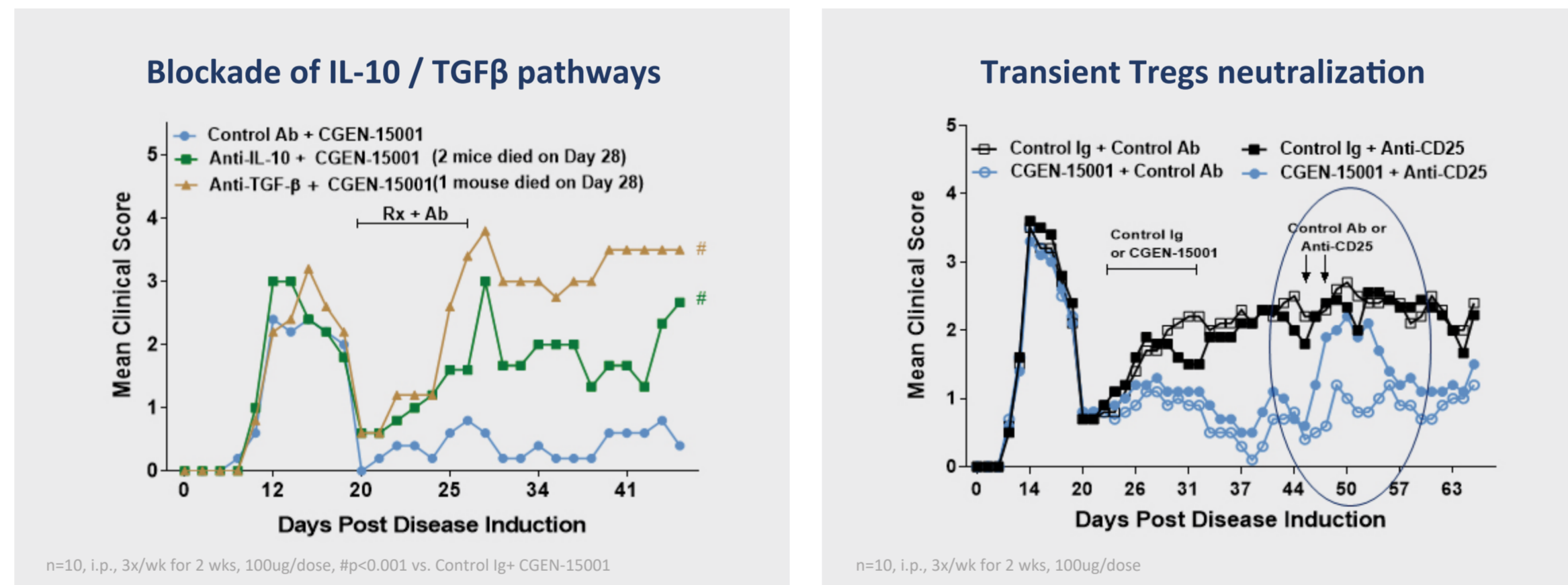
- Suggests tolerance induction

INDUCTION OF ANTIGEN-SPECIFIC TOLERANCE BY CGEN-15001



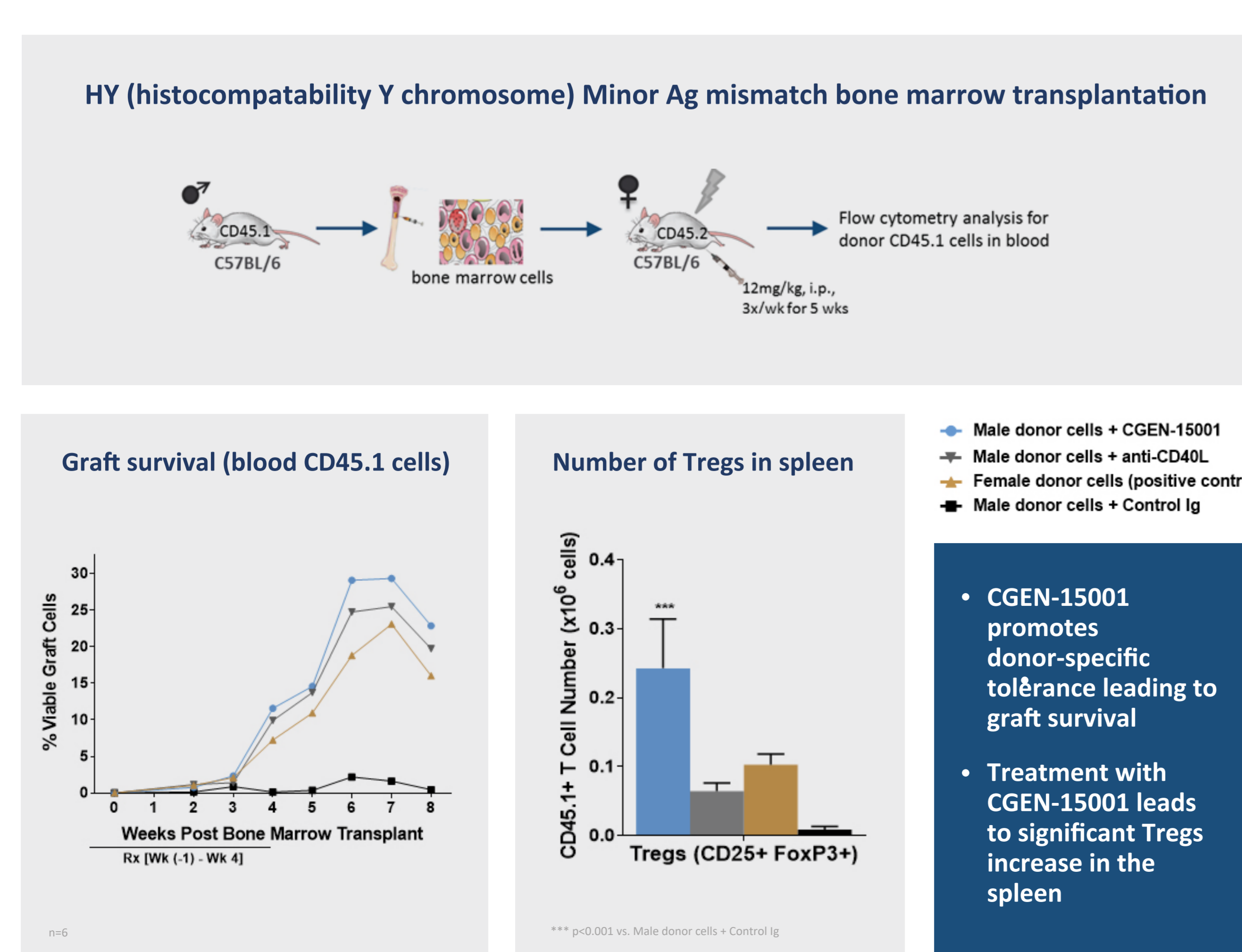
- T cells from CGEN-15001-treated mice protect recipients only when disease is driven by the same epitope present during CGEN-15001 treatment of donors (PLP178-191)
- CGEN-15001 induces tolerance in treated mice, which can be transferred to recipient mice
- The immune tolerance induced by CGEN-15001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

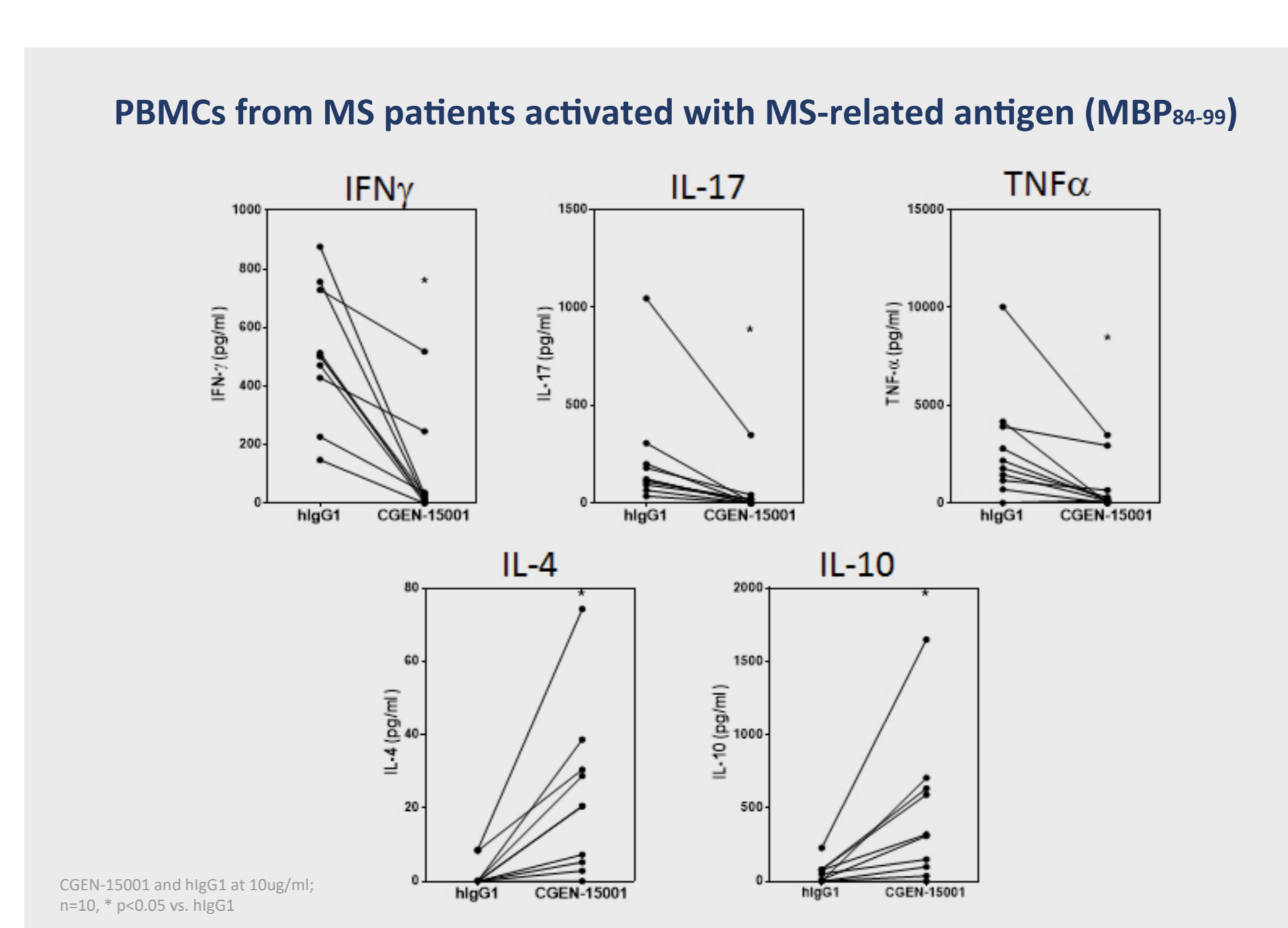


CGEN-15001 promotes donor-specific tolerance leading to graft survival

- Treatment with CGEN-15001 leads to significant Tregs increase in the spleen

TRANSLATIONAL STUDIES

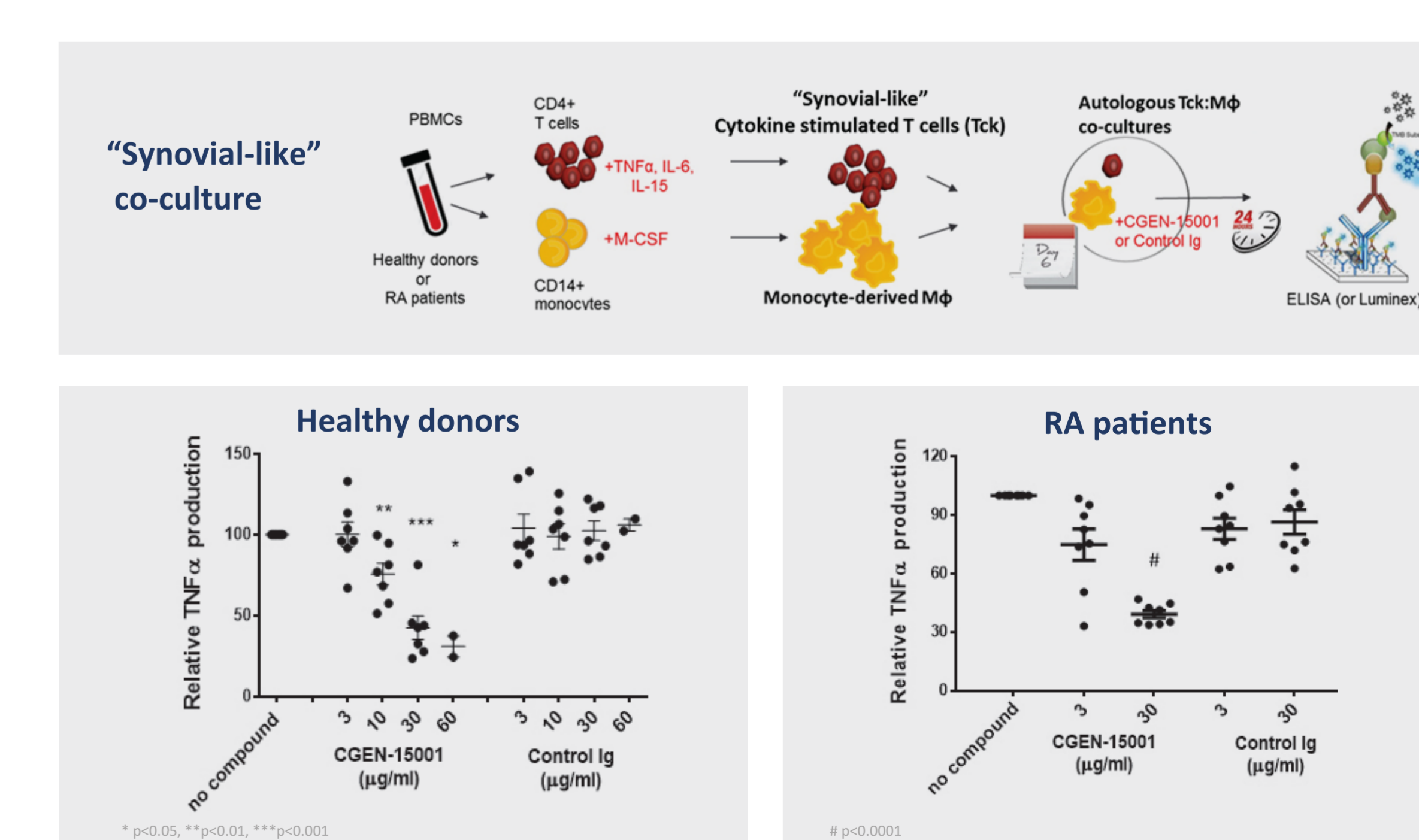
CGEN-15001 PATHWAY IS FUNCTIONAL AND RESPONSIVE IN MS PATIENTS –TH1/TH17 TO TH2 SHIFT



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

- Inhibits proliferation and secretion of IFN γ , IL-17 and TNF α
- Increase anti-inflammatory and regulatory cytokines IL-4 and IL-10

CGEN-15001 PATHWAY IS FUNCTIONAL AND RESPONSIVE IN RA PATIENTS



Translational assay mimicking T-cell and macrophage interactions in RA synovium

- Inhibition of TNF α secretion
- Other pro-inflammatory cytokines and chemokines were also reduced