Overexpression of PD-1 on T cells promotes tolerance in cardiac transplantation via an ICOS-dependent mechanism

Thiago J. Borges et al.
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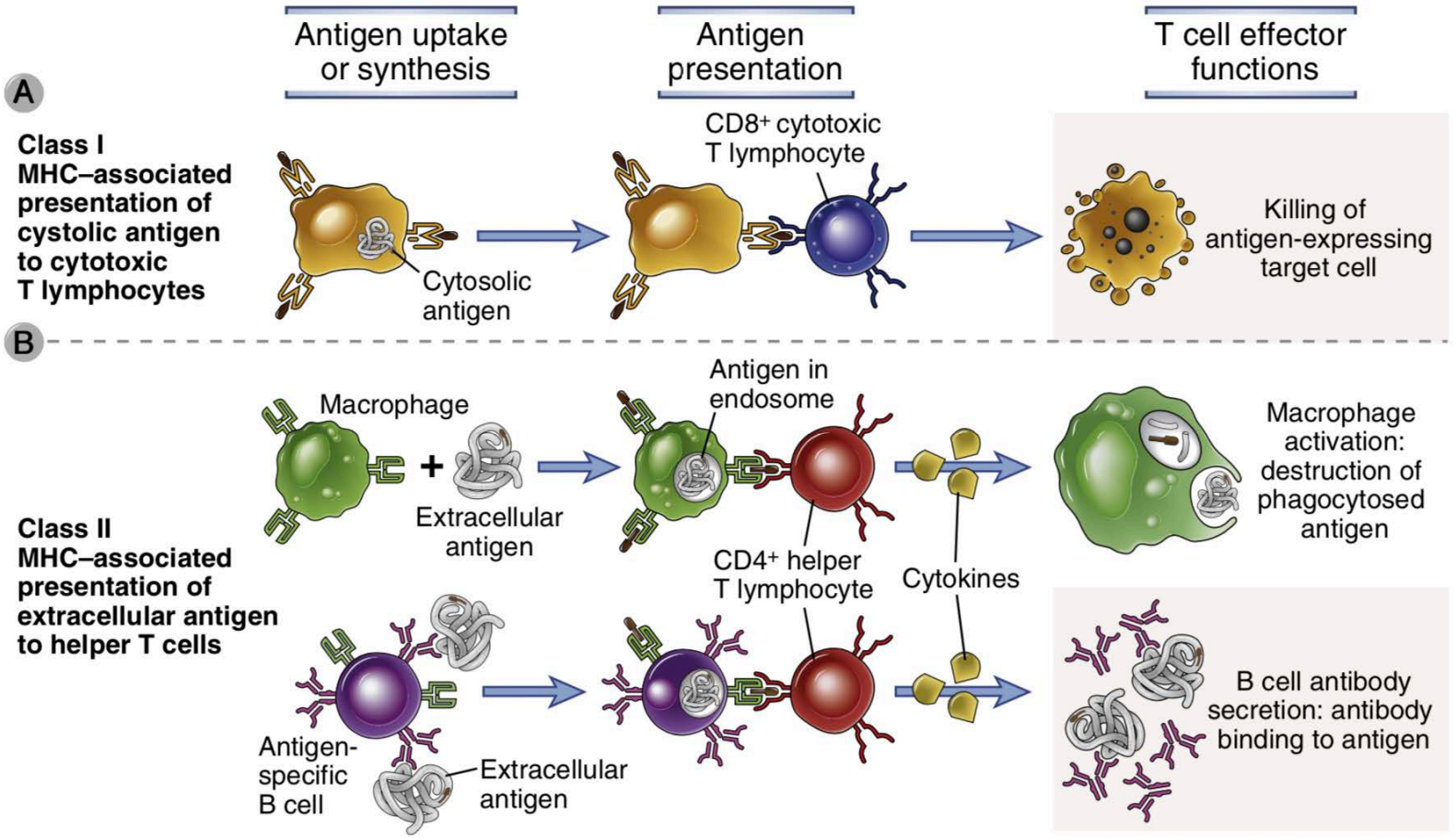
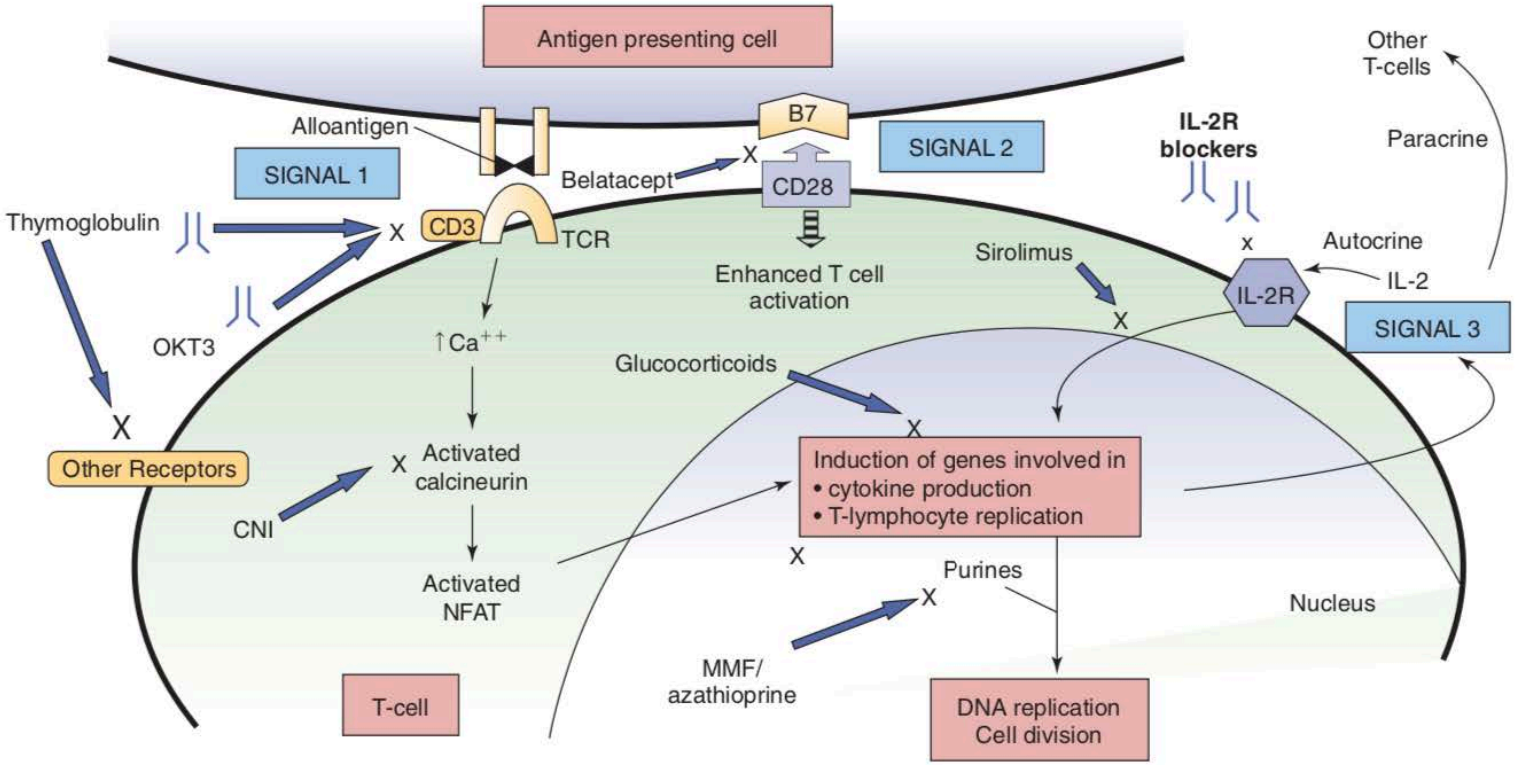
Presenter: Dragan Copic

Antigen presentation via MHC- class I & II molecules and resulting responses



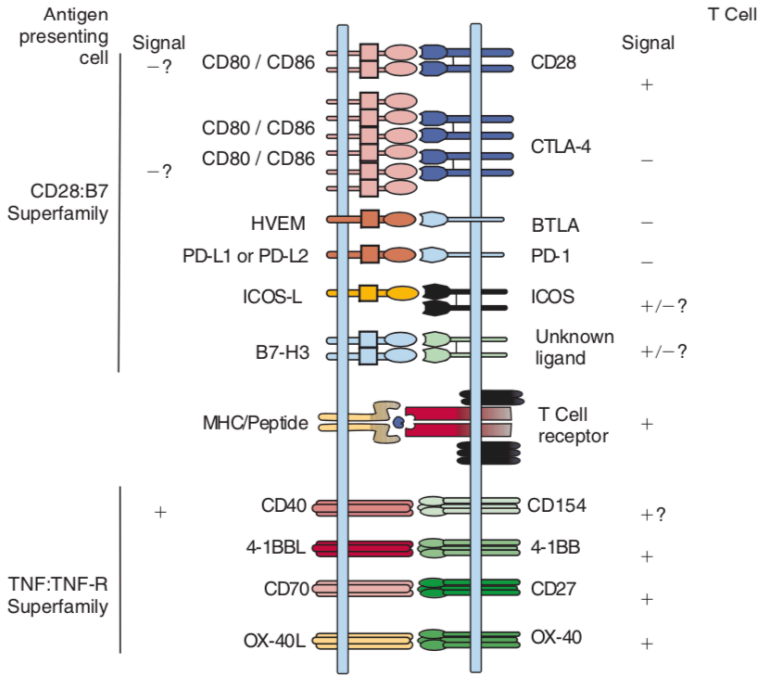
Abbas, Cellular and Molecular Immunology, 8th Edition, Philadelphia: Saunders Elsevier, 2015

Immunological synapse of APC:T-cells interaction and how to target it



Barry M. Brenner, Brenner & Rectors The Kidney, 8th Edition, Philadelphia: Saunders Elsevier, 2008

Costimulatory receptors in T-cell responses



One signal is transduced by the antigen-specific TCR when it recognizes processed antigen bound to an MHC molecule on the surface of an APC

The second signal is mediated by costimulatory molecules and is independent of antigen.

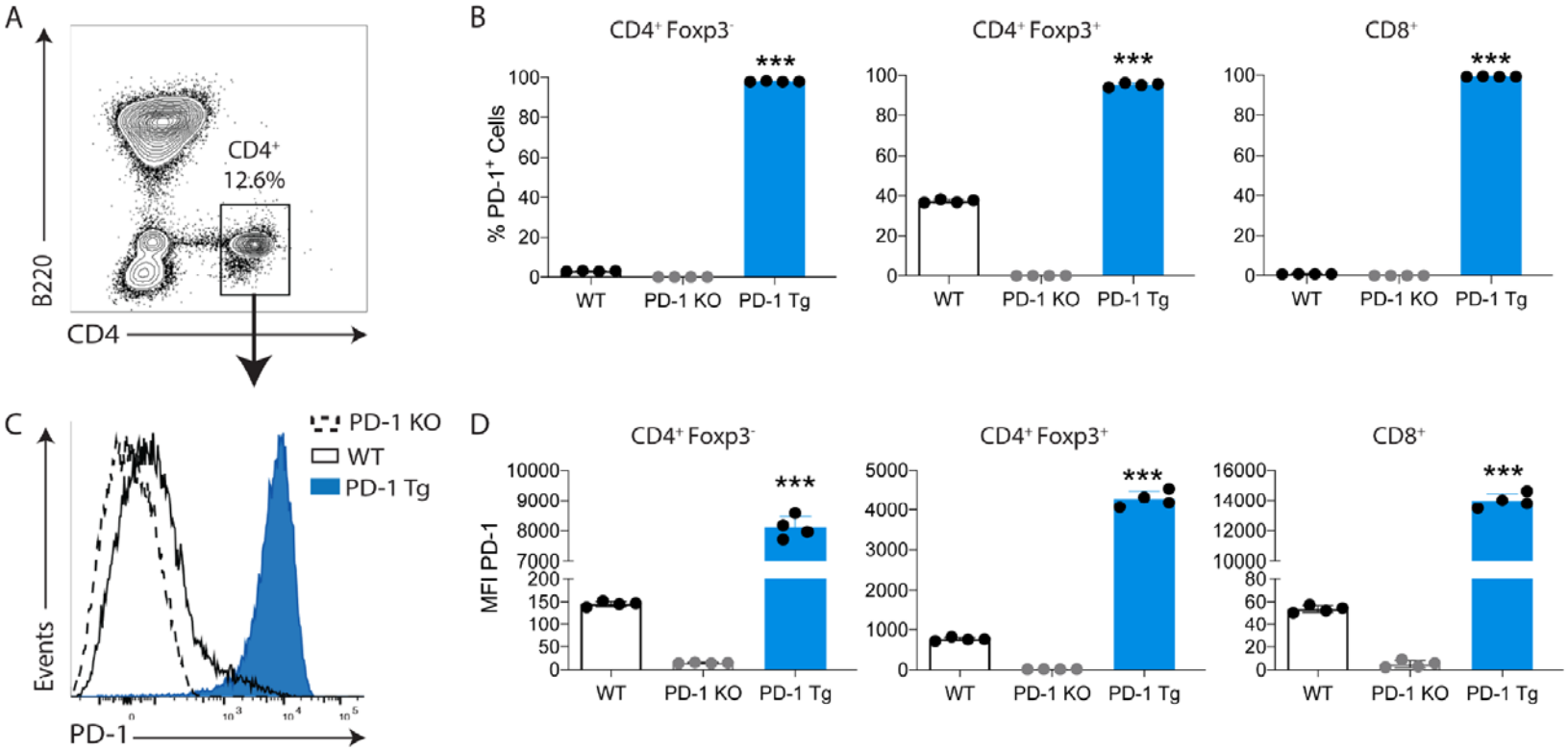
(+) stimulatory effect
(-) inhibitory effect

Barry M Brenner, Brenner & Rectors The Kidney, 8th Edition, Philadelphia: Saunders Elsevier, 2008

Targeting PD1:PDL-1 to achieve graft tolerance

- PD-1:PDL-1 interaction has inhibitory effect on T cell
  - activation
  - proliferation
  - differentiation
- Antigen presentation to TCR modulates PD-1 expression
- Targeted blockade of PD-1:PDL-1 in immuno-oncology
- PD-1 signaling is critical to protect against graft rejection following mouse heart, liver and skin transplantation

T-cell-specific overexpression in PD-1 transgenic mice (PD-1 Tg)



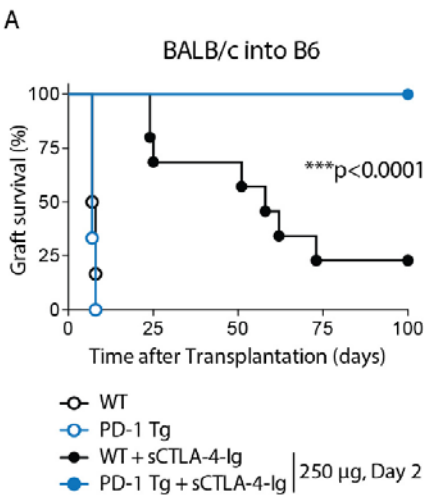
Higher expression of PD-1 in $CD4^+Foxp3^-$, $CD4^+Foxp3^+$, $CD8^+$ -T cells compared to WT and PD-1 KO T cells

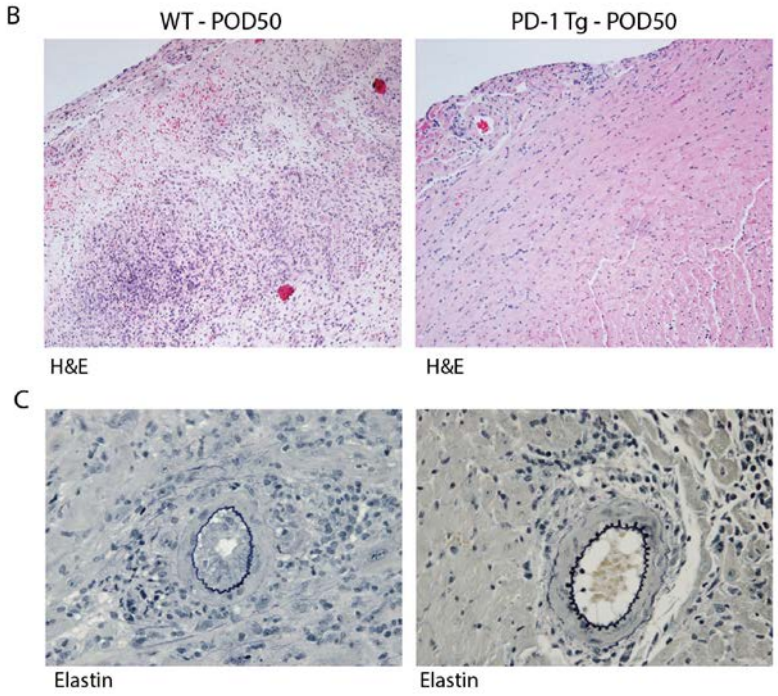
PD-1 is highly expressed on T cells of PD-1 Tg

PD-1 overexpression combined with one-time administration of CTLA-4-Ig prevents acute rejection reactions and depends on PDL-1 expression on donor cells

BALB/c (H-2d) hearts were transplanted into WT or PD-1 Tg B6 (H-2b) mice +/- a single dose of CTLA-4-Ig

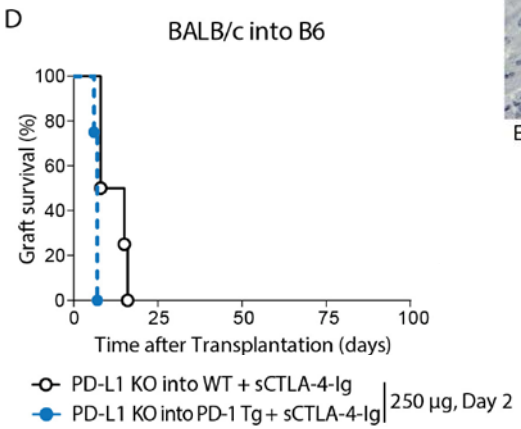
Animals were fully MHC-mismatched





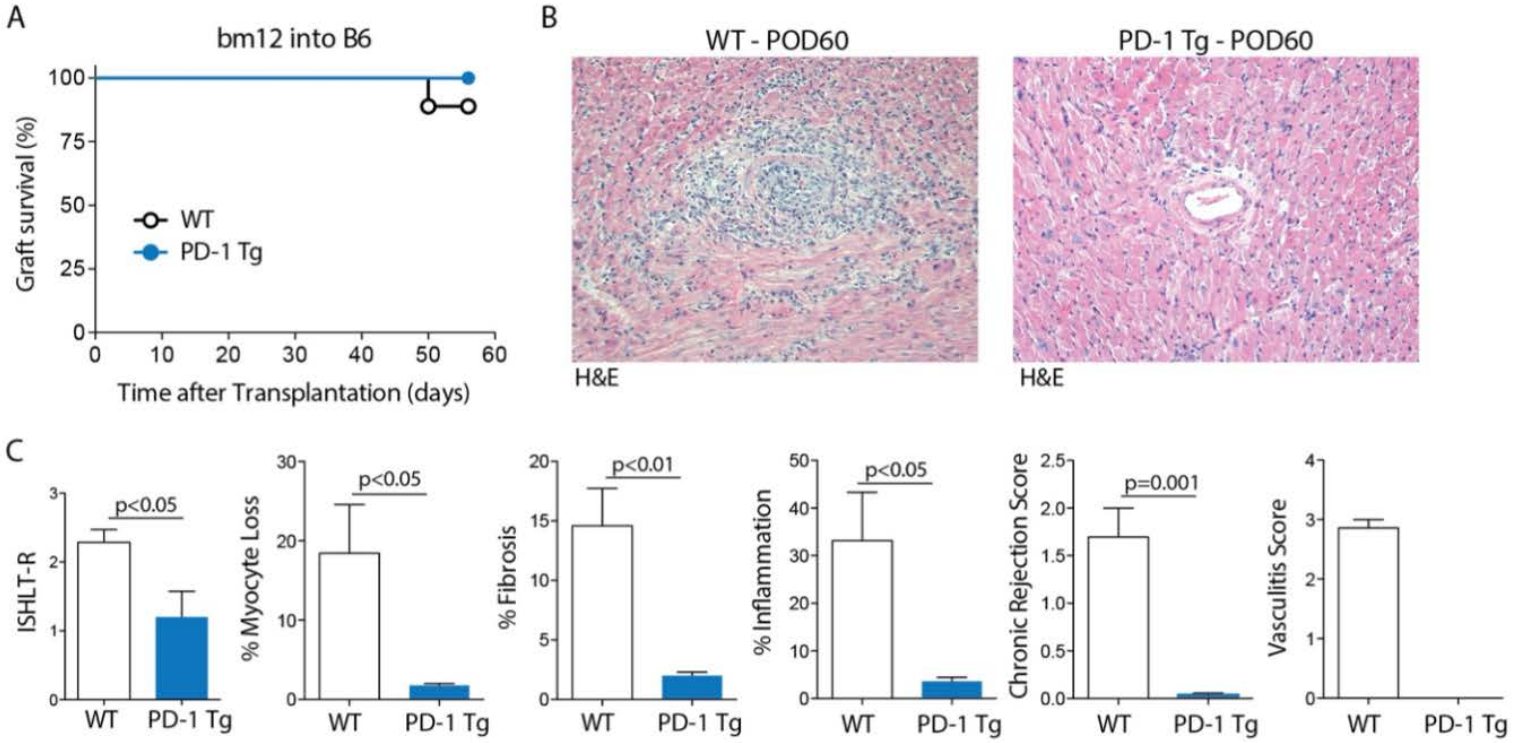
Kaplan-Meier curves of allograft survival in PDL-1 KO hearts (BALB/c) transplanted into WT or PD-1 Tg mice

Interaction of PD-1:PDL-1 promotes long term graft survival in PD-1 Tg



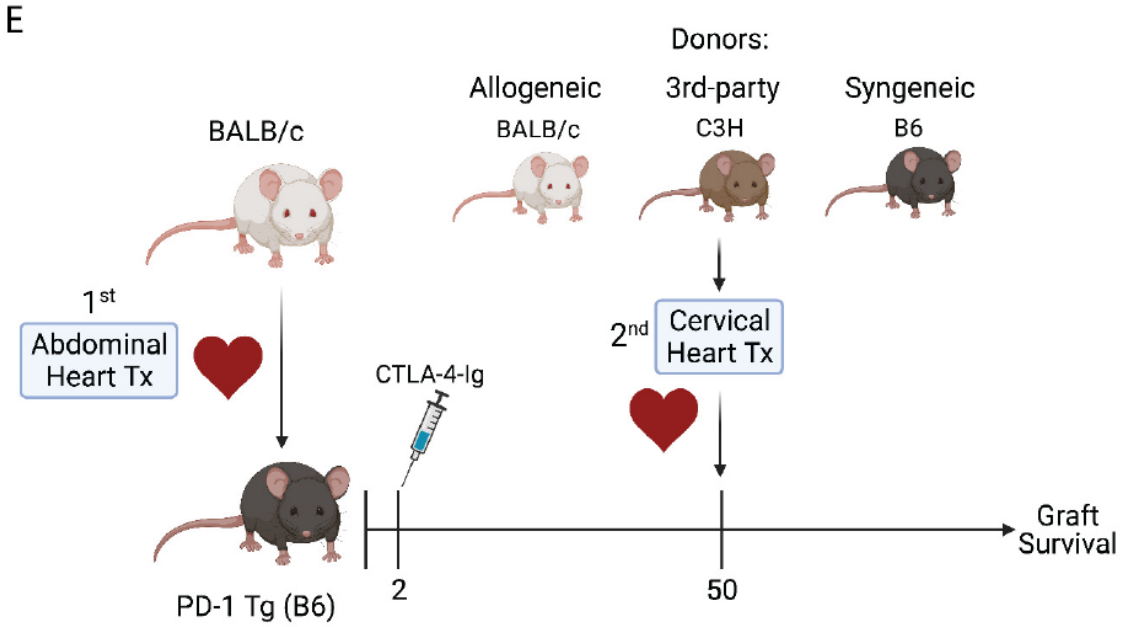
At 50 days post transplantation tolerized allografts
- revealed minimal inflammation,
- low fibrosis percentage
- vasculopathy score (<1)

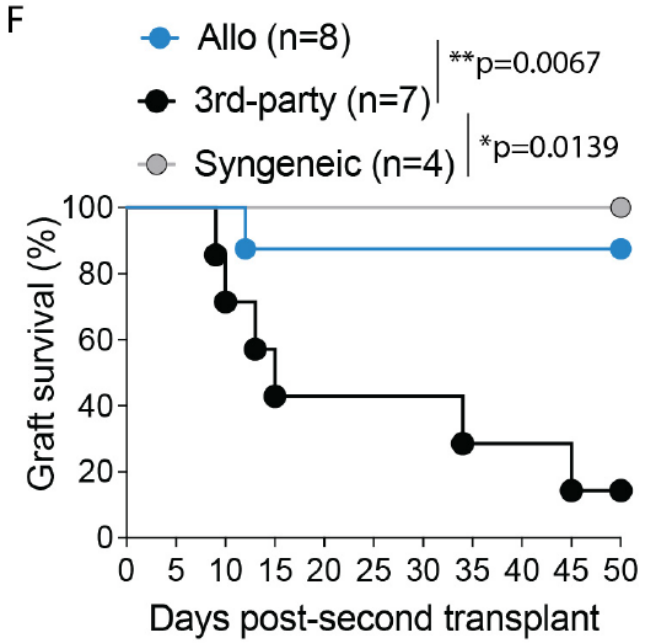
Effect of PD-1 overexpression in a model of chronic graft rejection



Bm12 into B6 to mimic single MHC II mismatch
Most grafts survived
Histopathological evaluation of PD-1 Tg

Long-term survival of allo-grafts is donor-specific



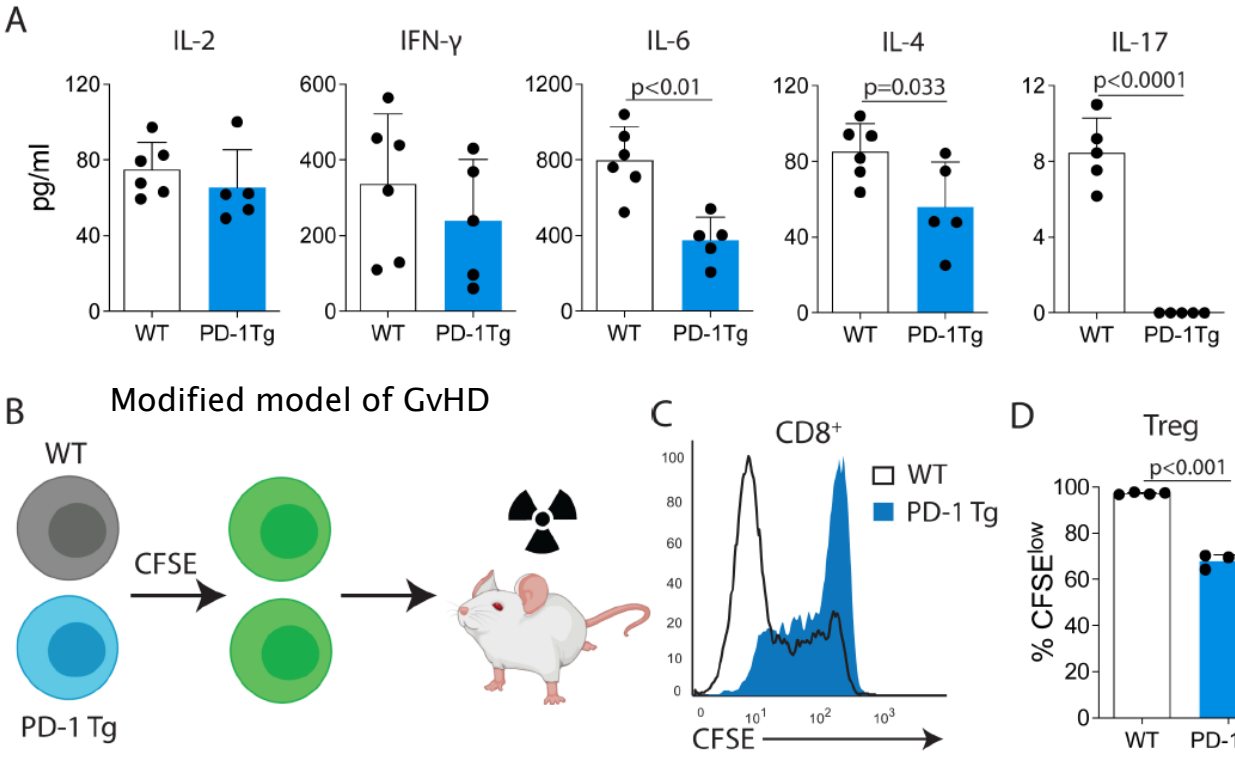


Schematic experimental design of abdominal and cervical heart co-transplantation in PD-1 Tg mice

Recipients PD-Tg B6 transplanted with abdominal BALB/c (H-2^b) hearts 2^{nd} transplantation fifty days later

PD-1 Tg effector T-cells are less primed and proliferate significantly less compared to WT T-cells *in vitro* and *in vivo*

WT or PD-1 Tg splenocytes were harvested 14 days after cardiac allograft transplantation + CTLA-4 Ig infusion
Co-culture with allogeneic irradiated donor type stimulator cells for 72h



Cytokine production is reduced in PD-1 TG splenocytes

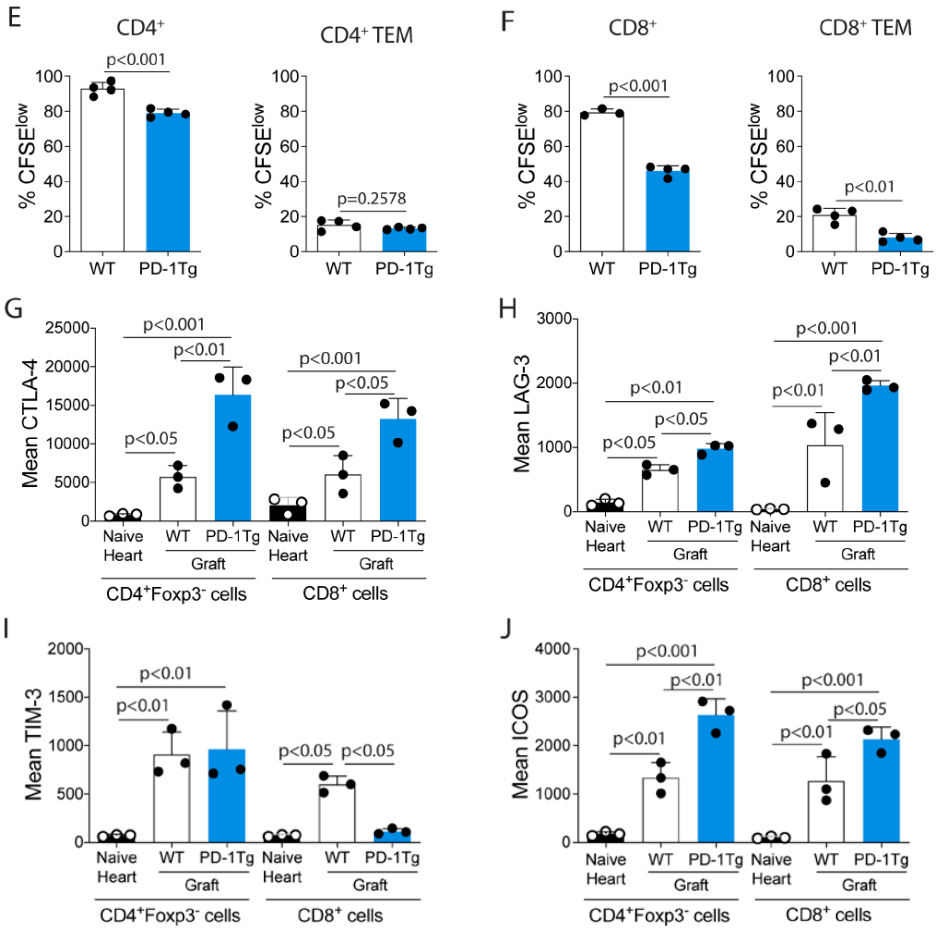
T-cell proliferation is decreased

Proliferation was assessed 72h after adoptive transfer by Measurement of CFSE dilution

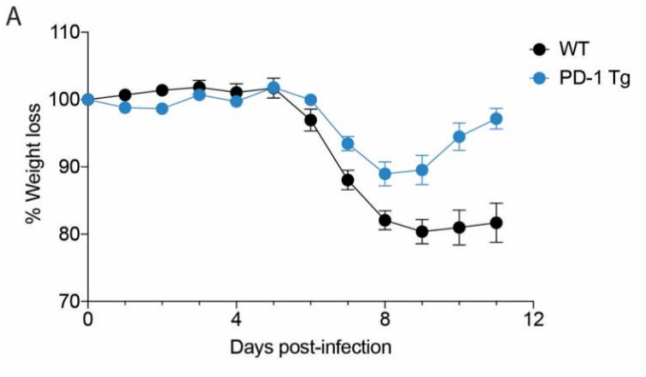
Proliferation of T-cell subsets is decreased and exhaustion markers are increased in PD-1 Tg mice

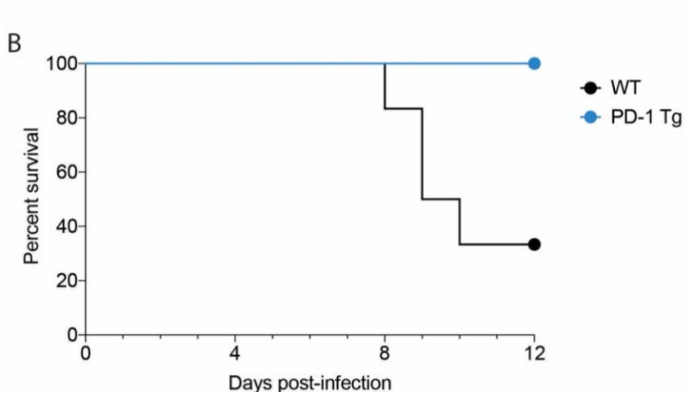
With the exception od CD4+ TEM all T cells in PD-1Tg animals showed less proliferation

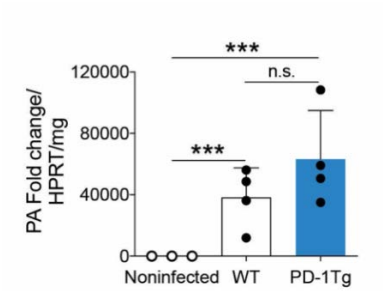
Increased expression of CTLA-4, LAG-3 and ICOS suggests a partially exhausted Phenotype of PD-1 Tg T-cells mice



Immunological response to acute viral infection is not impaired in PD-1 Tg mice





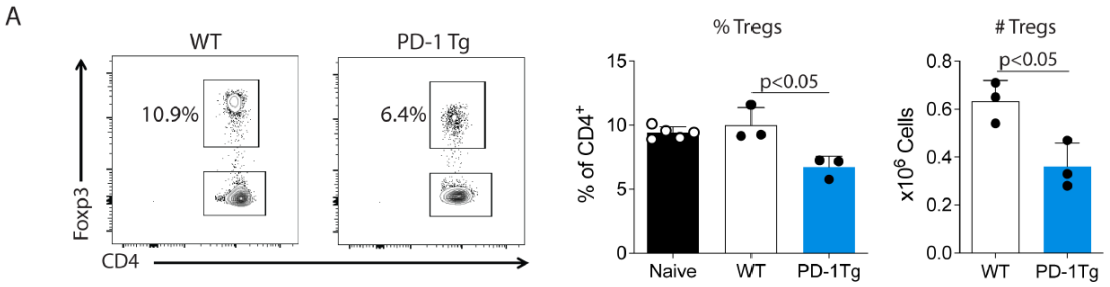


PD-1 pathway is important for the response to viral infection

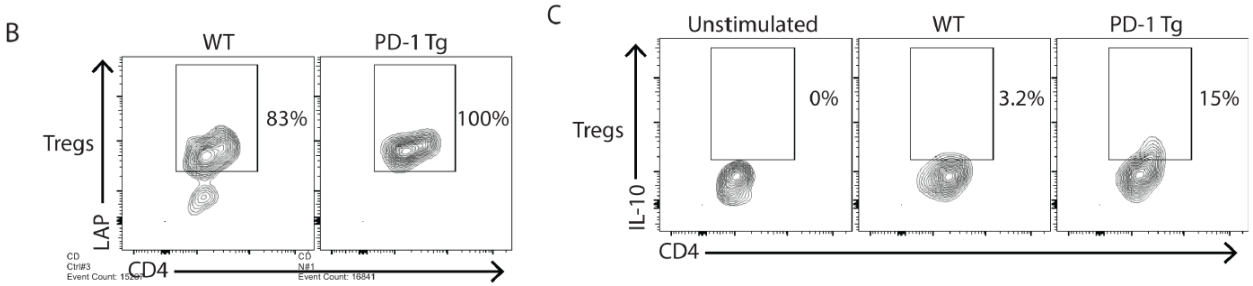
Naïve WT or PD-1 Tg were infected with sublethal doses of Influenza A
PD-1 Tg control viral infection equal to matched WT controls

- Weight loss
- Survival
- Viral load 7 days post infection

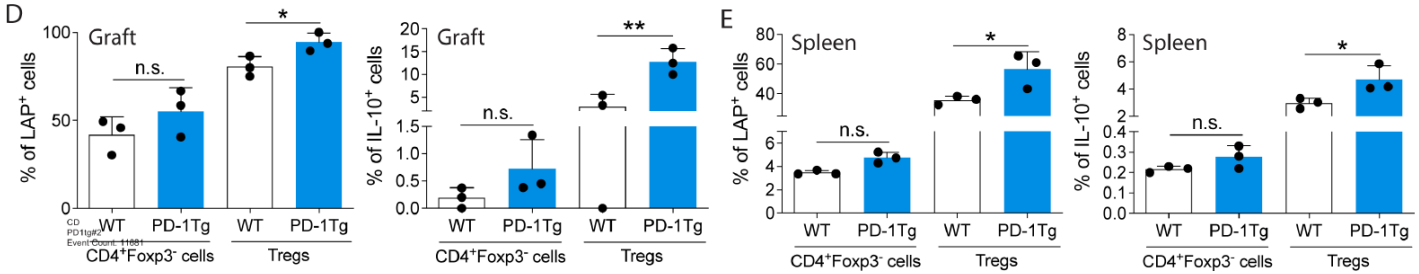
T_{regs} are lower in PD-1 Tg but express higher levels of IL-10 and LAP



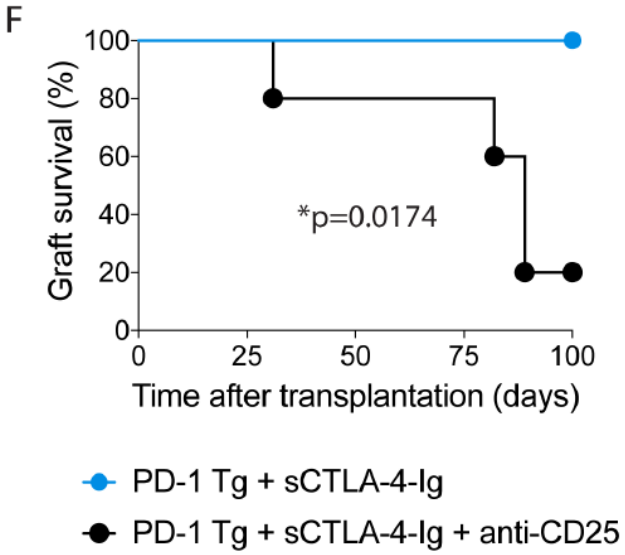
7 days after heart transplant T_{regs} in spleen and thymus were assessed

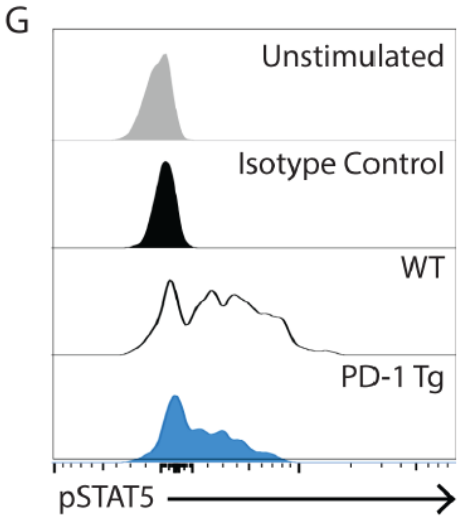


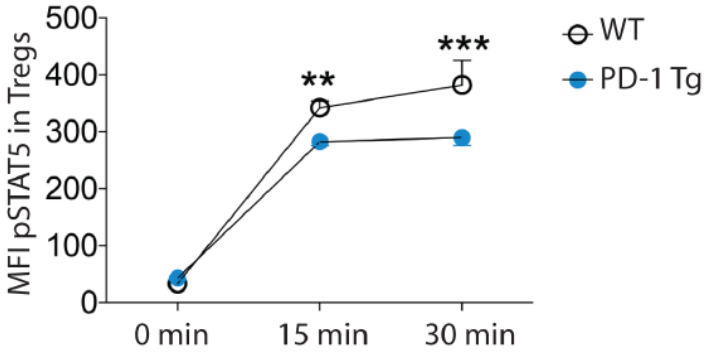
Expression of LAP and IL-10 is increased In PD-1 Tg T_{regs}



T_{regs} are crucial for graft survival of PD-1 Tg mice





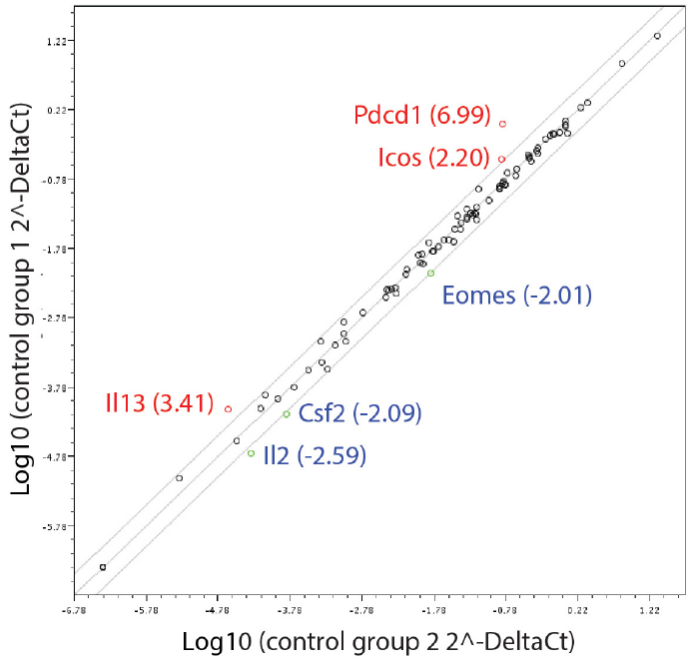


Depletion of Tregs before transplantation shortens graft survival of PD-1 Tg recipients treated with co-stimulation blockade (MST 89 vs >100 days)

STAT5 signaling is crucial for T_{regs} function
Phosphorylation of STAT-5 is reduced in PD-1 Tg T_{regs} after treatment with IL-2

ICOS is upregulated in Tregs from PD-1 Tg recipients treated with CTLA-4-Ig

A



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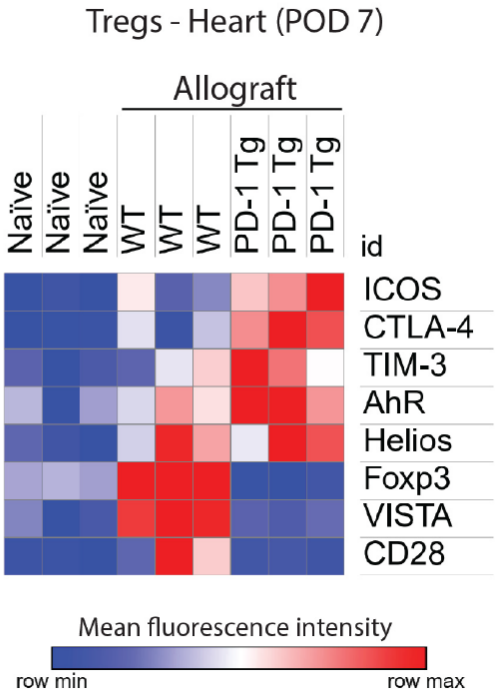

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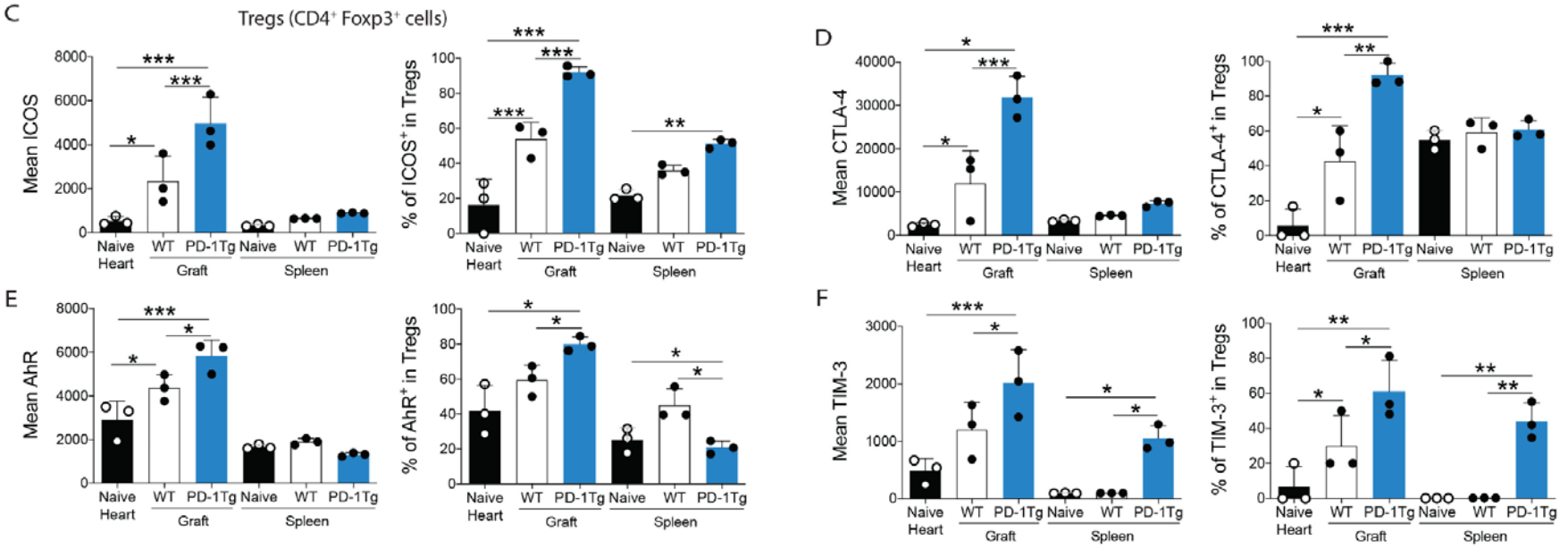
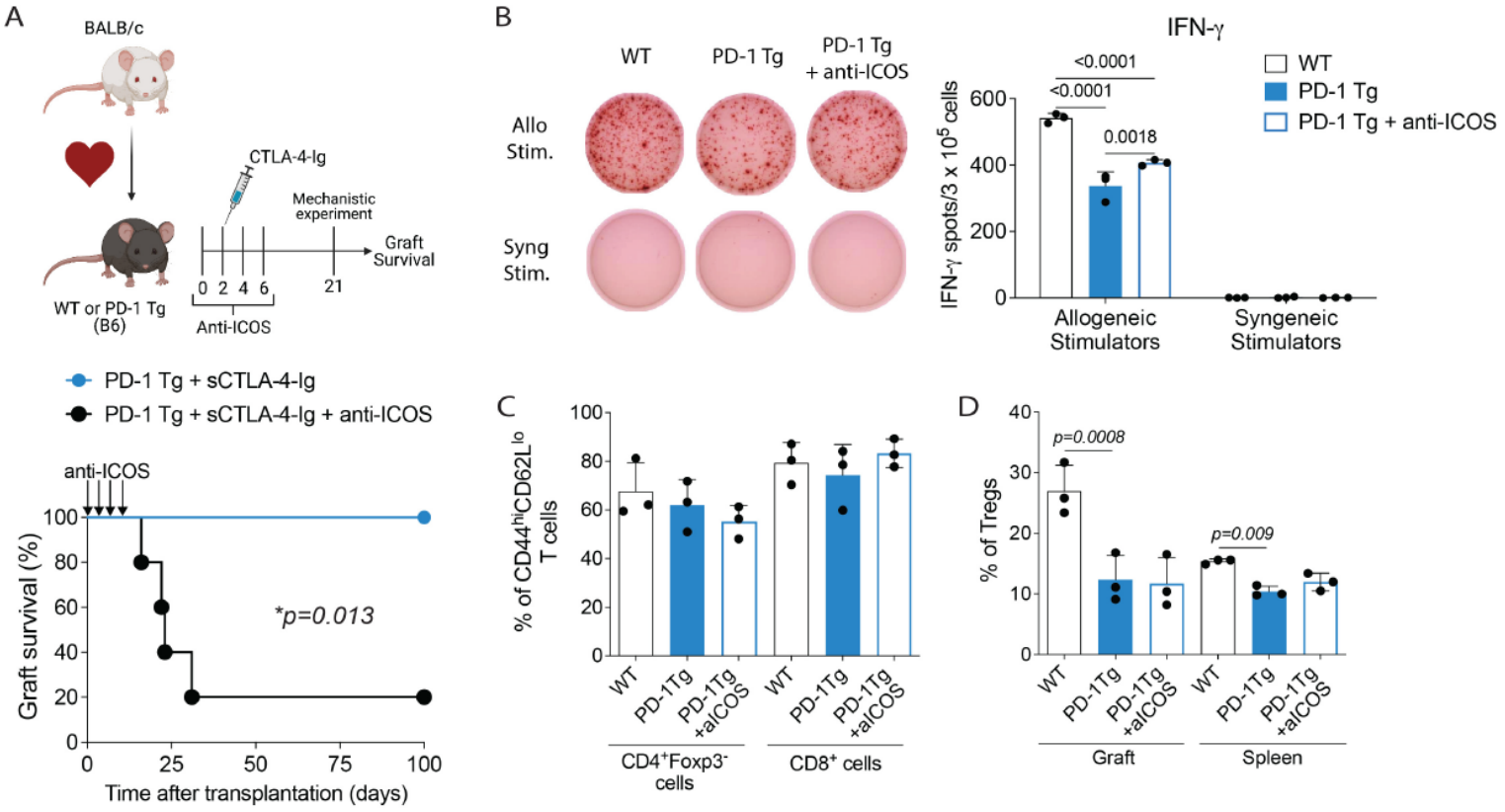


Immunophenotyping of Tregs from naïve hearts, cardiac grafts and spleens from WT or PD-1 Tg recipients 7 days post surgery

Increased expression of ICOS, CTLA-4, AhR and TIM-3

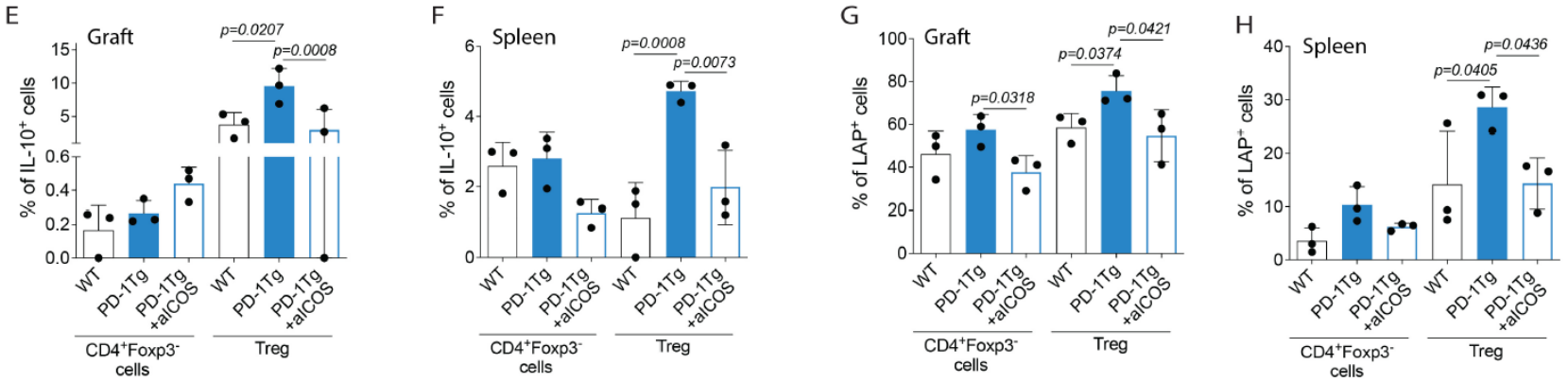
Induction of tolerance in PD-1 Tg recipients treated with CTLA-4-Ig is ICOS-dependent

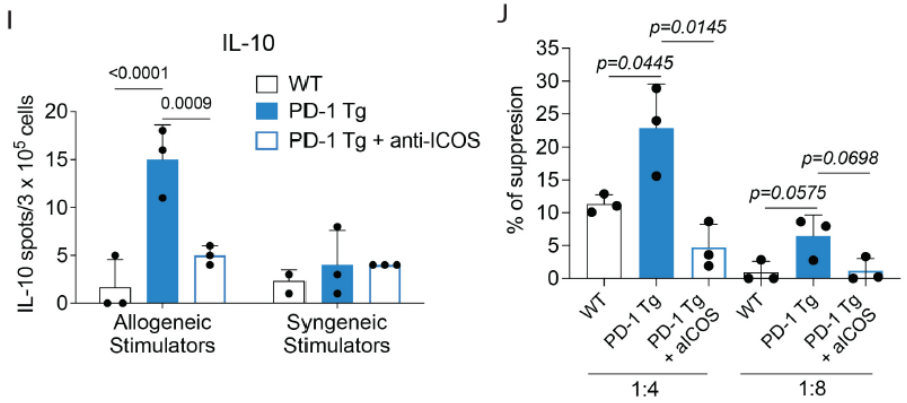


Blocking antibody approach against ICOS
Prolongation of graft survival was abrogated when ICOS was targeted

ICOS blockade had no effect on CD4+ and CD8+ TEM or Treg frequencies

Suppressive functions of PD-1 Tg T_{regs} are decreased when ICOS is blocked





IL-10 production and LAP expression is reduced in PD-1Tg Tregs treated with anti-ICOS

Non-Treg cells were not affected by ICOS blockade

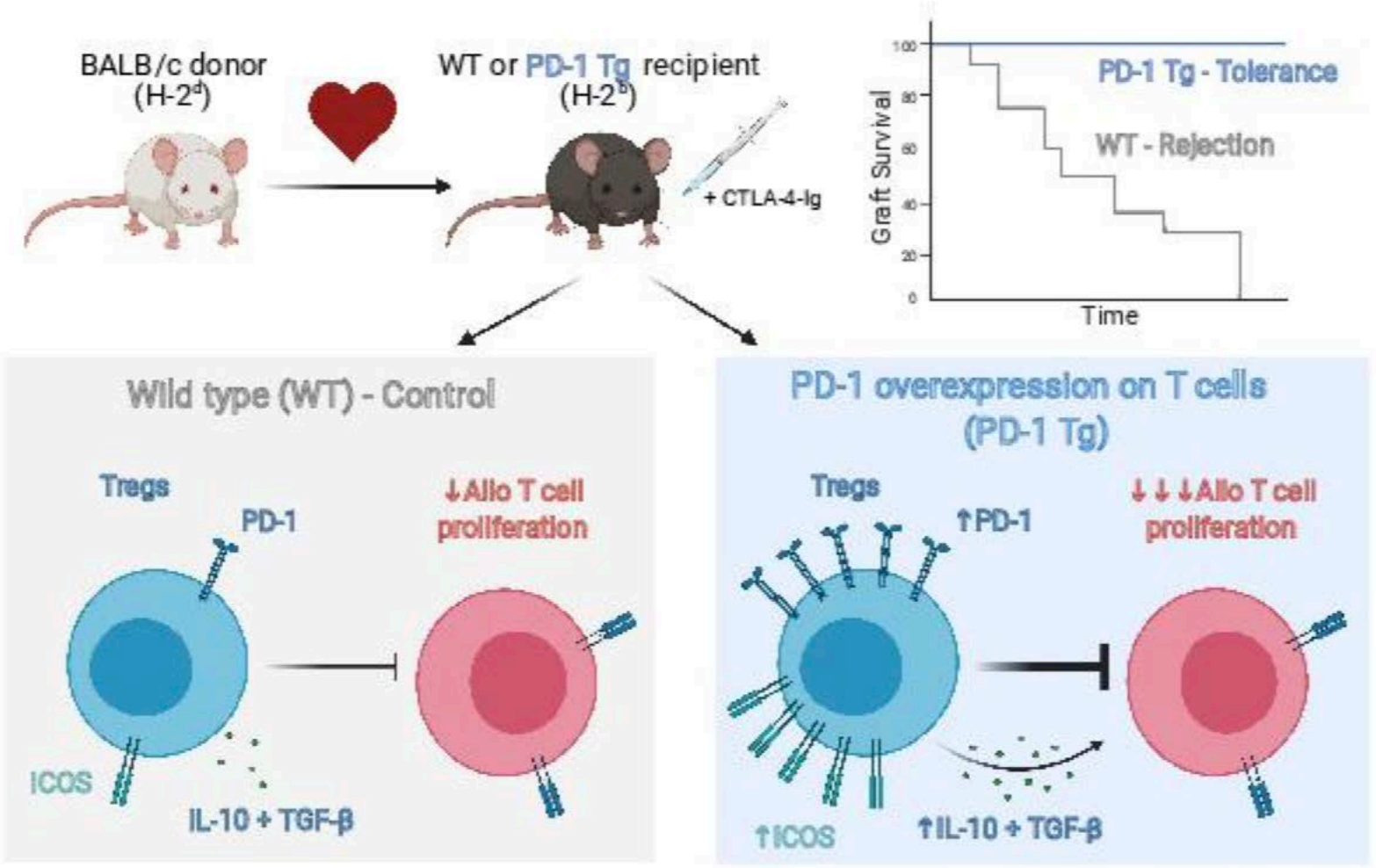
IL-10 production is allo-specific and inhibited by ICOS Blockade

Tregs from PD1 Tg mice inhibit T-cell proliferation
This effect is significantly reduced when ICOS is blocked

Keypoints

- T cell-specific overexpression of PD-1 promoted tolerance in an MHC-fully mismatched murine cardiac transplant model
- PD-1 Tg conventional T cells proliferated significantly less and produced less pro-inflammatory cytokines compared to WT
- Allograft PD-L1 expression was required for this survival benefit
- Graft-infiltrating PD-1 Tg Tregs expressed significantly higher levels of ICOS

Graphical summary



Thank you for your attention !