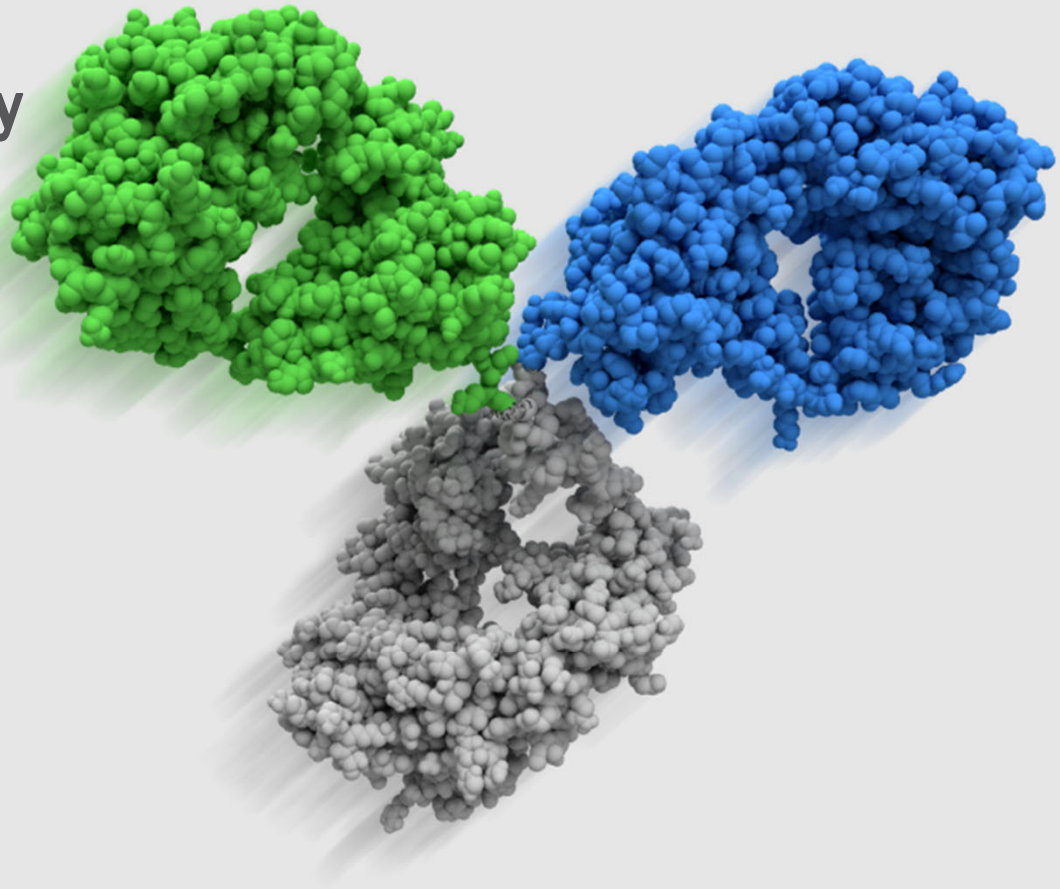
T-Body™ Trispecific TAA/CD3/CD28 Co-Stimulatory Antibody Optimization Drives Superior Tumor-Directed T-Cell Engagement



8th T-cell Engager Therapeutics Summit

Invenra Nonconfidential

Contact bd@invenra.com

Novel Monoclonal, Bispecific, and Trispecific Antibodies: Discovered, Optimized, and Ready for the Clinic

Why Invenra?

Innovative

Science–first mentality | 10+ years multispecific expertise

Proven

20+ partners | 2 clinical-stage

Easy

Flexible and transparent business terms from fee-for-service to strategic collaboration

		Accelerated timelines with transparent pricing and terms
1	**Best multispecifics start with quality mAbs**	>30 diverse, optimized human libraries
		Achieve desired affinity, specificity, and functional profile goals
		Transfer easily to our multispecifics platforms
		Accelerate lead identification
2	**B-Body® bispecific antibodies deliver unrivaled yield**	Reduce manufacturing risks
		Make IgG modifications using a fully human IgG-like scaffold
		Overcome manufacturability challenges
3	**T-Body™ trispecific antibodies yield powerful solutions for complex disease**	Optimize performance based on desired target density, therapeutic window, and manufacturing
		Support advanced therapeutics: ADCs, next generation Immuno-Oncology & Cell Engagers

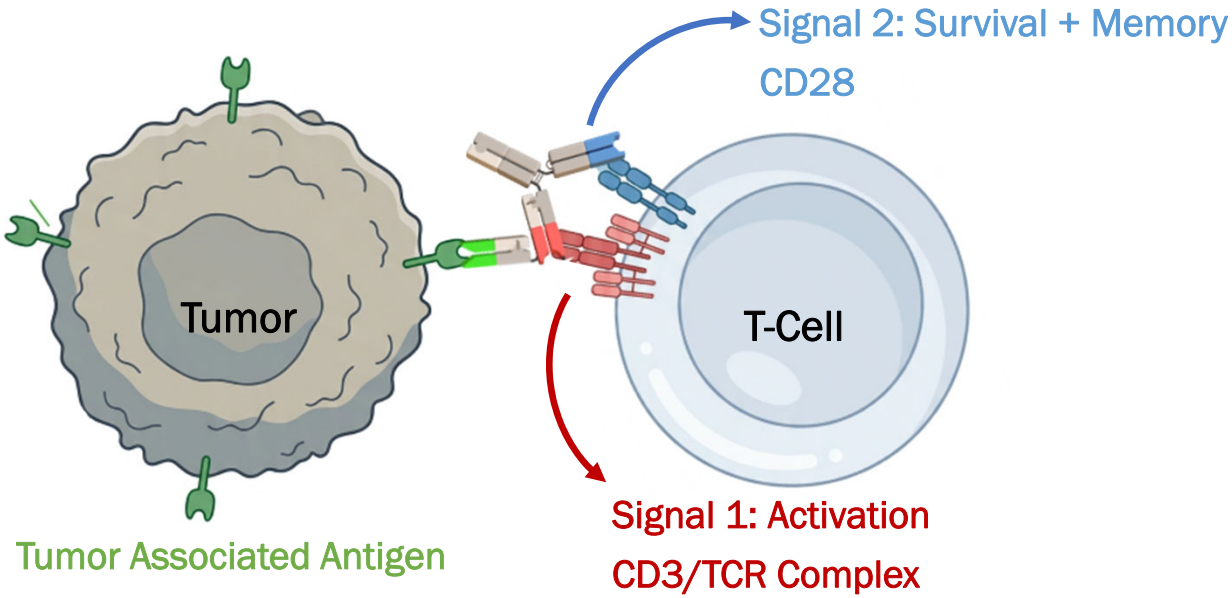
T-Cell Engager Challenges: Optimizing Therapeutic Index for Treating Solid Tumors

Advancing next-generation TCEs requires addressing three interconnected challenges.

Narrow Therapeutic Window	T-Cell Exhaustion in Solid Tumors	Development Bottlenecks
CRS remains dose-limiting despite step-up dosing strategies	35-68% of tumor-infiltrating CD8+ T-cells express high PD-1 (exhausted phenotype)	Traditional antibody discovery and optimization: 6-12 months
On-target, off-tumor toxicity limits maximum tolerated doses	PD-1+/TIM-3+ co-expression indicates severe exhaustion	Affinity, epitope, format, and valency require empirical testing
CD3 affinity tuning critical but complex—narrow optimization window	CD3 engagement alone may be insufficient to reactivate exhausted T-cells	Iterative cycles extend timelines by 4+ months per reformatting
Need enhanced tumor selectivity to decouple efficacy from toxicity	Co-stimulatory signals needed for durable anti-tumor responses	Critical barrier to exploring new targets and disease indications

Bispecific TCE programs in solid tumors have achieved 0–7% ORR across multiple Phase 1 trials, with many discontinued before reaching therapeutic dose due to toxicity.

Two Signals Drive Superior T-Cell Responses



Signal 1 (CD3): T-Cell Activation

- Initiates cytotoxicity
- Limited proliferation alone
- Susceptible to apoptosis

Signal 2 (CD28): Co-Stimulation & Survival

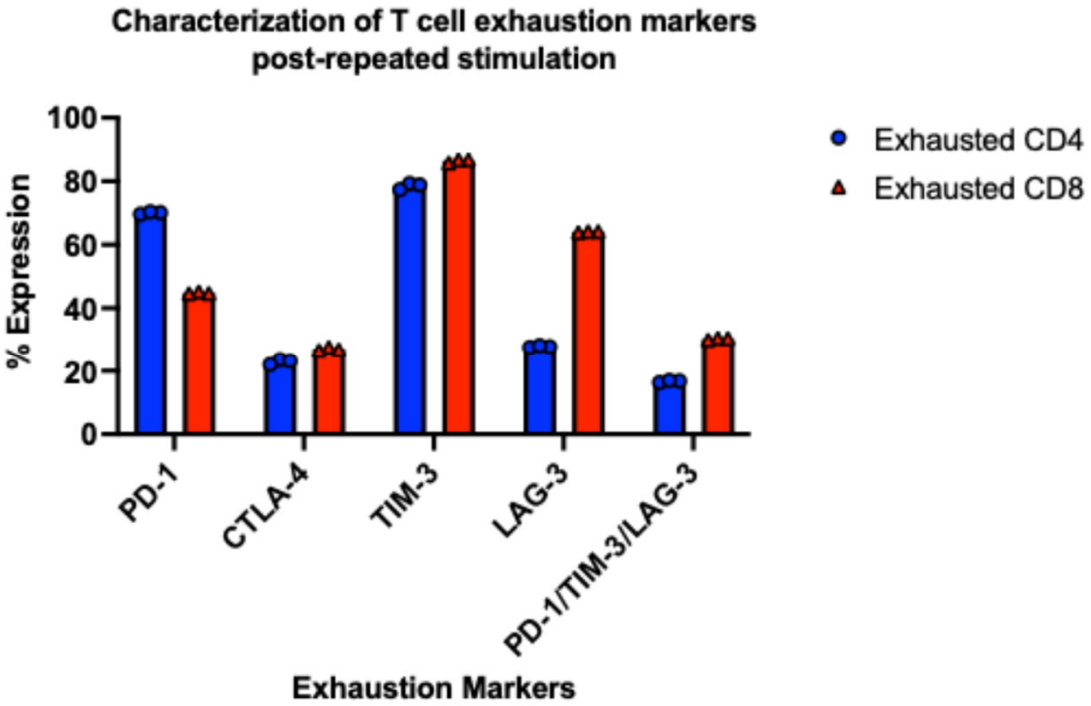
- Prevents apoptosis (Bcl-xL ↑)
- Sustained proliferation
- Memory formation
- **Reactivates exhausted T-cells**

Impact in Trispecific TCEs: Enhanced Activity

- >30-fold increased T-cell activation
- **2-4-fold** improved T-cell survival
- Critical for reinvigoration of PD-1+ exhausted T-cells

CD28 co-engagement transforms TCE activity and is particularly critical for reactivating exhausted T-cells in solid tumors

Repeated CD3 Stimulation Drives T cell Exhaustion



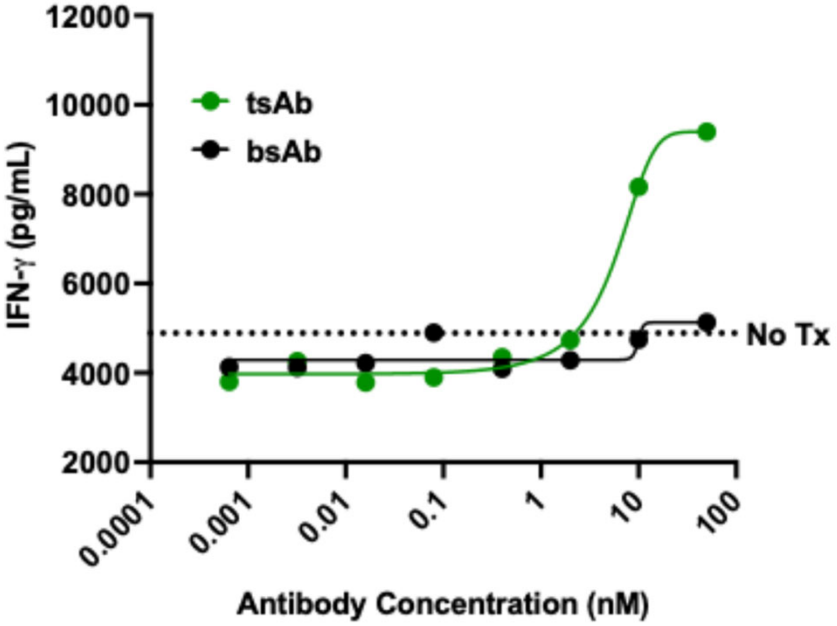
- Chronic TCR/CD3 stimulation, a key driver of T-cell exhaustion
  - Metabolic derangement
  - Upregulation of ICs
  - Hyporesponsiveness

Can CD3/CD28 Co-Engagement Reactivate Exhausted T-Cells?

CD3/CD28 Co-Engagement Reactivates Exhausted T-Cells

PD-1⁺ exhausted T-cells require CD28 co-stimulation for reactivation

T-Body trispecific TCE vs B-Body bispecific TCE



TsAb (CD3×CD28×TAA) Performance:

✓ IFN-γ production from PD-1⁺ exhausted T-cells
- TsAb TCE has significant increase vs. bsAb TCE

✓ Enhanced exhaustion marker modulation
- Demonstrates engagement of PD-1+ T-cell population
- Bispecifics (CD3×TAA): minimal activation

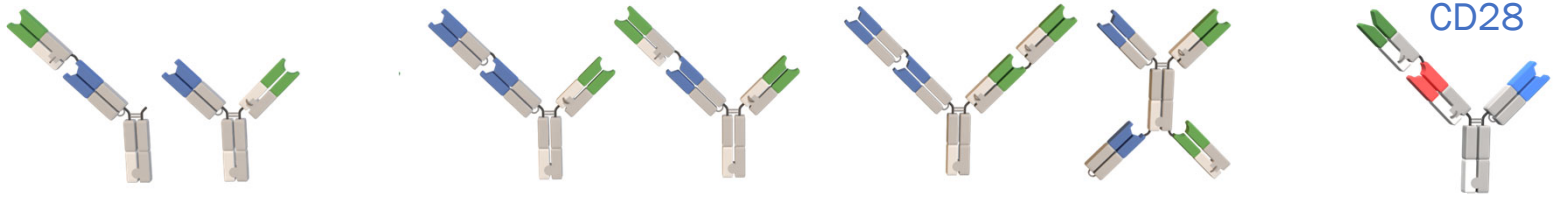
✓ Maintained safety profile
- No cytokines detected in absence of tumor cells
- Tumor-dependent activation preserved

How do we identify optimal CD3/CD28 combinations?

TCE Format Selection: Context-Dependent Optimization

Target density, therapeutic window, and manufacturing drive choice of optimal format

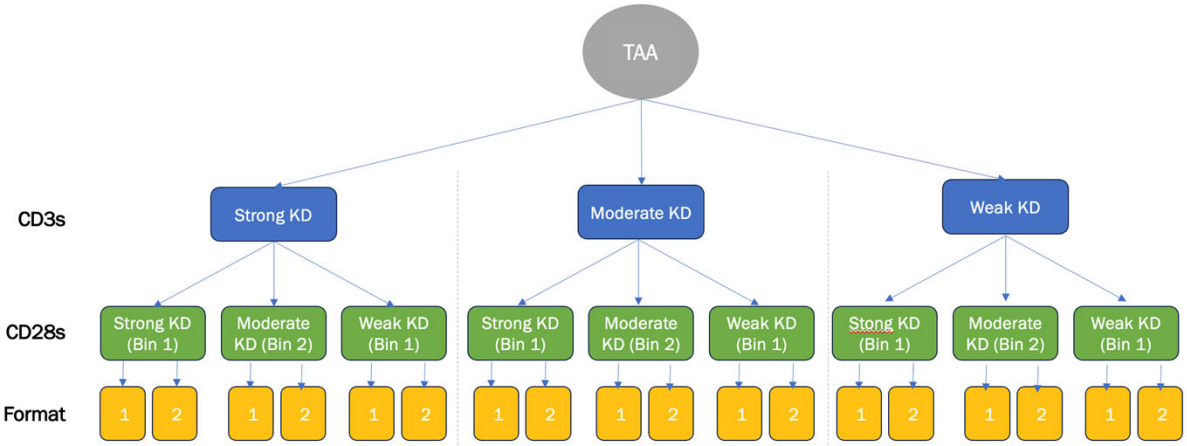
Invenra's B-Body® Bispecific & & T-Body™ Trispecific Family



	B-Body® Bispecific 1x1	B-Body® Bispecific 2x1	B-Body® Bispecific 2x2	T-Body™ Trispecific
Key Feature	Monovalent CD3 & TAA	Bivalent TAA	Bivalent CD3 & TAA	CD3 + CD28 + TAA
Advantage	Simple, IgG-like	Stronger tumor binding	Avidity to both	Co-stimulation enabled
Trade Off	No avidity	More complex	CD3 avidity toxicity risk	Molecular complexity

Invenra's platforms enable parallel format testing in final configuration & functional data in weeks, not months.

T-Body Trispecific Platform Enables Rapid Systematic Optimization of TCEs



Performed in collaboration with Alloy Therapeutics®

Experimental Design:

18 trispecific variants in final T-Body trispecific format

- 3 CD3 affinities (Strong, Moderate, Weak)
- 3 CD28 affinities (Strong, Moderate, Weak) across 2 epitope bins
- 2 molecular orientations

Platform Advantages:

- Plug-and-play variable domain design
- All variants tested in final trispecific format
- No reformatting required between screening and characterization
- Parallel expression and functional testing

All 18 variants expressed and functionally characterized in 10 weeks.

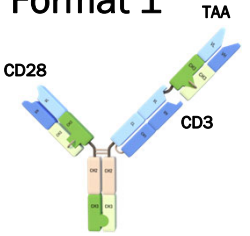
B-Body Bispecific and T-Body Trispecific Antibody Expression and Developability

Identity	Orientation	Expression (ug/mL)	PDI	Z-Ave D (nm)	Tm (°C)	Tagg266 (°C)	Tagg473 (°C)	SEC	SCX	HIC
CD3 (Strong) + CD28 (Weak, Bin 1)	CD28 x TAA + CD3	112.8	0.023	13.63	54.18	65.9	65.95	Pass	Pass	Pass
CD3 (Strong) + CD28 (Strong, Bin 1)	CD28 x TAA + CD3	75.1	0.06	13.69	62.24	65.91	65.11	Pass	Pass	Pass
CD3 (Strong) + CD28 (Mod, Bin 2)	CD28 x TAA + CD3	91.75	0.006	14.23	63.29	64.81	64.94	Pass	Pass	Pass
CD3 (Mod) + CD28 (Weak, Bin 1)	CD28 x TAA + CD3	46.95	0.031	13.77	54.27	65.5	66.13	Watch	Pass	Pass
CD3 (Mod) + CD28 (Strong, Bin 1)	CD28 x TAA + CD3	65.3	0.038	13.94	62.15	65.5	65.84	Pass	Pass	Pass
CD3 (Mod) + CD28 (Mod, Bin 2)	CD28 x TAA + CD3	65.2	0.019	14.5	63.46	64.46	65.07	Pass	Pass	Pass
CD3 (Weak) + CD28 (Weak, Bin 1)	CD28 x TAA + CD3	65.7	0.041	13.76	54.07	66.3	66.39	Watch	Pass	Pass
CD3 (Weak) + CD28 (Strong, Bin 1)	CD28 x TAA + CD3	48.7	0.01	13.89	62.45	65.7	65.78	Pass	Pass	Pass
CD3 (Weak) + CD28 (Mod, Bin 2)	CD28 x TAA + CD3	66.9	0.041	14.19	63.66	65.47	65.83	Pass	Pass	Pass

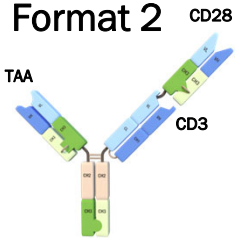
Identity	Orientation	Expression (ug/mL)	PDI	Z-Ave D (nm)	Tm (°C)	Tagg 266 (°C)	Tagg473 (°C)	SEC	SCX	HIC
CD3 (Strong) + CD28 (Weak, Bin 1)	TAA x CD28 + CD3	28.85	0.045	13.34	53.73	64.54	66.01	Pass	Pass	Pass
CD3 (Strong) + CD28 (Strong, Bin 1)	TAA x CD28 + CD3	72.1	0.01	13.17	65.56	66.79	65.67	Pass	Pass	Pass
CD3 (Strong) + CD28 (Mod, Bin 2)	TAA x CD28 + CD3	52.15	0.035	13.11	64.76	65.56	65.21	Pass	Pass	Pass
CD3 (Mod) + CD28 (Weak, Bin 1)	TAA x CD28 + CD3	54.3	0.01	13.52	53.23	65.43	64.81	Pass	Pass	Pass
CD3 (Mod) + CD28 (Strong, Bin 1)	TAA x CD28 + CD3	116	0.025	13.23	65.39	66.52	65.51	Pass	Pass	Pass
CD3 (Mod) + CD28 (Mod, Bin 2)	TAA x CD28 + CD3	57.15	0.07	13.54	65.8	66.2	65.48	Pass	Pass	Pass
CD3 (Weak) + CD28 (Weak, Bin 1)	TAA x CD28 + CD3	32.3	0.021	13.09	53.33	66	65.38	Pass	Pass	Pass
CD3 (Weak) + CD28 (Strong, Bin 1)	TAA x CD28 + CD3	69.9	0.018	13.38	65.88	67.18	66.82	Pass	Pass	Pass
CD3 (Weak) + CD28 (Mod, Bin 2)	TAA x CD28 + CD3	125.25	0.093	13.03	65.2	65.84	65.8	Pass	Pass	Pass

Identity	Orientation	Expression (ug/mL)	PDI	Z-Ave D (nm)	Tm (°C)	Tagg 266 (°C)	Tagg473 (°C)	SEC	SCX	HIC
Her2 x CD3 (Strong)	Null x TAA X CD3	116.5	0.03	12.37	66.97	68.07	68.54	Pass	Pass	Pass
Her2 x CD3 (Mod)	Null x TAA x CD3	74.3	0.009	12.57	68.16	68.79	69.25	Pass	Pass	Pass
Her2 x CD3 (Weak)	Null x TAA x CD3	70.95	0.039	12.6	67.97	68.78	69.47	Pass	Pass	Pass

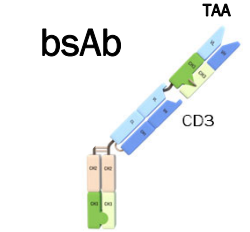
tsAb Format 1



tsAb Format 2

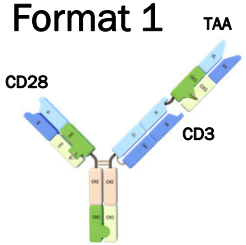


bsAb

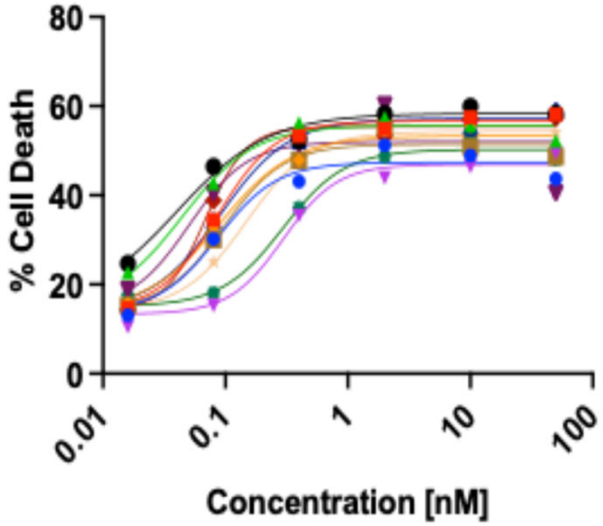


Comparison of T-Body Trispecific vs B-Body Bispecific TCEs Killing of Target Cells

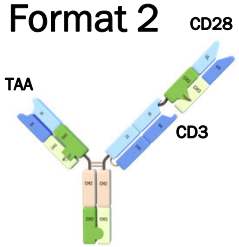
Format 1



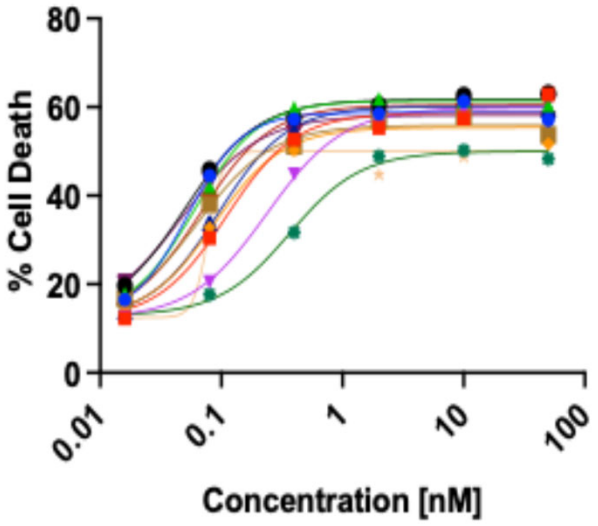
CD28 ::x:: TAA x CD3



Format 2

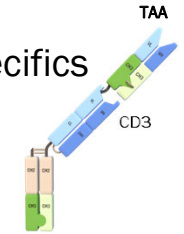


TAA ::x:: CD28 x CD3



T-Body™ Trispecifics

B-Body Bispecifics (TAA x CD3)



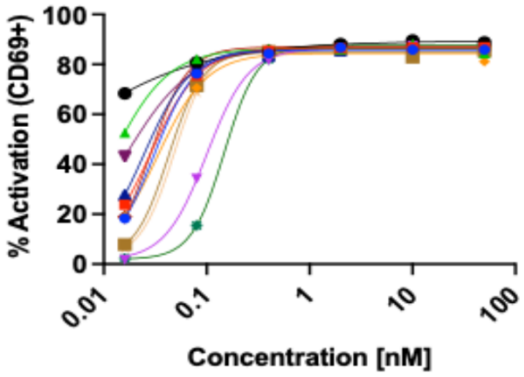
- Trispecific TCEs outperformed bispecific TCEs
- Optimization of CD3 and CD28 KDs and epitope was important for enhancing efficacy

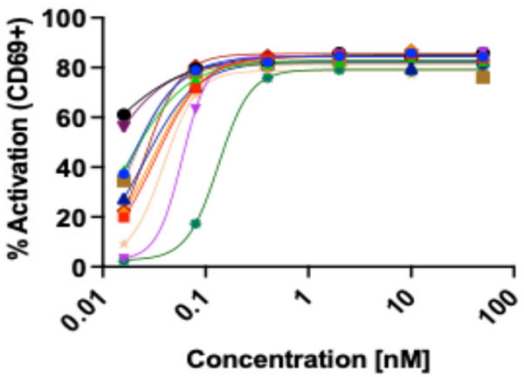
Comparison of T-Body Trispecific vs B-Body Bispecific TCEs Activation of CD8+ and CD4+ T-Cells in Presence of Tumor Cells

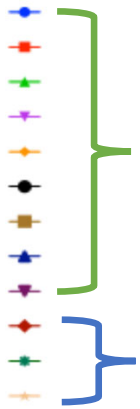
CD28 ::x:: TAA x CD3

TAA ::x:: CD28 x CD3

CD8+ T-cells



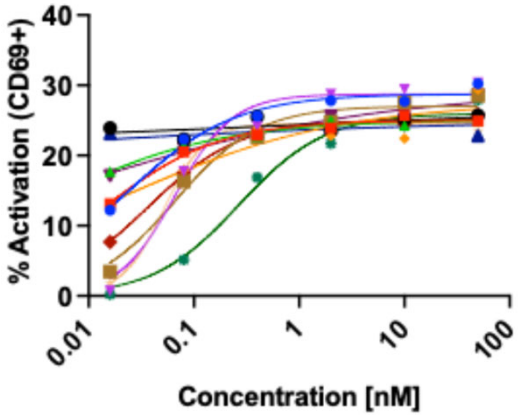


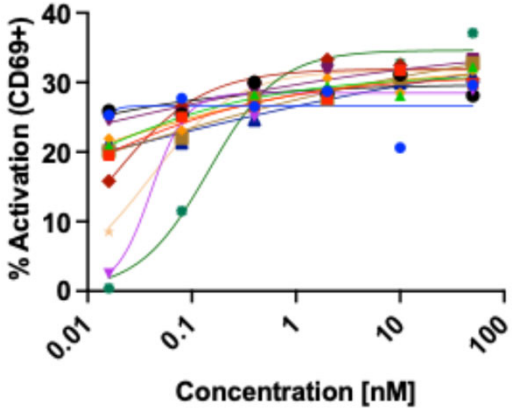


T-Body™ Trispecifics

B-Body Bispecifics (TAA x CD3)

CD4+ T-cells



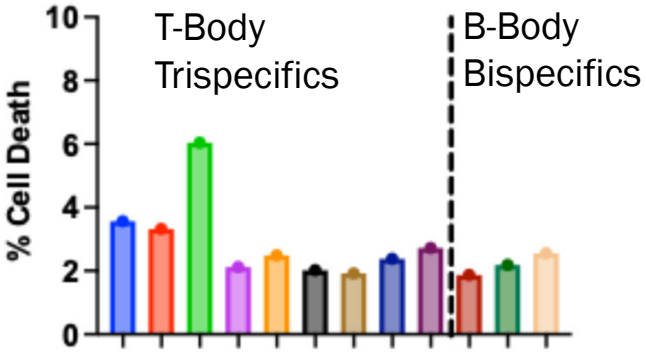


- Combinations of CD3 and CD28 KDs and epitope generated a range of T-cell activation

Comparison of T-Body Trispecific vs B-Body Bispecific TCE Induced Fratricide of CD8 + CD4 T-Cells (No Tumor)

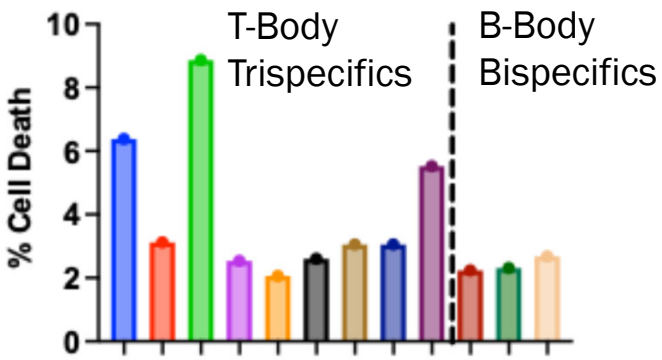
CD28 ::x:: TAA x CD3

Effectors Alone (Fratricide)

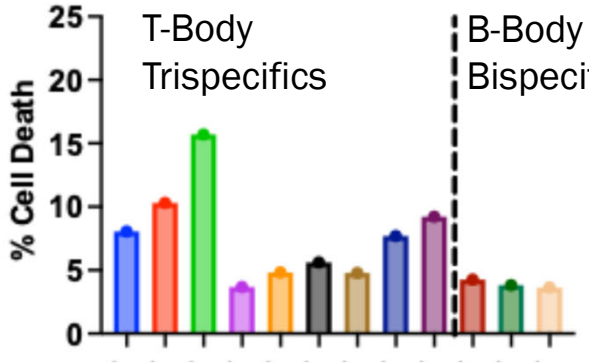


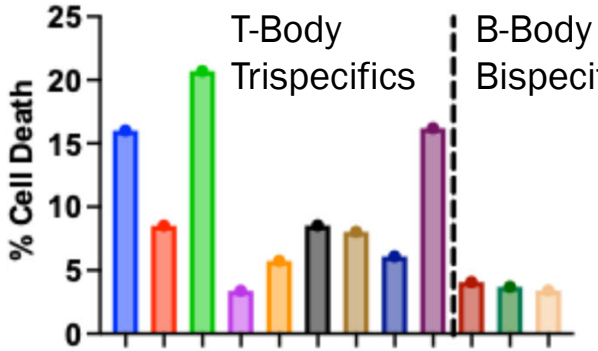
TAA ::x:: CD28 x CD3

Effectors Alone (Fratricide)



CD8⁺ T-cells





CD4⁺ T-cells

- Testing of CD3 and CD28 combinations was critical to identify low T-cell fratricide.

Comparison of T-Body Trispecific vs B-Body Bispecific TCE Auto-Activation of CD8 + CD4 T-Cells (No Tumor)

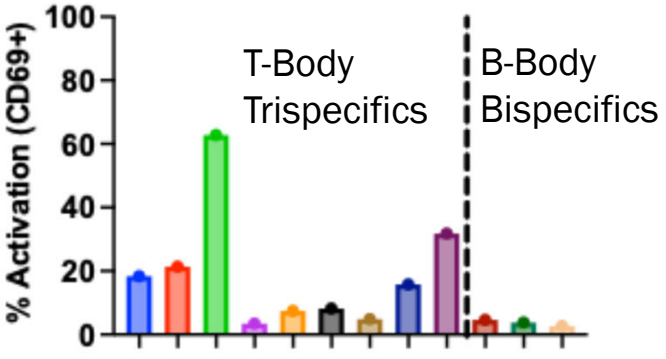
CD28 ::x:: TAA x CD3

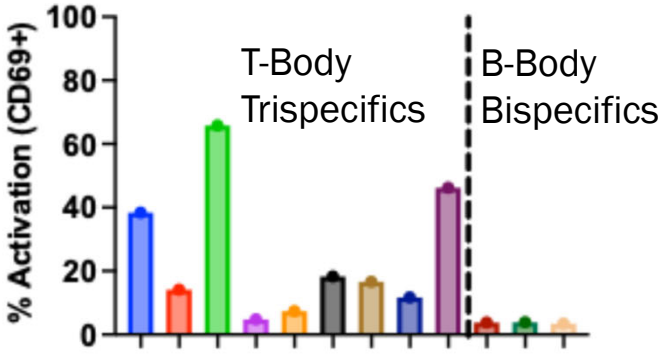
Effectors Alone (Activation)

TAA ::x:: CD28 x CD3

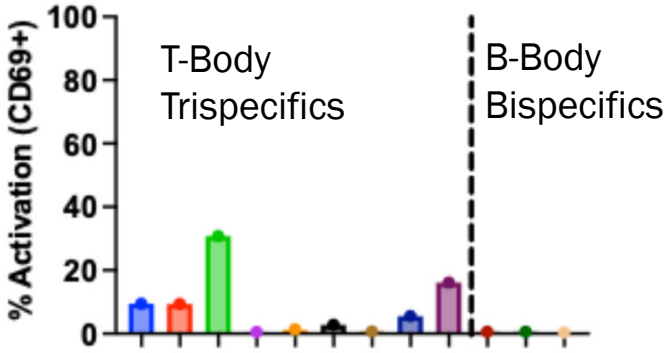
Effectors Alone (Activation)

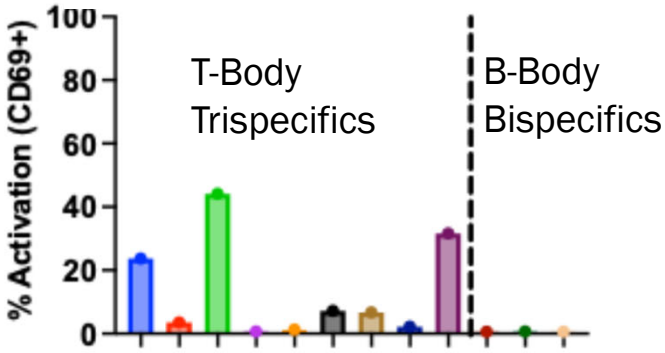
CD8+ T cells





CD4+ T cells

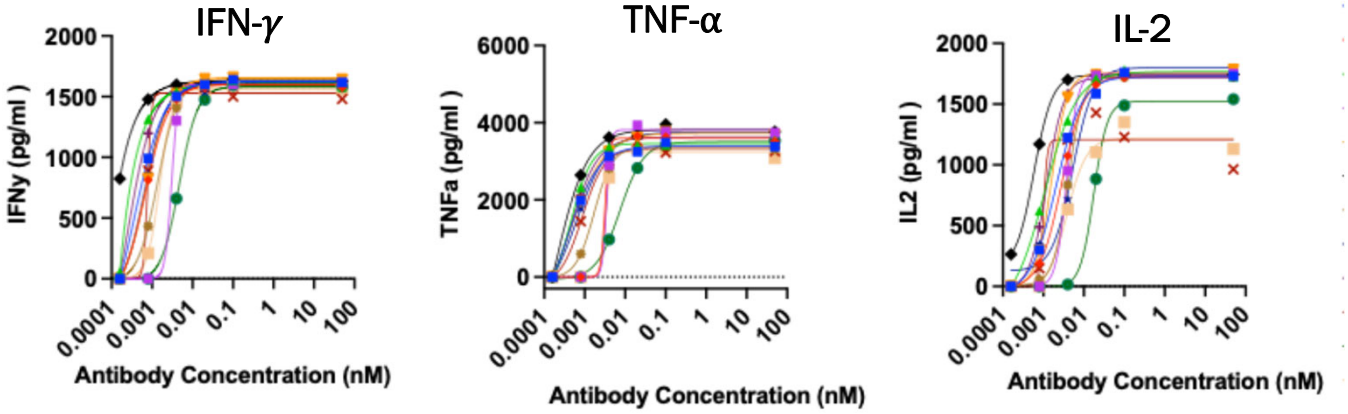




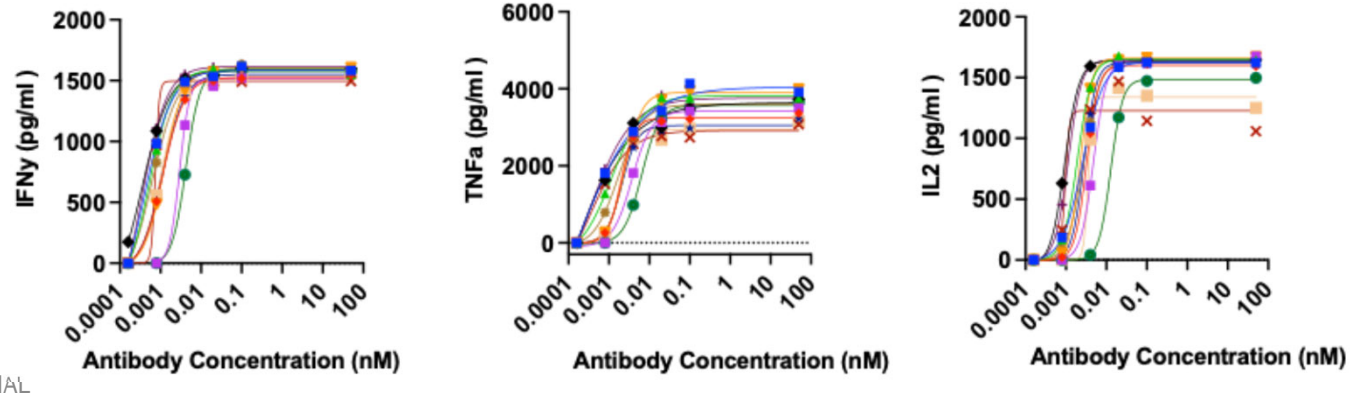
- Most CD3/CD28 combinations activated T-cells more than bispecifics when no tumor was present.
- Optimized combination was low in this assay.

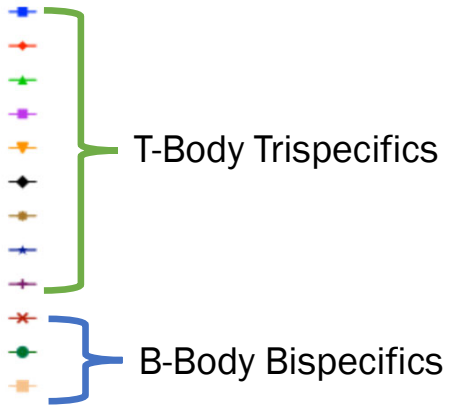
Comparison of T-Body Trispecific vs B-Body Bispecific TCE Induction of Cytokines

CD28 ::x:: TAA x CD3



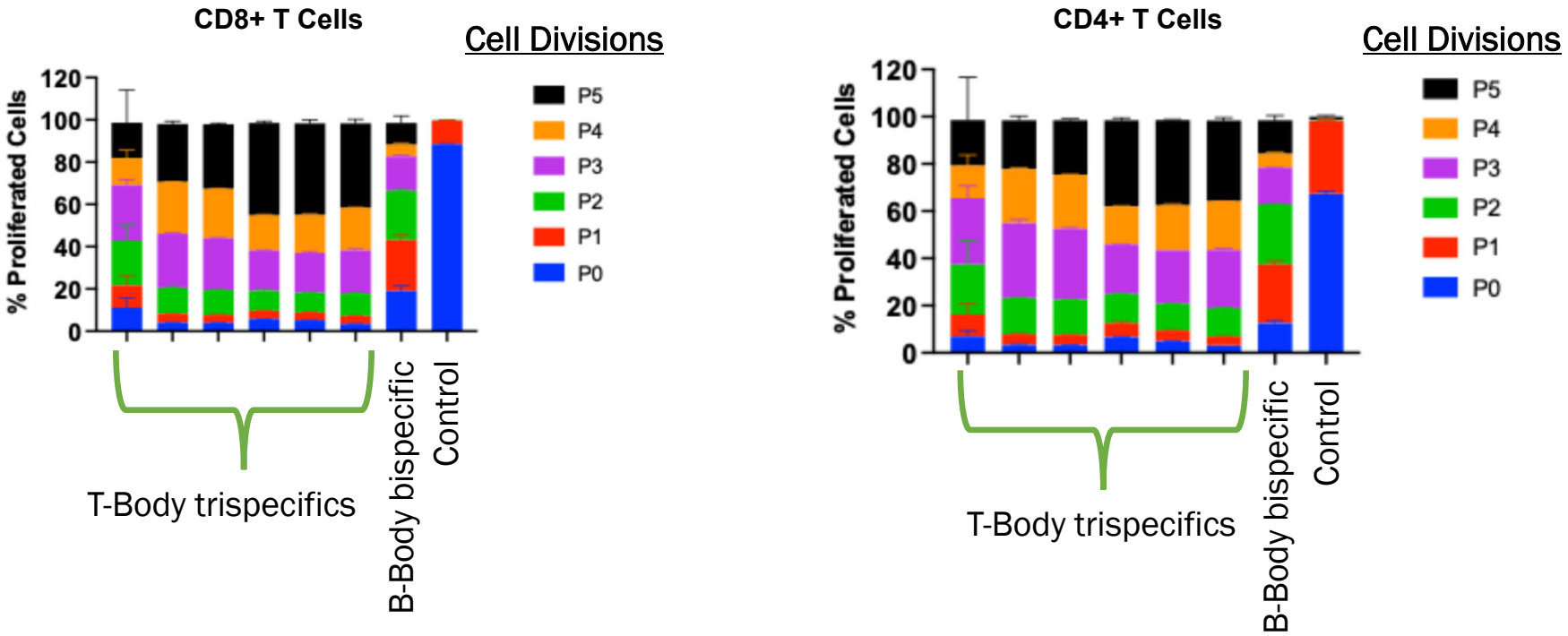
TAA ::x:: CD28 x CD3





Note: no cytokines were detected in the absence of tumor cells

Comparison of T-Body Trispecific vs. B-Body Bispecific Impact on T cell Proliferation (5 Days)

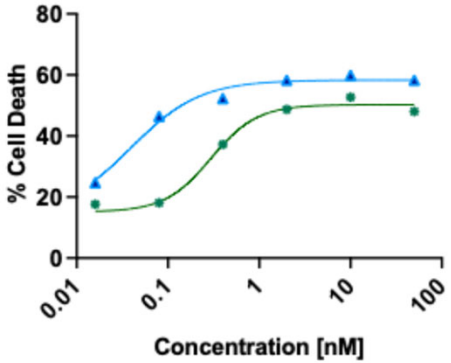


- Trispecific TCEs outperformed bispecific TCEs.
- Optimization of CD3 and CD28 KDs and epitope was important for enhancing proliferation.

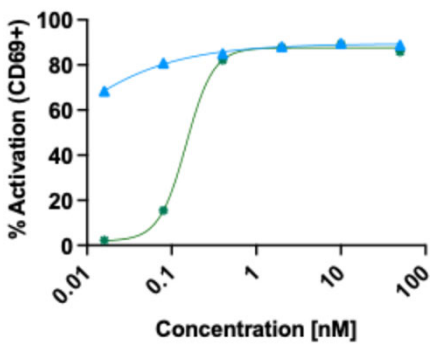
Comparing the Optimized T-Body Trispecific to the Top B-Body® TCE

PBMCs + Tumor Cells + Trispecific Abs or Bispecific Abs

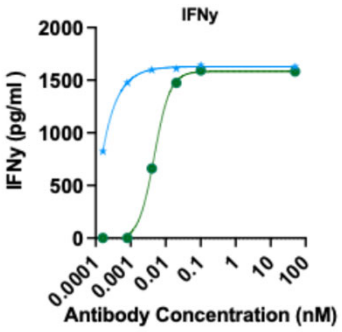
Cytotoxicity

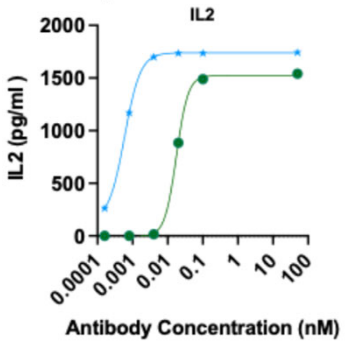


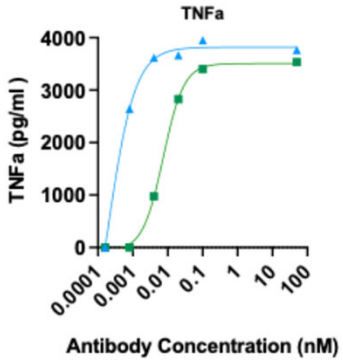
CD8+ T-cell Activation



Cytokines

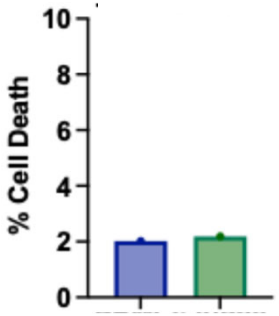




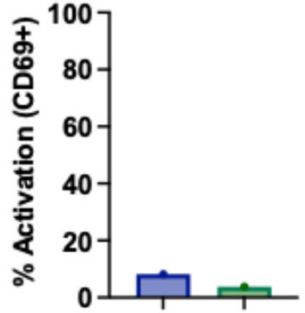


PBMCs Alone + Trispecific Abs or Bispecific Abs

CD8 T-cell Fratricide



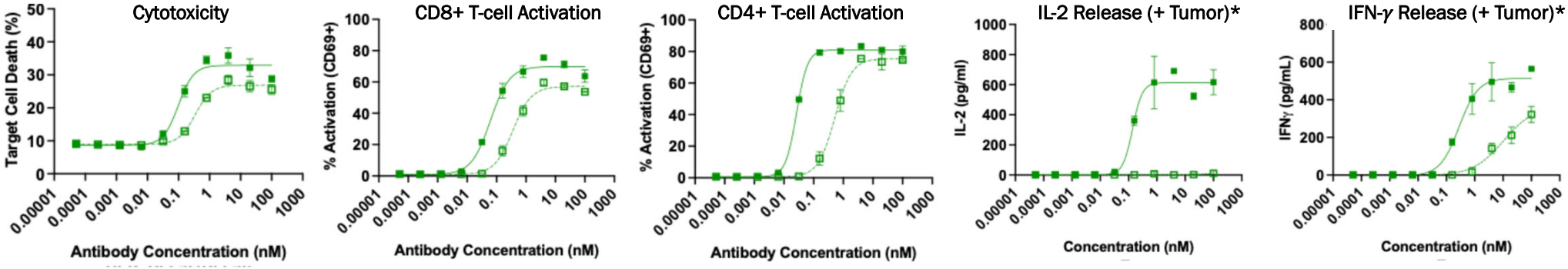
CD8 T-cell Auto-Activation



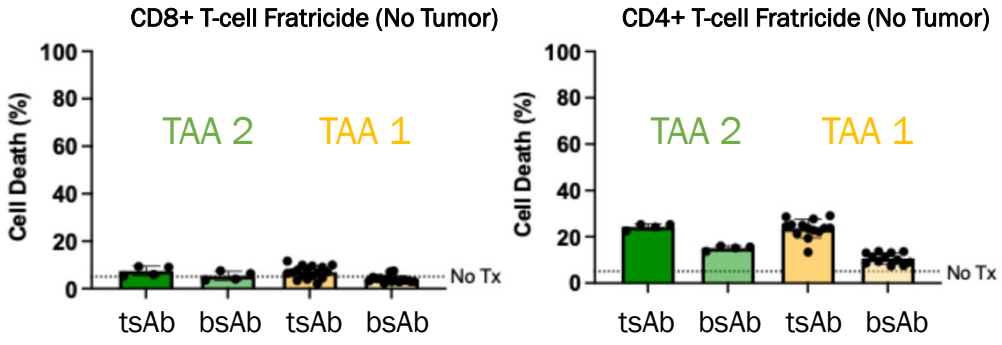
Tested at 50 nM

No cytokines detected in absence of tumor cells

Testing Optimized CD3/CD28 Pair with Additional TAA



*No IL-2 or IFN-γ release detected with PBMCs alone in the absence of tumor target cells



- Top panels: Using TAA 2, the optimized TsAb TCEs showed increased cytotoxicity, T-cell activation, and cytokine release compared to the BsAb TCEs across all assays tested
- Bottom panels: T-cell fratricide remained low across both tsAb TCEs tested.

Summary

- Addition of a CD28 costimulatory molecule to TCE in a tsAb format can:
  - Overcome exhaustion
  - Promote enhanced T cell proliferation
  - Enhance cytotoxicity, T-cell activation, and cytokine production

- Fratricide and cytokine release in the absence of TAA engagement remained low or undetectable for optimized CD3/CD28 pairing.

Platform Power: From Concept to Candidate in Weeks

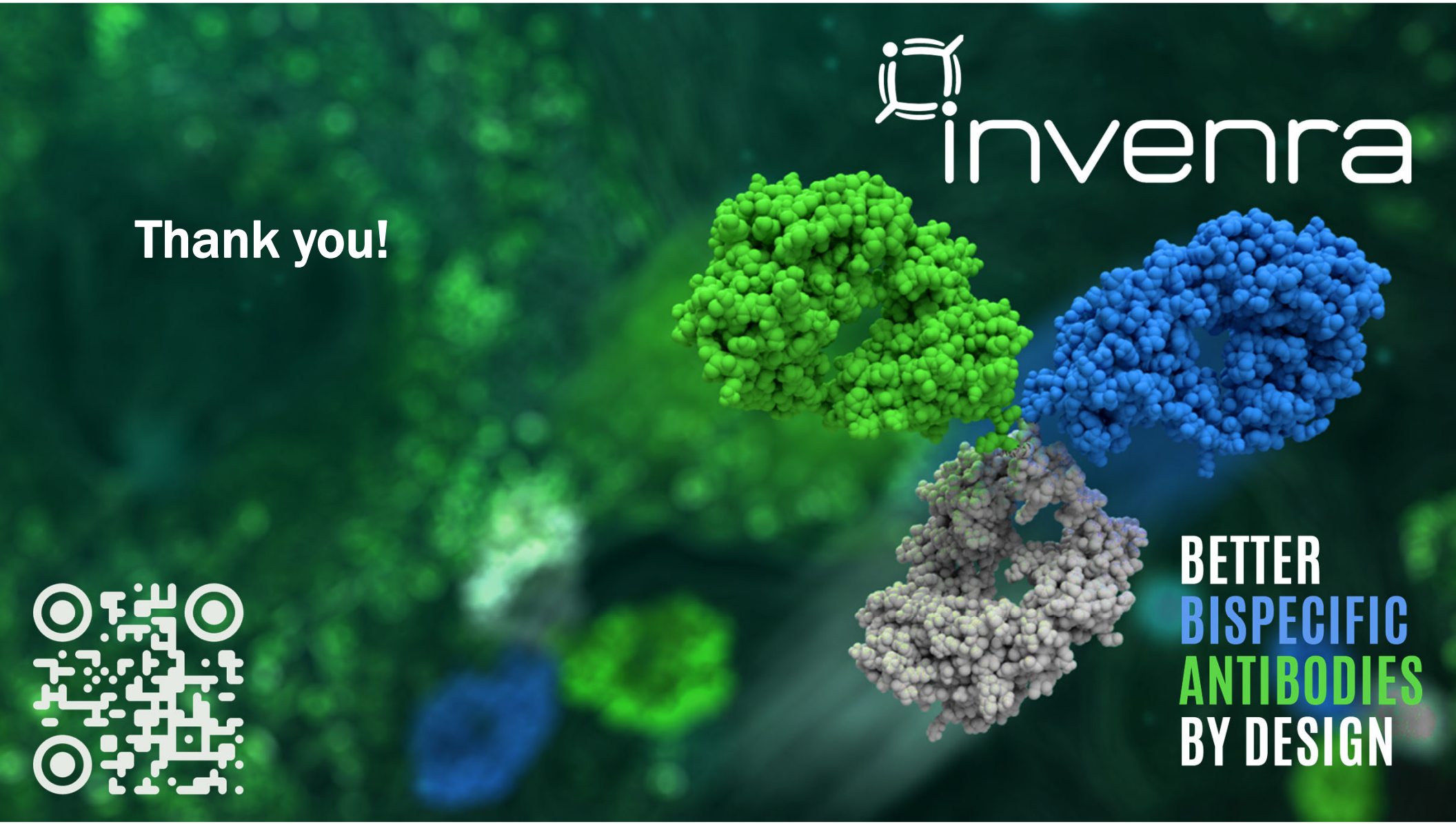
What you just saw:

- Rapid optimization of 18 trispecific TCE variants
- Systematic CD3×CD28 optimization
- Complete developability profiling
- Timeline: 10 weeks

This same platform approach applies to:

- Any bsAb or tsAb combination
- Any new target (multiple tumor targets or different co-stim.)
- Any therapeutic modality (TCEs, ADCs, IO, checkpoints)

Next: Assess PK and measure in vivo efficacy using humanized mice + tumor xenograft models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Thank you!
BETTER
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