Enhancing The Activity of T-Cell Engagers In Solid Tumors With CD28 Co-Stimulation

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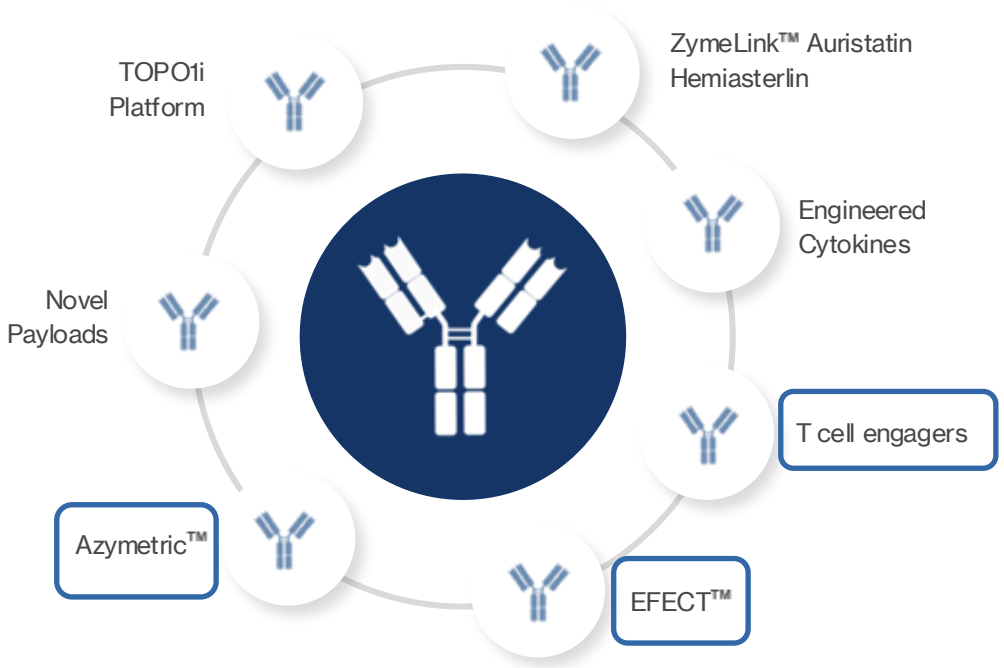
JUNE 24, 2026

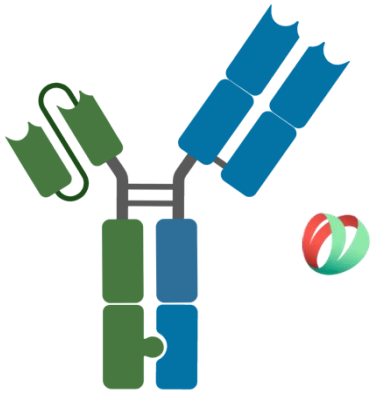
Developing Best In Class Antibodies Across Indications

PLATFORM AND DISCOVERY PARTNERSHIPS

Leverage partnerships to extend the reach of Zymeworks' best-in-class platforms and capabilities



MERCK Daiichi-Sankyo Johnson&Johnson GSK



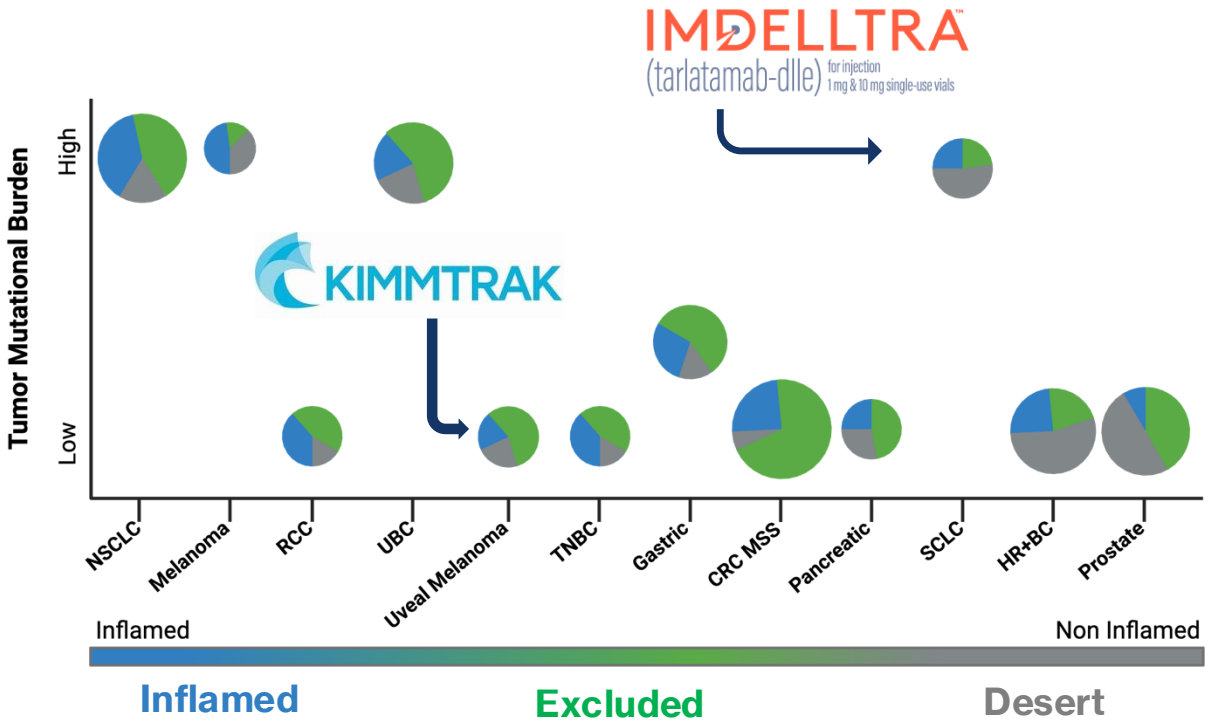
ZIIHERA® (zanidatamab-hrii) 50mg/ml Injection for IV

Biparatopic Antibodies

ADCs

TCEs

Limited Number of TCE Approved in Solid Tumors And Unmet Need Remains



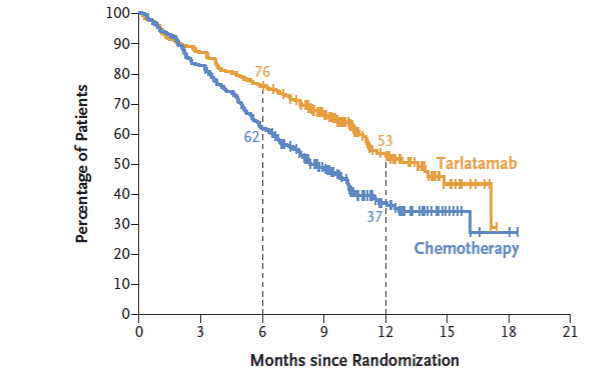
Adapted from Hedge and Chen 2020 Immunity 52

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tarlatamab in Small-Cell Lung Cancer after Platinum-Based Chemotherapy

N ENGL J MED 393;4 NEJM.ORG JULY 24, 2025



No. at Risk							
Tarlatamab	254	220	192	131	60	17	0
Chemotherapy	255	210	156	97	42	9	2	0

	Median Overall Survival (95% CI) *mo*
Tarlatamab (N=254)	13.6 (11.1–NR)
Chemotherapy (N=255)	8.3 (7.0–10.2)

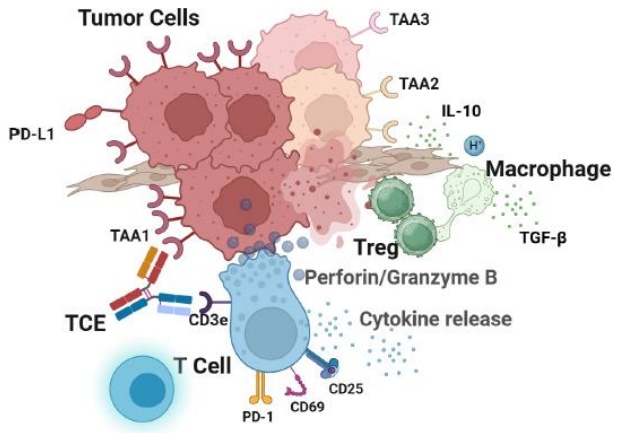
Stratified hazard ratio for death, 0.60 (95% CI, 0.47–0.77)
P<0.001

	ORR	PFS	OS	Gr3 AE
Tarlatamab	35%	4.2m	13.6m	54%
Chemotherapy	20%	3.7m	8.3m	80%

Gen 1 TCE Are Limited by Narrow Therapeutic Window & Solid Tumors Present Additional Challenges

Key Problem 1:
Tumor heterogeneity and limitations due to concomitant cytokine release

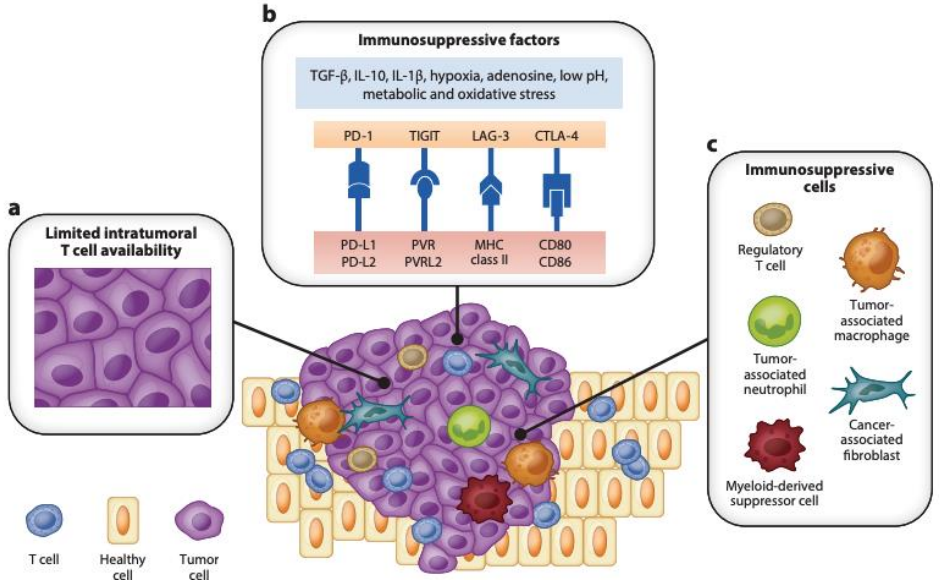
Solution 1:
Target selection and molecular design



Cao L et al Front Immunol 2025

Key Problem 2:
Low T cell infiltration, T cell anergy and immunosuppressive microenvironment

Solution 2:
Addition of co-stimulatory signal to T-cell engagers



Arvedson T et al Ann Rev Cancer Biol 2022

Why Is CD28 The Ideal Co-Stimulatory Target?

	CD28	4-1BB	CD2
Naïve / recently recruited T cells [1-3]	✓	✗	✓
Anergy prevention [4-6]	✓	✗	⚠ *Moderate (NFAT-dominant)*
Ability to expand & maintain T_{pex} [7,8,6]	✓	✗	✓
No signaling in absence of Signal 1 (monovalent engagement) [9,8,6]	✓	✗	⚠ *NF-κB yes / NFAT no*
Limited / no detrimental trans-cell interactions [10-12]	✓	✗	⚠ *NK-T bridging potential*
Low TMDD risk	✓	⚠	⚠
Clinically validated [13-16]	✓	✓	✗

1. Esensten, 2016, Immunity, vol. 44 2. Pollok, 1993, J Immunol, vol. 150 3. Leitner, 2015, J Immunol, vol. 195 4. Skokos, 2020, Sci Transl Med, vol. 12 5. Saoulli, 1998, J Exp Med, vol. 187 6. De Sousa Linhares, 2024, iScience, vol. 27 7. Humblin, 2023, Sci Immunol, vol. 8 8. Enamorado, 2023, Immunity, vol. 56 9. Dennehy, 2006, J Immunol, vol. 176 10. Esensten, 2016, Immunity, vol. 44 11. Wang, 2009, Immunol Rev, vol. 229 12. Quastel, 2022, Nat Rev Immunol, vol. 22 13. Korfi, 2025, Cancer Res (AACR), vol. 85 14. Segal, 2018, Clin Cancer Res, vol. 24 15. Cappell & Kochenderfer, 2021, Nat Rev Clin Oncol, vol. 18 16. Chon, Phase 1 (BGB-B2033), ASCO 2026 (first disclosure)

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Trispecific T-Cell Engagers

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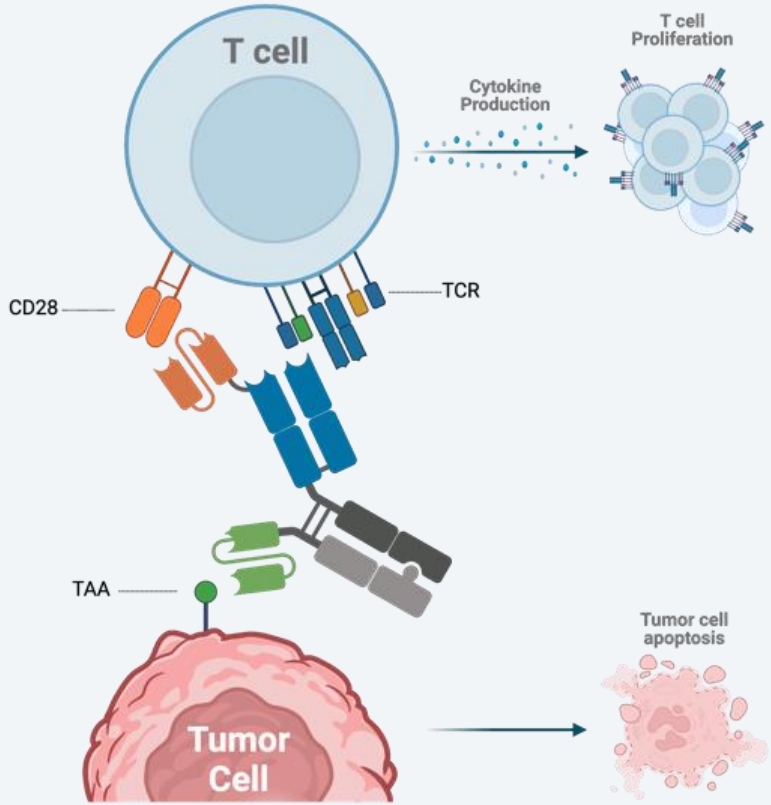
TriTCE Co-stim Are Designed For Optimal Anti-Tumor Activity And Maximal Safety

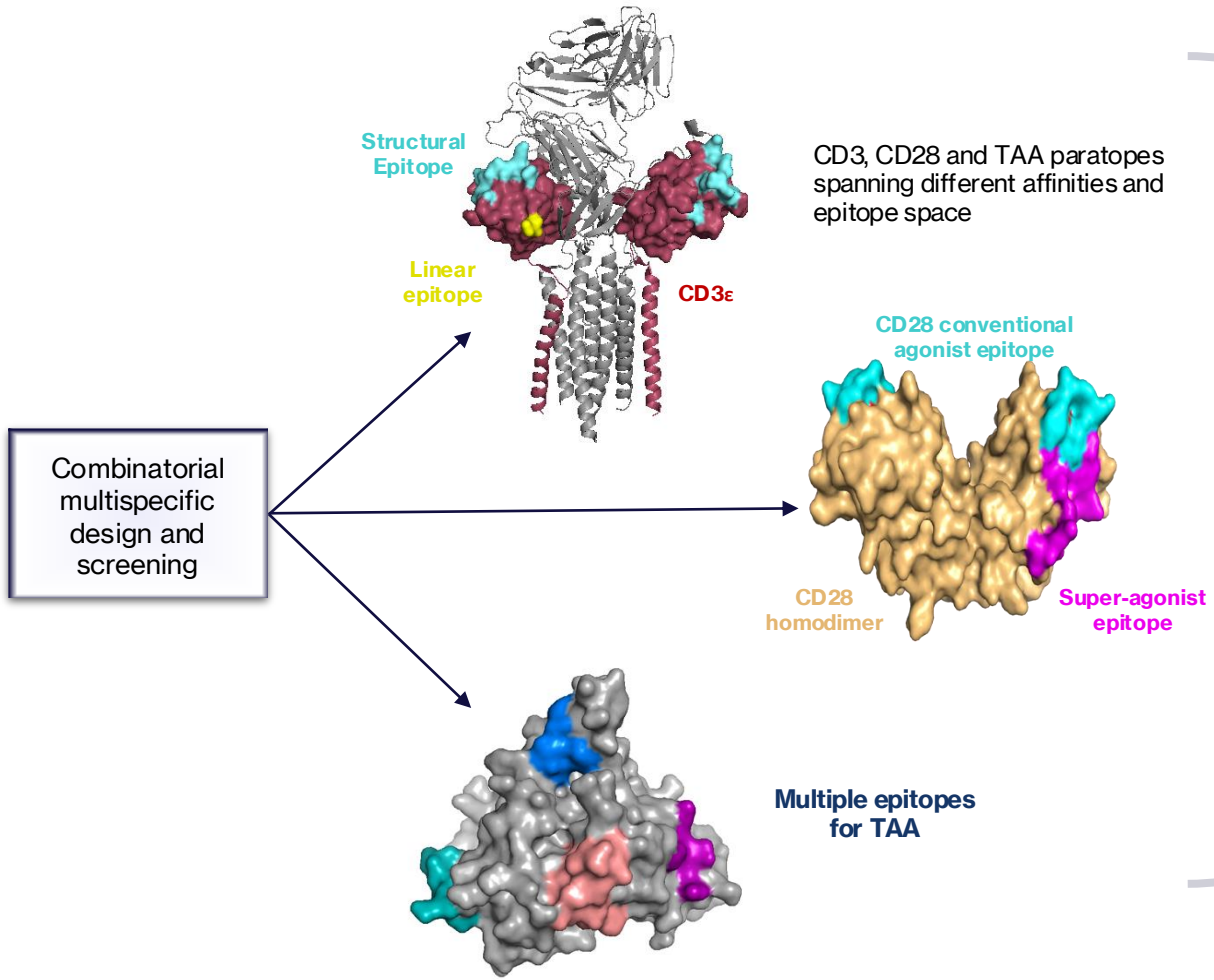


	Design Feature	Expected Benefit
1	**Balanced activation of CD3 and CD28**	Potential to provide more durable responses and activate T cell responses in 'cold' tumors with lower T cell infiltration
2	**Low affinity, Conditional CD28 engagement**	Requires co-engagement of CD3
3	**Obligate *cis*-T cell (CD3xCD28) binding**	No T cell-to-T cell bridging or T cell fratricide
4	**Target-dependent activity**	Low T cell binding and no T cell activation in absence of tumor target

CRS: Cytokine release syndrome; irAEs: immune-related adverse events

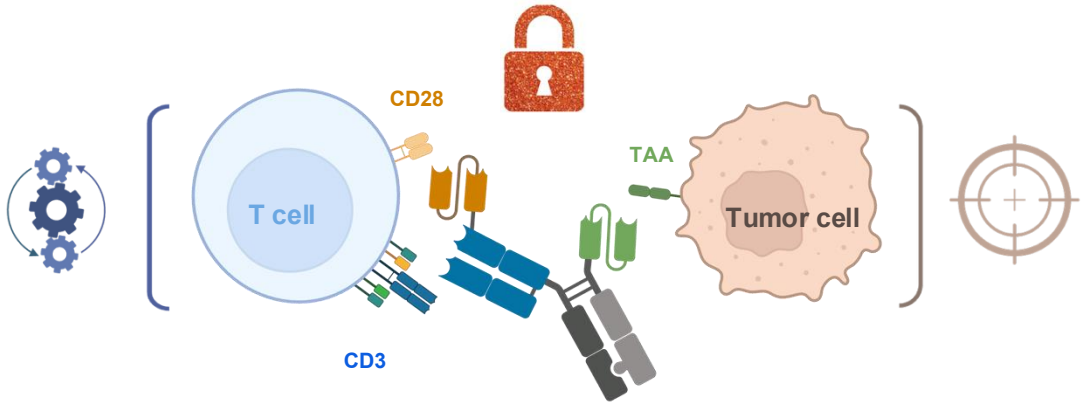
Extensive Paratope And Format Exploration Enables Discovery Of Best TriTCEs

Selection of Diverse Paratopes and Affinities



CD3, CD28 and TAA paratopes spanning different affinities and epitope space

Locked CD3/CD28 geometry:
optimized for efficient conditional *cis* CD28 co-stimulation and strict TAA dependence



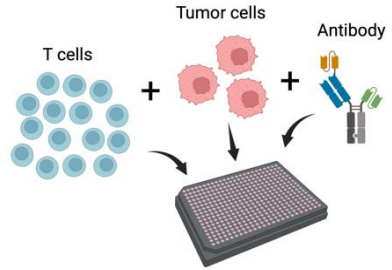
Fine-tune CD3 and CD28 affinity:

- Cytotoxic potency
- T cell activation
- Cytokine production
- T cell proliferation

Versatile tumor targeting solutions:

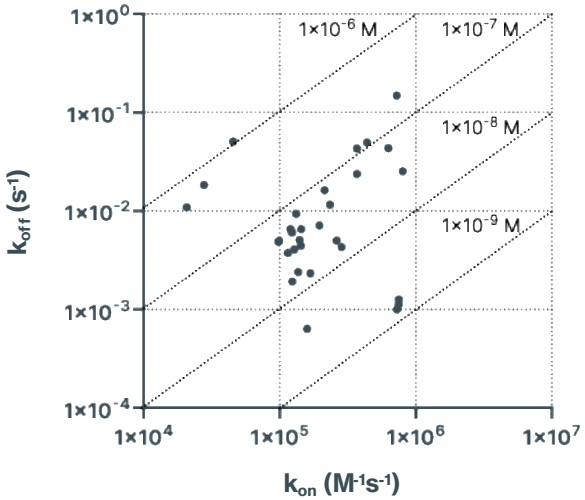
- Monovalent/bivalent Fab, scFv, VHH
- Multi-TAA logic-gated designs
- pMHC targeting

Optimizing CD3 And CD28 Affinities For Best Trispecific TCEs

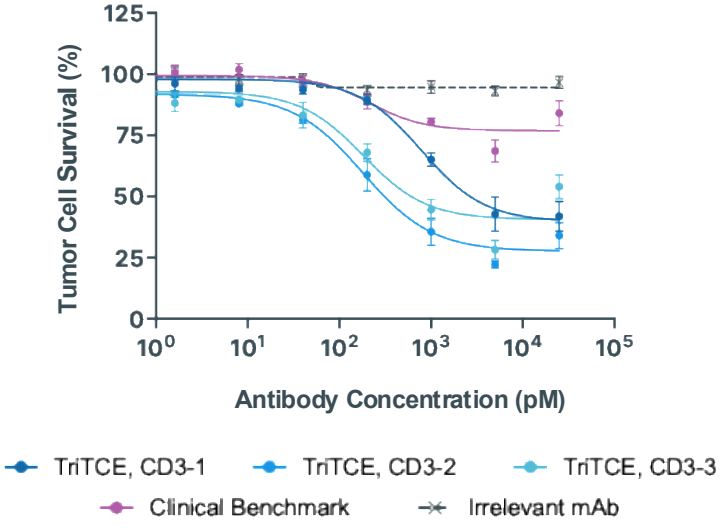


Fine-tuning CD3 kinetics

CD3 affinity library

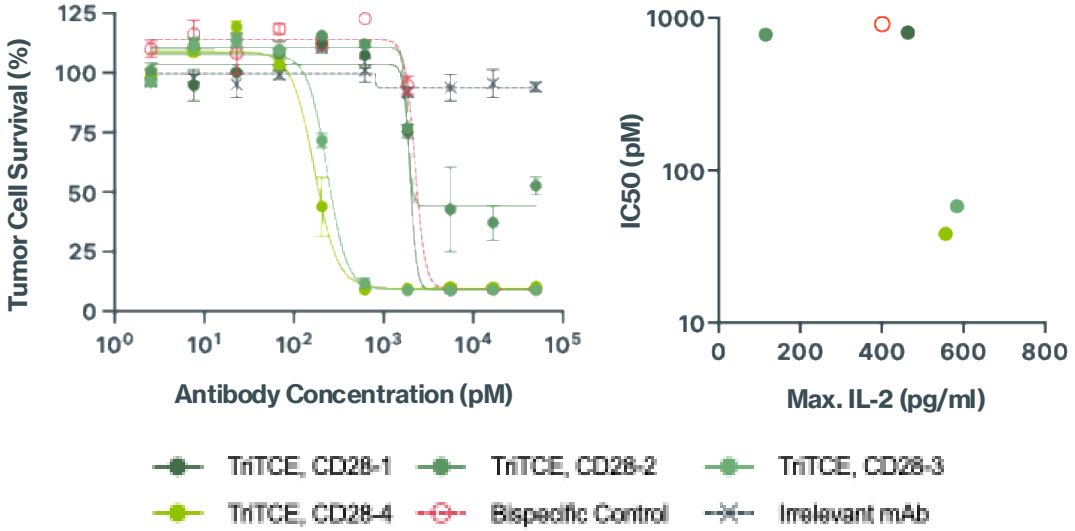


T-Cell Dependent Cytotoxicity



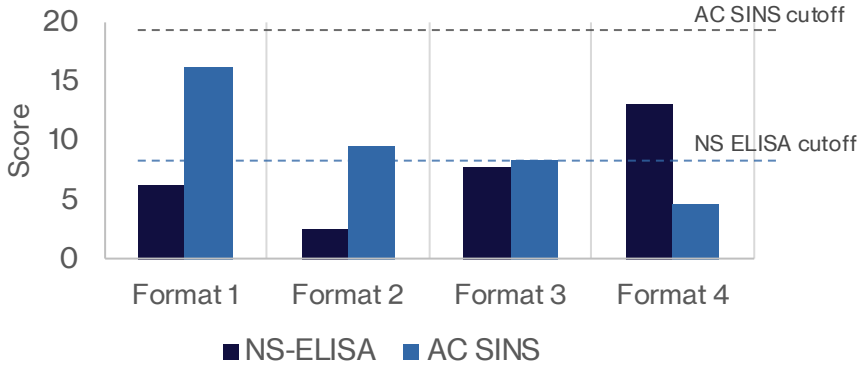
Fine-tuning CD28 co-stimulation

T-Cell Dependent Cytotoxicity

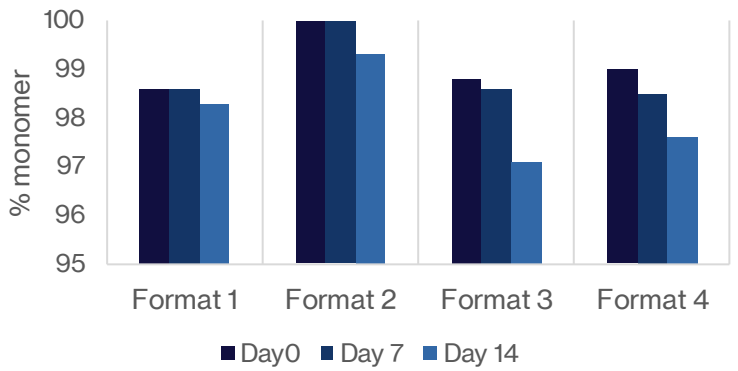


Multispecific Antibodies Must be Engineered For Optimal Activity And Developability

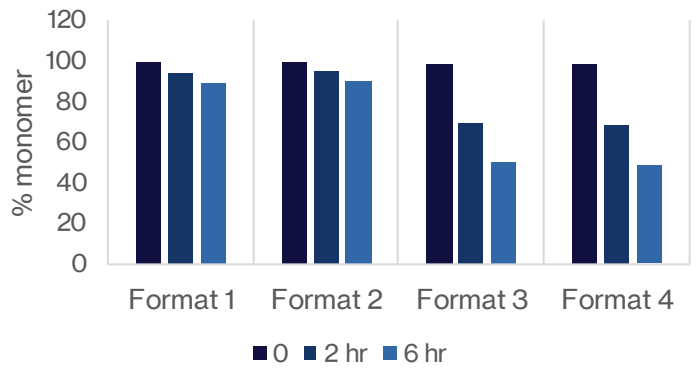
Non-specific Interactions



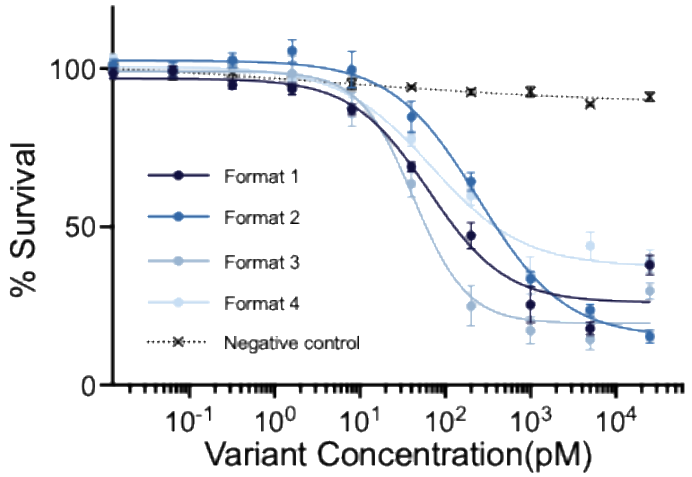
Accelerated Stability (T°C)



Accelerated Stability (pH)



T-cell Dependent Cytotoxicity



- Engineering liabilities out of paratopes and selecting the right format is key to making robust multispecific therapeutics.
- Potency is key for T cell engagers, but the developability profile will indicate how easily it can be manufactured.

A DLL3-Targeted TCE with Co-Stimulation

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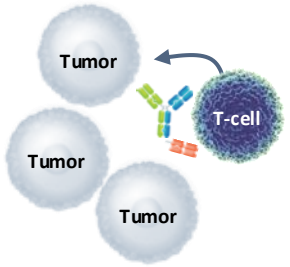
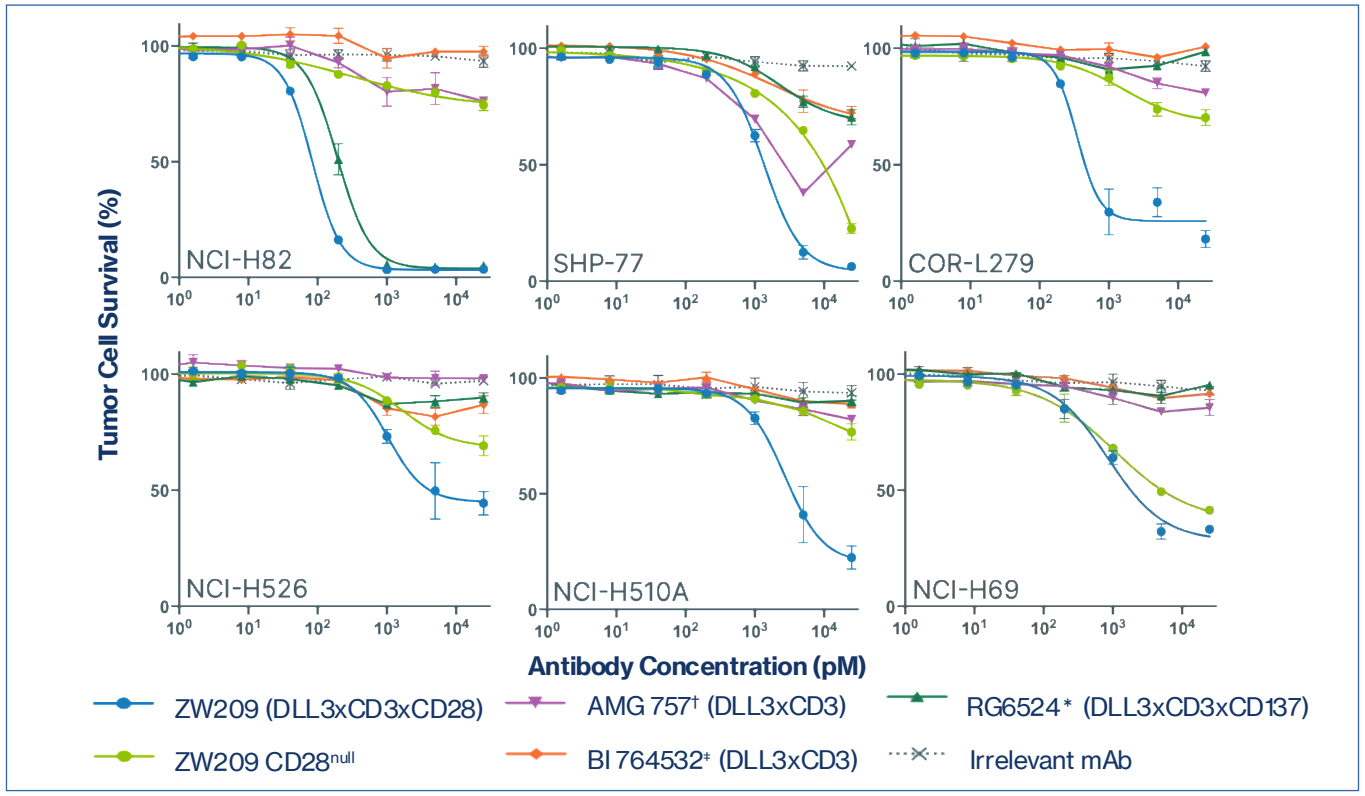
ZW209 Exhibits Improved Potency Relative To Bispecific And Trispecific Clinical Benchmarks At Low Effector: Target Ratios



Low E:T Assay System

Cytotoxicity and T cell proliferation



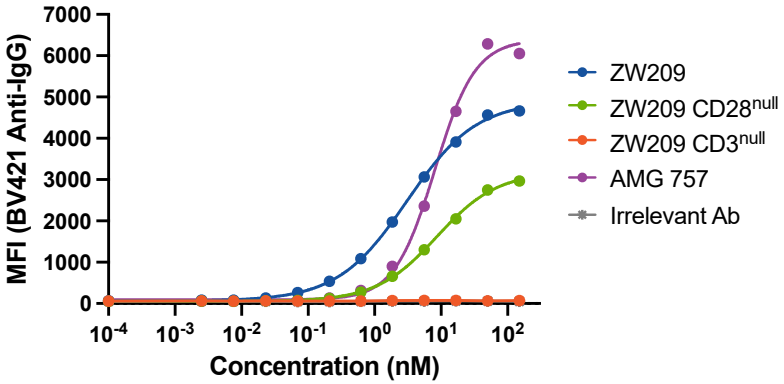
Test articles were incubated with T cells co-cultured with DLL3-expressing SCLC tumor cell lines at low E:T ratio for 7 days and evaluated for cytotoxicity.

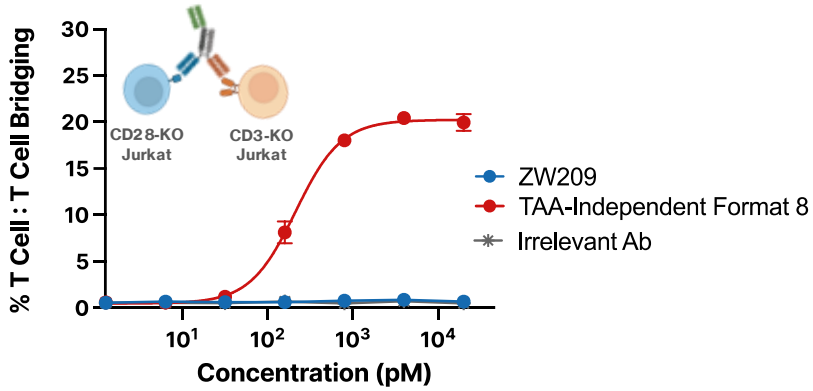
ZW209: DLL3 x CD3 x CD28 Trispecific T Cell Engager Designed For Treatment Of Small Cell Lung Cancer

ZW209 design facilitates desirable T cell engagement

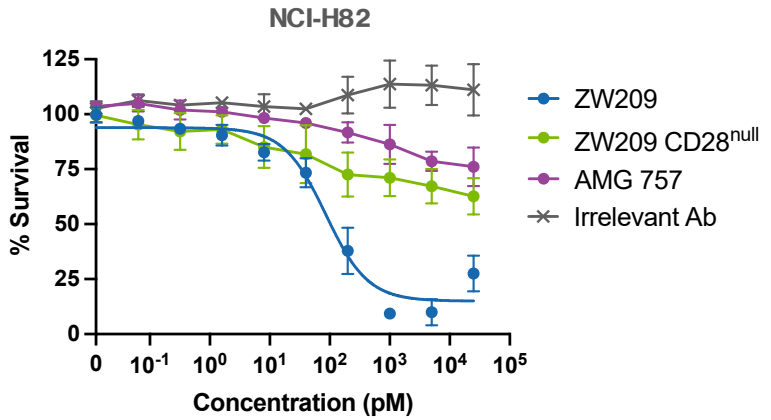
Design Feature
☑ Balanced activation of CD3 and CD28
☑ Low affinity, Conditional CD28 engagement
☑ Obligate *cis*-T cell (CD3xCD28) binding
☑ Target-dependent activity

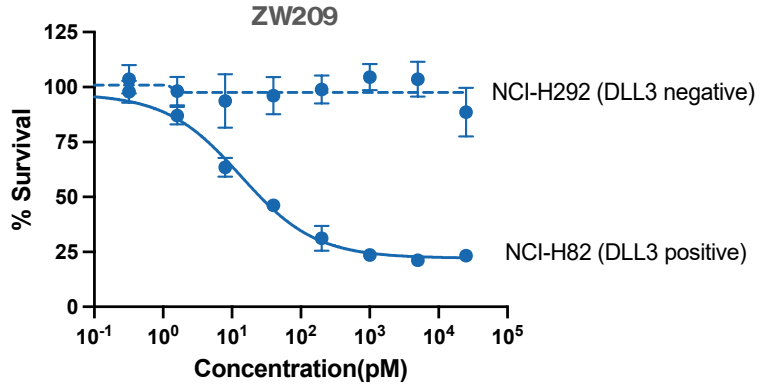
Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate Cis Binding



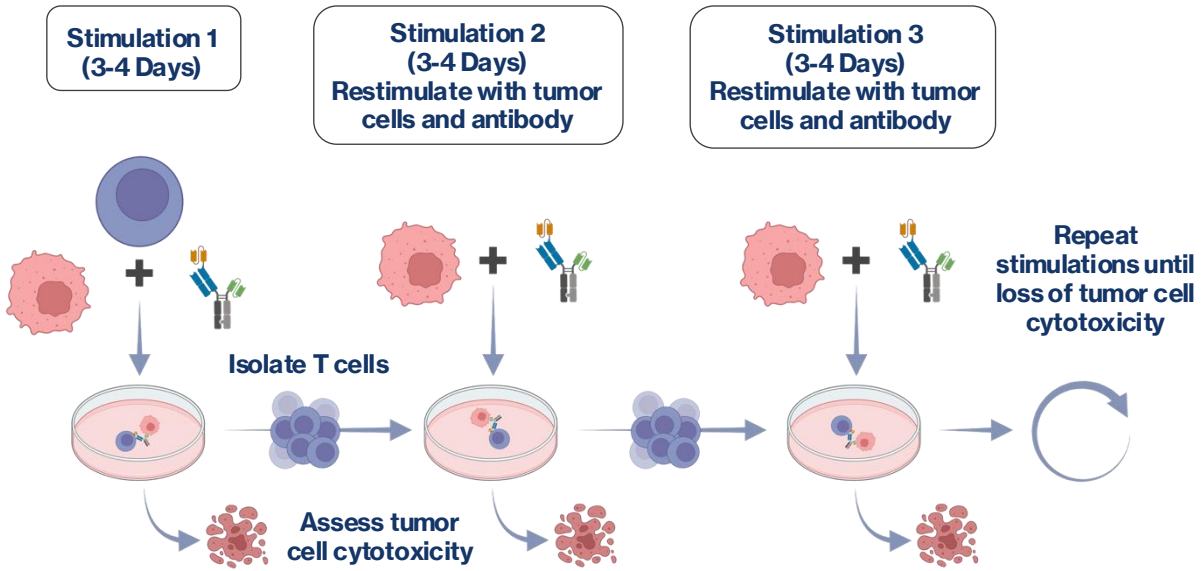


Improved Cytotoxicity Over Bispecifics in Low E:T Conditions

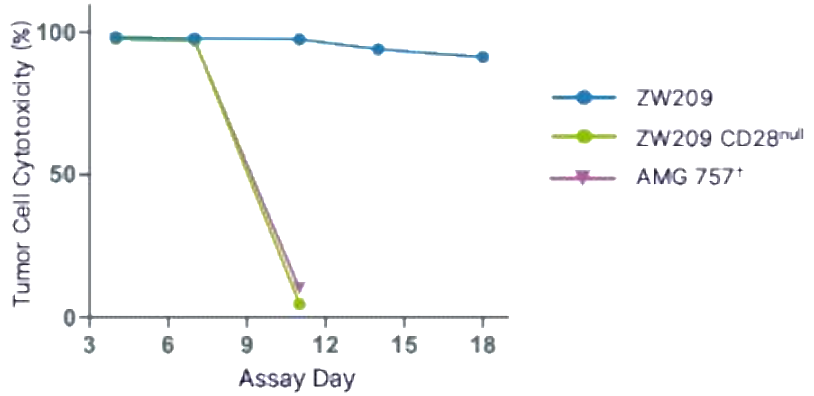




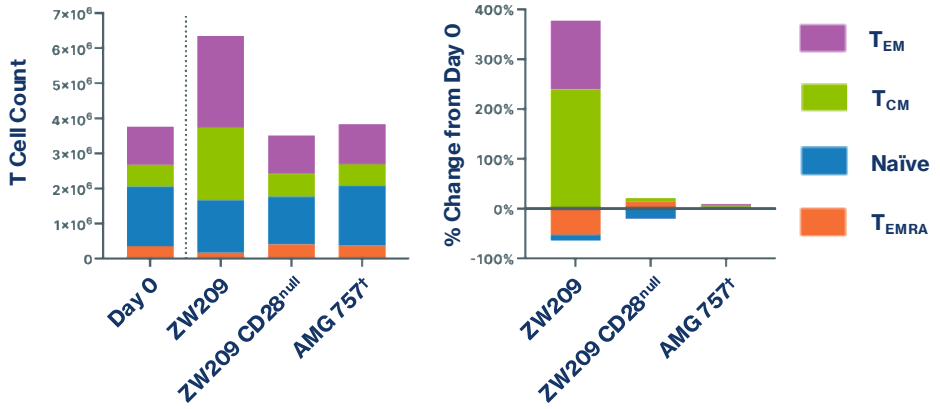
ZW209 Demonstrates Prolonged T cell Cytotoxicity In Repeat Challenge Assay



Sustained cytotoxicity relative to bispecific TCEs

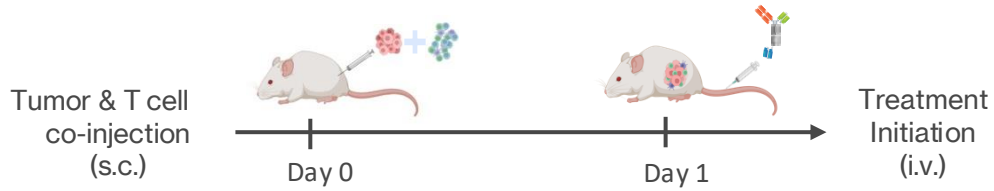


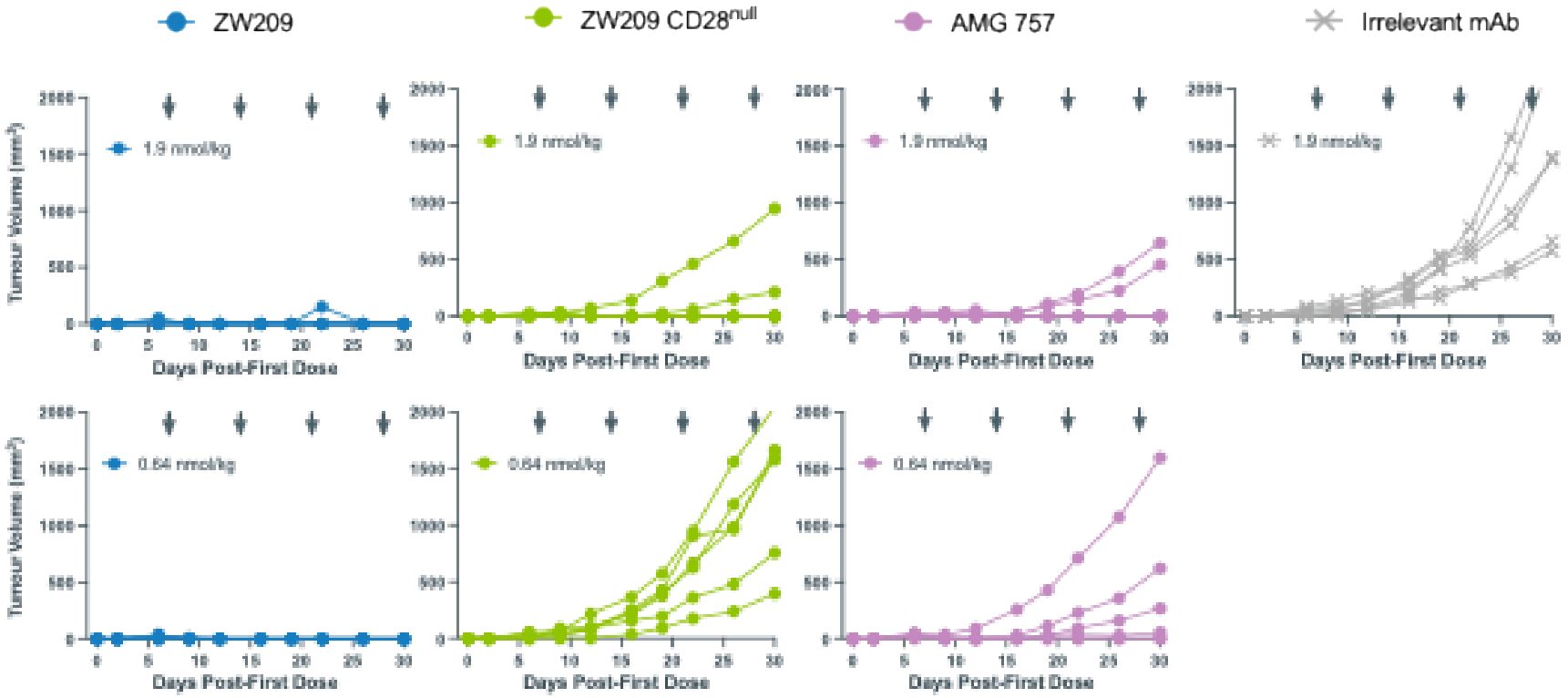
Expanded effector memory (T_{EM}) and central memory (T_{CM}) T cell populations after 2nd stimulation (Day 7)



† AMG 757 (DLL3/CD3 BiTE) produced in-house

ZW209 Mediates Enhanced Antitumor Activity Compared To Bispecific And Benchmark Antibody

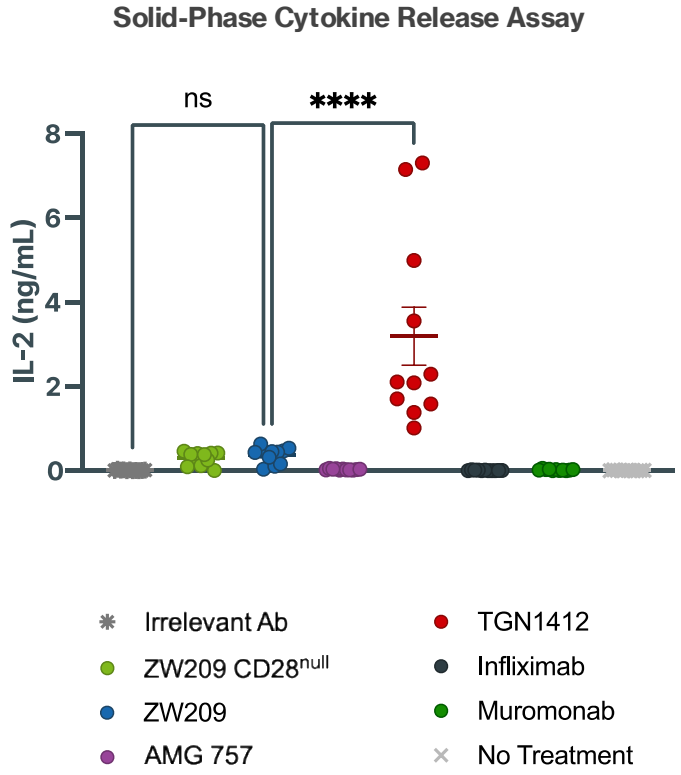




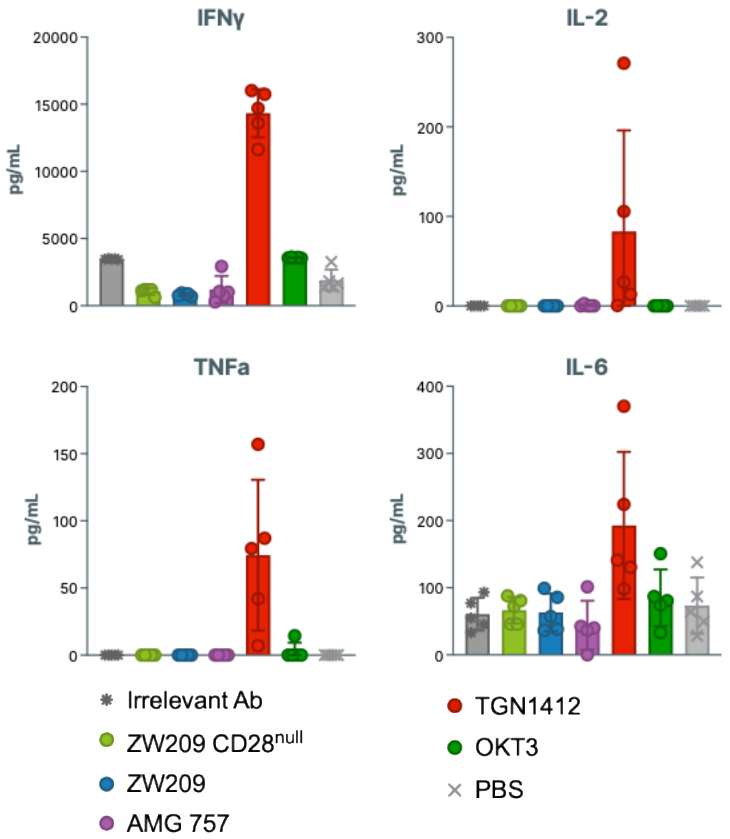
ZW209 shows superior anti-tumor activity compared to the bispecific and benchmark antibody in NCI-H82 admixture xenograft model

ZW209 Has A Favorable Safety Profile *In Vitro* And In Animal Studies

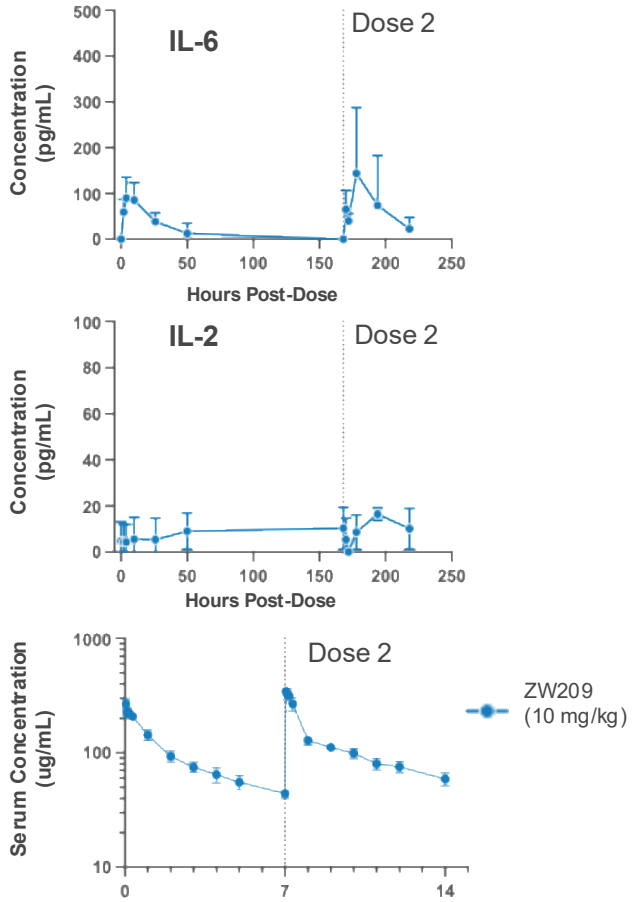
No Cytokine Activation With PBMCs Alone



Induces Minimal Systemic Cytokine In An *In Vivo* Cytokine Release Model



Well-Tolerated In Cynomolgus Monkeys



TGN1412 positive control
All dosed at 2 mg/kg except OKT3 (0.25 mg/kg)

A Co-Stim Story For Many Indications And Targets

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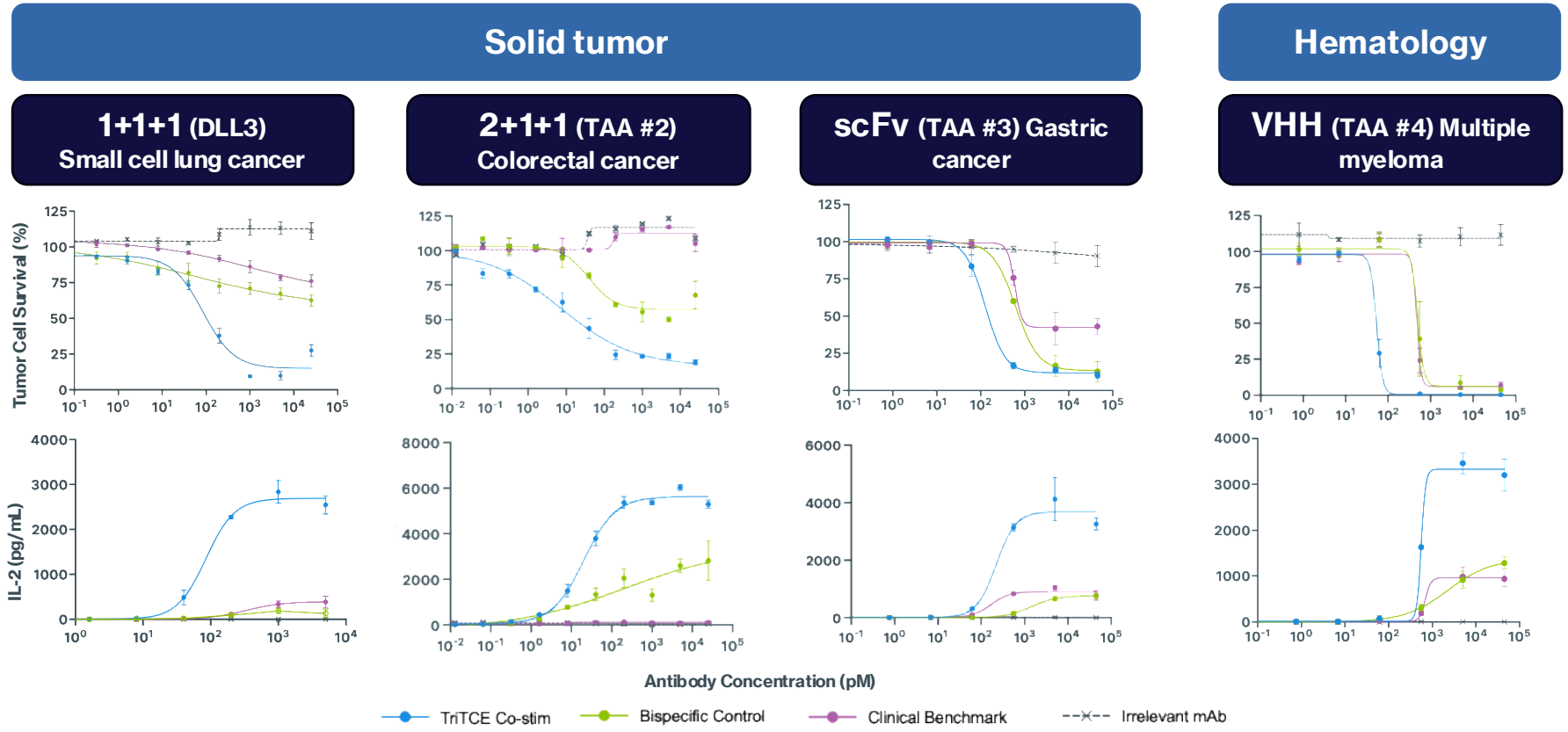
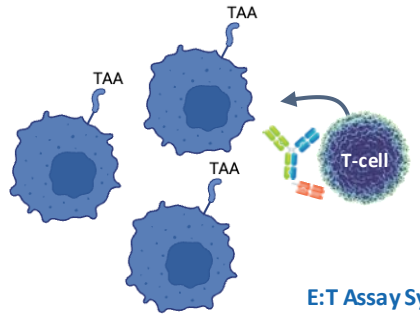
TriTCE Co-Stim Platform Is Versatile And Applicable Across Diverse Indications



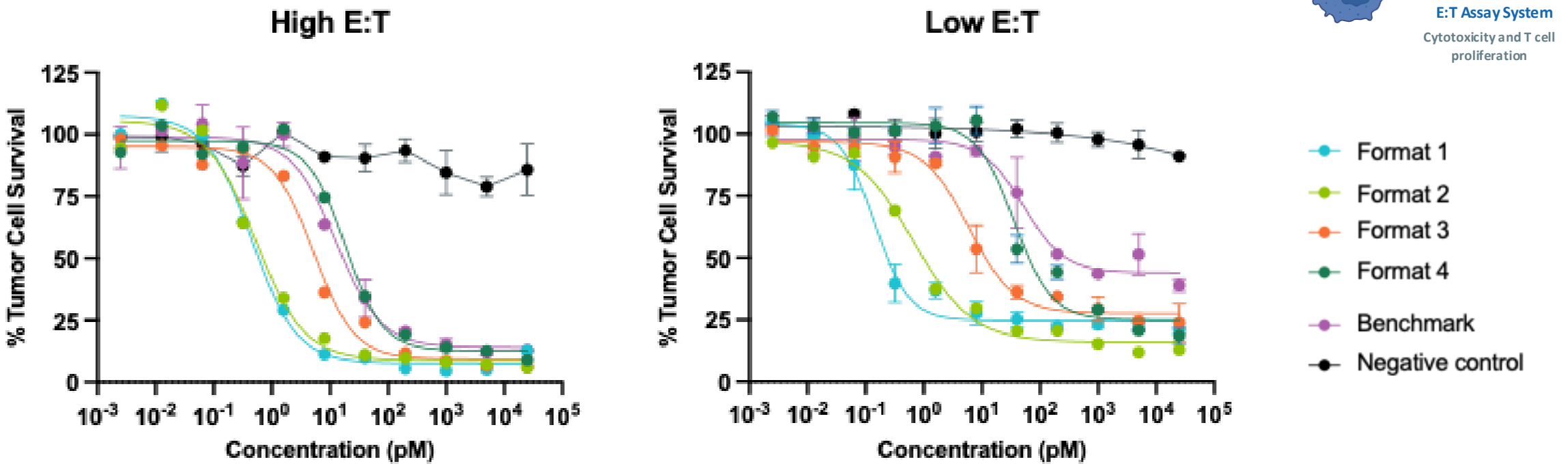
Optimal format and valency changes based on target and indication

Format Has A Significant Impact On Activity Of T cell Engager



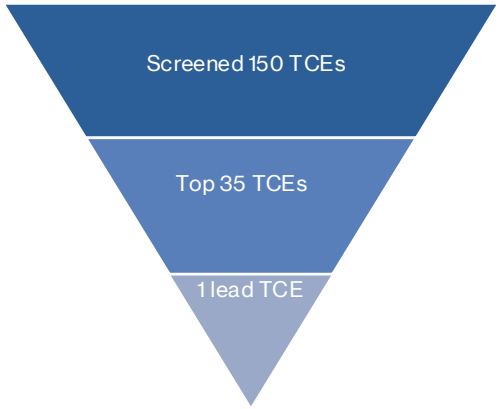
E:T Assay System

Cytotoxicity and T cell proliferation

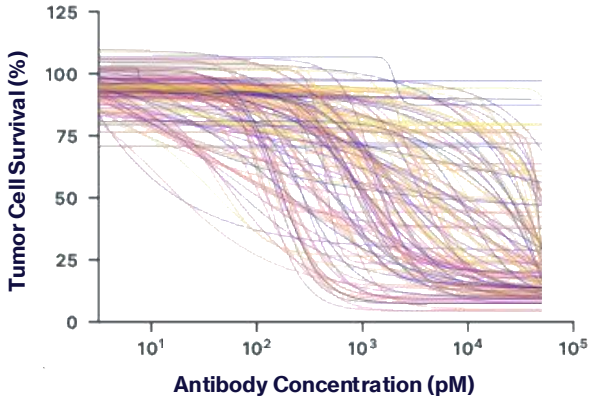


Targeting Peptide-MHC Using TriTCE Co-Stim Platform

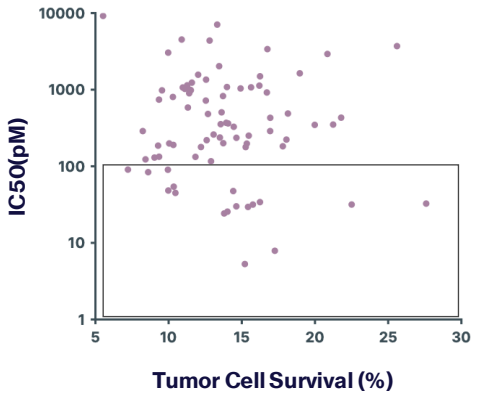
pMHC TriTCE Screening Funnel



HTP *in vitro* assessment of 150 TCEs

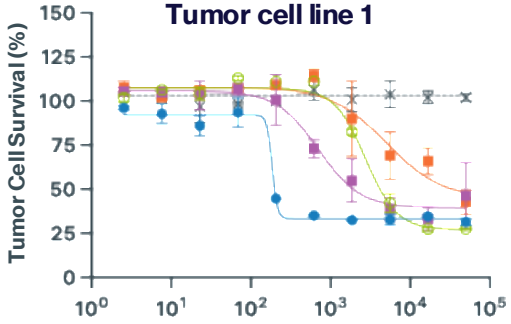


Selection based on cytotoxicity and potency

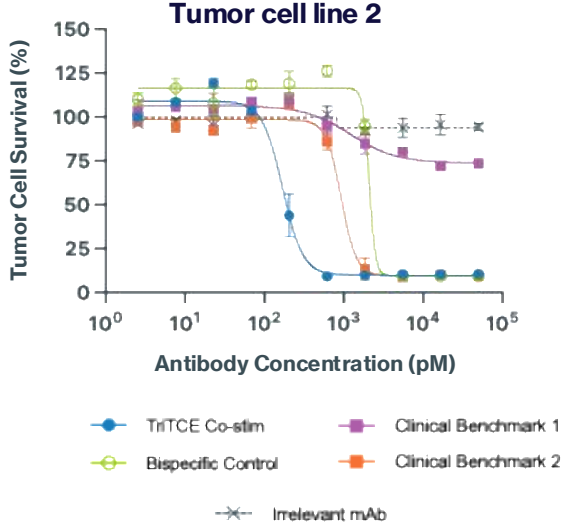


Lead TCE selection

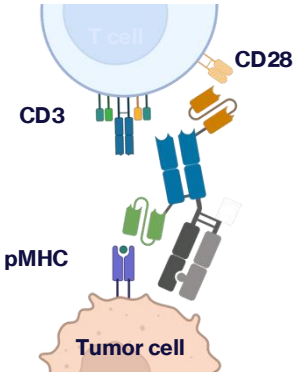
Tumor cell line 1



Tumor cell line 2



Identification of Lead αpMHC TriTCE format*

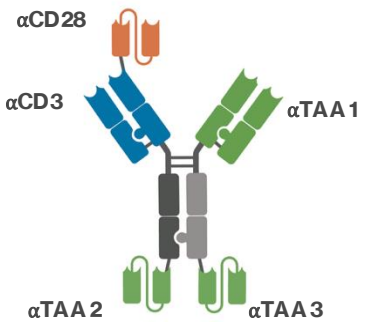


*representative format

Logic-Gated TriTCE Co-Stim Platform Can Overcome Antigen Escape In Acute Myeloid Leukemia

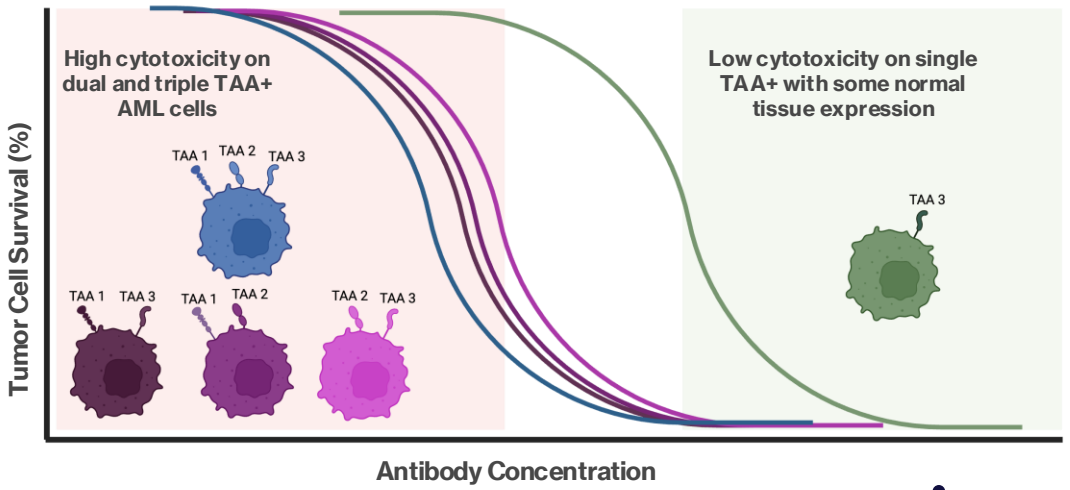
Biological Challenge	Limitation of Mono-antigen Targeted Therapies
Heterogeneous intertumoral antigen expression	Antigen escape
Lack of a clean single target between AML blast, LSCs and healthy cells	Narrow therapeutic window

Screened logic-gated TriTCE antibody formats for selective tumor cytotoxicity in the presence of two or three TAAs



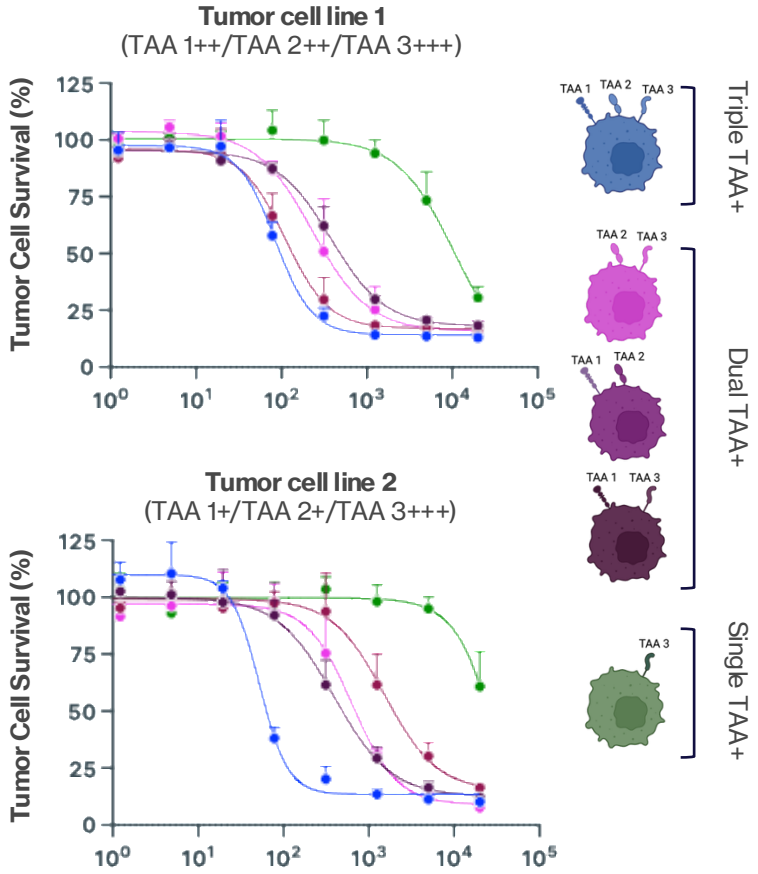
*representative format

TAA expression profile	TAA	Cytotoxicity
Triple positive	TAA 1 & TAA 2 & TAA 3	✅
Dual positive	TAA 1 & TAA 2 OR TAA 2 & TAA 3 OR TAA 1 & TAA 3	✅
Single positive	TAA 3	❌



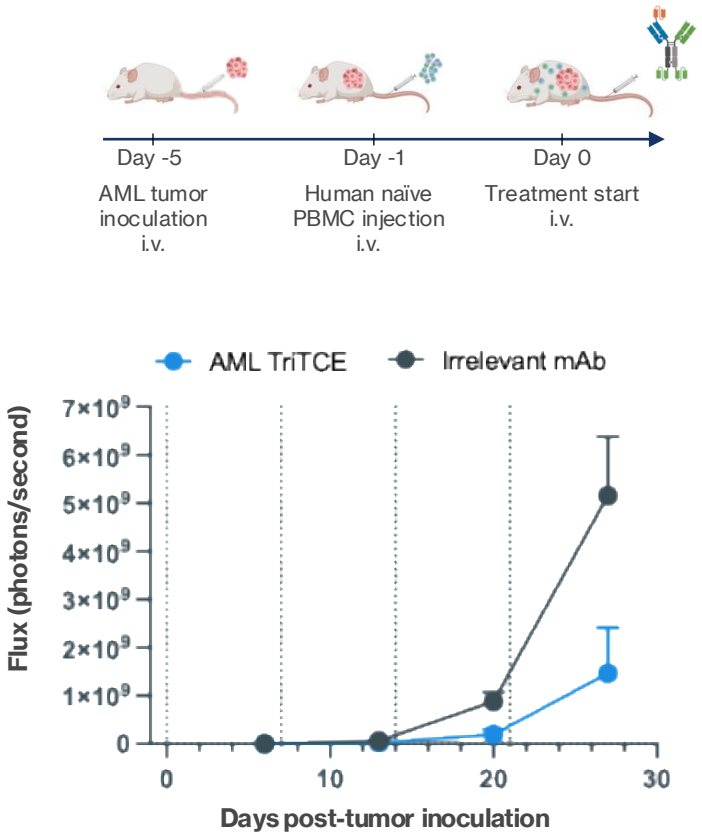
Logic-Gated TriTCE Co-Stim Platform Can Overcome Antigen Escape In Acute Myeloid Leukemia

Lead logic-gated TriTCE demonstrates desired TAA-selective cytotoxicity

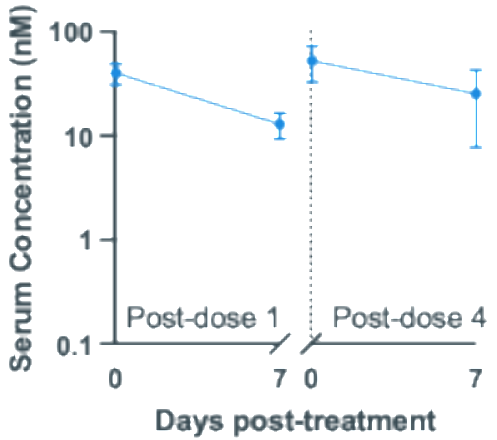


In vivo anti-tumor activity of AML TriTCE in disseminated AML xenograft model

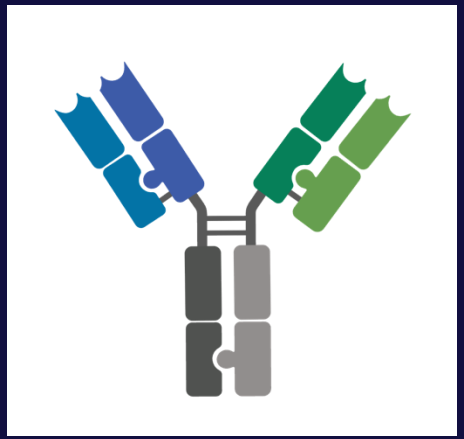
(TAA 1+/TAA 2++/TAA 3+++)



Antibody-like serum PK of AML TriTCE



Summary



Azymetric™ platform for bispecific antibodies and beyond

Design

- TriTCE Co-stim platform optimized for strict TAA dependent T cell activation with efficient conditional *cis* CD28 co-stimulation for maximal activity and safety

Advanced Protein Engineering Solutions

- Flexibility of Azymetric™ enables easy high throughput screening of multispecific formats to identify novel therapeutics with desired biology

Making A Difference In Indications With High Unmet Need

- Plug and play co-stimulation platform facilitates design of next generation T cell engagers to overcome complex biological challenges in oncology and autoimmune diseases

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