UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): June 6, 2024

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On June 6, 2024, the Company announced two oral presentations (each, a "Presentation") and a poster presentation (the "Poster") at the American Transplant Congress 2024, held June 1-5, 2024 ("ATC"). A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. Copies of the Presentations and Poster are furnished hereto as Exhibits 99.02, 99.03 and 99.04, and incorporated herein by reference

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.01 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On June 6, 2024, the Company announced data from the Presentations and Poster at the ATC. In the Presentation entitled, "Combined Blockade of the CD154 and CD28 Co-Stimulation Pathways Attenuates Pathogenic Alloimmunity and Prolongs Survival in Cynomolgus Cardiac Allografts", data demonstrated that the combined use of the Company's TNX-1500 product candidate for the prevention of allograft and xenograft rejection, for the prevention of graft-versus-host disease after hematopoietic stem cell transplantation and for the treatment of autoimmune diseases, and anti-CD28 monoclonal antibody, VEL-101, is associated with durable protection and graft survival and function in a nonhuman primate model.

In the Presentation entitled, "Extended Survival of 9- and 10-Gene-Edited Pig Heart Xenografts with Ischemia Minimization and CD154 Costimulation Blockade-Based Immunosuppression", data demonstrated that TNX-1500 has potential to prevent rejection of 9-, or 10-genetically-edited pig hearts.

The Poster titled, "Experience with a Novel Delayed Immune Tolerance Protocol in Nonhuman Primates Based on Anti-CD154, Anti-CD2, and Anti-CD28", evaluated whether a modified protocol based on targeting CD28 and CD2 promotes expansion of peripheral regulatory T-cells and is sufficient to promote heart allograft acceptance.

Forward- Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description.
99.01	Press Release of the Company, June 6, 2024
99.02	Combined Blockade of the CD154 and CD28 Co-Stimulation Pathways Attenuates Pathogenic Alloimmunity and Prolongs Survival in
99.03	Cynomolgus Cardiac Allografts
99.04	Extended Survival of 9- and 10-Gene-Edited Pig Heart Xenografts with Ischemia Minimization and CD154 Costimulation Blockade-Based
104	Immunosuppression
	Experience with a Novel Delayed Immune Tolerance Protocol in Nonhuman Primates Based on Anti-CD154, Anti-CD2, and Anti-CD28
	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: June 6, 2024

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

Exhibit 99.01

Tonix Pharmaceuticals Announces Two Oral Presentations and One Poster Presentation Involving TNX-1500 (Fc-modified humanized anti-CD40L mAb) at the American Transplant Congress 2024

TNX-1500 displays potential as a monotherapy or combination therapy to prevent rejection in organ transplantation in allograft and xenograft animal models

Research Directed by Faculty of the Center for Transplantation Sciences, Massachusetts General Hospital

Transplantation is also believed to be a model for treating autoimmunity

CHATHAM, N.J., June 6, 2024 – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a fully-integrated biopharmaceutical company with marketed products and a pipeline of development candidates, announces two oral presentations and a poster presentation at the American Transplant Congress 2024, held June 1-5, 2024 at the Pennsylvania Convention Center, Philadelphia, Pa. A copy of the oral and poster presentation is available under the Scientific Presentations tab of the Tonix website at www.tonixpharma.com.

"We remain encouraged by the potential of our TNX-1500, Fc-modified humanized anti-CD40L monoclonal antibody therapy for the prevention of rejection in solid organ transplantation," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "Despite advancements in the field of solid organ transplantation, there remains a significant need for new treatments with improved activity and tolerability. Several lines of research indicate that anti-CD40L therapy may improve outcomes for allograft acceptance, and that anti-CD40L therapy may be required for long term xenograft acceptance. We are excited about the broad potential of TNX-1500, on the prevention of allograft and xenograft rejection and also for the treatment of autoimmune diseases like systemic lupus erythematosus and Sjögren's Syndrome."

In the oral presentation titled, "*Combined Blockade of the CD154 and CD28 Co-Stimulation Pathways Attenuates Pathogenic Alloimmunity and Prolongs Survival in Cynomolgus Cardiac Allografts*", by Kinoshita, K. *et al*., data demonstrated that the combined use of TNX-1500 and anti-CD28 monoclonal antibody, VEL-101 is associated with durable protection and graft survival and function in a nonhuman primate model.

In the oral presentation titled, "*Extended Survival of 9- and 10-Gene-Edited Pig Heart Xenografts with Ischemia Minimization and CD154 Costimulation Blockade-Based Immunosuppression*", Sanatkar, A. *et al*., data demonstrated that TNX-1500 has promise to prevent rejection of 9-, or 10-genetically-edited (GE) pig hearts.[1,2]

The poster presentation titled, "*Experience with a Novel Delayed Immune Tolerance Protocol in Nonhuman Primates Based on Anti-CD154, Anti-CD2, and Anti-CD28*", by Ileka, I. evaluated whether a modified protocol based on targeting CD28 and CD2 promotes expansion of peripheral regulatory T-cells and is sufficient to promote heart allograft acceptance.

In February 2024, Tonix announced completion of the clinical stage of its Phase 1 single ascending dose study of TNX-1500 in healthy volunteers. The primary objectives of the study are to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous TNX-1500. This first-in-human study is intended to support dosing in a planned Phase 2 trial in kidney transplant recipients.

About TNX-1500

TNX-1500 (Fc-modified humanized anti-CD40L mAb) is a humanized monoclonal antibody that binds and blocks the CD40-ligand (CD40L), also known as CD154. TNX-1500 is being developed for the prevention of allograft and xenograft rejection, for the prevention of graft-versus-host disease (GvHD) after hematopoietic stem cell transplantation (HCT) and for the treatment of autoimmune diseases. A first-in-human Phase 1 trial of TNX-1500 has completed the clinical phase. The primary objective of the Phase 1 trial is to assess the safety, tolerability, PK, and pharmacodynamics of intravenous (*i.v.*) TNX-1500. Eligible participants enrolled in the Phase 1 trial were distributed across three dosing cohorts (3 mg/kg, 10 mg/kg, and 30 mg/kg, respectively) and evaluated regularly over a 120-day period after dosing. The Phase 1 trial is intended to support dosing in a planned Phase 2 trial in kidney transplant recipients. Two published articles in the *American Journal of Transplantation* demonstrate TNX-1500 prevents rejection, prolongs survival and preserves graft function as a single agent or in combination with other drugs in non-human primate renal and heart allografts.[3,4]

1. Revivicor 9-GE pigs: GalKO.β4GalNT2KO.GHRKO.hCD46.hCD55.hTBM.hEPCR.hCD47.hHO-1
2. Revivicor 10-GE pigs: GalKO.β4GalNT2KO.CMAHKO.GHRKO.hCD46.CD55.hTBM.hEPCR.hCD47.hHO-1.
3. Lassiter G., et al. *Am J Transplantation*. 2023. https://doi.org/10.1016/j.ajt.2023.03.022
4. Miura S., et al. *Am J Transplantation*. 2023. https://doi.org/10.1016/j.ajt.2023.03.025

Tonix Pharmaceuticals Holding Corp.*

Tonix is a fully-integrated biopharmaceutical company focused on developing, licensing and commercializing therapeutics to treat and prevent human disease and alleviate suffering. Tonix's development portfolio is focused on central nervous system (CNS) disorders. Tonix's priority is to submit a New Drug Application (NDA) to the FDA in the second half of 2024 for Tonmya[1], a product candidate for which two statistically significant Phase 3 studies have been completed for the management of fibromyalgia. TNX-102 SL is also being developed to treat acute stress reaction as well as fibromyalgia-type Long COVID. Tonix's CNS portfolio includes TNX-1300 (cocaine esterase), a biologic designed to treat cocaine intoxication that has Breakthrough Therapy designation. Tonix's immunology development portfolio consists of biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. Tonix also has product candidates in development in the areas of rare disease and infectious disease. Tonix Medicines, our commercial subsidiary, markets Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg for the treatment of acute migraine with or without aura in adults.

*Tonix's product development candidates are investigational new drugs or biologics and have not been approved for any indication.

[1]Tonmya™ is conditionally accepted by the U.S. Food and Drug Administration (FDA) as the tradename for TNX-102 SL for the management of fibromyalgia. Tonmya has not been approved for any indication.

This press release and further information about Tonix can be found at www.tonixpharma.com.

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate,” “expect,” and “intend,” among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (the “SEC”) on April 1, 2024, and periodic reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

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Exhibit 99.02

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Combined blockade of CD154 and CD28 co-stimulation pathways attenuates pathogenic alloimmunity and prolongs survival in cynomolgus cardiac allografts

K. Kinoshita[1], A. Maenaka[1], Z. A. Habibabady[1], M. Ma[1], V. L. Diaz[1], I. Ileka[1], T. Zhang[2], N. O'Neill[2], I. A. Rosales[3], S. Fogarty[4], P. Maguire[4], B. Daugherty[4], S. Lederman[4], U. Meier-Kriesche[5],N. Poirier[6], A. Azimzadeh[1], R. N. Pierson III[1]

[1]Department of Surgery, Center for Transplantation Sciences, Massachusetts General Hospital, Boston, MA, [2]Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, [3]Department of Pathology, MGH, Boston, MA, [4]Tonix Pharmaceuticals, Inc., Chatham, NJ, [5]Veloxis Pharmaceuticals, Cary, NC, [6]OSE Immunotherapeutics, Nantes, France

KK has no financial relationships with commercial interests to disclose. SF, BD, and SL are Tonix employees, PM is a Tonix consultant, UMK is Veloxs employee, and NP is OSE employee. This work was supported by Tonix through a Sponsored Research Agreement.

MASSACHUSETTS GENERAL HOSPITAL
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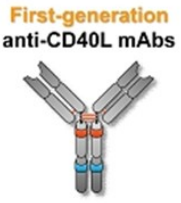
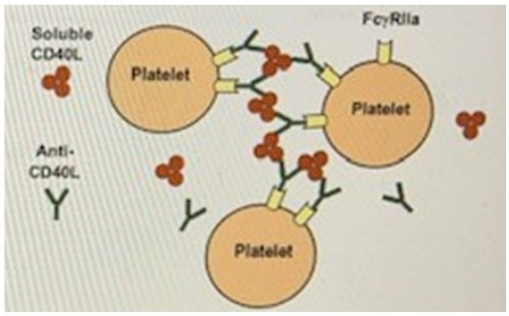
Background

- 1st generation anti-CD154 mAb
  prolonged graft survival in NHP Tx model (heart/Kidney/Islets/skin)
- Major thrombotic events in the clinical trial
  hu5c8 mAb forms immune complexes with soluble-CD154 via FcγRIIa
  crosslinked sCD154:hu5c8 via FcγRIIa activates platelets
  (Robles-Carrillo L et al 2010)



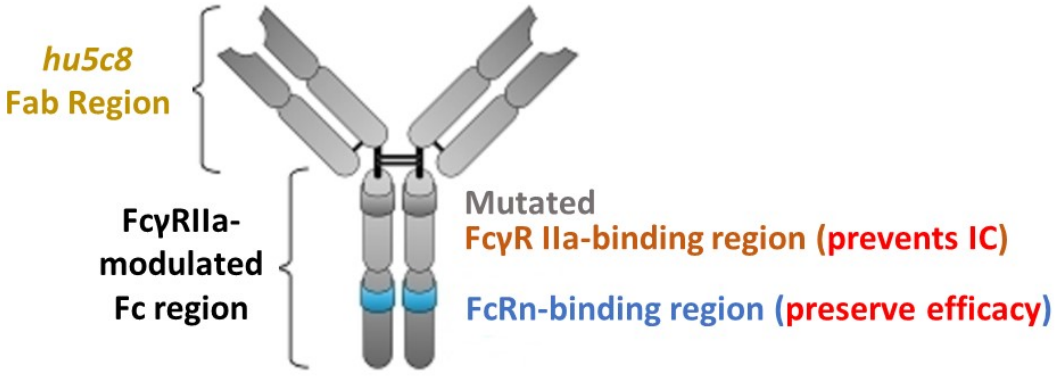
- 2nd generation aCD154 reduced efficacy
  Aglycosyl IgG1 aCD154 Ab (NHP allo islet)
  (Ferrant et al 2004)
  FcgR silenced aCD154 domain Ab (NHP allo kidney)
  (Kim et al 2016)



TNX-1500: αCD154 IgG4 with retained hu5c8 Fab

- 3rd generation: Fc-modified aCD154 mAb

TNX-1500 reduced binding to FcγRIIa and retained FcRn binding.
(prevents IC) (preserved efficacy)



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

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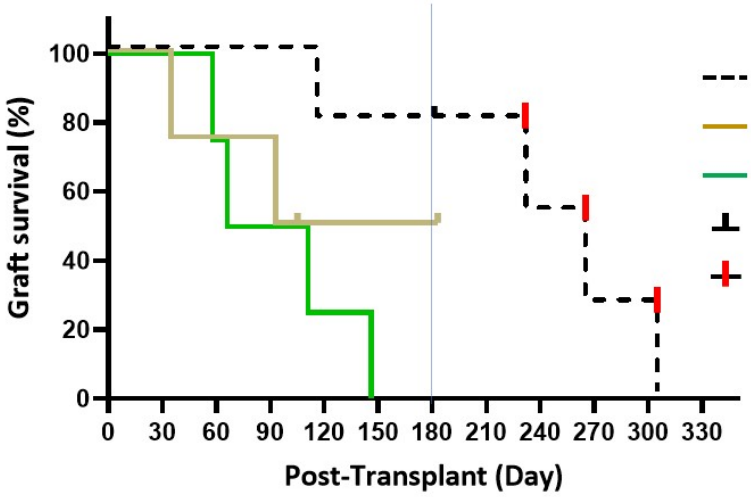
Costimulation Blockade: aCD154

NHP Heart Allograft Survival was significantly prolonged with standard dose TNX-1500 (stTNX) vs low-dose (loTNX)



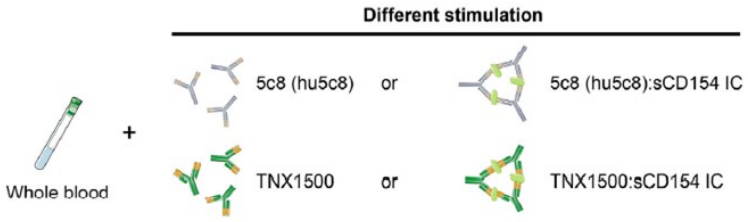
	Median survival (range)
stTNX	>265 (116-305)
loTNX	99 (35-183)
loTNX+MMF	88 (58-146)

⊥ Explant of beating graft

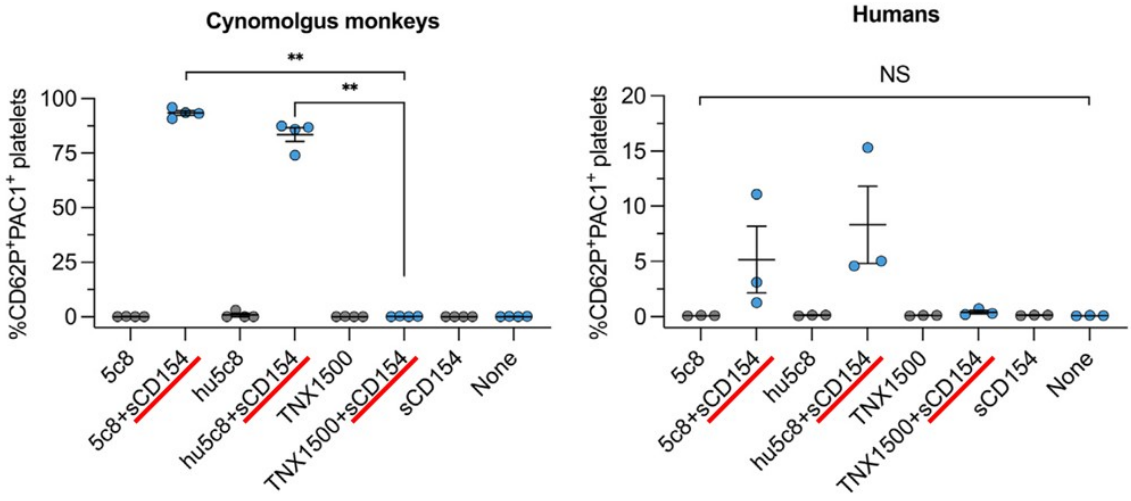
+ Rejection after cessation of stTNX treatment

P<0.05 for all comparisons against stTNX

Miura et al, AJT 2023



Platelet activation with hu5c8+soluble CD154 is not seen with TNX-1500



- **TNX-1500**

  Safe, Effective at 20 mg/kg weekly (Standard Dose)

  Equivalent to 5c8 at 20 mg/kg monthly (Low Dose)

  Miura et al, AJT 2023
  Heart Tx model in NHP study

- **VEL-101 (FR 104): anti-CD28 PEGylated monovalent Fab molecule**

  Safe, Effective at 5 or 10 mg/kg weekly

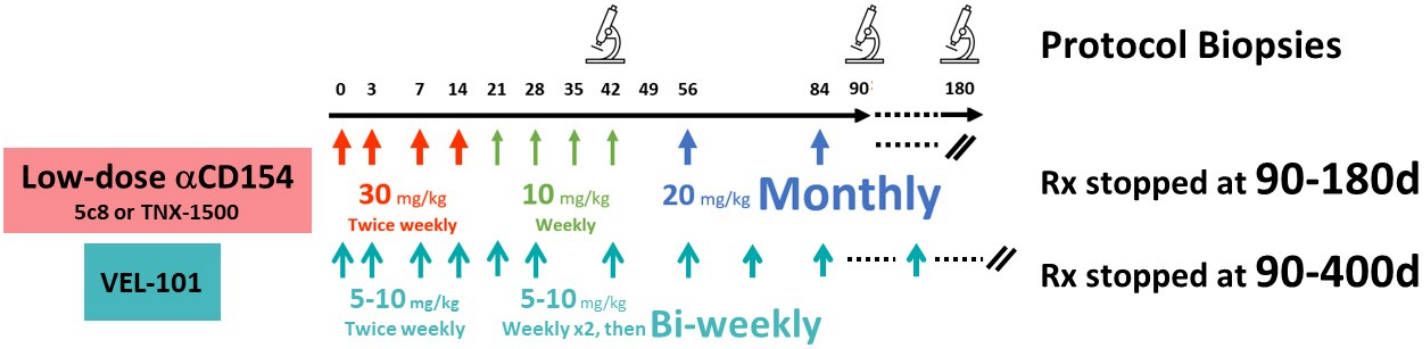
  Poirier et al, Sci Trans Med 2012
  Kidney Tx model in NHP study

- **Synergy between VEL-101 and TNX-1500 or 5c8 explored with TNX-1500/5c8 at 20 mg/kg monthly ('Low Dose')**

Methods – Cyno Hetero Heart AlloTx

Anti-CD154 monoRx 'Low Dose'
Anti-CD28 monoRx
Anti-CD154 + Anti-CD28

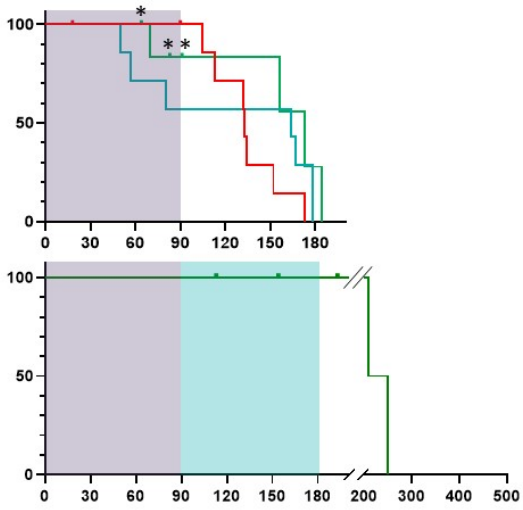
hu5c8 | TNX | VEL-101 | 5c8+VEL-101 | TNX+VEL-101



Results

Vel-101+5c8 prevented graft loss during Rx period

Vel-101 monoRx after dual Rx 'induction' prolonged graft survival



5c8 (n=9)
VEL-101 (n=7)
5c8+VEL-101 (n=7)
On treatment, stopped d90

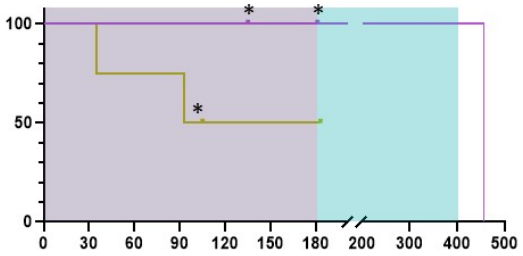
5c8+VEL-101 (extended) (n=5)
On dual treatment, 5c8 stopped d90
On VEL-101 monoRx

* Euthanized by protocol for unexplained weight loss

Vel-101+TNX prevented graft loss during Rx period

Vel-101 monoRx after dual Rx 'induction' prolonged graft survival

No alloantibody, generally low ISHLT ACR and CAV scores



loTNX (n=4)

loTNX+VEL-101 (n=3)

On treatment

On VEL-104 monoRx

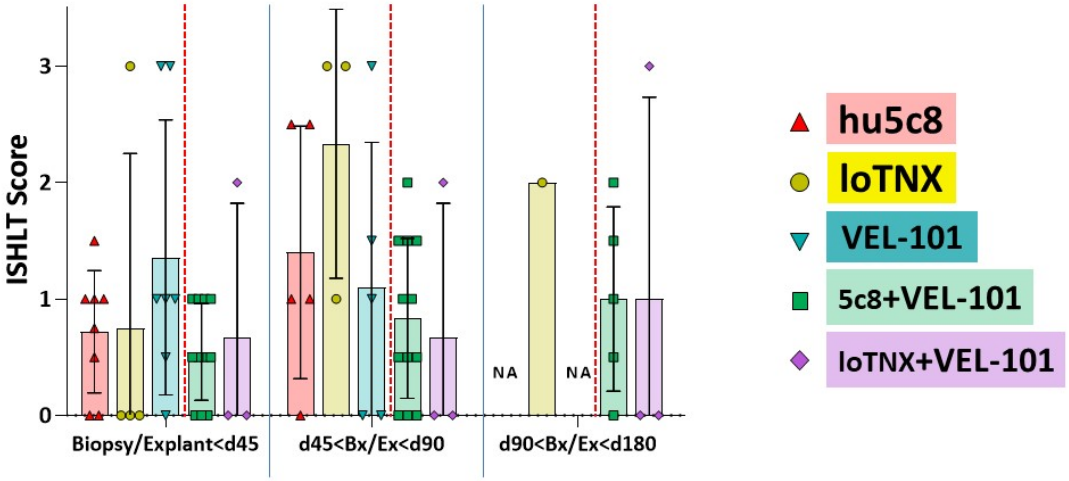
*Euthanasia with beating graft
(surgical complication, unexplained weight loss)

TNX-1500 or hu5c8 with VEL-101 inhibited alloantibody elaboration, class switching

	Anti-donor IgM	Anti-donor IgG
hu5c8	0/5	0/5
loTNX	1/4 (MHC I + II)	2/4 (MHC I + II)
VEL-101	2/7 (MHC I)	2/7 (MHC I + II)
5c8+VEL-101	0/5	0/5
loTNX+VEL-101	0/3	0/3

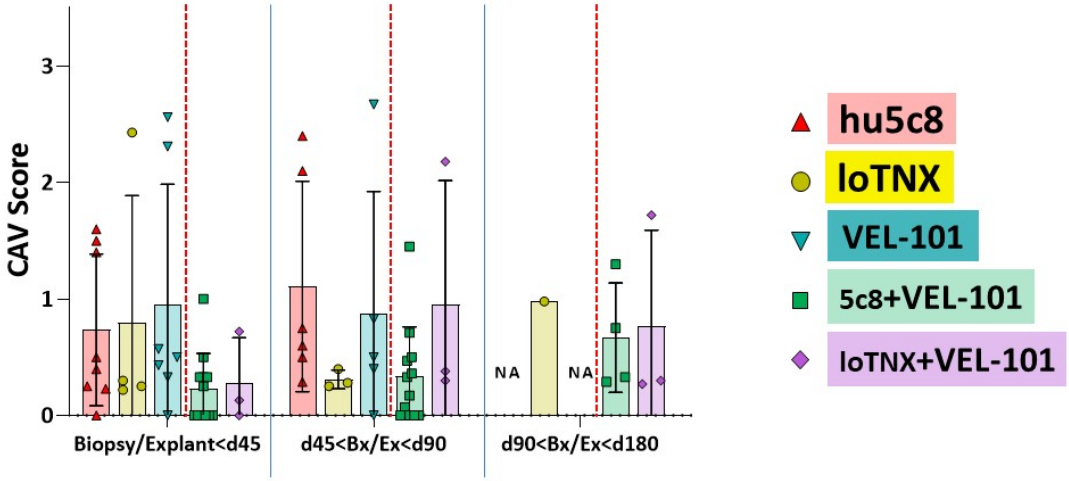
***NB: Assay in older h5c8 studies was less sensitive than in contemporary VEL/TNX studies**

VEL-101 with either 5c8 or loTNX reduced ISHLT ACR score



VEL-101 with 5c8 reduced CAV score

Further study of TNX+VEL-101 is warranted



Conclusions

- **TNX-1500 efficacy is similar to hu5c8 parent molecule <u>in NHP study</u>**
  - **No procoagulant phenotype**
  - **Well tolerated: no increase in viral infections or PTLD**
- **αCD154 with αCD28 has synergistic effects**
  - **durable protection from pathogenic allo-immunity**
  - **promising for clinical translation.**

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Thank you!

- Pierson and Cooper lab
  - Dr Richard N. Pierson III
  - Dr David K. Cooper
  - Shannon Pratts
  - Zahra Abady
  - Akihiro Maenaka
  - Madelyn Ma
  - Victoria Lynn Diaz
  - Ikechukwu Ileka
  - Maho Terashita
  - Gweneth Eliza Lavalla
  - Shuhei Miura
  - Franzi Pollok
  - Gannon McGrath
  - Ryan Chaban
- Kawai lab
  - Dr Tatsuo Kawai
  - Ryo Otsuka
  - Ahmad Karadagi
  - Toshihide Tomosugi
  - Andrea Yanulevich
  - Grace Lassiter
  - Ashley D'Attilio
- Madsen lab
  - Dr Joren C. Madsen
  - Jane M. O
  - Cynthia L. Miller
  - James T. Nawalaniec
  - Samantha M. Landino
- Markmann lab
  - Dr James F. Markmann
  - Rudy Matheson
  - Olivia Bourgeois
  - Katsuhiro Tomofuji
  - Daniel Cloonan
  - Taylor M. Coe
- Pathology team
  - Dr Robert B. Colvin
  - Ivy A. Rosales
- Knight surgery
  - Michael J. Duggan
  - Jessica Marie Burke
  - Anet T. Calisir
  - Nelson Marquez
  - Eli Smith
  - Erin B. Marx
  - Carolyn B. Wike
  - Nicholas M. Deluca
- CCM
  - Joanne Morris
  - Desiree N. Meuse
  - Diane Chen
  - Timothy Jones
  - Stephen M. McElroy
  - Lauren Marie Romero

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Exhibit 99.03

ATC2024

Extended Survival of 9- and 10-Gene Edited Pig Heart Xenografts with Ischemia Minimization and CD154 Costimulation Blockade –Based Immunosuppression

Amir Sanatkar MD.

[1]Center for Transplantation Sciences, Massachusetts General Hospital and Harvard Medical School, Boston, MA

June 4, 2024

Relevant Disclosures

- ***R. Chaban was supported by the Benjamin Research Fellowship from the German Research Foundation (DFG)***
- ***I. Ileka is supported by T32 5T32 AI007529-24***
- ***Gene edited pigs were provided by Revivicor and NSRRC (NIH grant U42OD011140)***
- ***Tonix Pharmaceuticals provided TNX-1500*, a humanized, Fc-modified, dimeric anti-CD154 mAb***
- ***This work was supported by NIH grants UO1 AI153612 (Pierson), U19 AI090959 (Cooper), and sponsored research agreements with Tonix Pharmaceuticals***

HARVARD MEDICAL SCHOOL

ATC2024 AMERICAN TRANSPLANT CONGRESS PHILADELPHIA, PA • JUNE 1-5

MASSACHUSETTS GENERAL HOSPITAL CENTER FOR TRANSPLANTATION SCIENCES

* TNX-1500 is an investigational new biologics and is not approved for any indication

Background

- Gene-edited (GE) pigs for Xenotransplantation.
  - **Removal of** CHO antigen targets of preformed Ab
    - TKO (Gal-1,3-αGal, Neu5Gc, β4Gal)
  - **Addition of** human regulatory molecules
    - Complement: CD46, CD55, CD59
    - Coagulation: TBM, EPCR, TFPI
  - **Addition of** human anti-inflammatory 'transgenes'
    - CD47, HLA-E/β2μg, HO-1, A20, CD39

HARVARD MEDICAL SCHOOL

ATC2024 AMERICAN TRANSPLANT CONGRESS PHILADELPHIA, PA • JUNE 1-5

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Methods

- Current study:
  - 3-, 9-, or 10-GE pig hearts
  - novel costimulation-based immunosuppressive (TONIX-1500)
  - cold-perfused storage technique designed to minimize graft ischemia.
- Eight **baboon** recipients received heterotopic heart transplants
- 3 Reference pig hearts (National Swine Resource & Research Ctr: NSRRC)
  - 3-GE pigs (n=3): GalKO.β4GALNT2KO.Hcd55
- 5 Multi-GE pig hearts (Revivicor)
  - 9-GE pigs (n=3): GalKO.β4GalNT2KO.GHRKO.hCD46.hCD55.hTBM.hEPCR.hCD47.hHO-1
  - 10-GE pigs (n=2): GalKO.β4GalNT2KO. CMAHKO.GHRKO.hCD46.CD55.hTBM.hEPCR.hCD47.hHO-1.

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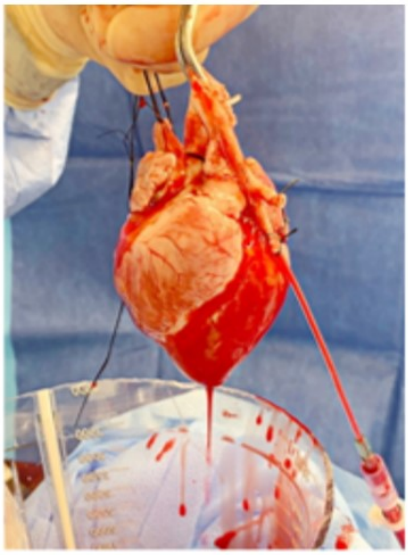
Preservation Methods: Steen Ischemia Minimization

- battery-powered portable perfusion circuit
- 4°C Steen Solution buffered extracellular solution (laboratory-made)
- Protocol 2-hr perfusion
- 240ml of washed human RBCs + 760 ml Steen solution
- Aortic perfusion at 4°C, 40-50 mmHg, immersed in reservoir; LV vent



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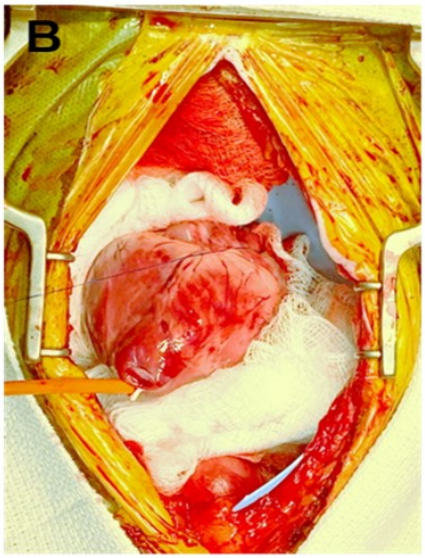
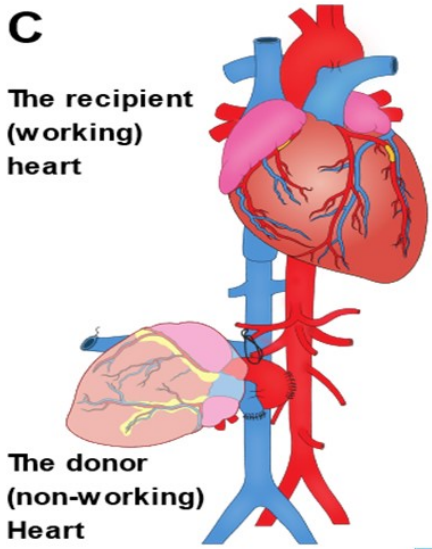
Methods: Heterotopic Heart Transplantation





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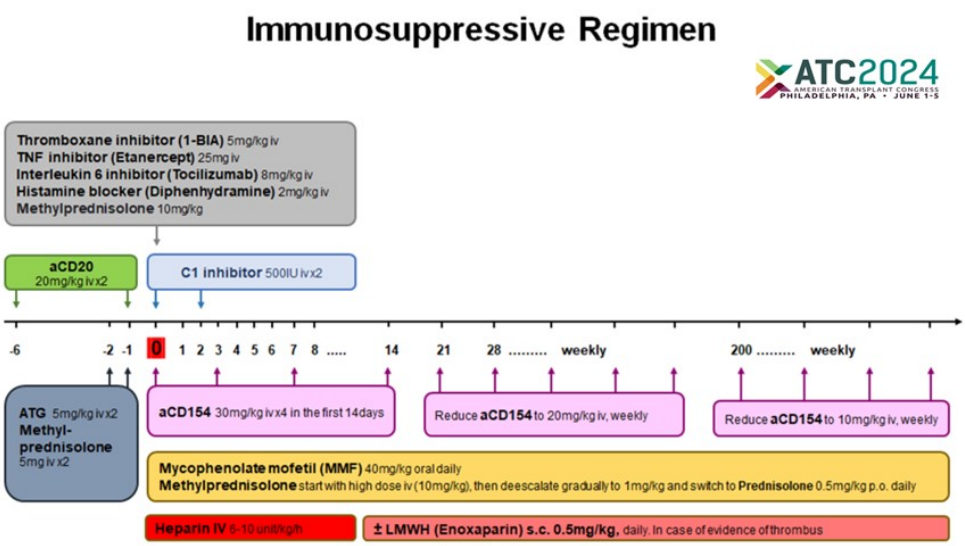
Methods: Recipient Immunosuppressive Treatment Regimen

- **Induction**:
  - ATG
  - αCD20
- **Day 0**:
  - TNF (inh)
  - IL-6 (inh)
  - Thromboxane inhibitor (BIA)
- **Maintenance Therapy**:
  - αCD154 (TNX-1500)
  - MMF
  - Corticosteroids
  - IL-6 (inh)



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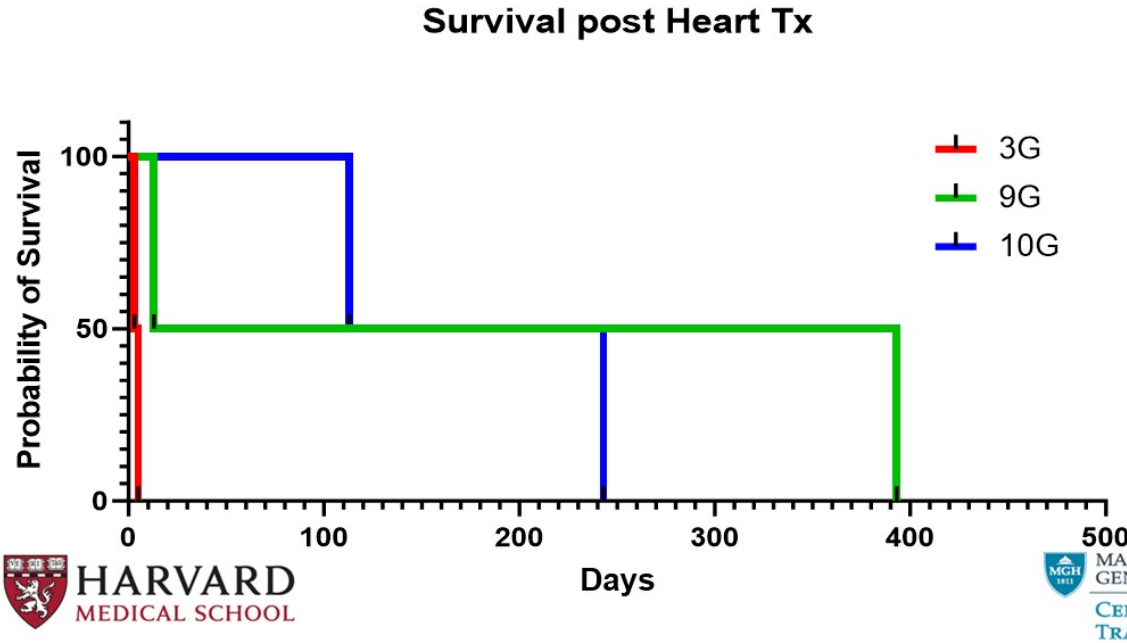
Results: Xenograft survival



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Results: Summary

Animal ID	GE	Anticoagulation	Major complication	Graft Survival (Days)	Final Biopsy
B3022	3G	Heparin IV	Graft rupture	3	Antibody mediated rejection
B2922	3G	Heparin IV	Graft rupture	5	Antibody mediated rejection
B8522	3G	Heparin IV	Refractory Ventricular fibrillation	0	No evidence of rejection
B7421	9G	No	Refractory Ventricular fibrillation	0	Antibody mediated rejection (Inadequate IRI protection)
B2721	9G	Heparin IV for 10 days	None	393	No evidence of rejection
B6921	9G	Heparin IV for 10 days	None	13	Antibody mediated rejection (High preformed IgM)
B7221	10G	Heparin IV for 8 days, then heparin sc for 2 weeks, ASA po daily	None	113	Antibody mediated rejection (Grade 3), Acute cellular rejection (3R)
B2622	10G	Heparin IV for 8 days, then heparin sc continue, ASA po daily	None	243	No evidence of rejection (FTT, Loss of abdominal domain?)

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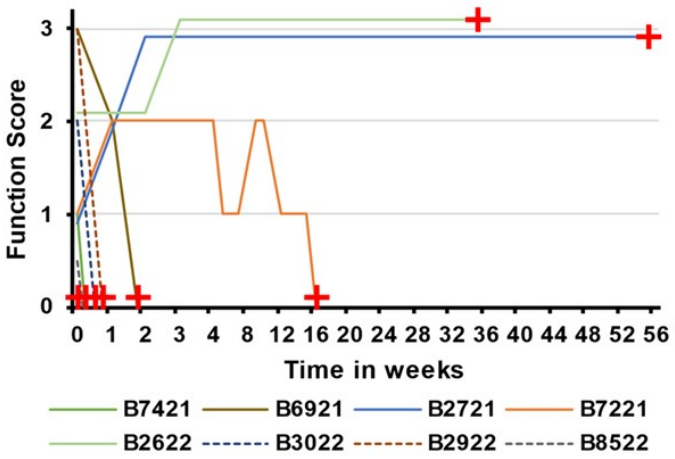
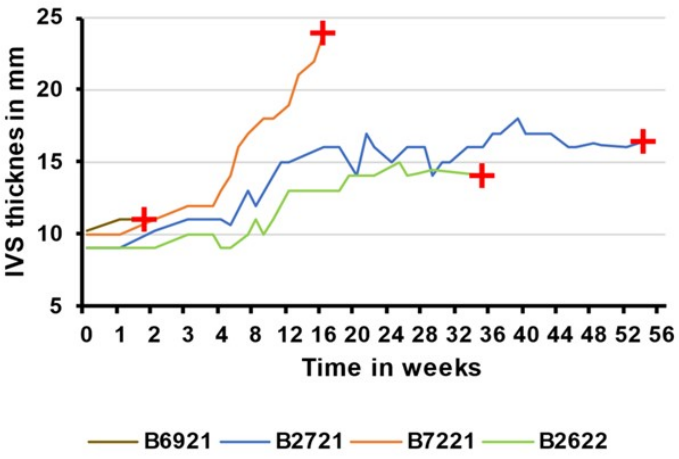
Results: Graft Survival, Function, and Morphology

A) Graft Contractility and Survival



B) Interventricular Septum (IVS)



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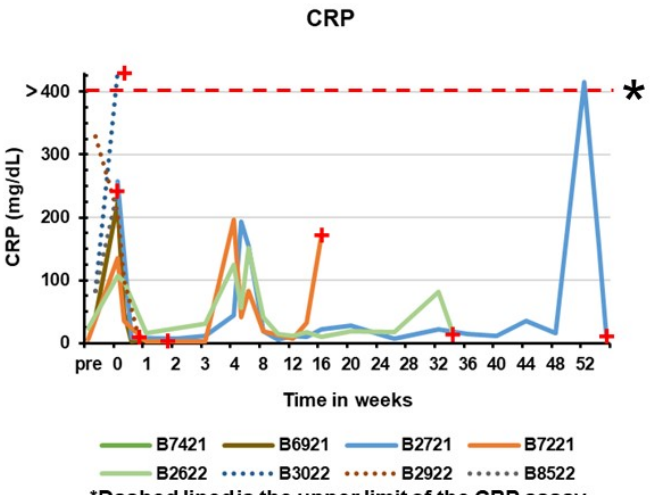
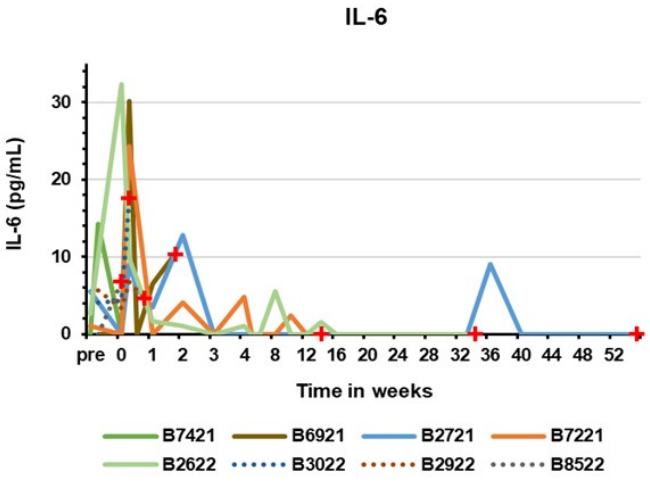
Results: CRP, IL-6



*Dashed lined is the upper limit of the CRP assay



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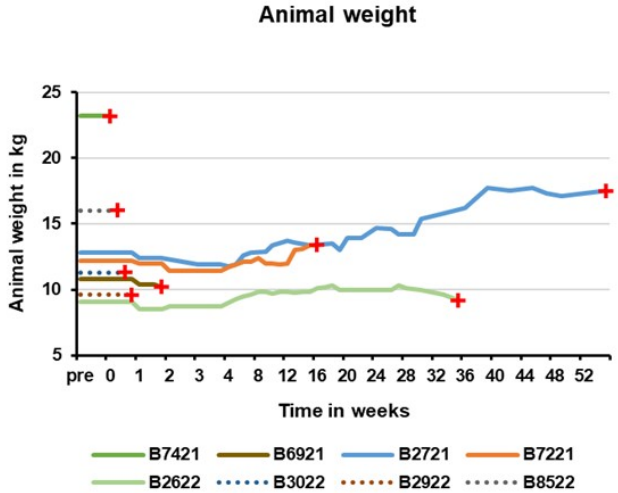
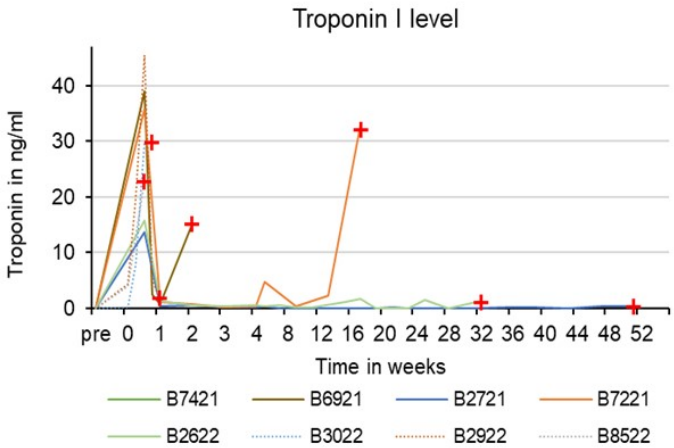
Results: Clinical condition, cardiac injury





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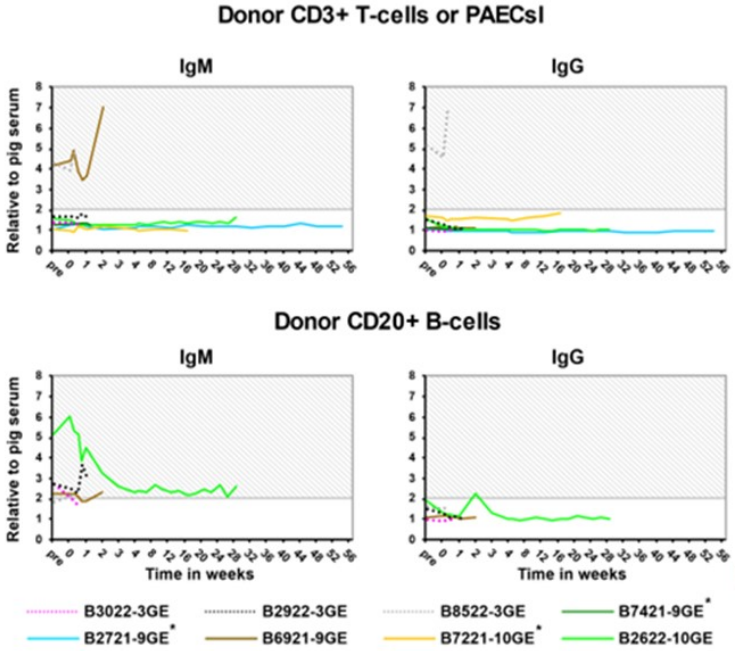
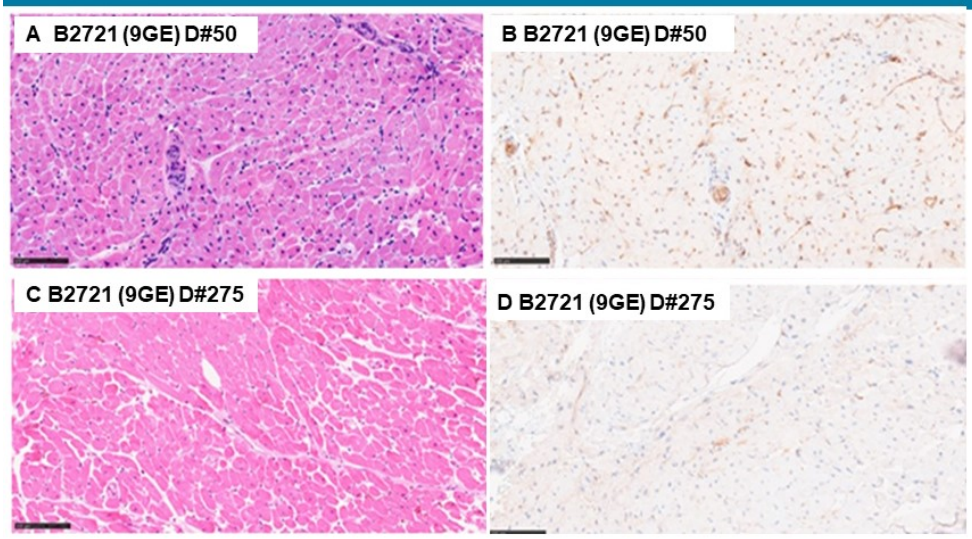
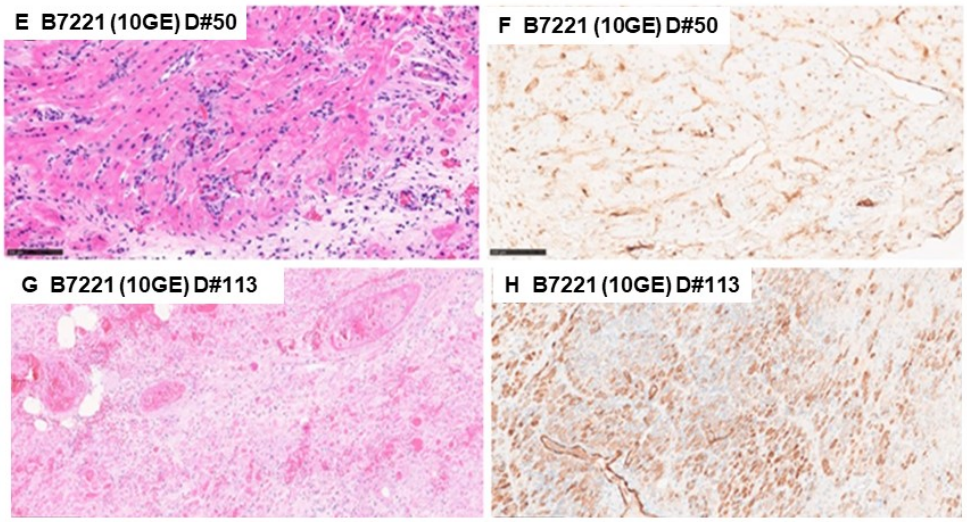
Anti-donor antibody levels:



Results: Histology



Results: Histology



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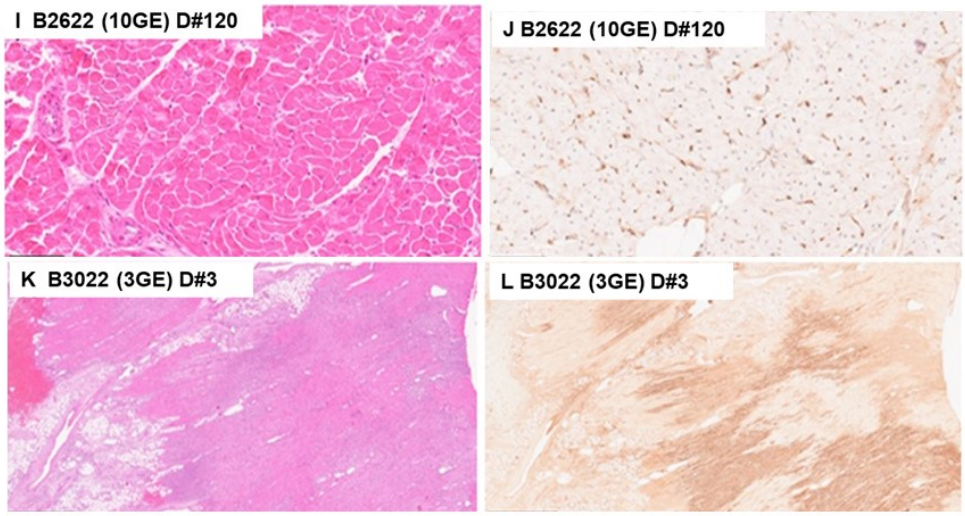
Results: Histology



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Conclusions

- 9- or 10-GE pig hearts exhibit promising performance.(Compared to reference basic genetics) in a clinically applicable regimen
- Peri-transplant myocardial injury and systemic inflammation occur consistently, However; recovery and survival can be achieved using Gene modifications and Ischemia minimization.
- Further evaluation in an orthotopic heart model.

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Acknowledgments

TONIX PHARMACEUTICALS

Revivicor A UNITED THERAPEUTICS COMPANY

NIH

NSRRC National Swine Resource & Research Center

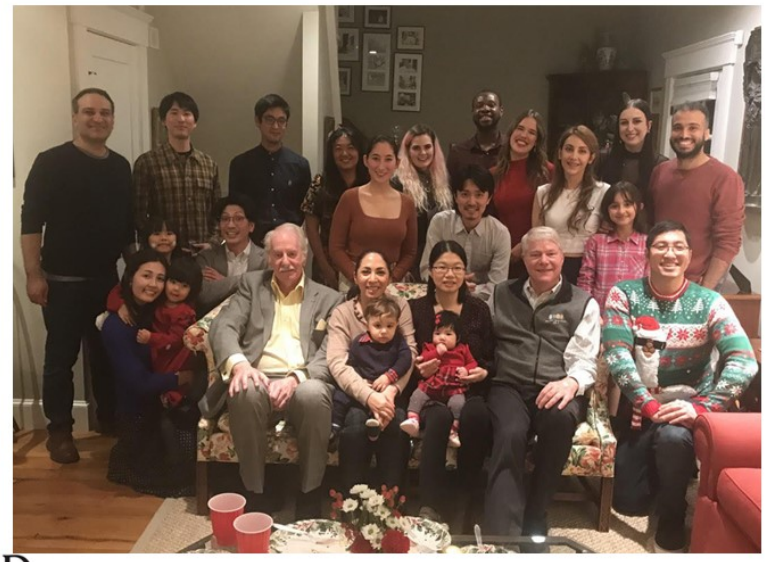

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Exhibit 99.04

Delayed Immune Tolerance for Cardiac Allografts in Nonhuman Primates by Targeting CD154, CD2, and CD28 Costimulation Pathways

Amir Sanatkar MD[1], I. Ileka MD[1], R. Chaban MD[1,2], K. Kinoshita MD[1], G. McGrath MD[1], Z. Habibabady MD[1], A. Maenaka PhD[1], M. Ma[1], V. Diaz[1], S. Lederman[3], J. Madsen MD, PhD[1,4], R.N. Pierson III MD[1,4]

1. Center for Transplantation Sciences, Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
2. Department of Cardiovascular Surgery, University Hospital of Mainz, Mainz, Germany
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Introduction

Long-term renal allograft acceptance has been achieved in macaques using a pioneering mixed-chimerism protocol, but similar regimens have proven unsuccessful in heart allograft recipients unless a renal graft was performed simultaneously. Here we test whether a modified protocol based on targeting CD28 and CD2 promotes expansion of peripheral regulatory T-cells and is sufficient to promote heart allograft acceptance.

Method

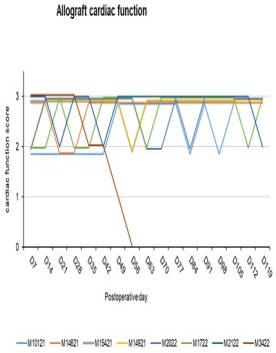
Donor bone marrow transplantation (BMT) was administered to recipients of MHC-mismatched heterotopic heart allografts after a 4-month delay period under TNX-1500 (anti-CD154). BMT induction was comprised of one (Group 1) or two (Group 2) doses of total body irradiation, thymic irradiation, and horse anti-thymocyte globulin (ATG) followed by two (Group 1) or five (Group 2) weekly doses of anti-CD2 and five weekly treatments with anti-CD28 and TNX-1500.

Results

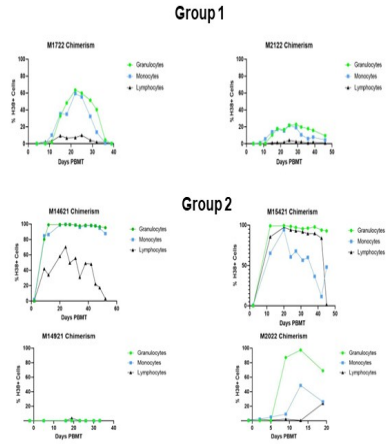
One Group 1 graft was rejected during the delay period; one in Group 1 and one in Group 2 with normal graft function exhibited moderate rejection on protocol biopsy prior to BMT, while five others exhibited normal histology. Lymphocyte chimerism >5% was observed in three of the five Group 2 animals but not in either Group 1 recipient. One Group 1 animal rejected 44 days after BMT while another succumbed to disseminated CMV infection. In Group 2, two monkeys succumbed to CMV disease or bacterial infection during the post-BMT treatment period. Two of three Group 2 animals developed >35% lymphocyte chimerism but succumbed to post-transplantation lymphoproliferative disease (PTLD) at 37, 41, and 51 days after BMT, with normal graft function and histology in all 3 at euthanasia.

Conclusion

The combination of anti-CD28 with multi-dose anti-CD2 often promotes lymphocyte chimerism in this delayed BMT model at levels that predict prolonged graft survival or long-term acceptance in kidney recipients. However, the high incidence of PTLD and opportunistic infection prevented assessment of the regimen's effectiveness in promoting alloimmune tolerance. Strategies to improve CMV control and PTLD prophylaxis merit investigation in this delayed heart allograft tolerance model



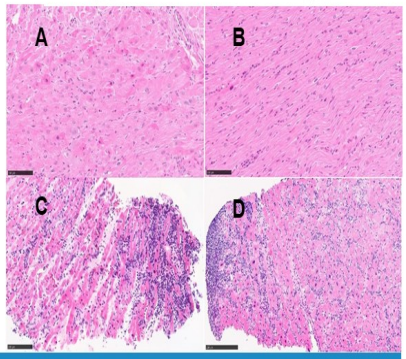
Graft survival was followed by ultrasound (USG) and palpation, and the contractility was subjectively classified as good [3], moderate [2], weak [1], or absent [0]



Heart biopsy histology:

A) In group 1 (M2122); there was no evidence of rejection. B) In group 2 (M10121, M14621, M14921, M2022); there was no evidence of rejection.

C) M1722 (group 1) had acute cellular rejection grade 1 along with antibody-mediated rejection. D) M15421 (group 2) exhibited acute cellular rejection grade 2.



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