

Efficacy Of CD154 Blockade With TNX-1500 To Prevent Heart Allograft Immune Injury

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Relevant Disclaimers

- S. Fogarty, B. Daugherty, and S. Lederman are employees of Tonix Pharmaceuticals Inc.
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Background: Rationale

α CD154 Co-stimulation Blockade

Suppresses pathogenic alloimmunity

Avoid CNJ toxicity

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ARTICLES

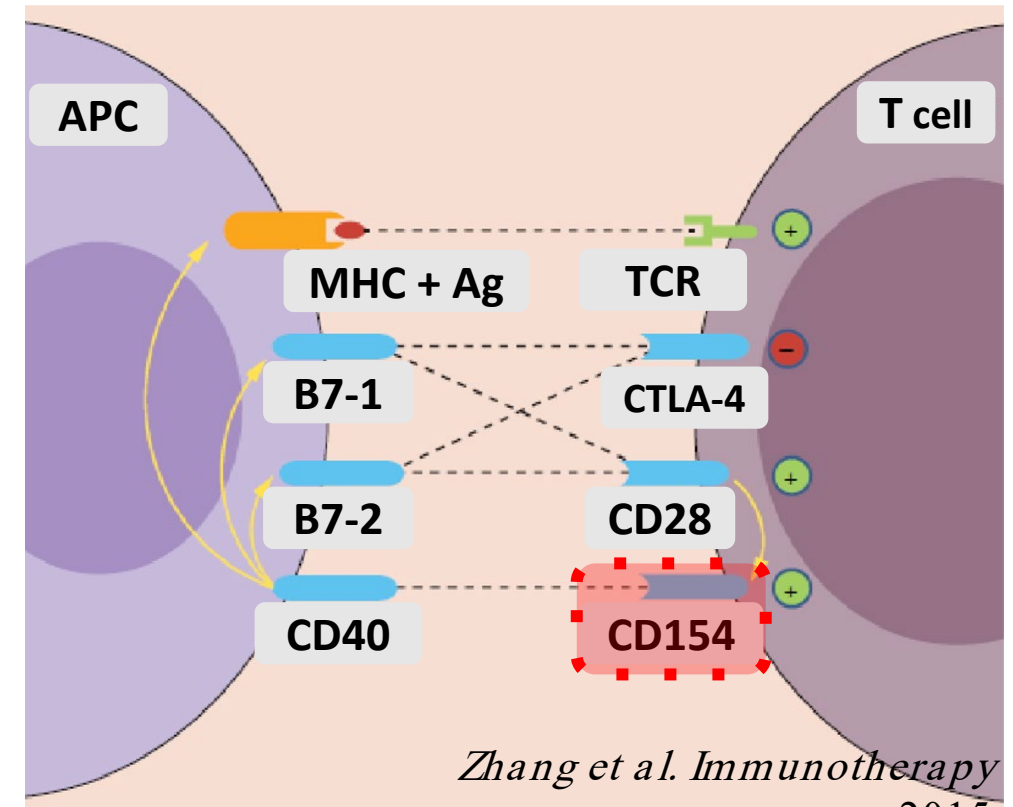
Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates

ALLAN D. KIRK^{1,2,3}, LINDA C. BURKLY⁴, D. SCOTT BATTY³, ROXANNE E. BAUMGARTNER¹, JUSTIN D. BERNING¹, KELVIN BUCHANAN¹, JOHN H. FECHNER, JR.², RHONDA L. GERMOND¹, ROBERT L. KAMPEN¹, NOELLE B. PATTERSON¹, S. JOHN SWANSON³, DOUGLAS K. TADAKI¹, CHRISTOPHER N. TENHOOR⁴, LEONARD WHITE¹, STUART J. KNECHTLE² & DAVID M. HARLAN¹

Transplantation. 1999 Dec 15;68(11):1800-5. doi: 10.1097/00007890-199912150-00026.

Prolongation of primate cardiac allograft survival by treatment with ANTI-CD40 ligand (CD154) antibody

R N Pierson 3rd¹, A C Chang, M G Blum, K S Blair, M A Scott, J B Atkinson, B J Collins, J P Zhang, D W Thomas, L C Burkly, G G Miller



Zhang et al. Immunotherapy
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Background

- **1st & 2nd generations α CD154 mAb prolongs allograft in multiple NHP Txp models (Heart/ Kidney /Islet /Skin)**

1st Gen: Venous, arterial thrombotic events

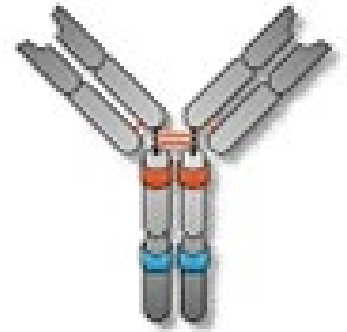
Ruplizumab, IDEC-131

α CD154/sCD154 ICs activate plts via **FcyRIIa**

2nd Gen: Reduced efficacy

aglycosyl Ruplizumab

Fc-silent domain antibody



hu5c8

Background: TNX 1500

■ 3rd generation α CD154 mAb

Fc-modified IgG4

Fc γ RIIa-binding region modified

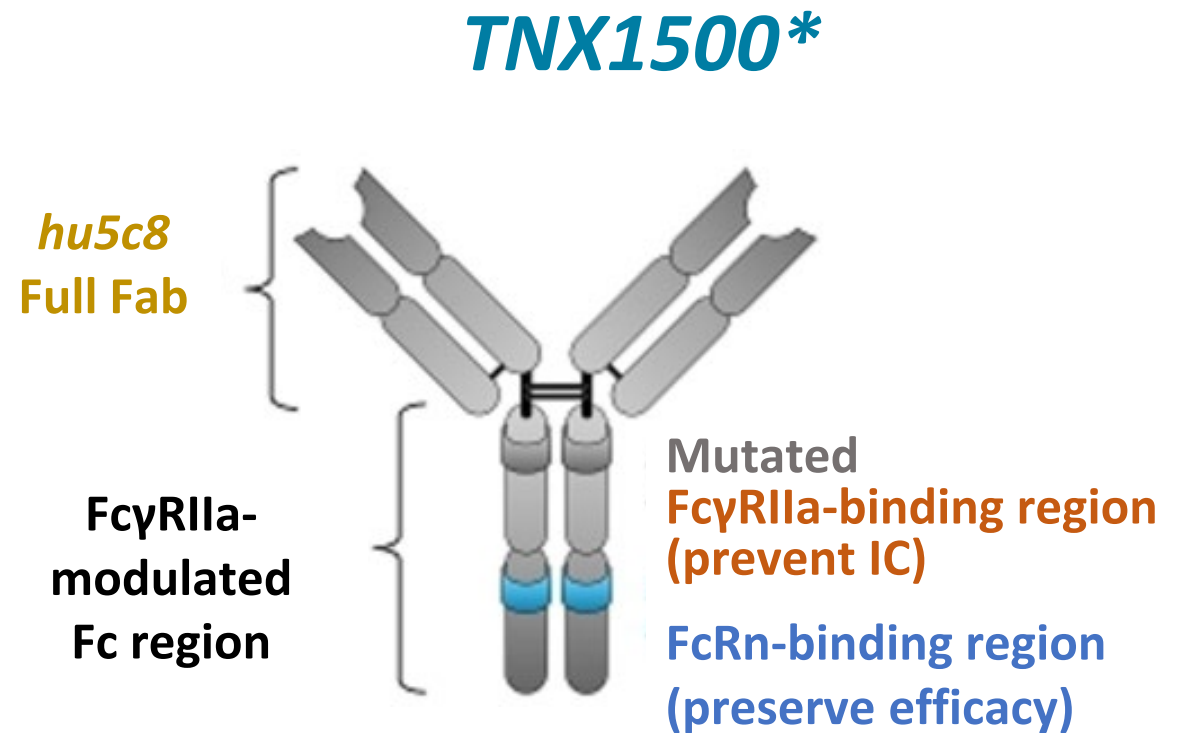
Avoid TE complications

FcRN binding retained

Ruplizumab Fab binding region

Designed for preserved efficacy

compared to Gen 2

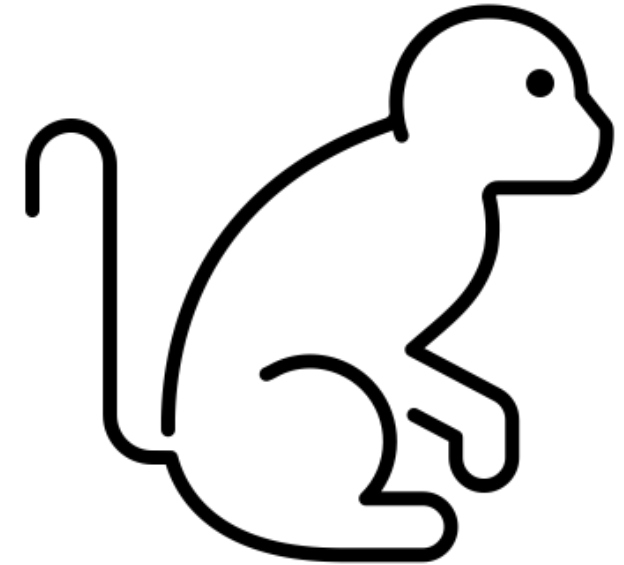


*TNX-1500 is an investigational new biologic and has not been approved for any indication

Study design

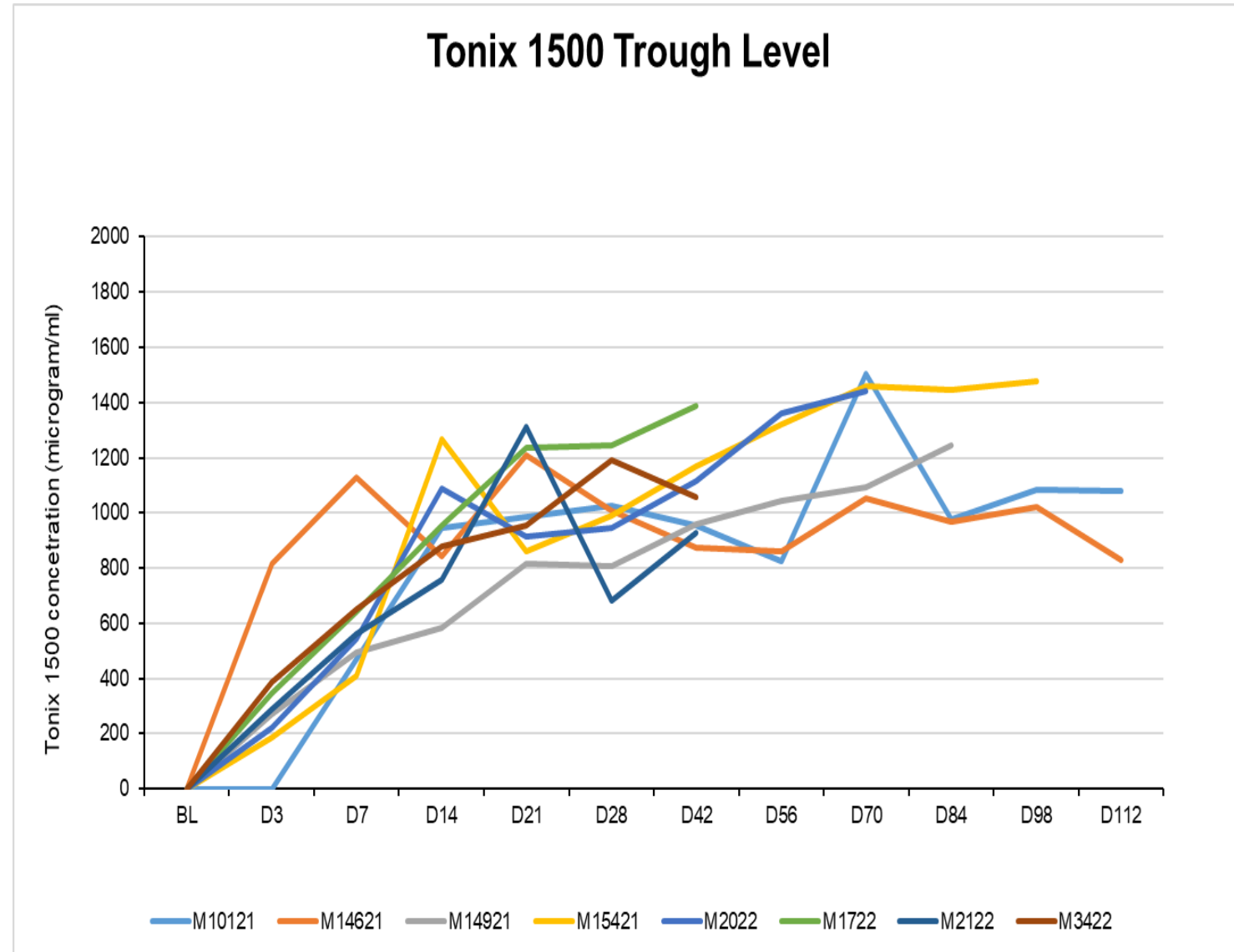
25 cyno heterotopic abdominal heart allografts

- TNX monoRx (n=17) through EOS *d120 (n=12) or d180 (n=5)*
30mg/kg on days 0, 3, 7 and 14; then
20mg/kg/wk
- TNX+additional Rx until EOS at d180
TNX+MMF (40mg/kg/d; n=4)
TNX+Rapa (5-10ng/ml target trough; n=4)



Results: TNX-1500 Trough Levels

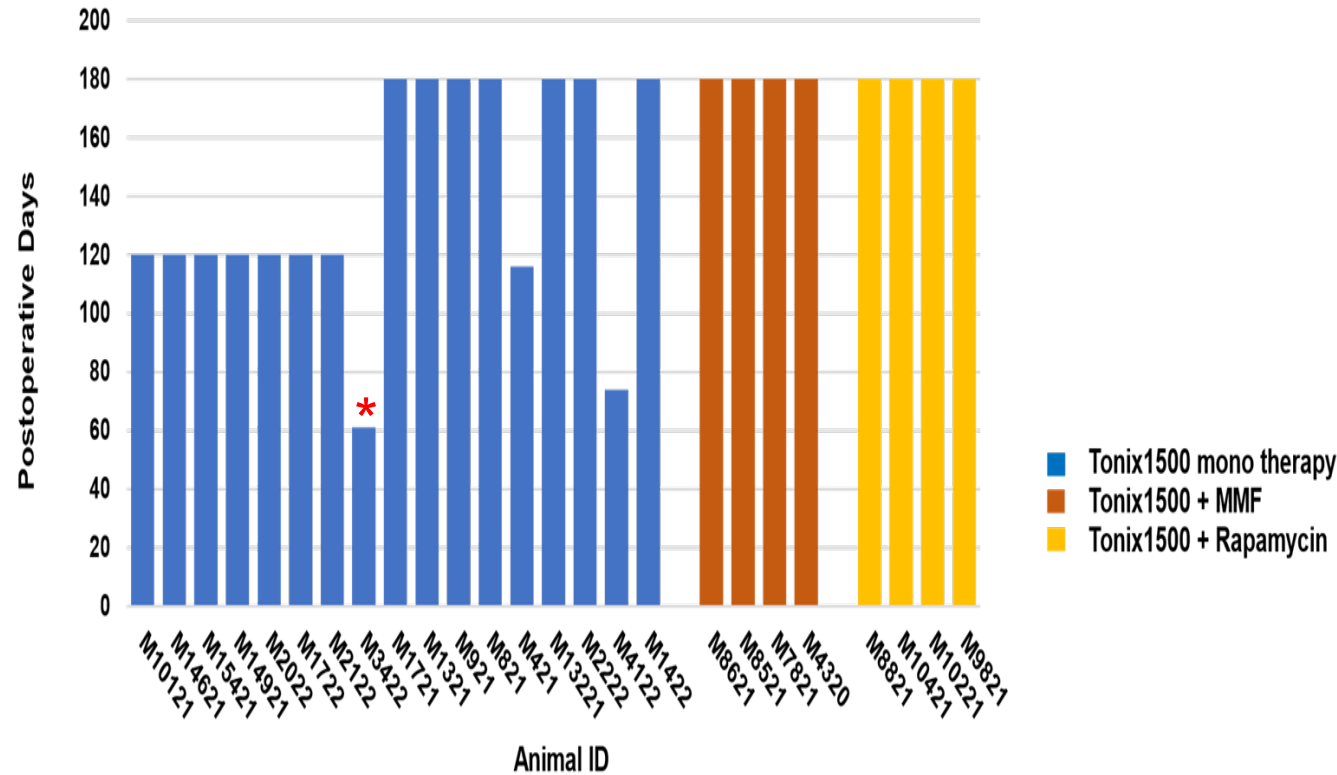
- TNX-1500 troughs:
0.7-1.5 µg/mL after 2nd week
- *No allergic, thrombotic, or administration-related complications were observed*



Results: Graft Survival

- 3/17 TNX monoRx rejected before EOS
on days 61, 74, and 116
 - Cardiac function stable through EOS in the remaining 22 animals

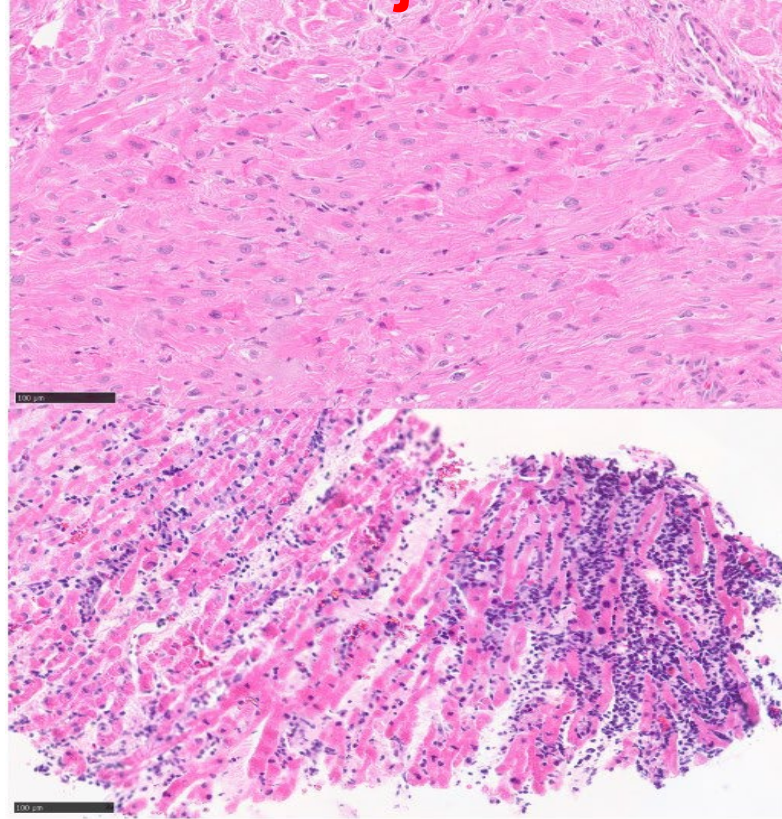
Comparison of Graft Survival According to Treatment Group



Results: Histology at EOS

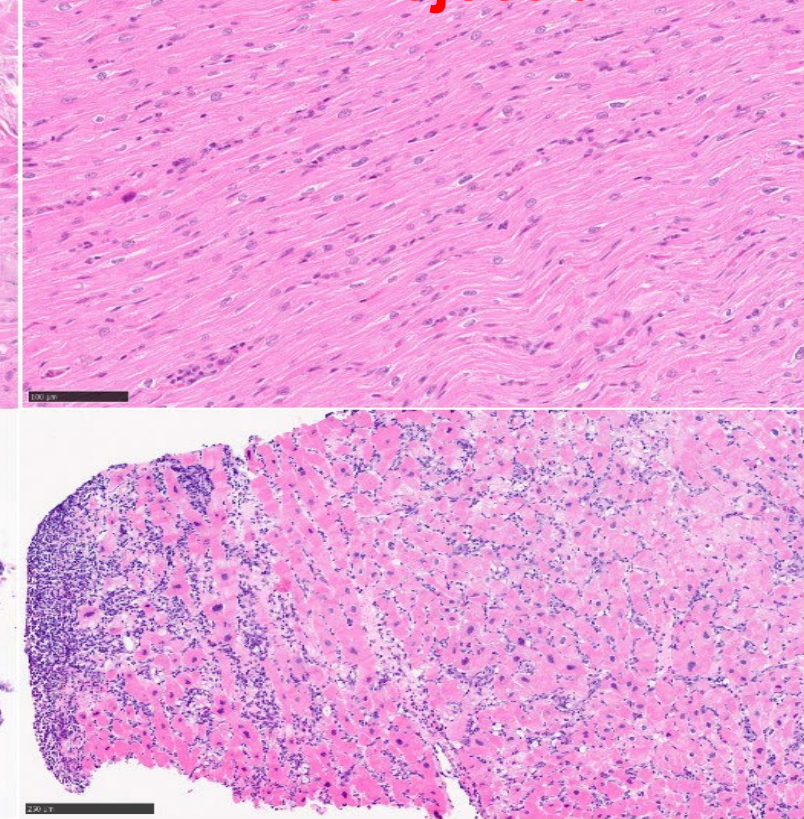
- Protocol Bx day 90-100
 - ACR0 in 15
 - ACR1 in 4
 - ACR2 in 3
- ACR incidence by EOS, by group:
 - TNX monoRx 5/17
 - TNX+MMF 2/4
 - TNX+Rapa 0/4

No rejection



ACR 1

No rejection



ACR 2

Results: Anti-donor Ab; Complications

- Anti-donor antibody
 - Unusual before EOS with TNX monoRx except with graft rejection
 - 2/4 with TNX+MMF Rx; 0/4 with TNX+Rapa
- Complications
 - Anemia in 1/25 (TNX+Rapa); resolved with supportive care
 - No thromboembolic complications

Conclusion

- **TNX monotherapy is effective and well tolerated**
 - 12/17 ACR0 by EOS
 - 14/17 graft survival to EOS
- **TNX+MMF and TNX+Rapa prevent graft loss by EOS**
 - Rapa co-Rx: 0/4 ACR; 0/4 alloAb
 - MMF co-Rx: 2/4 ACR; 2/4 alloAb

Reproducibility, Mechanism, and Significance under study

Thank you

