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The History and Promise of α-CD154 Monoclonal Antibody Immunomodulation for Transplantation

61st Annual Congress of the Japan Society for Transplantation
October 9, 2025

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Form 1-B Conflict of Interest Requiring Disclosure

The 61th Annual Congress of the Japan Society for Transplantation COI Disclosure

Name of Presenter: Seth Lederman, MD

Conflict of interest requiring disclosure in relation to the presentation:

① Research was funded by Tonix Pharmaceuticals, Inc.
③ Dr. Lederman is CEO of Tonix

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Introduction

CD40L (also called CD154) was Identified in 1992
Mediates "T-Helper" Function

- **Identified as "5c8 Antigen"[1]**
- **Monoclonal antibody 5c8 blocks helper function**

Identification of a Novel Surface Protein on Activated CD4+ T Cells That Induces Contact-dependent B Cell Differentiation (Help)

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Summary

CD4+ T lymphocytes provide contact-dependent stimuli to B cells that are critical for the generation of specific antibody responses in a process termed T helper function. The surface structures on activated CD4+ T cells that mediate this function are not fully known. We previously reported the isolation of a functionally unique subclone of the Jurkat leukemic T cell line (D1.1) that constitutively expressed contact-dependent helper effector function. To identify T cell surface molecules that mediate contact-dependent T helper function, a monoclonal antibody (mAb), designated 5c8, was generated that inhibits D1.1-mediated B cell activation and immunoprecipitates a novel 30-kD protein structure from surface-iodinated D1.1 cells. Normal CD4+ T cells express 5c8 antigen (Ag) transiently after activation by phorbol myristate acetate and phytohemagglutinin with maximal expression 5–6 h after activation and absence of expression by 24 h. In contrast, neither resting nor activated CD8+ T cells express 5c8 Ag. In functional studies, mAb 5c8 inhibits the ability of fixed, activated CD4+ T cells to induce B cell surface CD23 expression. In addition, mAb 5c8 inhibits the ability of CD4+ T cells to direct terminal B cell differentiation driven by pokeweed mitogen. Taken together, these data suggest that 5c8 Ag is a novel, activation-induced surface T cell protein that is involved in mediating a contact-dependent element of the helper effector function of CD4+ T lymphocytes.

1091 J. Exp. Med. © The Rockefeller University Press • 0022-1007/92/04/1091/11 $2.00
Volume 175 April 1992 1091–1101

[1]Lederman & al. *J Exp Med.* 1992 175(4):1091-1101.

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CD40L is a Transiently Expressed 32 kD Surface Protein on a Subset of CD4+ T cells

- **Transiently expressed on the surface of a subset of activated CD4+ T cells[1]**
  - Mediates T cell help
  - CD40L+ cells are:
    - T-helper cells (T_h)
    - T-effector cells (T-eff)
- **32 kD protein**

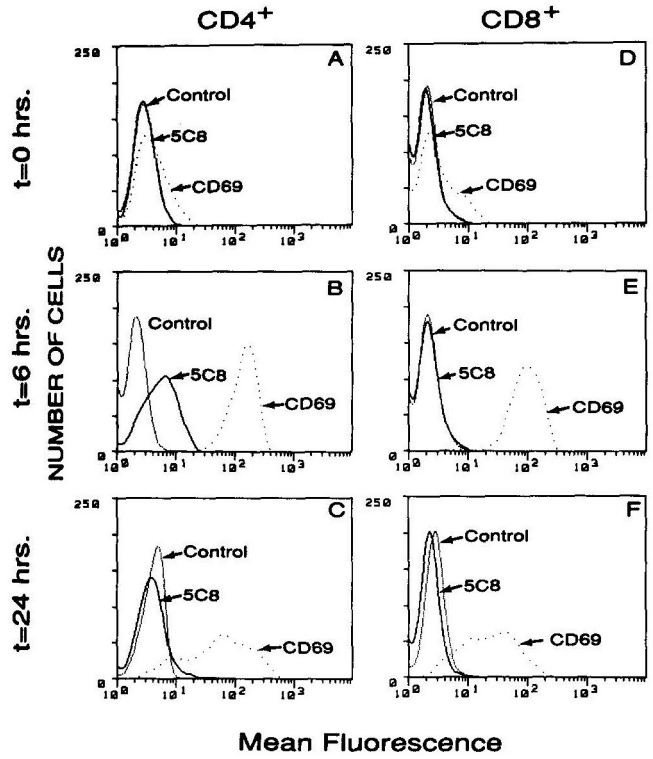
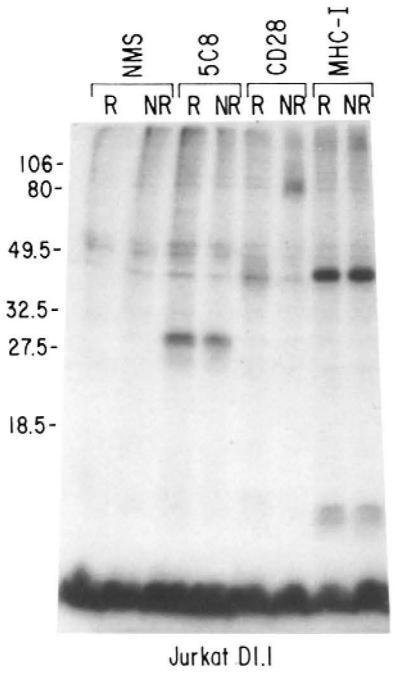


Figure 4. Kinetics of expression of 5c8 Ag on isolated CD4+ or CD8+ T cell subsets. Shown are fluorescence histograms of CD4+ cells or CD8+ cells at the indicated time points after freshly purified T cell subsets were activated with PHA (10 μg/ml) and PMA (10 ng/ml). *Solid line*, 5c8 binding; *dashed line*, IgG2a control; *dotted line*, anti-CD69.



[1]Lederman & al. *J Exp Med.* 1992 175(4):1091-1101.

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About CD40L

CD40L is a transiently expressed T cell surface molecule and is also called CD154[1-4]

- Predominantly expressed by T cells and interacts with CD40 on B cells and macrophages

Mediates T cell helper function[1-4]

- Activates B cells for humoral (antibody-mediated) immune response (isotype switching)
- Activates macrophages and dendritic cells
- Provides T cell help to activated CD8+ T cells

X-linked hyper-IgM syndrome is caused by a defective CD40L gene[5-6]

- Lack T helper function with only IgM serum antibodies but no IgG or IgE
- If maintained on gamma globulin, patients are otherwise healthy

Member of the TNFα superfamily[4]

- TNFα, RANKL, TL1a and CD30L are other family members that are drug targets
  - α-TNFα, and α-RANKL approved (*e.g.*, Humira® for RA and Prolia® for osteoporosis)

α-CD40L mAb prevent rejection of allo-transplants

- Humanized (Hu) 5c8 as monotherapy prevents rejection in non-human primates (NHPs)[7,8]
- Primatized (Pr) 5c8 controls antibody-mediated rejection in highly sensitized NHPs[9]

[1]Lederman S, et al. *J Exp Med*. 1992;175(4):1091-1101.
[2]Lederman S, et al. *J Immunol*. 1992;149(12):3817-3826.
[3]Lederman S, et al. *J Immunol*. 1994;152(5):2163-2171.
[4]Covey LR, et al. *Mol Immunol*. 1994;31(6):471-484
[5]Ramesh N, et al. *Int Immunol*. 1993;5(7):769-773.
[6]Callard RE, et al. *J Immunol*. 1994;153(7):3295-3306.
[7]Kirk AD, et al. *Nat Med*. 1999. (6):686-93.
[8]Pierson RN 3rd, et al. *Transplantation*. 1999 68(11):1800-5.
[9]Anwar IJ, et al. *Sci Transl Med*. 2025. 17(779):eadn8130.

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α-CD40L Treatment is CD4⁺ Foxp3⁺ Treg Sparing and α-CD40L-induced Tolerance is at Least Partially Treg-Dependent

CD4⁺ CD25⁺ Foxp3⁺ regulatory T cells (Treg) play roles in tolerance[1-3]

- Mary Brunkow, Fred Ramsdell and Shimon Sakaguchi were awarded the Nobel Prize in Physiology or Medicine 2025 for *peripheral immune tolerance*
- Tregs are generally unable to express CD40L

α-CD40L treatment induces, preserve and expand CD4⁺ CD25⁺ Foxp3⁺ Tregs[4-10]

- In transplantation models, α-CD40L is repeatedly linked to higher frequencies or preserved pools of CD4⁺Foxp3⁺ Tregs
- α-CD40L-induced experimental graft tolerance is Treg-dependent consistent with Tregs being spared and functionally competent
- α-CD40L treatment induced/preserves Tregs whereas CTLA4-Ig treatment decreases Tregs[7]
- α-CD40L treatment induces/preserves Tregs to a greater extent than α-CD11b[10]
- α-CD40L synergizes with CAR-Tregs to enforce infectious tolerance in a heart-allograft model[11]

[1] Brunkow ME, et al. *Nat Genet.* 2001 27(1):68-73.
[2] Ramsdell F. *Immunity.* 2003 19(2):165-8
[3] Sakaguchi S. *J Clin Invest.* 2003 112(9):1310-2.
[4] Pinelli DF, Ford ML. *Immunotherapy.* 2015;7(4):399-410.
[5] Muckenhuber M, et al. *Front Immunol.* 2022 13:969633.
[6] Haribhai D, et al. *Am J Transplant.* 2011; 11(9):1815–1824.
[7] Kim et al., *Am J Transplant* 2017. 17(5):1182-1192
[8] Pinelli et al., *Am. J. Transplant.* 2013. 13(11):3021-30
[9] Ferrer et al., *PNAS* 2011. 108(51):20701-6.
[10] Liu et al., *Am J Transplant.* 2024. 24(8):1369-1381.
[11] Durgam SS, et al. *JCI Insight.* 2025. 8;10(7):e188624.

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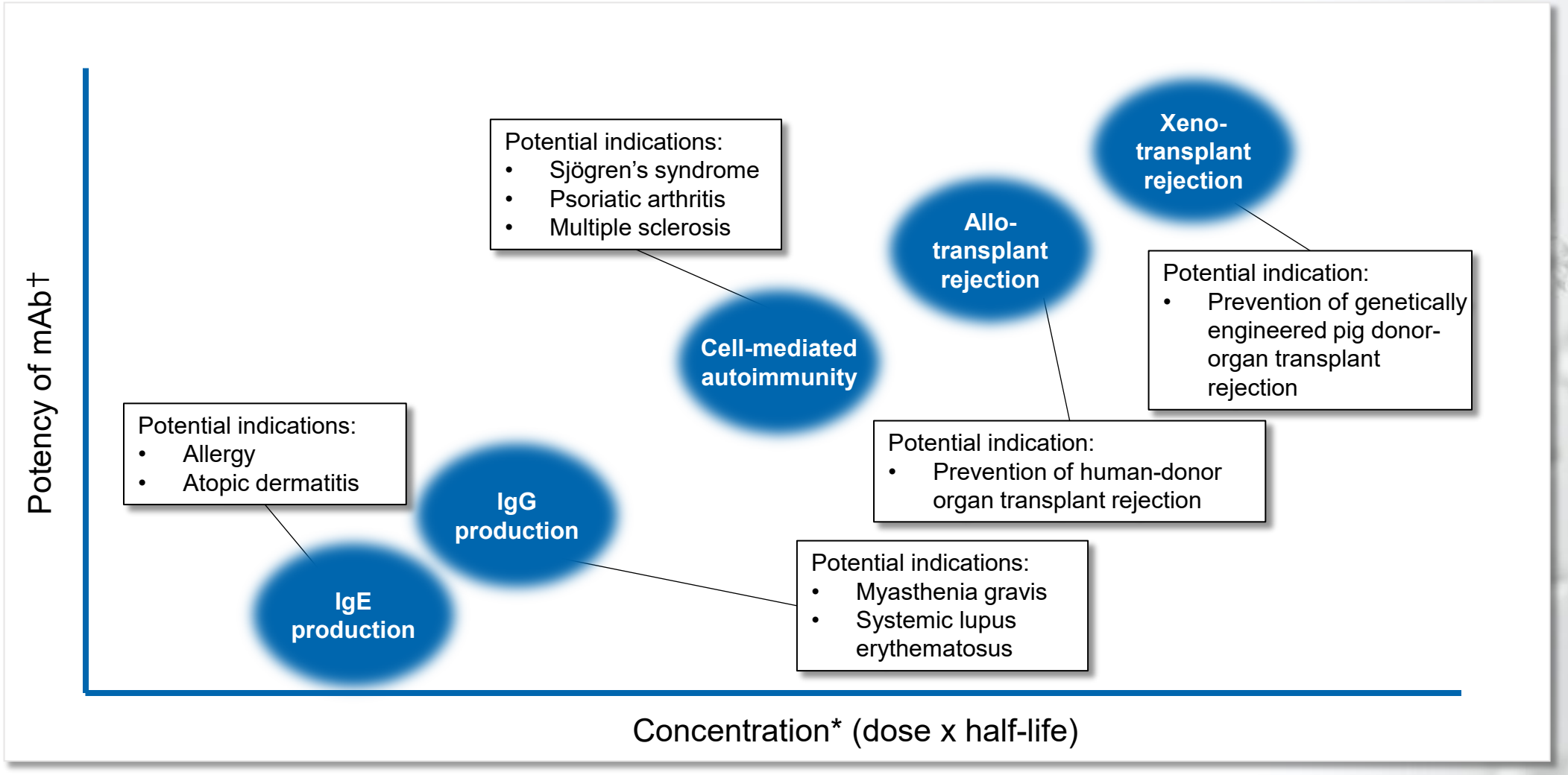
α-CD40L Effects on Humoral and Cellular Immunity in Animal Models Are Dependent on Potency and Concentration



*Concentration is dependent on dose and half-life.

†Potency depends on binding affinity and other factors, eg, neutralization of CD40L trimers.

IgE=immunoglobulin E; IgG=immunoglobulin G; mAb=monoclonal antibody.

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Structural Model of CD40/CD40L

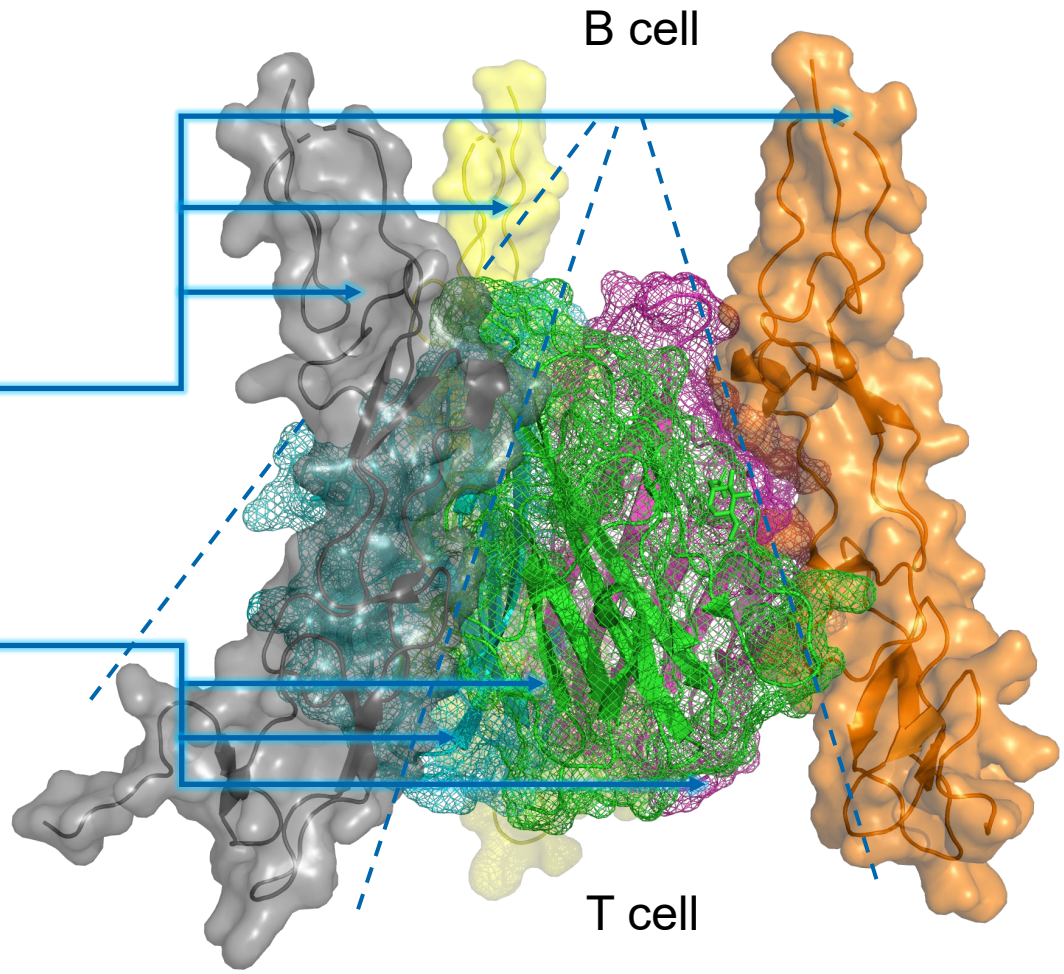
Model is based on
PDB ID: 3QD6

CD40

(gray, yellow, orange)

CD40L soluble trimer

(green, cyan, magenta)



PDB=Protein Data Bank.

An HJ. *J Biol Chem*. 2011;286(13):11226-11235.

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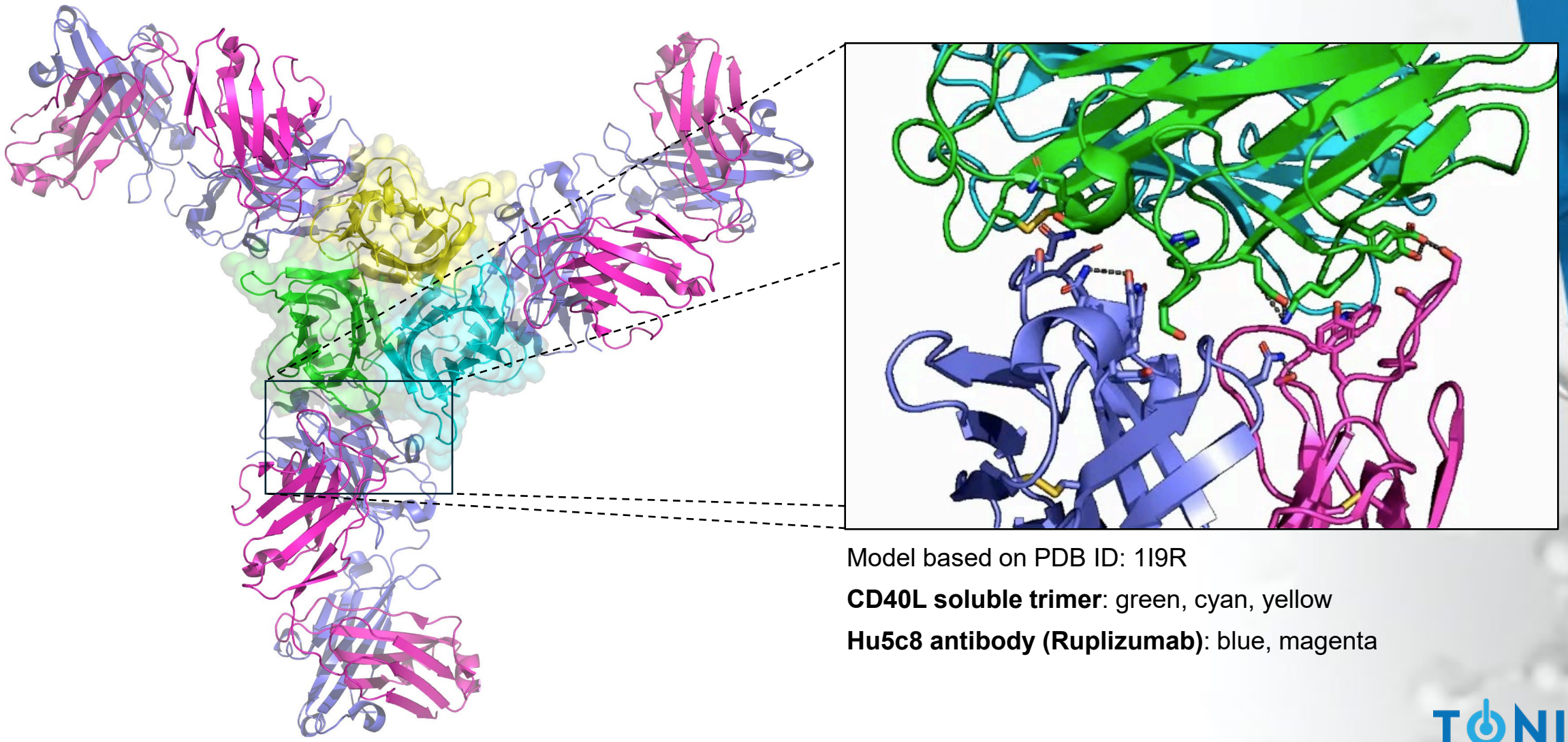
CD40L and Humanized 5c8/Ruplizumab Fab Complex



Model based on PDB ID: 1I9R

CD40L soluble trimer: green, cyan, yellow

Hu5c8 antibody (Ruplizumab): blue, magenta

PDB=Protein Data Bank.

Karpusas M, et al. *Structure.* 2001;9(4):321-329.

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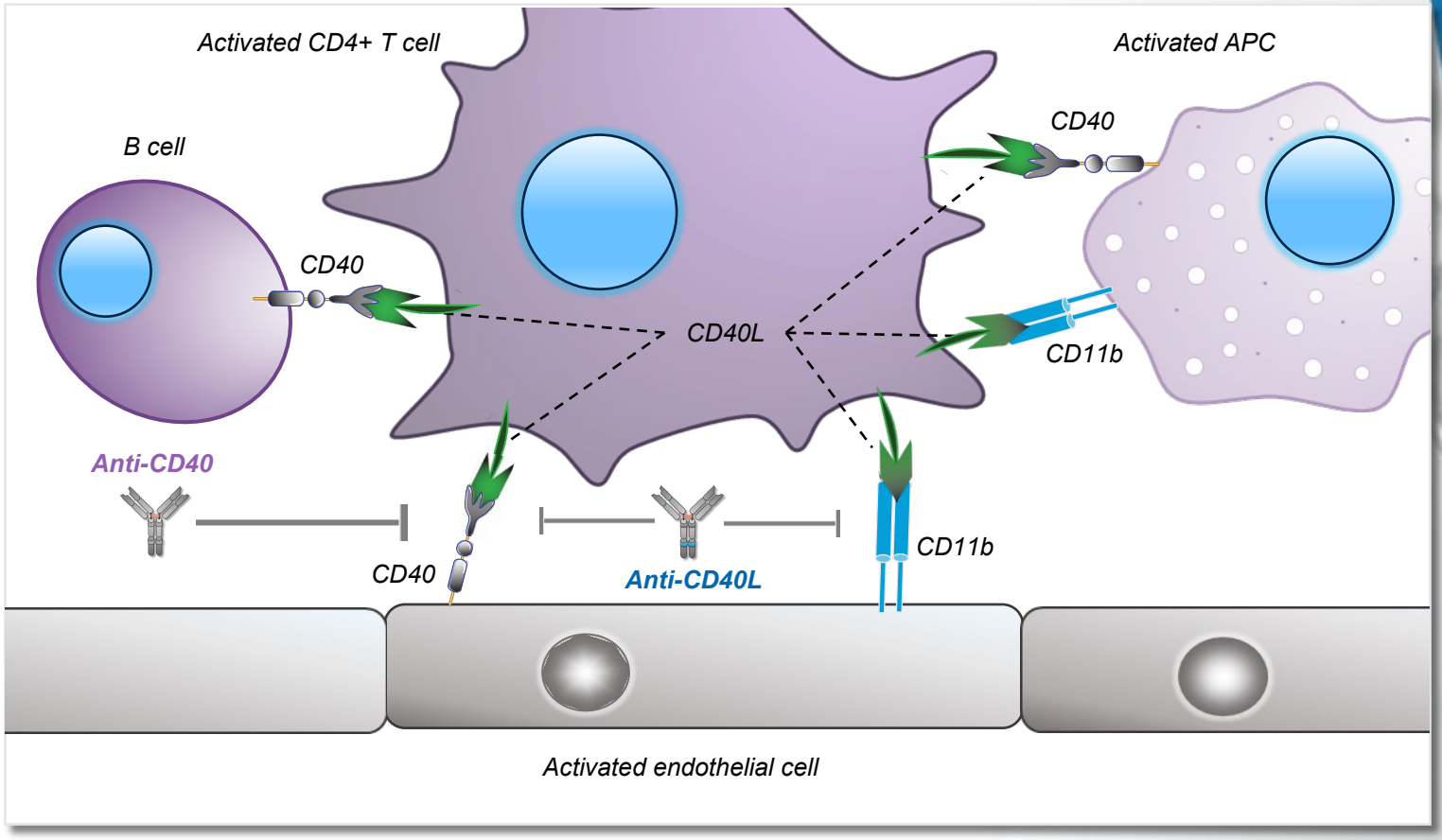
CD40L Binds to CD11b to Promote Graft-Specific T-Cell Activation

- **Blocking the interaction of CD40L and CD11b enhances efficacy of α-CD40 treatment in prolonging allograft survival**
  - **α-CD40 antibodies** block CD40/CD40L binding but do not affect CD11b/CD40L binding
- **α-CD40L antibodies offer the advantage of blocking interactions of CD40L with both CD40 and CD11b**



Liu D, et al. *Am J Transplant.* 2020;20(8):2216-2225.

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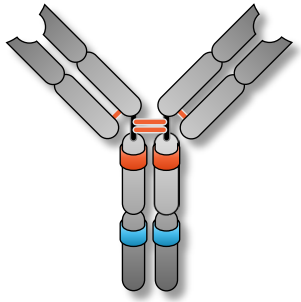
Engineering α-CD40L mAbs

3 Generations of α-CD40L Antibody (Ab) Development

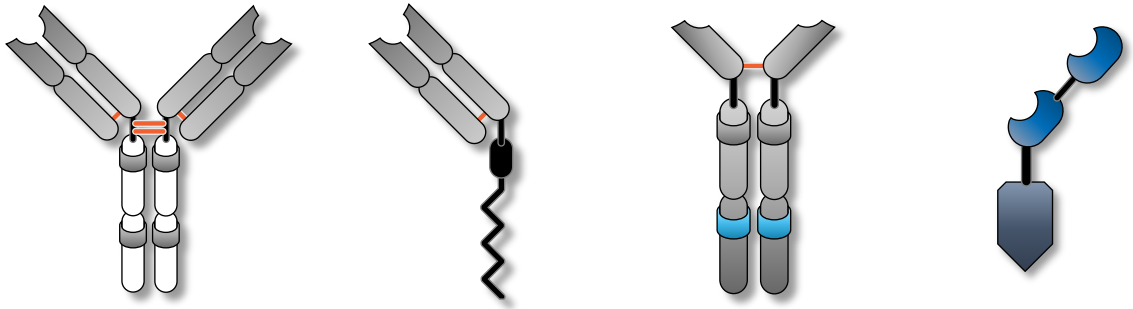
2nd and 3rd Generations Engineered to Decrease the Risk of Thrombosis

First-generation[1-2] anti-CD40L mAbs



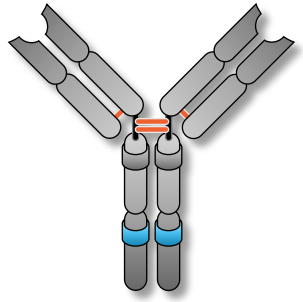
Ruplizumab "Humanized 5c8 IgG1"

Second-generation[3-12] anti-CD40L proteins



Aglycosyl Ruplizumab *Dapirolizumab* *Letolizumab* *Dazodalibep*

Third-generation[13] anti-CD40L mAbs



TNX-1500

[1]Pierson RN 3rd, et al. *Transplantation.* 1999 68(11):1800-5.
[2]Mirabet M, et al. *Mol Immunol.* 2008;45(4):937-944.
[3]Saxena A, et al. *Front Immunol.* 2016;7:580.
[4]Xie JH, et al. *J Immunol.* 2014;192(9):4083-4092.
[5]Ferrant JL, et al. *Int Immunol.* 2004;16(11):1583-1594.
[6]Daley SR, et al. *Am J Transplant.* 2008;8(11):2265-2271.
[7]Shock A, et al. *Arthritis Res Ther.* 2015;17(1):234.
[8]Tocoian A, et al. *Lupus.* 2015;24(10):1045-1056.
[9]Kim SC, et al. *Am J Transplant.* 2017;17(5):1182-1192. [10]Pinelli DF, et al. *Am J Transplant.* 2013;13(11):3021-3030.
[11]ClinicalTrials.gov identifier: NCT02273960. Updated July 16, 2019. Accessed August 20, 2025. https://clinicaltrials.gov/ct2/show/results/NCT02273960?view=results
[12]ClinicalTrials.gov identifier: NCT03605927. Updated June 5, 2025. Accessed August 20, 2025. https://clinicaltrials.gov/ct2/show/NCT03605927
[13]Data on File.

mAb=monoclonal antibody.

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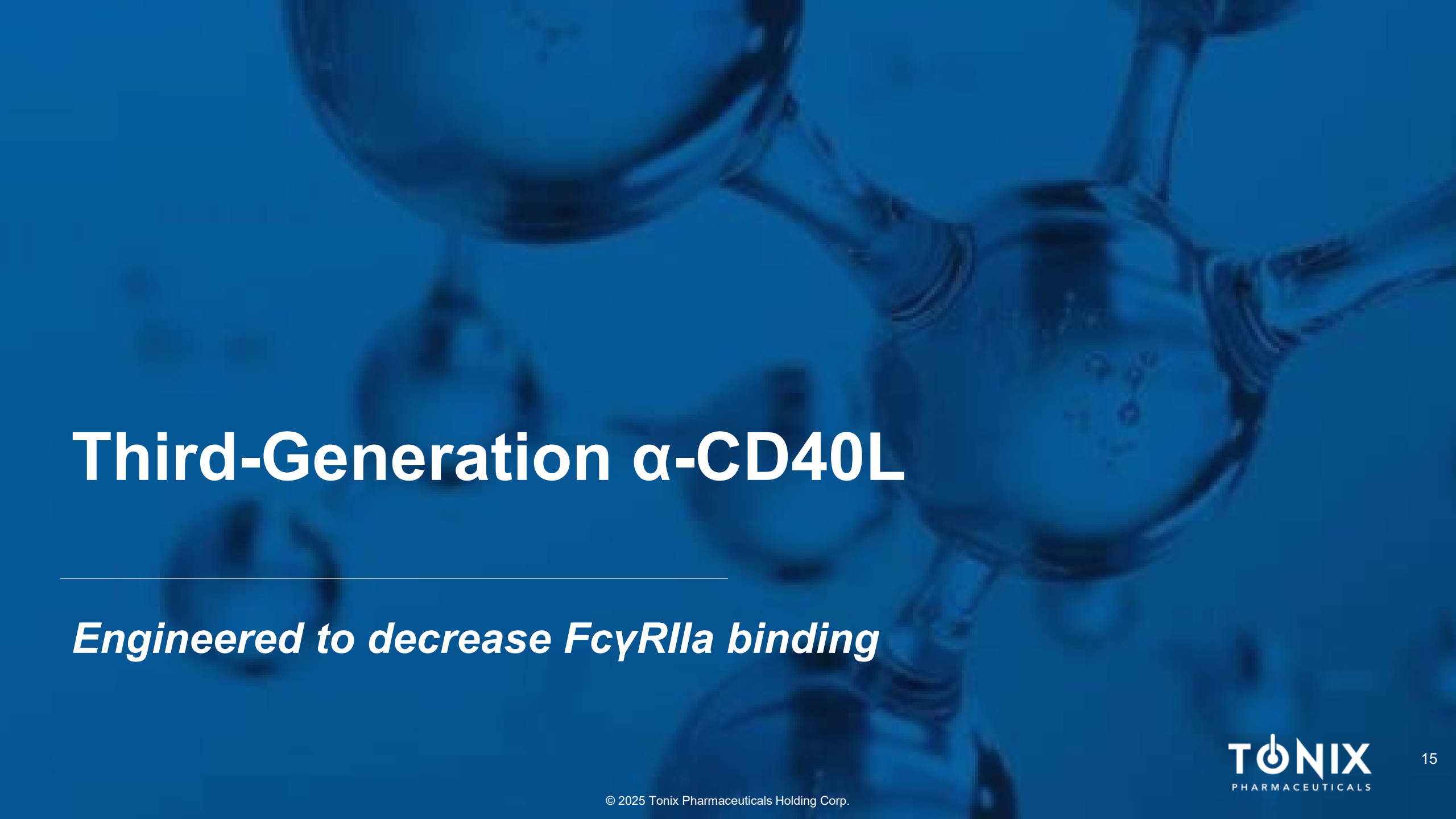

Third-Generation α-CD40L

Engineered to decrease FcγRIIa binding

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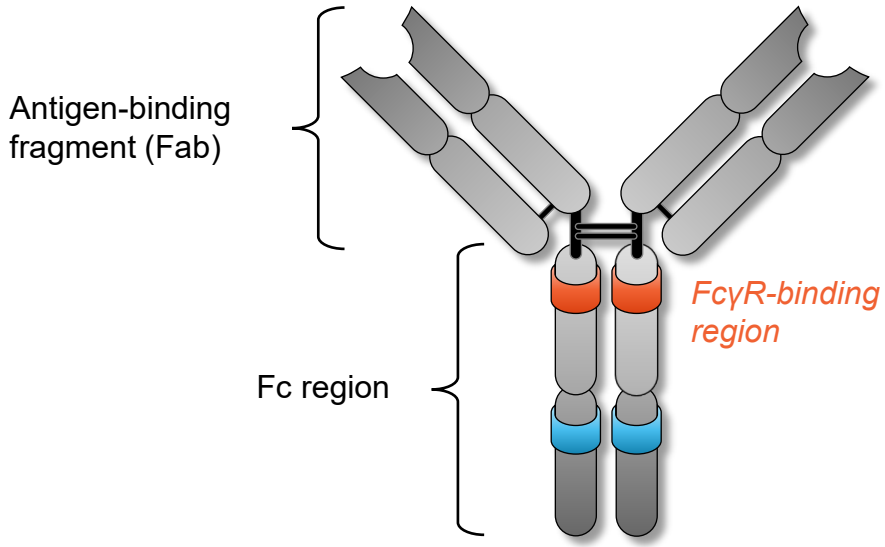
3rd Generation: Fc-modulated α-CD40L Abs

- Targeted amino acid substitutions to decrease FcR binding
- First-generation anti-CD40L Ab development was halted due to thromboembolic (TE) complications[1,2]
- TE complications were traced to interactions between the fragment crystallizable (Fc) gamma receptor (FcγR)-binding region and platelets[3]
- FcRγIIa was linked to the platelet activation effect[4]
- Some Fc function is required for the treatment effect[5]

First-Generation Anti-CD40L Abs[3]



Interaction of the FcγR-binding region with platelets leads to stabilization of platelet aggregates that can cause TE complications.[1,2]

[1]Koyama I, et al. *Transplantation.* 2004 77(3):460-2.
[2]Mirabet M, et al. *Mol Immunol.* 2008;45(4):937-944.
[3]Shock A, et al. *Arthritis Res Ther.* 2015;17(1):234.
[4]Robles-Carrillo L, et al. *J. Immunol.* 2010 185(3):1577–1583.
[5]Monk NJ, et al. *Nat Med.* 2003 9(10):1275-80.

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Generation of α-CD40L Variants to Decrease FcγRIIa (CD32A) Binding and Decrease Risk of Thrombosis

Variant	Fc	mAb	Hinge/CH2	CH3
TNX01	IgG1	N297Q	CDKTHTCPPCPAPELLGGP	QSTYR
TNX02	IgG1	WT – G1	CDKTHTCPPCPAPELLGGP	NSTYR
TNX03	IgG1	N297G	CDKTHTCPPCPAPELLGGP	GSTYR
TNX04	IgG1	C220S, C226S, C229S, P238S	SDKTHTSPPSPAPELLGGS	NSTYR
TNX05	IgG4	S228P, L235A	ESKYGPPCPPCPAPEFAGGP	NSTYR
TNX06	IgG4	WT – G4	ESKYGPPCPSCPAPEFLGGP	NSTYR
TNX07	IgG4	S228P	ESKYGPPCPPCPAPEFLGGP	NSTYR
TNX08	IgG4	S228P, L235E	ESKYGPPCPPCPAPEFEGGP	NSTYR
TNX09	IgG4	S228P, F234A, L235A	ESKYGPPCPPCPAPEAAGGP	NSTYR
TNX10	IgG1	L234A, L235A	CDKTHTCPPCPAPEAAGGP	NSTYR
TNX11	IgG1	C226S, C229S, P238S	CDKTHTSPPSPAPELLGGS	NSTYR
TNX12	IgG1	C229S, P238S	CDKTHTCPPSPAPELLGGS	NSTYR
TNX13	IgG1	C226S, P238S	CDKTHTSPPCPAPELLGGS	NSTYR

IgG=immunoglobulin G; mAb=monoclonal antibody.

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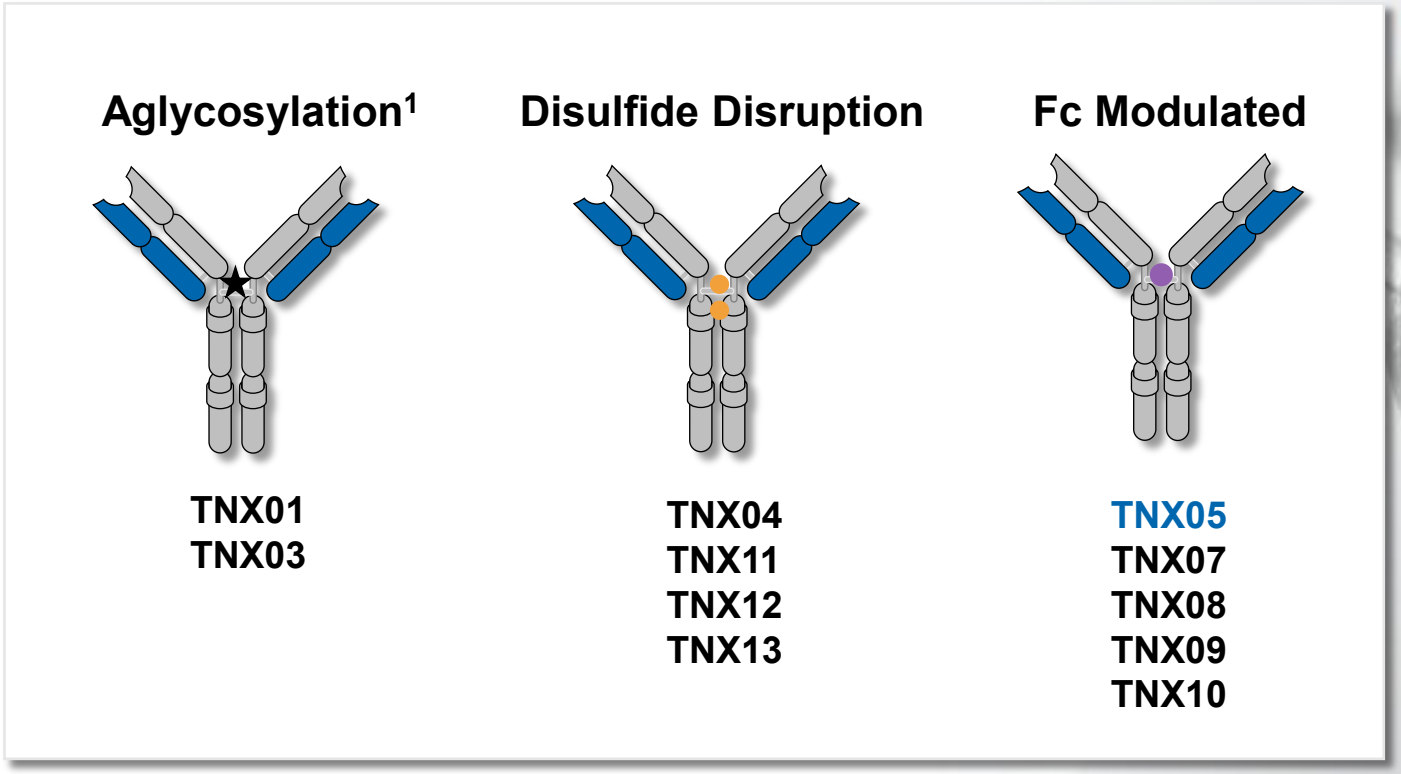
3rd Generation: Fine-turning α-CD40L Abs

- Heavy chain IgG1 and IgG4 variants were grouped by mutation result
- Analyzed for:
  - CD40L binding
  - FcγR binding
- Aglycosyl α-CD40L mAb was previously shown to lack activity in preventing transplant rejection, so were studied as controls[1]
- Thrombosis potential for α-CD40L mAbs was conferred to mice by expression of human FcγRIIa[2]



[1]Ferrant JL, et al. *Int Immunol.* 2004;16(11):1583-1594.
[2]Robles-Carrillo L, et al. *Journal of Immunology.* 2010 185(3):1577–1583.

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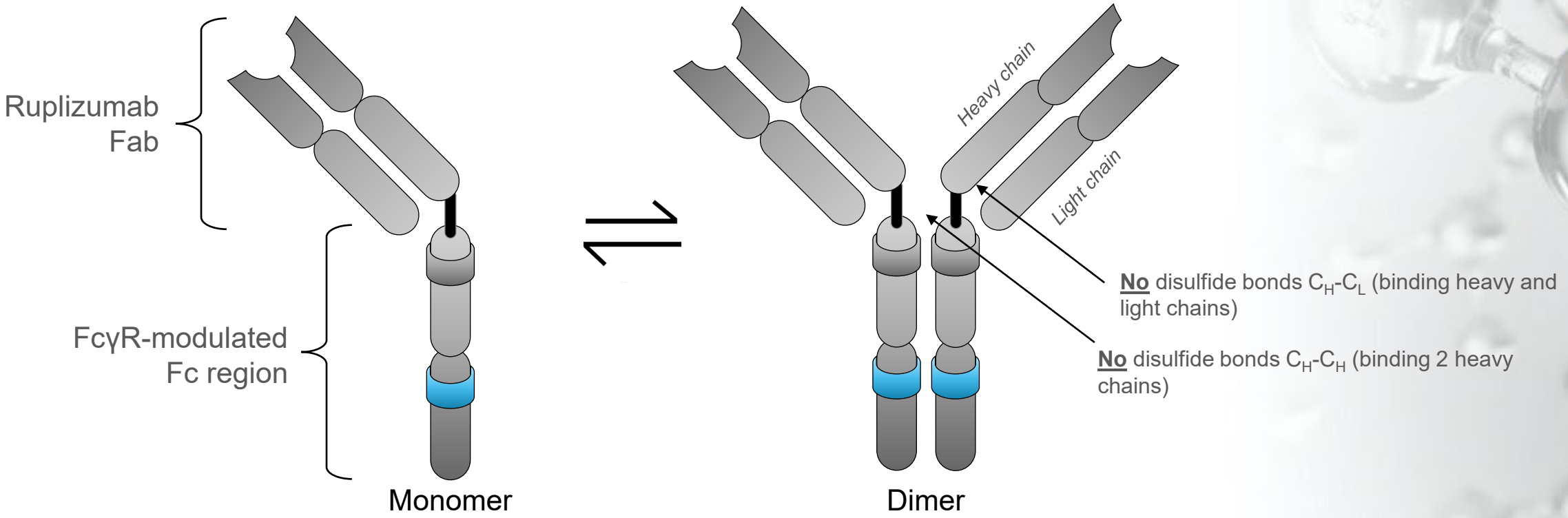
TNX04 (α-CD40L Candidate) without Disulfide Bonds

- No H-L and H-H interchain disulfide bridges by posttranslational modifications
- TNX04 heavy chains are expected to be in an equilibrium between monomers and a non-covalent dimer



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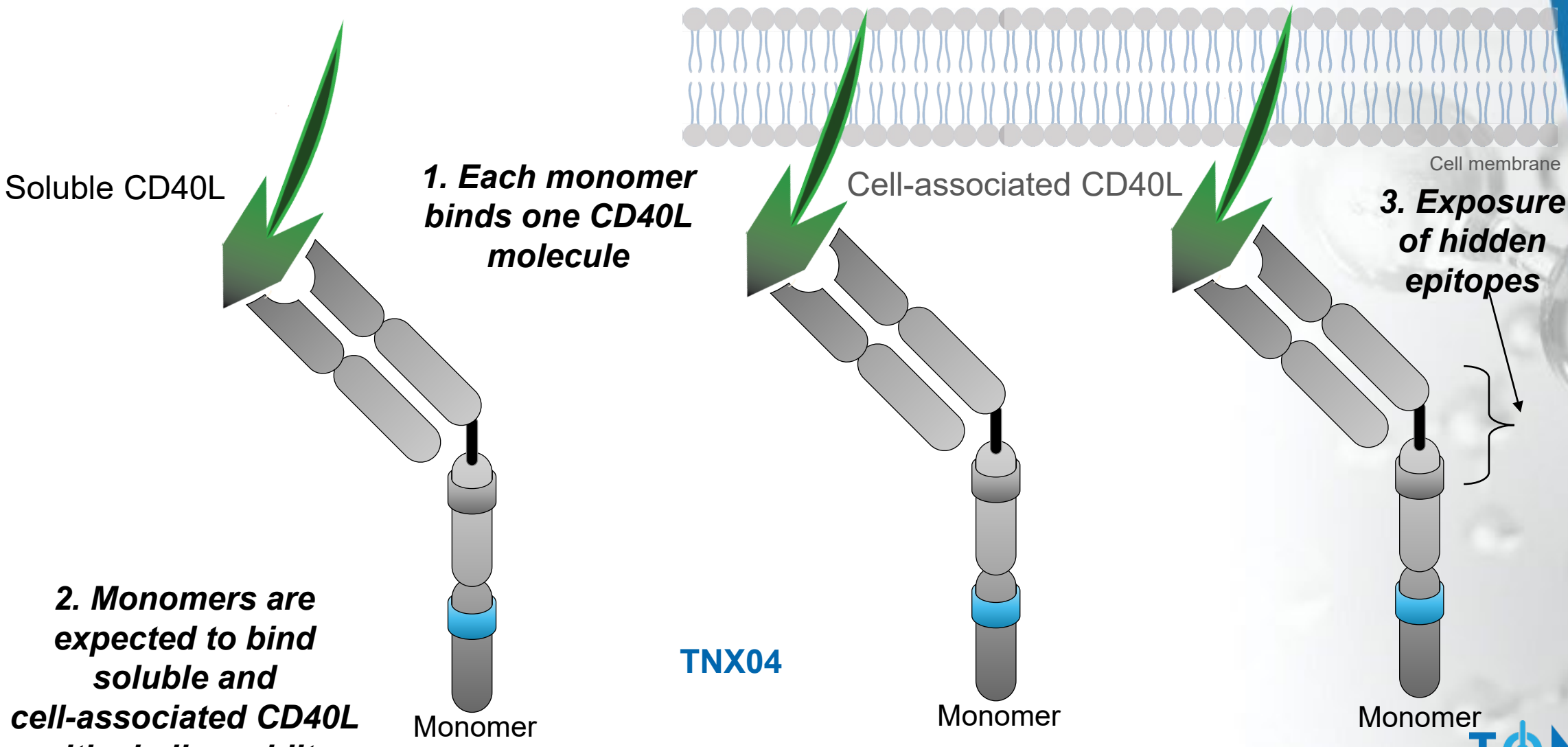
TNX04 Monomers without Disulfide Bonds



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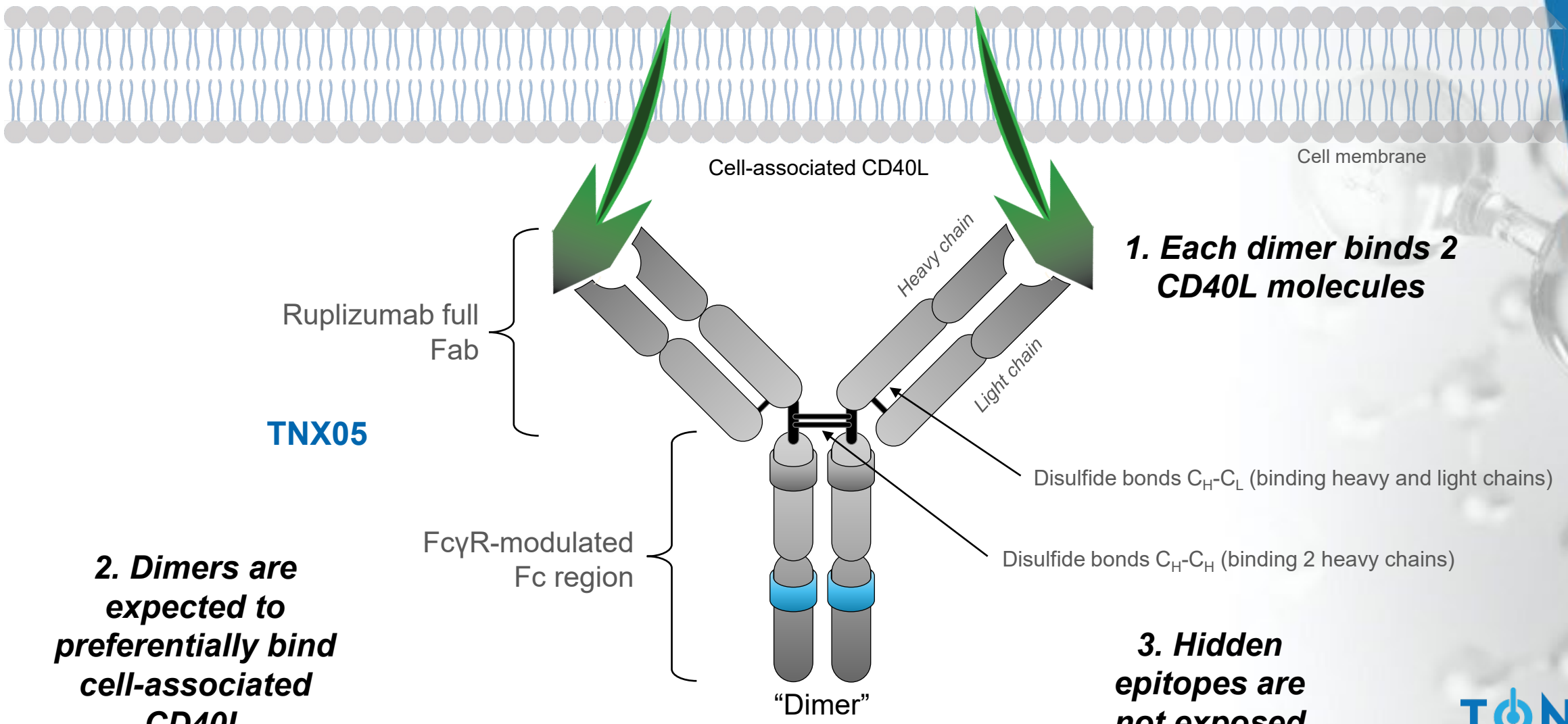
TNX05 (α-CD40L Candidate) Dimer with Disulfide Bonds



1. Each dimer binds 2 CD40L molecules

2. Dimers are expected to preferentially bind cell-associated CD40L

3. Hidden epitopes are not exposed

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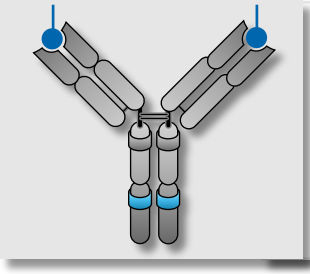
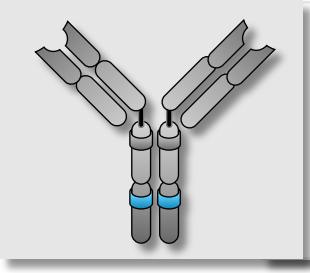
Potential Differences: Dimers (TNX05) vs Monomers (TNX04)



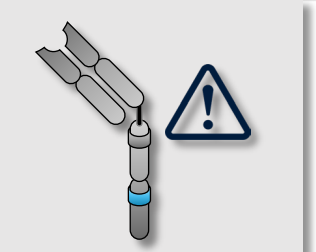
TNX05 dimer preferentially binds surface CD40L

Binding affinity of a dimer is ~monomer binding x monomer binding affinity (the square)



TNX04 may bind surface or soluble CD40L as a monomer

Binding affinity of a dimer is ~monomer binding affinity



The exposed internal-facing hinge region of TNX04 may increase risk of ADAs

Monomer conformer may expose epitopes normally hidden in the disulfide-linked dimer, which may explain high rate of ADAs

ADA=antidrug antibody.

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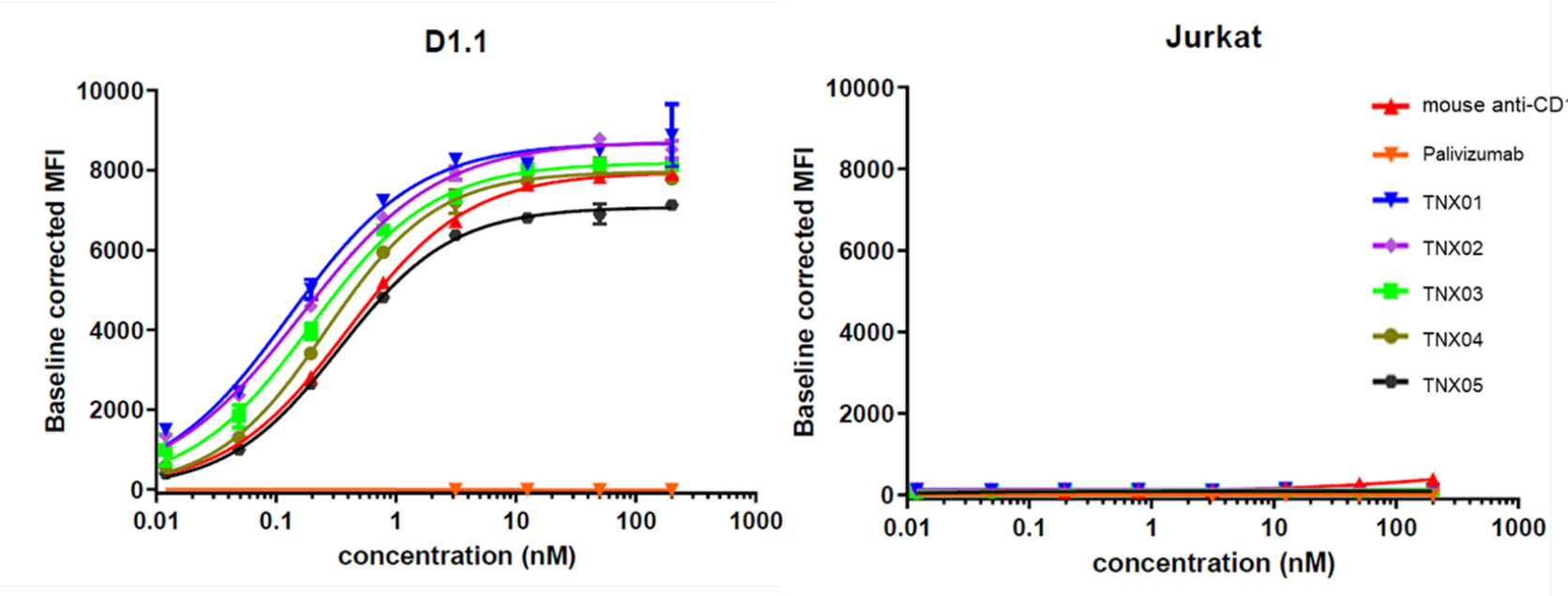
Binding of α-CD40L mAb Variants to CD40L⁺ Jurkat D1.1 Cells by Flow Cytometry



Variant	D1.1 Binding K_d (nM)
TNX01	0.128
TNX02	0.162
TNX03	0.195
TNX04	0.261
TNX05	0.338
TNX06	0.285
TNX07	0.296
TNX08	0.293
TNX09	0.278
TNX10	0.177
TNX11	0.213
TNX12	0.277
TNX13	0.268

Anti-CD40L antibodies (TNX01–TNX05) bound with high affinity to CD40L⁺ Jurkat D1.1 cells (left panel) by flow cytometry. Anti-CD40L antibodies (TNX01–TNX05) did not bind to CD40L⁻ Jurkat cells (right panel), confirming binding specificity. The table shows binding of each anti-CD40L variant to Jurkat D1.1 cells (K_d, nM). Palivizumab: negative control.

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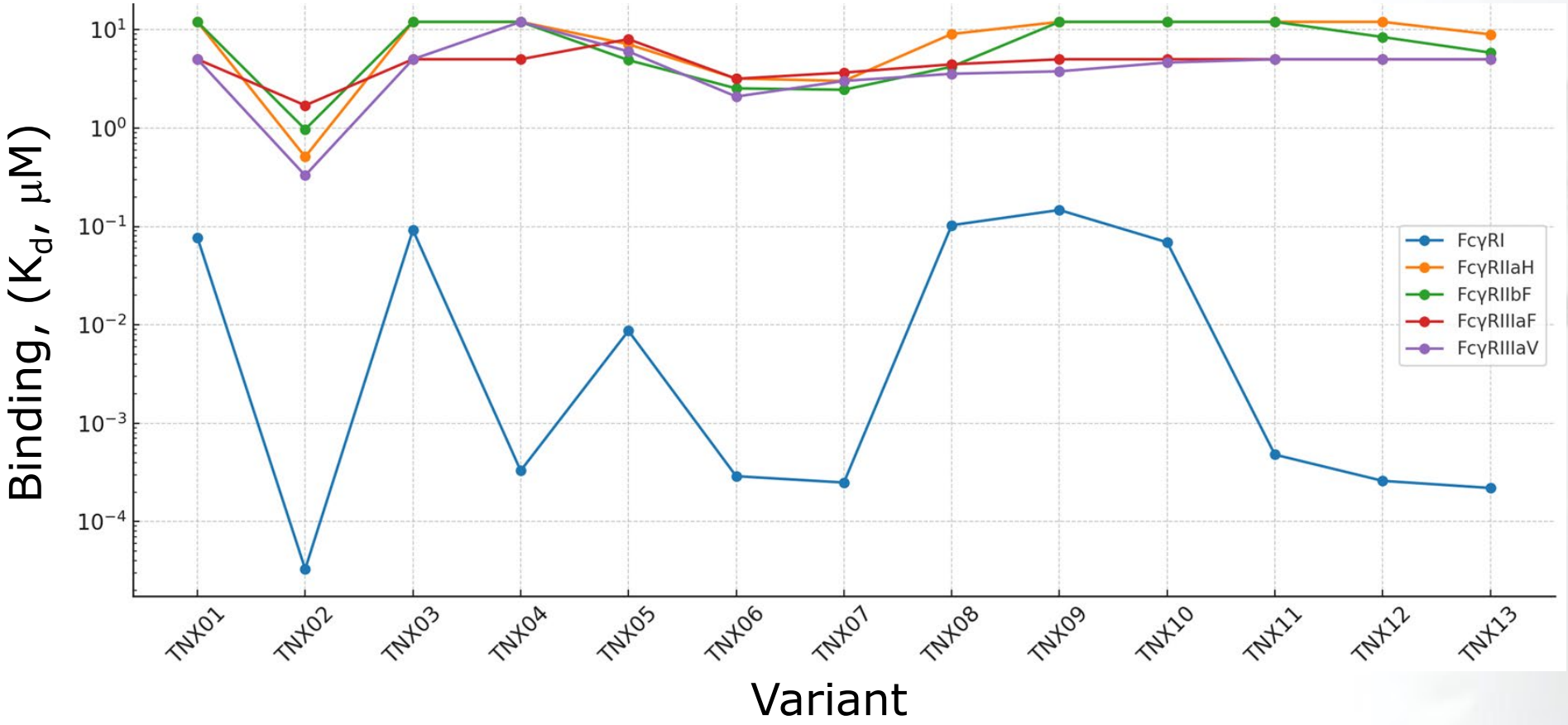
Binding of α-CD40L mAb Variants to FcγRI (and other FcγRs) by Surface Plasmon Resonance (SPR)



Binding of anti-CD40L antibodies to CD40L was measured by surface plasmon resonance (SPR) to FcγRI, FcγRIIaH, FcγRIIbF, FcγRIIIaF, and FcγRIIIaV. All variants bound FcγRI with lower affinity than TNX02 (ruplizumab).

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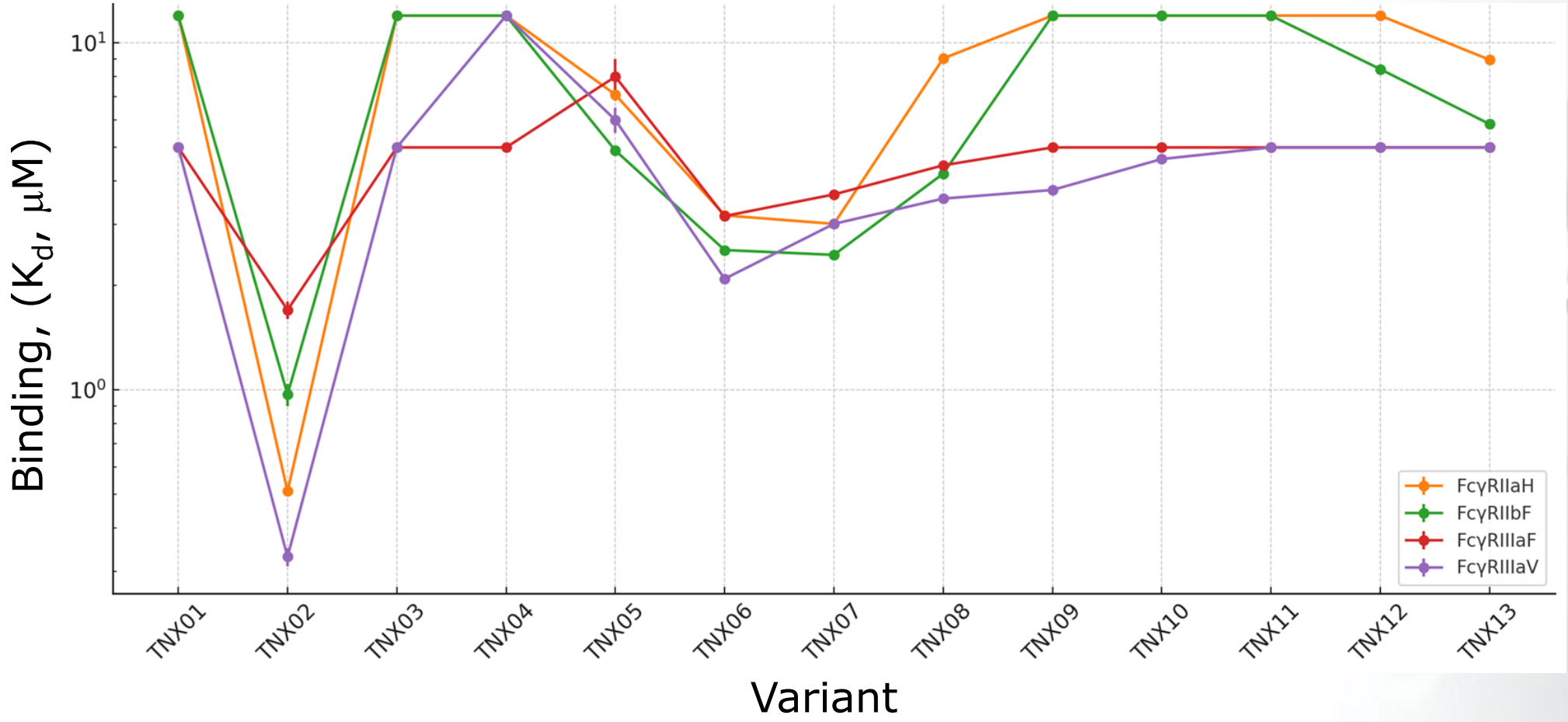
Binding of α-CD40L mAb Variants to Fc Receptors by Surface Plasmon Resonance (SPR)



Binding of anti-CD40L antibodies was measured by surface plasmon resonance (SPR) to FcγRIIaH, FcγRIIbF, FcγRIIIaF, and FcγRIIIaV peptides. All variants bound FcγRIIaH with lower affinity than TNX02 (ruplizumab).

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Binding of α-CD40L mAb Variants to FcRn and CD40L by Surface Plasmon Resonance (SPR)

Variant	FcRn	CD40L
TNX01	270 ±20	0.008 ±0.0005
TNX02	350 ±30	0.010 ±0.001
TNX03	310 ±90	0.013 ±0.001
TNX04	230 ±40	0.0095 ±0.001
TNX05	320 ±40	0.023 ±0.006
TNX06	300 ±20	-
TNX07	340 ±30	-
TNX08	340 ±40	-
TNX09	280 ±30	-
TNX10	330 ±50	-
TNX11	320 ±30	-
TNX12	300 ±7.0	-
TNX13	240 ±8.0	-

Binding affinities are K_D (nM)

mAb=monoclonal antibody.

Data on File.

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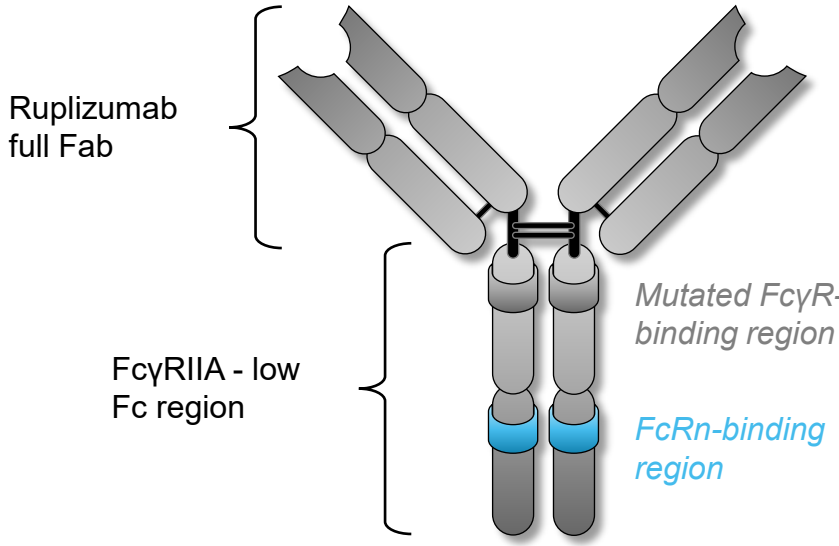
TNX05 Renamed TNX-1500: Chosen for Clinical Development

- TNX-1500 is a new, third-generation Ab targeted to CD40L
- Uses the full Fab from ruplizumab (hu5c8), the first-generation anti-CD40L Ab most consistently effective at delaying allograft rejection in primate models[1-3]
- Ab half-life is prolonged by functioning FcRn binding, which is blocked when the Fc region is fully blocked or eliminated[4]
- TNX-1500 has a selectively modified Fc region in which the FcγR-binding region is mutated, but the FcRn-binding region is intact

Selectively Modified Anti-CD40L Ab



TNX-1500* contains the full ruplizumab Fab and the mutated FcγR-modulated Fc region that preserves FcRn function.

*TNX-1500 has not been approved for any indication. Patents filed.

[1]Zhang T, et al. *Immunotherapy*. 2015;7(8):899-911.
[2]Kirk AD, et al. *Nat Med*. 1999;5(6):686-693.
[3]Kim SC, et al. *Am J Transplant*. 2017;17(5):1182-1192.
[4]Saxena A, et al. *Front Immunol*. 2016;7:580.

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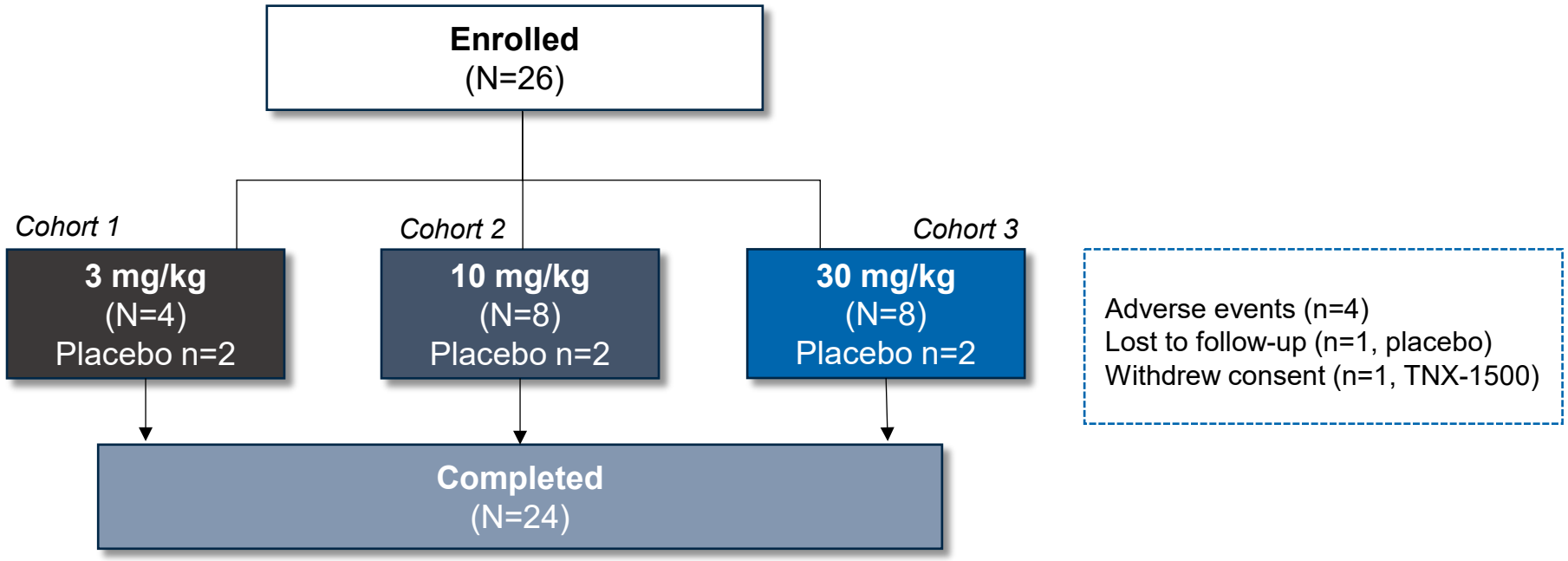
Phase 1 Topline Results

TNX-1500 Phase 1 Study Design

Goal: evaluate the safety, pharmacodynamics, and pharmacokinetics of TNX-1500



No adverse events led to discontinuation.

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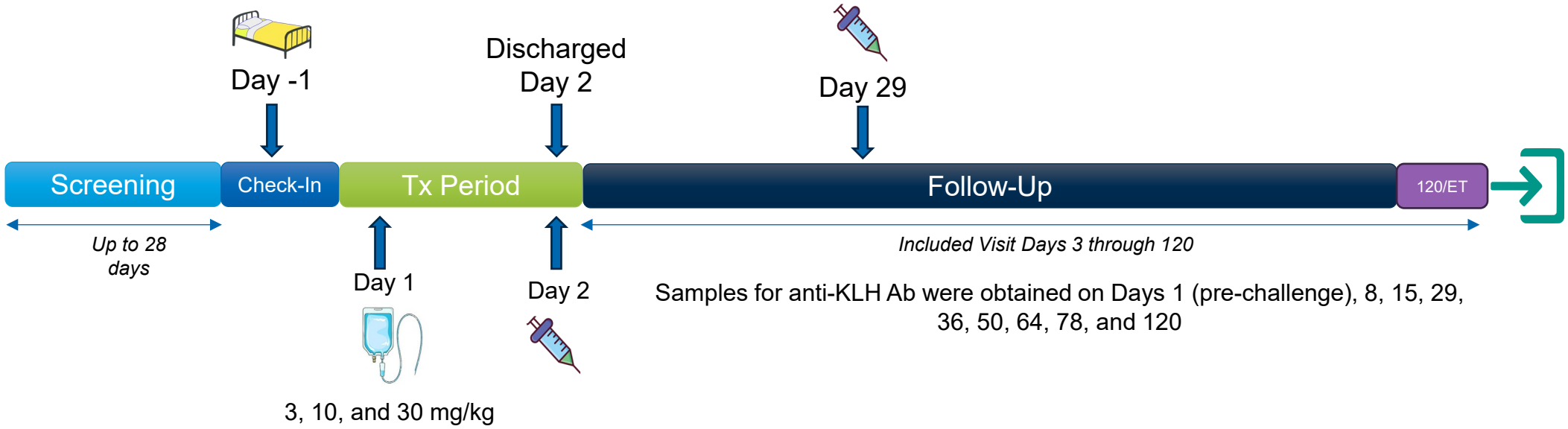
TNX-1500 Phase 1 Methods



Legend:

- Check-In Day at CRC
- TNX-1500/Placebo IV Administration
- KLH Challenge (IMMUCOTHEL®) SC Administration, Observed for 1 Hour Postdose
- Exit Study

IV=intravenous; KLH=keyhole limpet hemocyanin; SC=subcutaneous; Tx=treatment.

Data on File.

TNX-1500 Phase 1 Topline Results

Tolerability

	3 mg/kg	10 mg/kg	30 mg/kg	Placebo
TEAEs	1	1	1	0
Serious AE	0	0	0	0

- TNX-1500 was generally well tolerated with a favorable safety and tolerability profile
- The only treatment-emergent adverse event (TEAE) was aphthous ulcers; all rated as mild and possibly related
  - Resolved in 2 to 10 days
- No TEAEs were determined to be related to KLH administration
- There were no TE complications (prespecified as TEAEs of special interest)

KLH=keyhole limpet hemocyanin.

Data on File.

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TNX-1500 Phase 1 Topline Results (Cont.)

Pharmacokinetics and Pharmacodynamics

Dose mg/kg	Pharmacokinetics Mean (SD) half-life in days	Pharmacodynamics % Inhibition	
		KLH, 2-day challenge	KLH, 29-day challenge
0	-	0%	0%
3	19.6 (9.29)	100%	69%
10	37.8 (5.46)	100%	100%
30	33.7 (4.83)	100%	100%

KLH=keyhole limpet hemocyanin; SD=standard deviation.

Data on File.

TNX-1500 Phase 1 Conclusions and Future Directions

- Phase 1 completed; results support development for phase 2 trial (prevention of kidney transplant rejection)
  - Collaborations ongoing with Massachusetts General Hospital on allo-heart and kidney transplantation in nonhuman primates
- Engineered Fc modifications to TNX-1500 for safety did not attenuate the potency of TNX-1500 relative to humanized 5c8 (hu5c8, ruplizumab, BG9588)[1-3]
- The results of this study and our prior animal studies[4,5] suggest TNX-1500 is potentially best-in-class among anti-CD40L mAbs in development
- Prevention of xenograft rejection preclinical studies are underway
  - Collaborations ongoing with Massachusetts General Hospital on xeno-heart and kidney transplantation in nonhuman primates
- Prevention of allograft rejection in sensitized patients
  - Preclinical data published by Duke on Pr5c8[6]

mAb=monoclonal antibody.

[1]Lederman S, et al. *J Exp Med*. 1992;175(4):1091-1101.
[3]Boumpas DT, et al. *Arthritis Rheum*. 2003;48(3):719-727.
[3]Pierson RN 3rd, et al. *Transplantation*. 1999;68(11):1800-1805.
[4]Lassiter G, et al. *Am J Transplant*. 2023;23(8):1171-1181.
[5]Miura S, et al. *Am J Transplant*. 2023;23(8):1182-1193.
[6]Anwar IJ, et al. *Sci Transl Med*. 2025;17(779):eadn8130.

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Summary

- Calcinurin Inhibitors (CNIs) have enabled great success in transplantation by effectively preventing acute rejection; however, they also cause irreversible and progressive deterioration of kidney function in recipients of all types of solid organ transplants, which can be irreversible and progressive[1,2]
- CNI-sparing regimens with broader therapeutic windows that avoid CNI-induced nephrotoxicity could supplant current standard of care[3]
- The CD40-CD40L pathway is a pivotal immune system modulator and is a well-established and promising treatment target for more safely preventing allograft rejection[4]
- TNX-1500 is a modified anti-CD40L Ab, designed using targeted molecular engineering, expected to deliver efficacy without compromising safety
- Phase 1 study is complete, and results support moving to phase 2
- Further potential TNX-1500 applications include autoimmune conditions

mAb=monoclonal antibody.

1. Naesens M, et al. *Clin J Am Soc Nephrol.* 2009;4(2):481-508. 2. Nankivell BJ, et al. *N Engl J Med.* 2003;349(24):2326-2333.
3. Camilleri B, et al. *Exp Clin Transplant.* 2016;14(5):471-483. 4. Zhang T, et al. *Immunotherapy.* 2015;7(8):899-911.

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