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Novel Targetable Pathways in Costimulation Pathway Blockade

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No significant financial conflicts to declare

- Consultant, Moderna (not relevant to this presentation)
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- Chair, IXA Ethics Committee; NIH grants (heart, liver Xeno; allo tolerance)

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Costimulation Pathways:
Novel Regents Approaching the Clinic

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None of the reagents discussed are approved for any clinical indication

No (off-label) clinical use will be described

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Emerging Costimulation Blockade Approaches

CD154

- **TNX-1500 (Tonix)**
  - *BMS-986004 (BMS), AT-1501 (Eledon); HZN 4920 (dazodalibep, Horizon)*

CD28

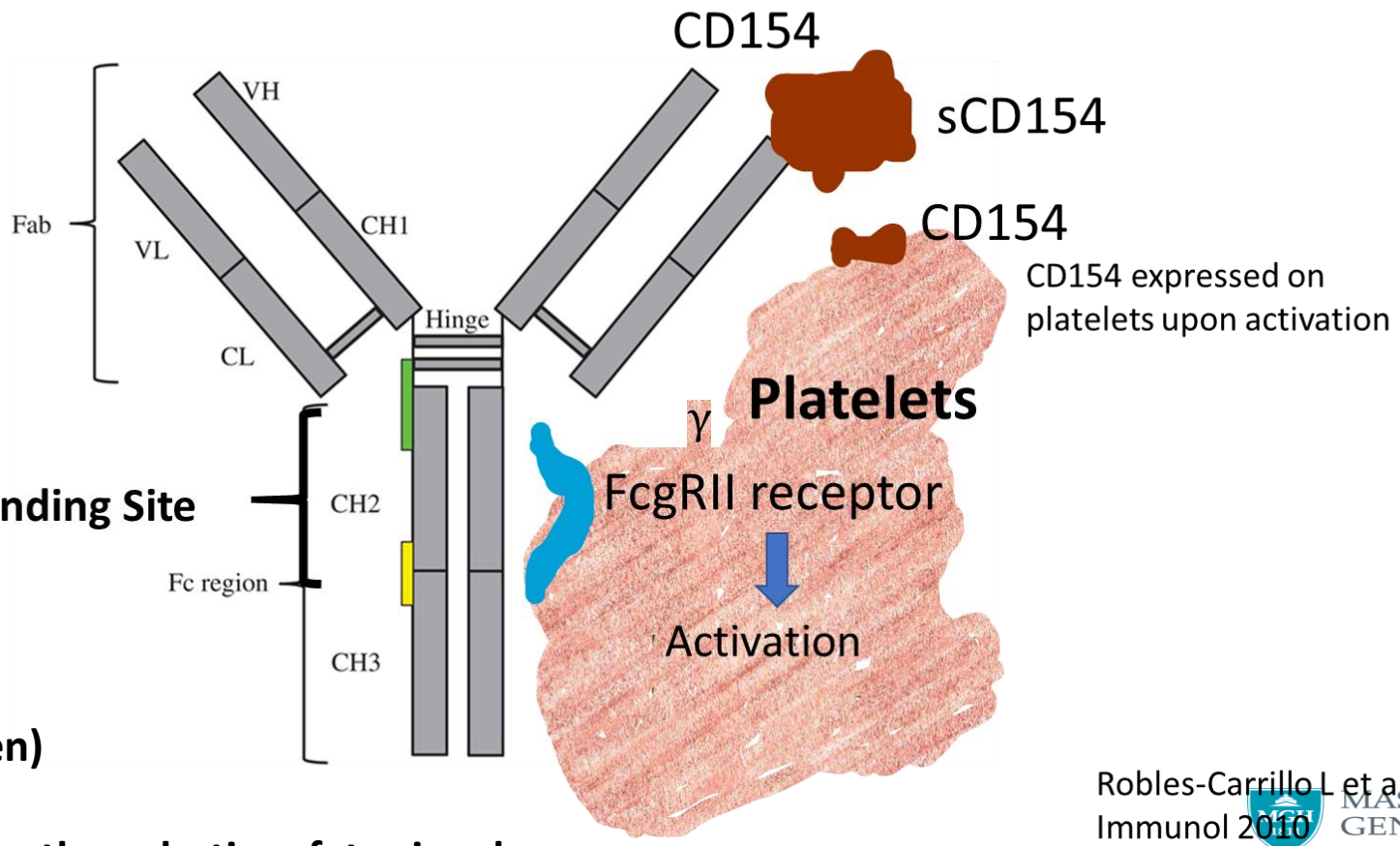
- **FR104 (OSE, Veloxis)**
  - *lulizumab (NCT04066114, BMS); Acazicolcept (Alpine, ICOSL vIgD-Fc)*

CD2

- **Primatized Rh-loCD2bR1 (NHP Reagent Resource Center)**
  - *Siplizumab (ITBMed)*

Emerging Costimulation Blockade: αCD154

IgG1 antibodies against CD154 form immune complexes with soluble CD154, activate platelets via FcγRIIa



hu5c8: Ruplizumab (Biogen)
IDEC-131: (Biogen/IDEC)
Clinical trials halted due to prothrombotic safety signal

Robles-Carrillo L et al. J Immunol 2010

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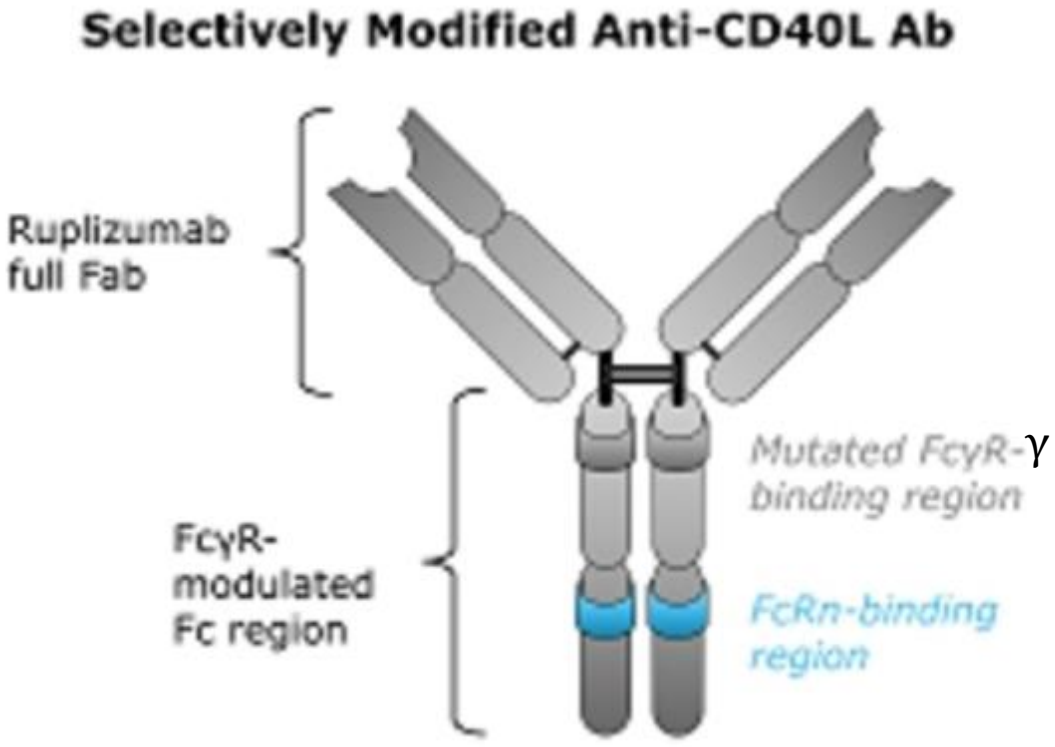
Emerging Costimulation Blockade: αCD154

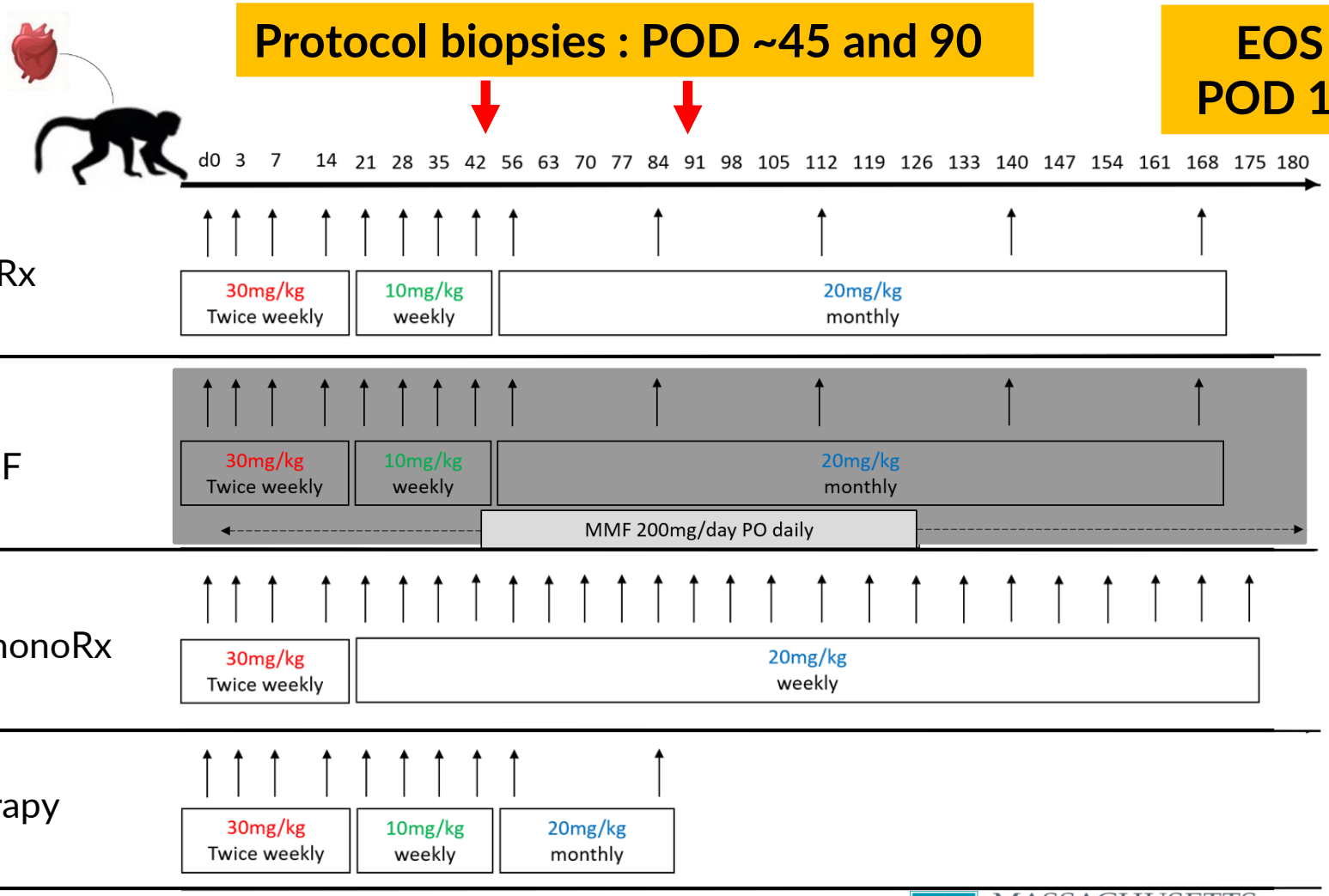
TNX-1500: αCD154 IgG4 with retained hu5c8 Fab



- Aglycosyl IgG1 αCD154 Ab exhibits reduced efficacy in allo islet model (Ferrant et al 2004)
- FcγR silenced αCD154 domain Ab exhibits reduced efficacy in allo kidney model (Kim et al 2016)
- **TNX-1500 is an Fc-modified IgG4 αCD154 with reduced binding to FcγRIIa**

Emerging Costimulation Blockade: αCD154

Heterotopic abdominal heart allotransplant model



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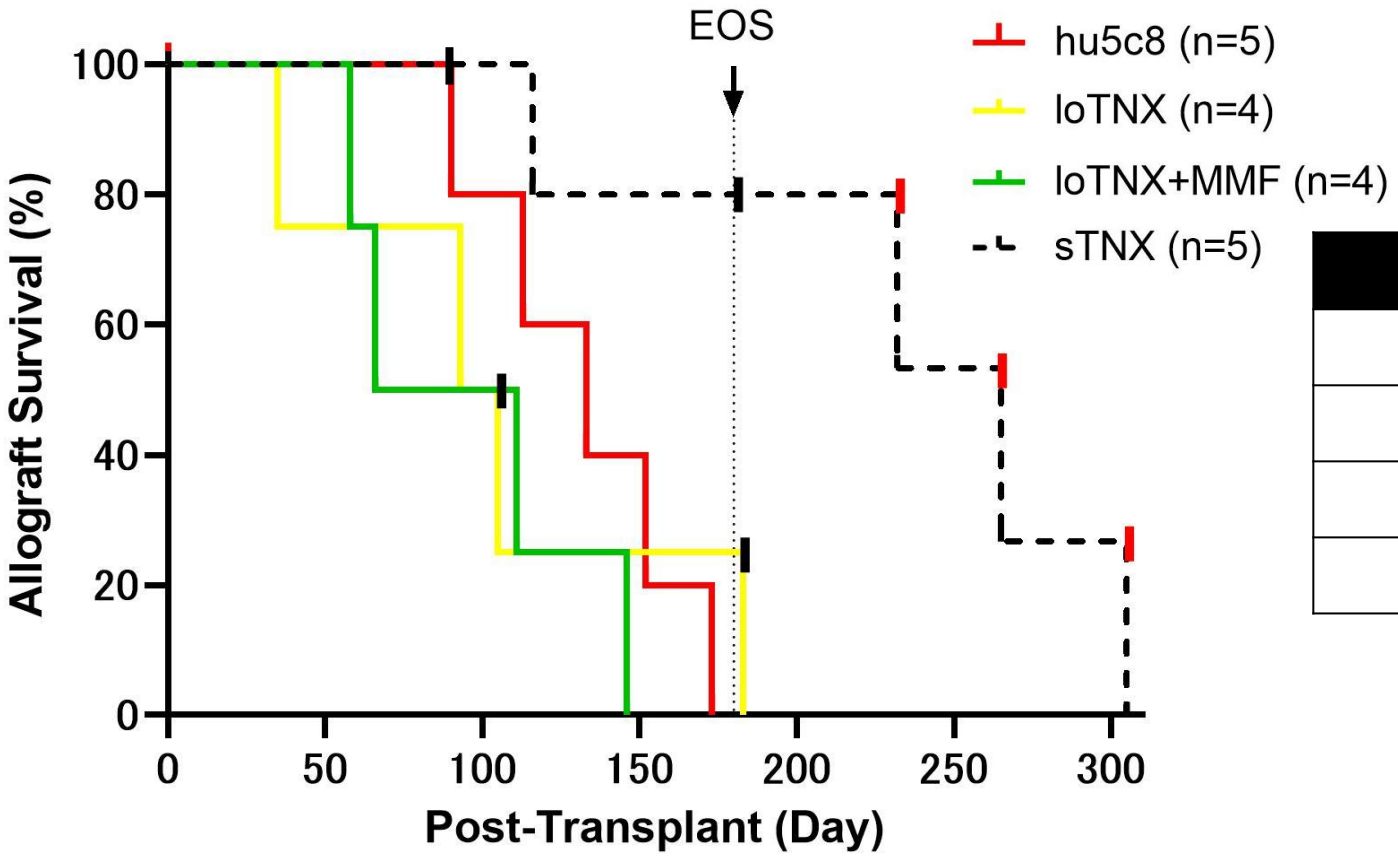
Emerging Costimulation Blockade: αCD154

Results - Heart Allograft Survival in NHPs is significantly prolonged with standard dose TNX-1500 (stTNX)



Explant of beating graft

Rejection after cessation of stTNX treatment

Treatment Group	MST (range)
hu5c8 (Rx off d90)	133 days (90-173)
loTNX	99 days (35-183)
loTNX + MMF	88 days (58-146)
stTNX	>265 days (116-305)

P<0.05 for all comparisons against stTNX

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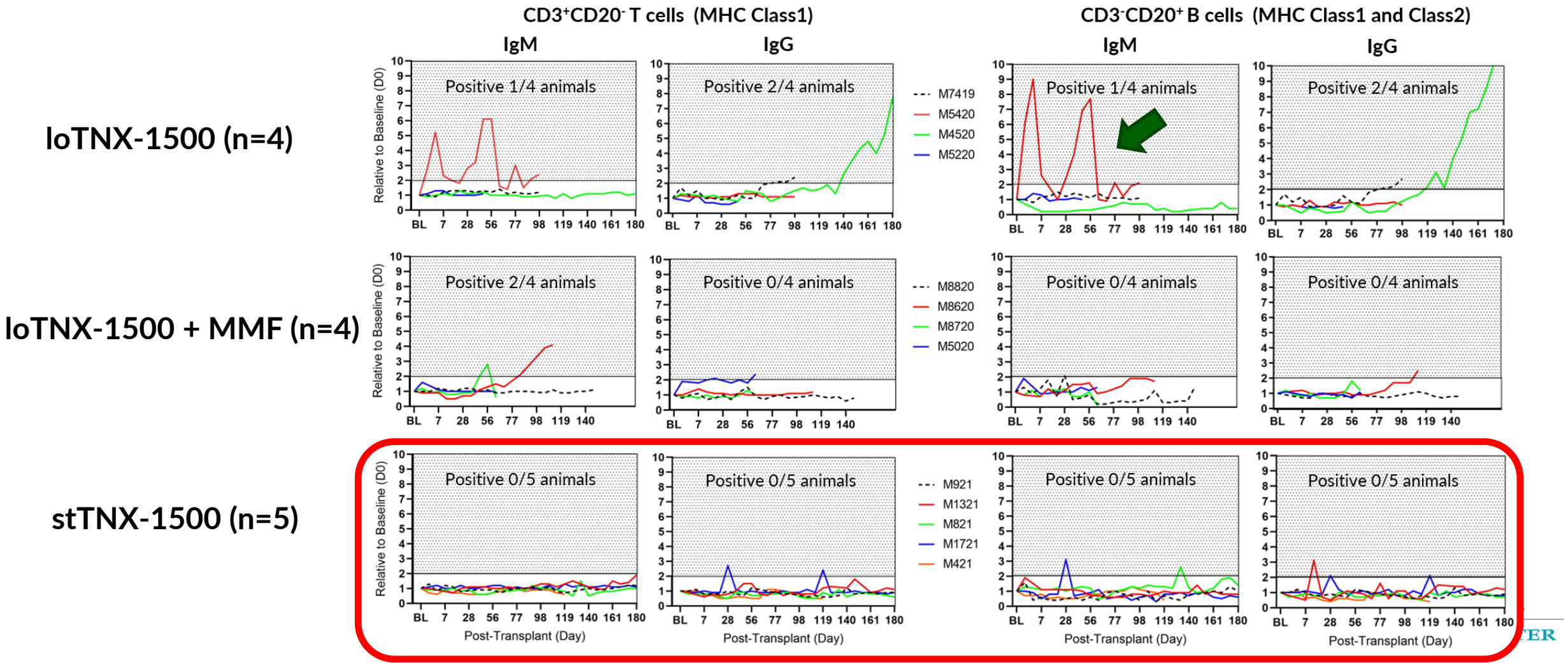
Emerging Costimulation Blockade: αCD154

Results- TNX-1500 suppresses anti-donor-alloantibody elaboration



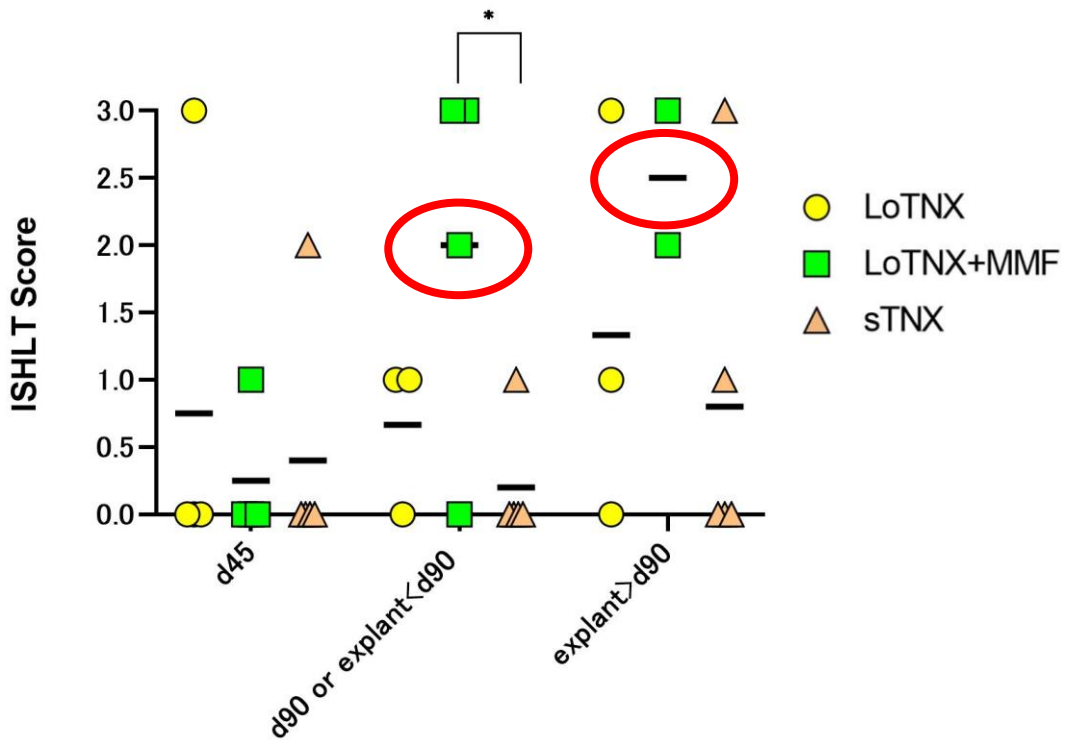
Emerging Costimulation Blockade: αCD154

Results- Immune Injury

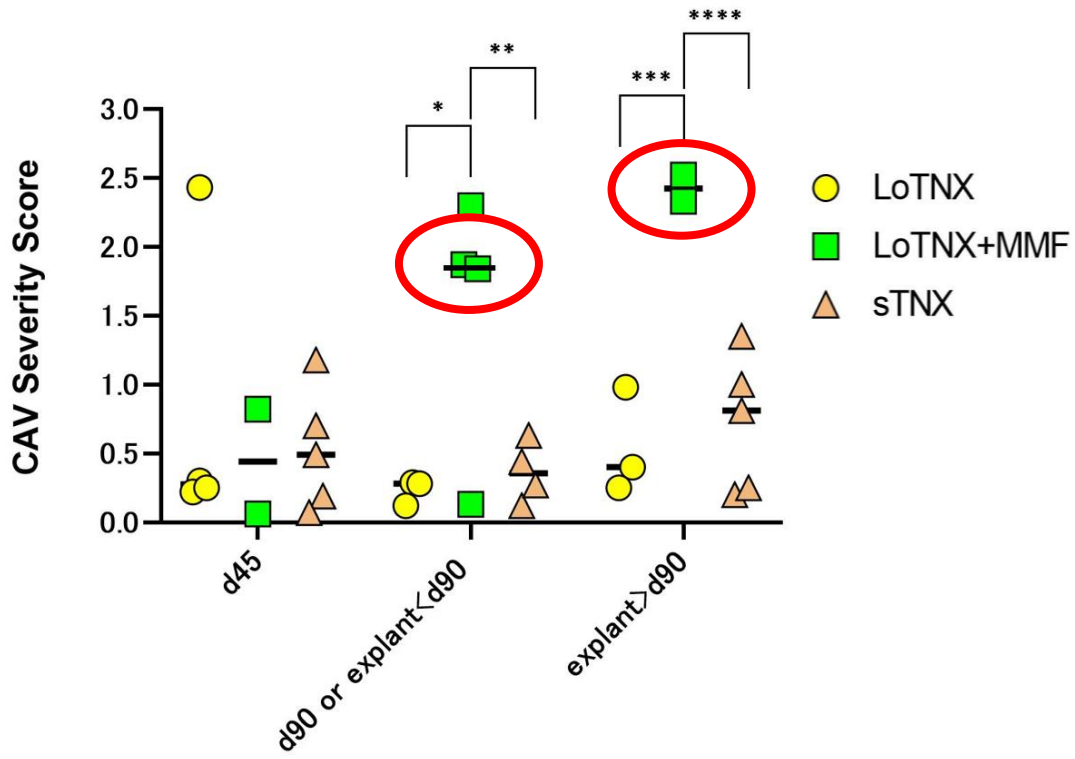
CAV significantly more severe with loTNX-1500+MMF

* P<0.05
** P<0.01
*** P<0.005
**** p<0.001

ISHLT scores



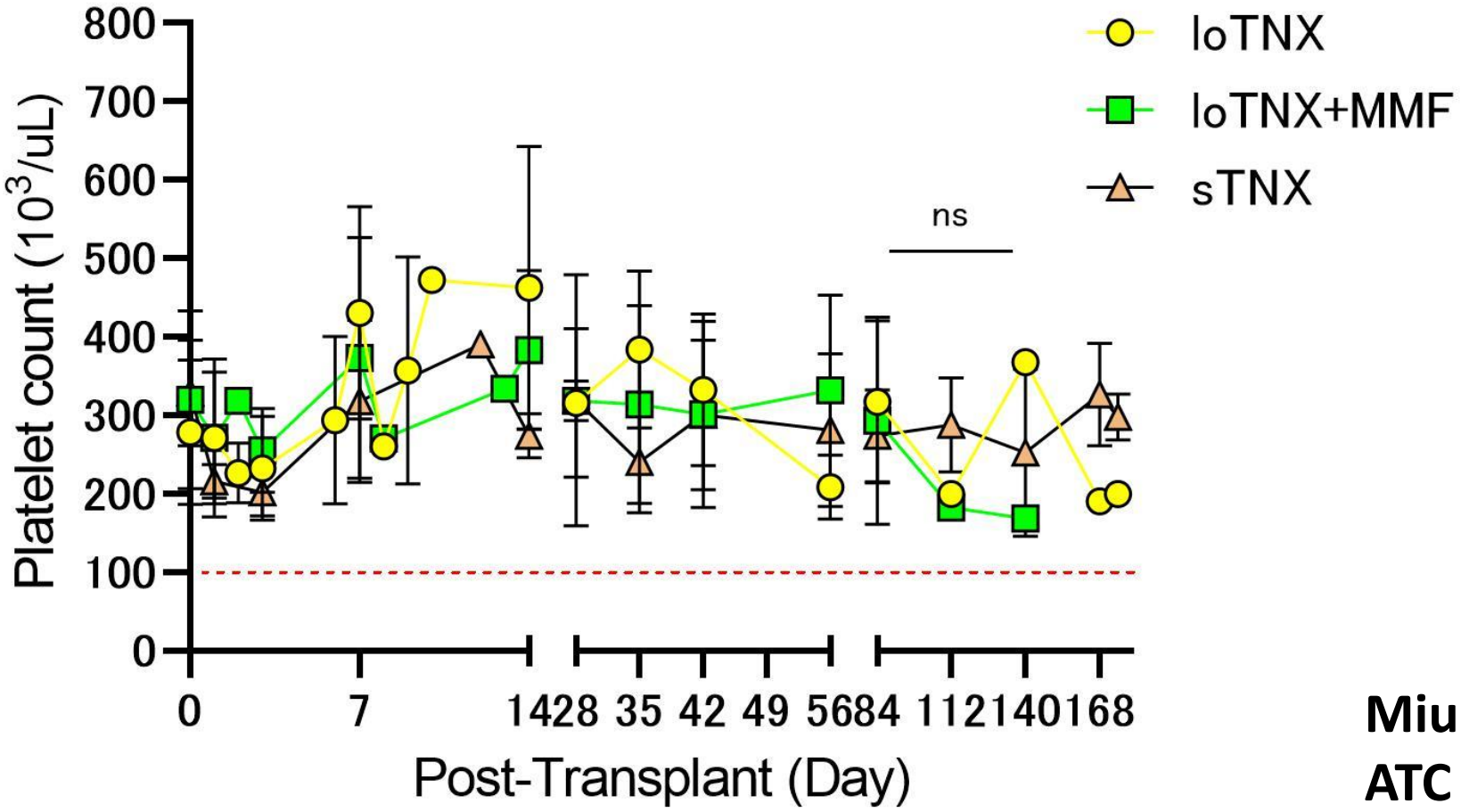
CAV severity scores



Emerging Costimulation Blockade: αCD154

Results- **Platelet counts stable**

No thromboembolic complications were observed

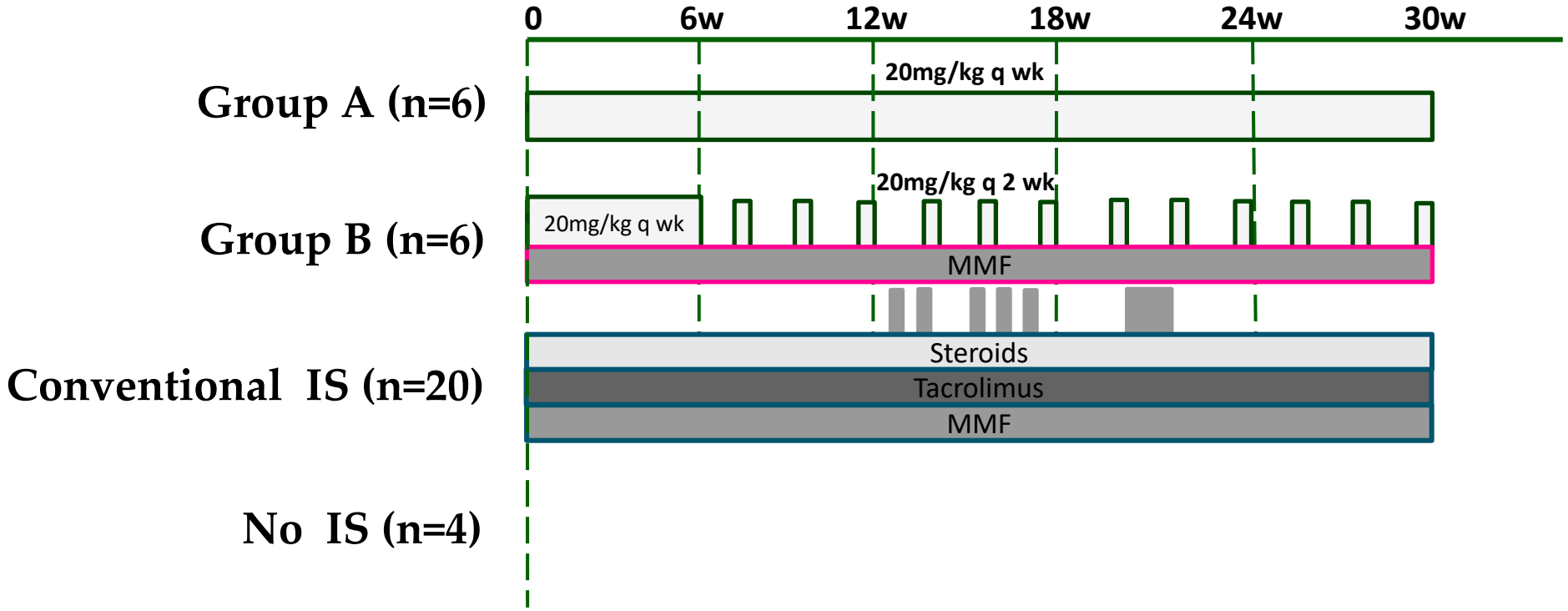


Miura S et al
ATC 2022, #582

Emerging Costimulation Blockade: αCD154

Lassiter G, Kawai T et al
ATC 2022, Abstract #172
Cyno Kidney AlloTxp

6 Standard Dose TNX-1500 (Group A)
6 Reduced-Dose TNX-1500+MMF (Group B)
Compared with Historical Results



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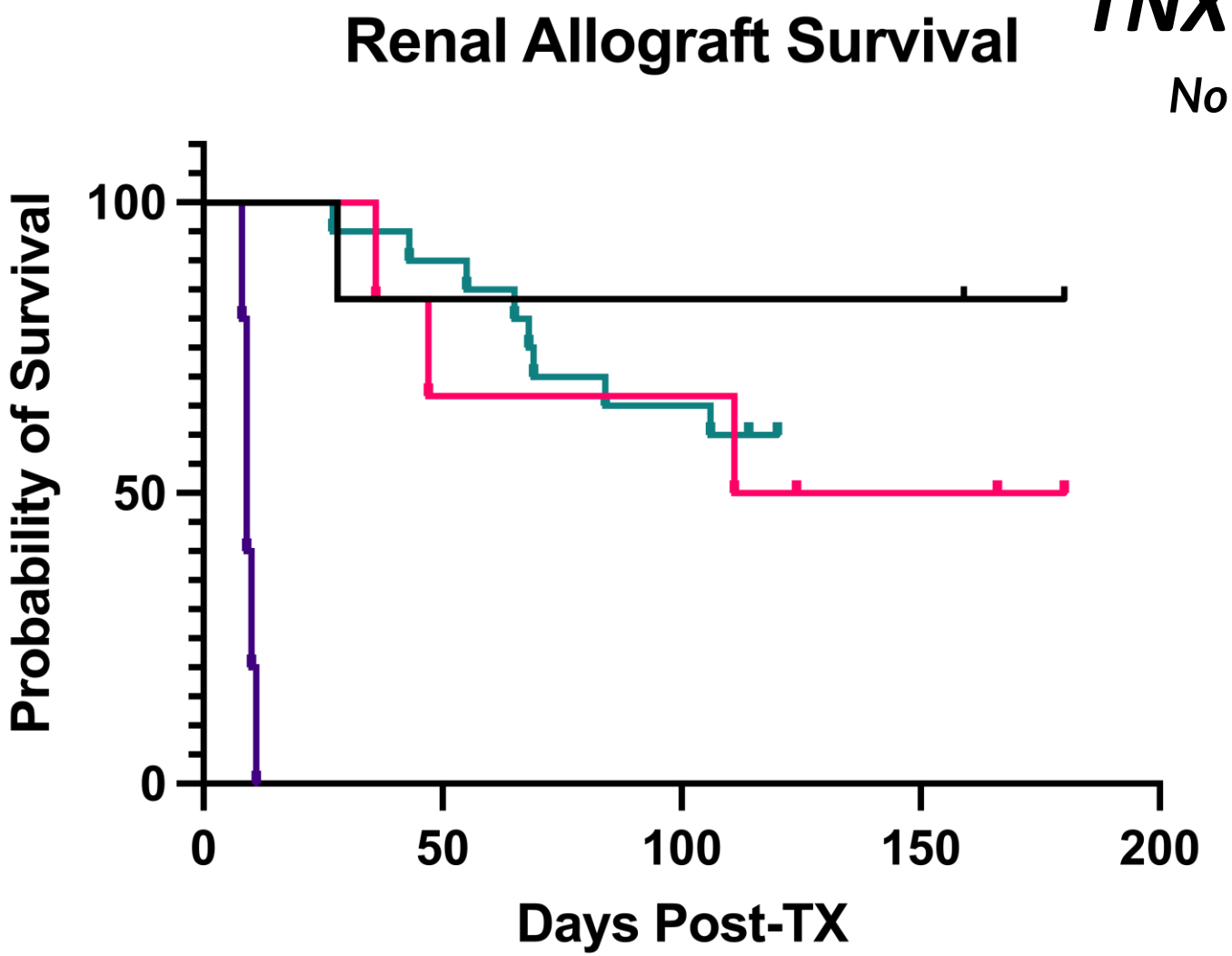
Emerging Costimulation Blockade: αCD154



TNX-1500 > loTNX-1500 + MMF

No thromboembolic complications were observed

- Group A (n=6) ***~stTNX***
- Group B (n=6) ***~loTNX+MMF***
- Conventional I.S. (n=20)
- No I.S. (n=4)

Lassiter G, Kawai T et al
ATC 2022, Abstract #172

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Emerging Costimulation Blockade: αCD154

Conclusions

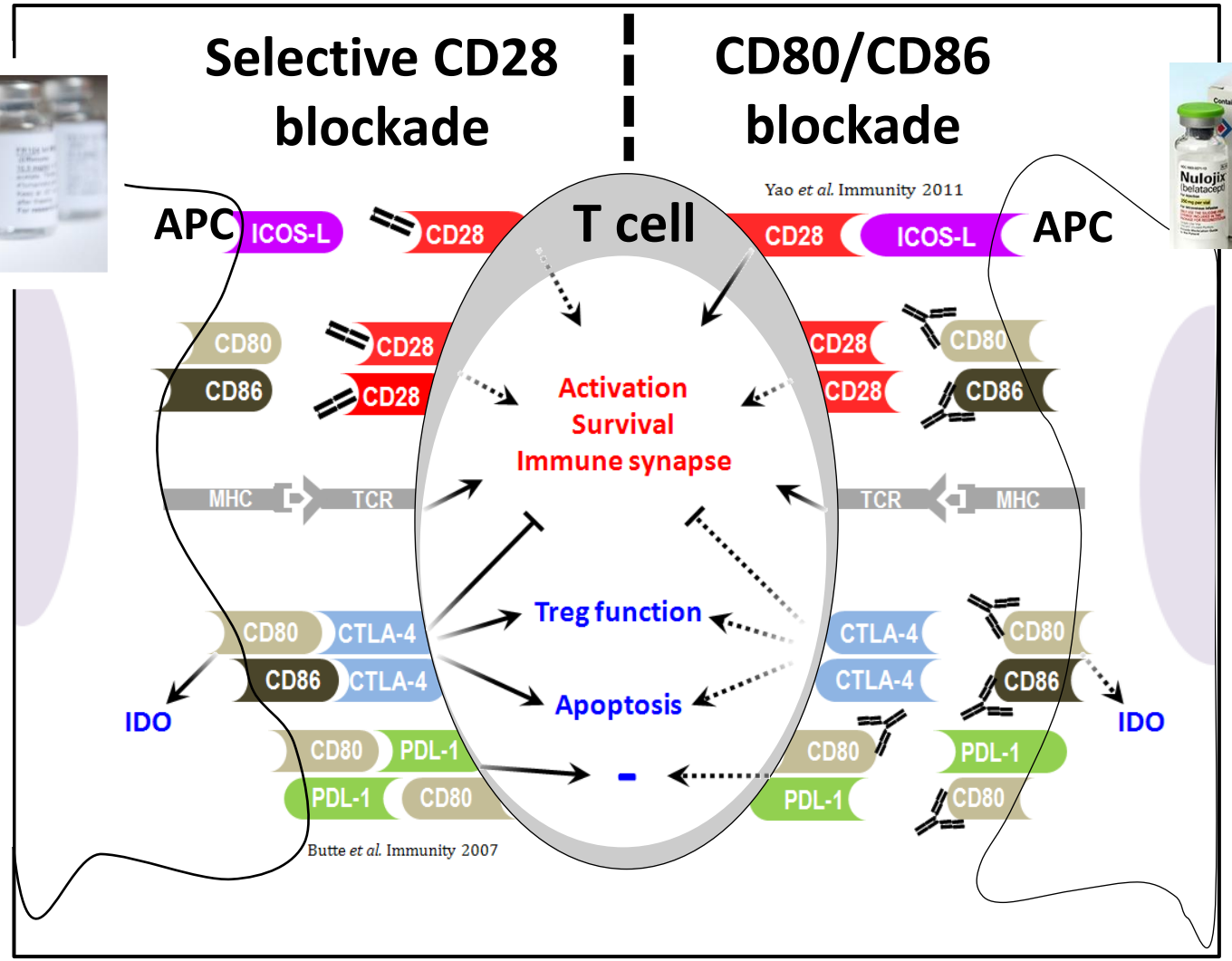
- Standard-dose TNX-1500 inhibits pathologic alloimmunity in NHPs
  - Consistently prolonged NHP cardiac and renal allograft survival
    - *Relative expansion of Tregs in peripheral blood*
    - *No CMV activation (no prophylaxis)*
    - *No clinical thrombotic events.*
- MMF does not improve heart results with low-dose TNX-1500
  - Similar findings for kidney
    - *Does MMF interfere with Treg expansion, function under αCD154 Rx? (Kirk AD et al)*
- TNX-1500 inhibits alloantibody elaboration, class switching
  - Dose-dependent effect

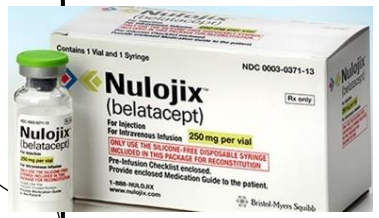
Emerging Costimulation Blockade : αCD28

αCD28

FR104:

domain-associated antibody, PEGylated





LEA29Y:

CTLA4-Ig

References: Poirier et al. Immunotherapy 2010; Transpl Int 2011; Am J Transplant 2012

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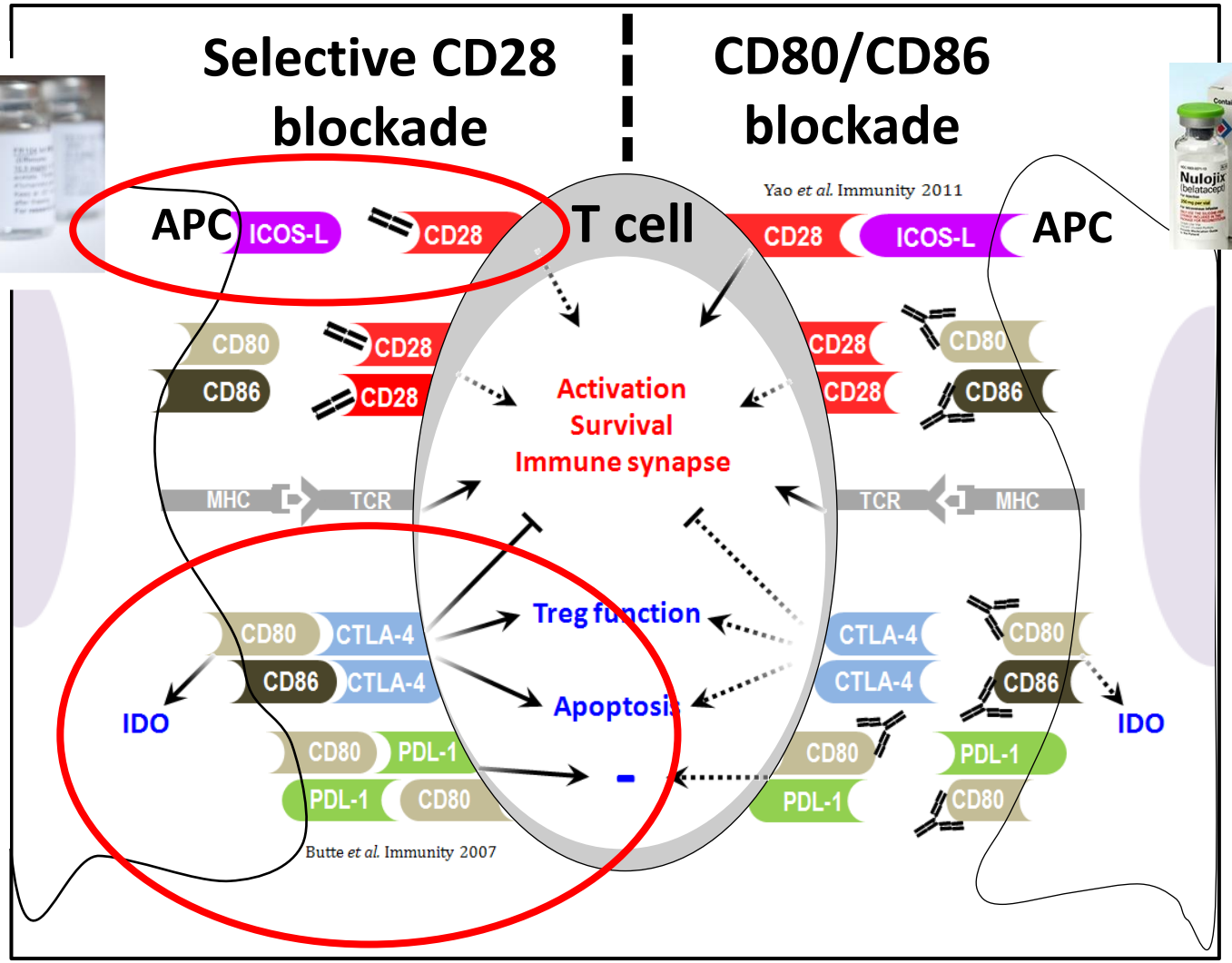
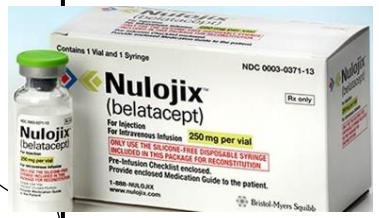
Emerging Costimulation Blockade : αCD28

αCD28

FR104:

domain-associated antibody, PEGylated





LEA29Y:

CTLA4-Ig

References: Poirier et al. Immunotherapy 2010; Transpl Int 2011; Am J Transplant 2012

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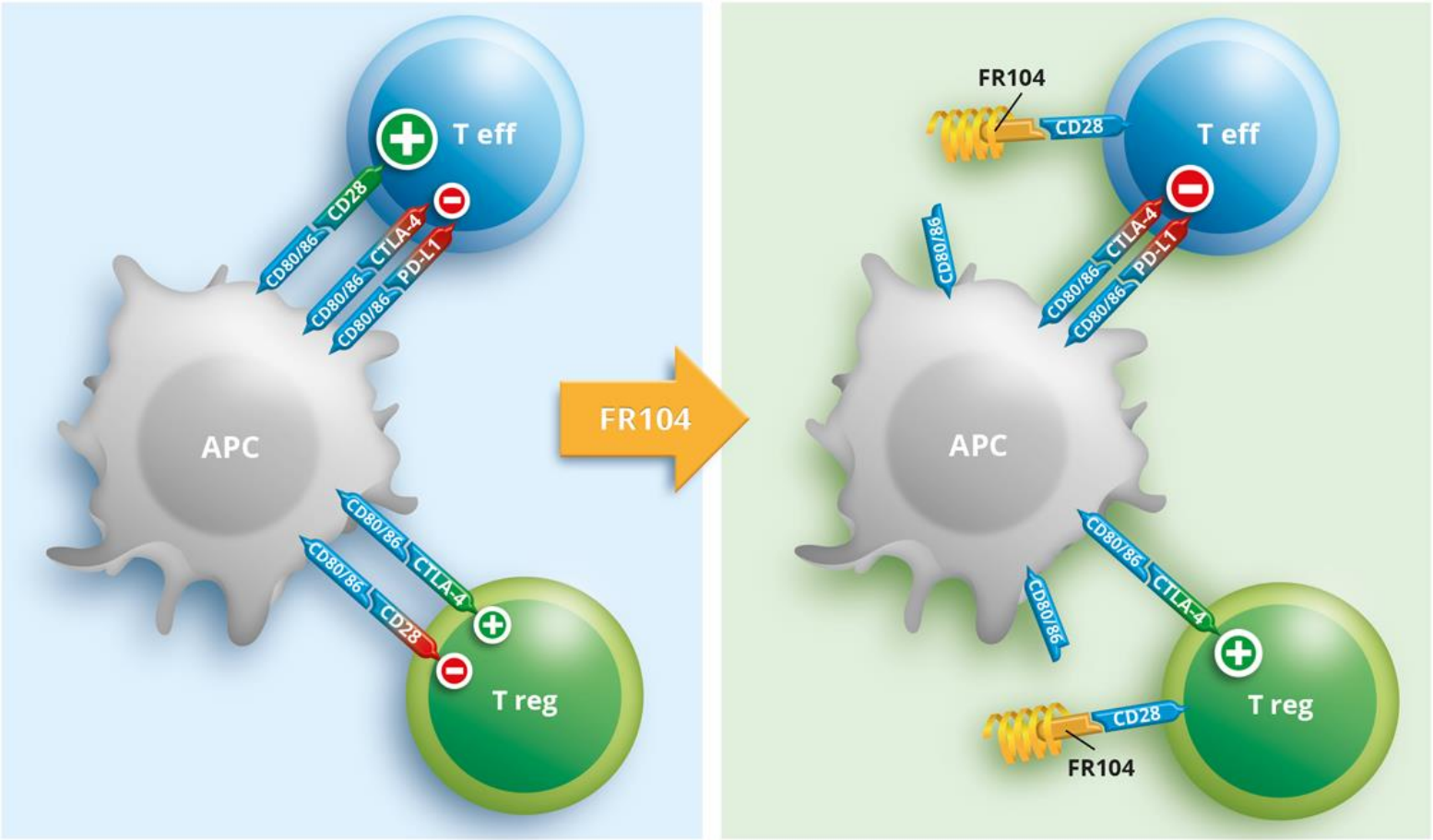
Emerging Costimulation Blockade: αCD28



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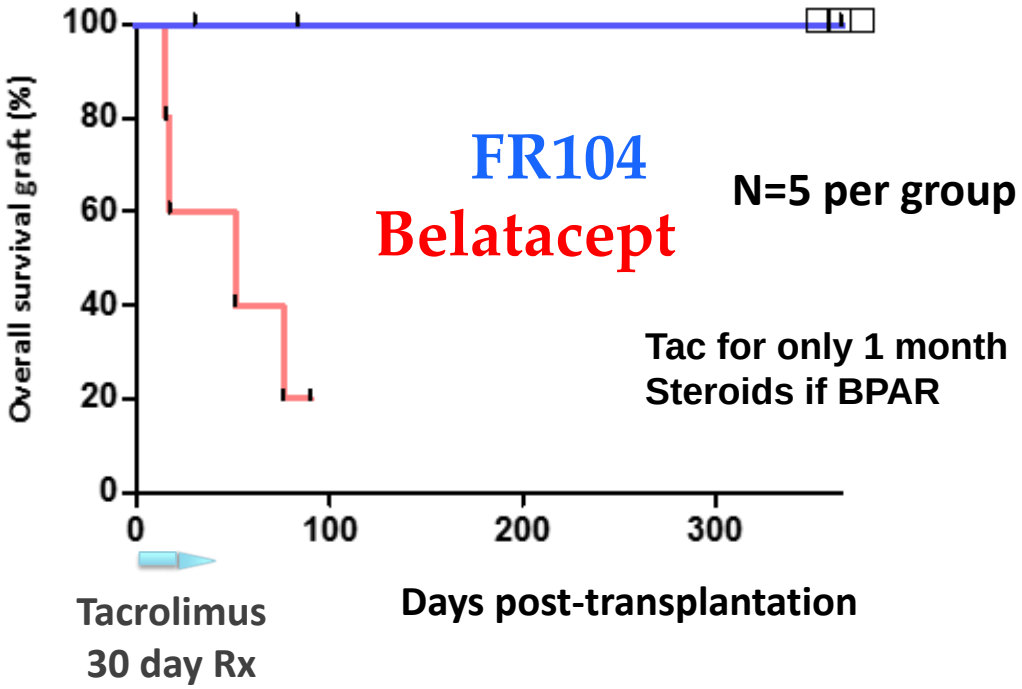
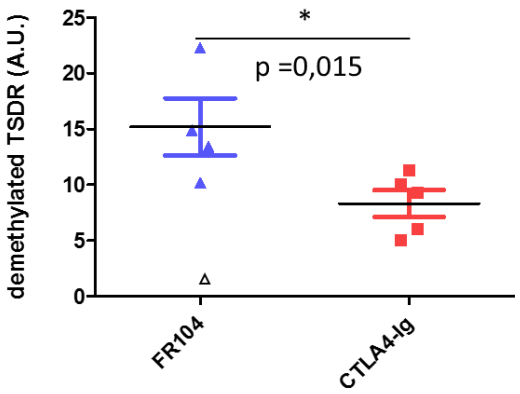
Emerging Costimulation Blockade: αCD28

FR104 monoRx promotes baboon kidney allo-Tx survival

Superior control of graft rejection vs Belatacept (steroid-resistant)

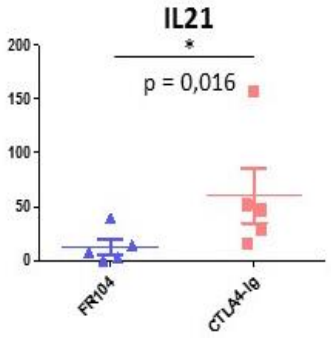


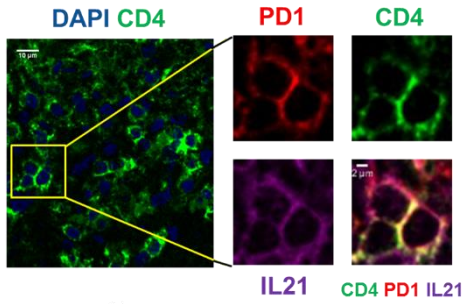
Expanded intragraft Tregs



Better control of intragraft Tfh

(decrease in IL-21 secreting cells)





Ville, Poirier et al, J Am Soc Nephrol 2016
Poirier et al, Am J Transplant. 2015
Poirier et al, Science Transl Med 2010

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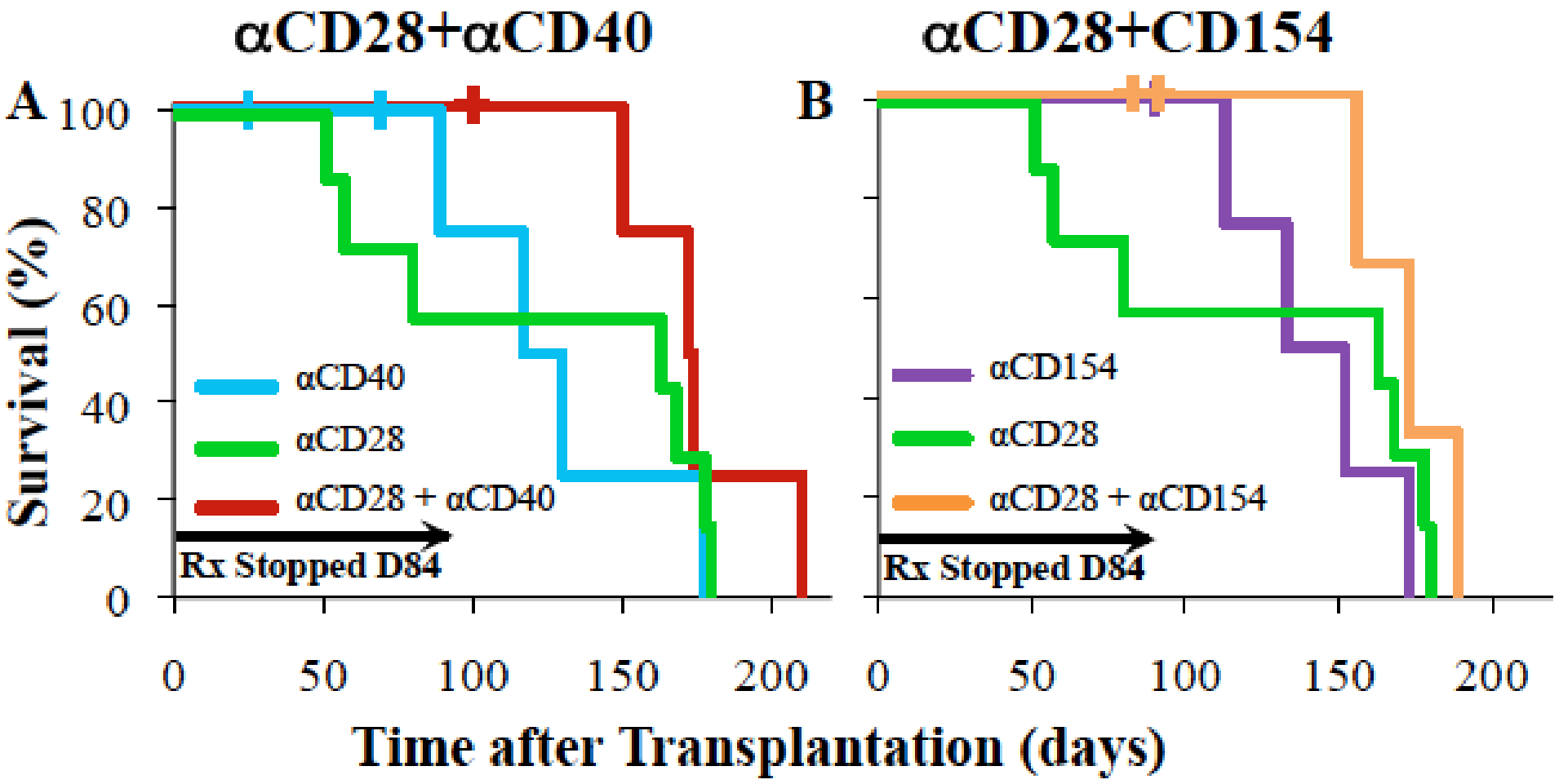
Emerging Costimulation Blockade: αCD28

FR104 Rx promotes monkey heart allo-Tx survival

Possibly synergistic when combined with αCD40 or αCD154



N=5-7 per group
Rx stopped after d84
No viral illness (no Rx)

Azimzadeh, Pierson, unpublished

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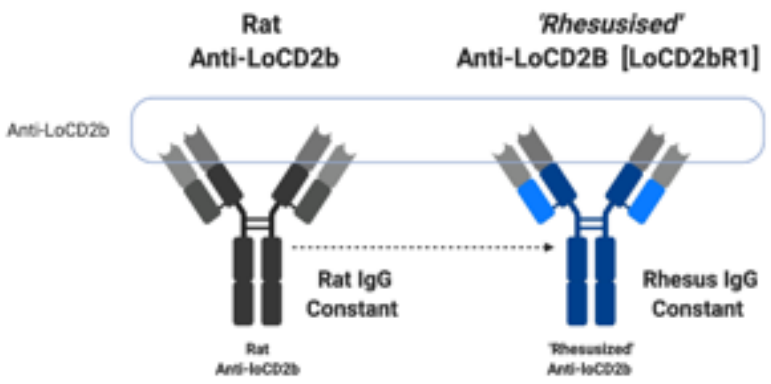
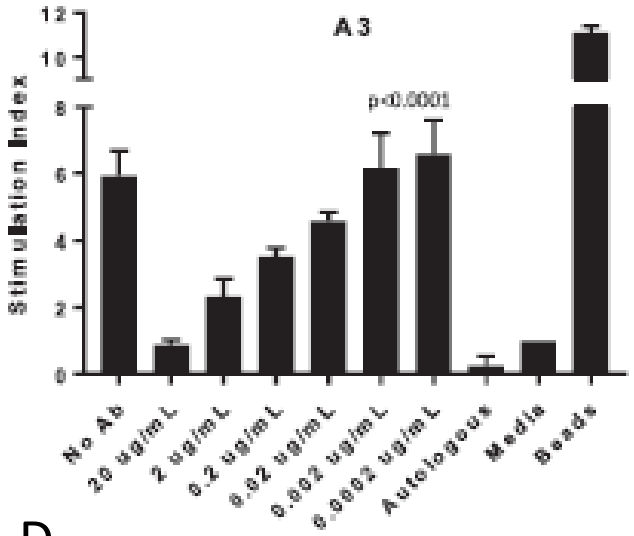
Emerging Costimulation Blockade: αCD2

CD2: α-loCD2 to replace αCD8 for tolerance induction in NHP

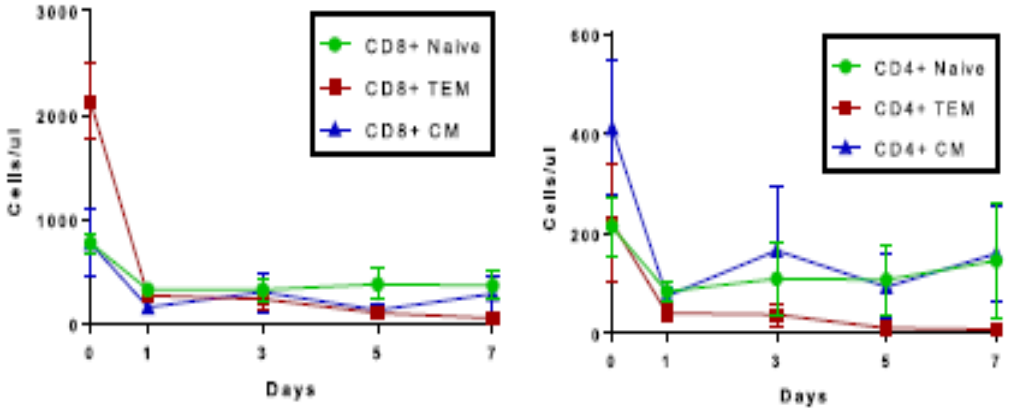
A



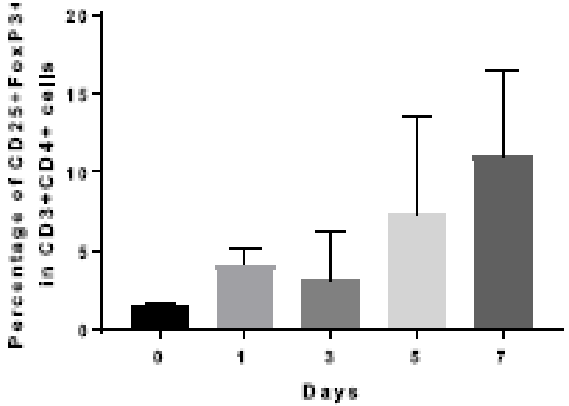
B



C



D



A. Engineered for NHP studies

B. Suppressive in MLR

C. Prolonged depletion of CD8 TEM, Relative sparing of CD4 N, CM

D. Predominance of T regs

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Emerging Costimulation Blockade Approaches

CD154

- **Tonix emphasizing transplantation (allo, xeno) for TNX-1500**
  - *Phase 1 targeted for 2022 pending IND approval*

CD28

- **OSE/Veloxis in Phase 2 for kidney transplantation with FR104**
  - *"Encouraging so far…"*

CD2

- **Primatized αloCD2 effective in kidney tolerance model**
- **Siplizumab for human kidney tolerance: in progress (MGH)**
  - *"Encouraging so far…"*

Emerging Costimulation Blockade Approaches

Thank you

for your attention!