



# TriTCE Co-Stim: A Differentiated T Cell Engager Platform With Conditional *Cis* CD28 Co-Stimulation

Genevieve Desjardins, PhD, Associate Director in Protein Engineering

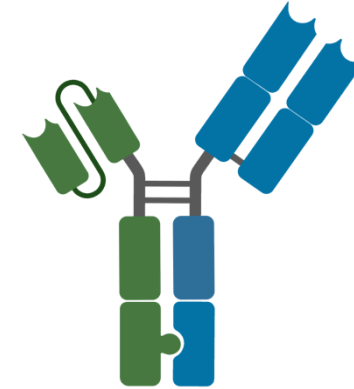
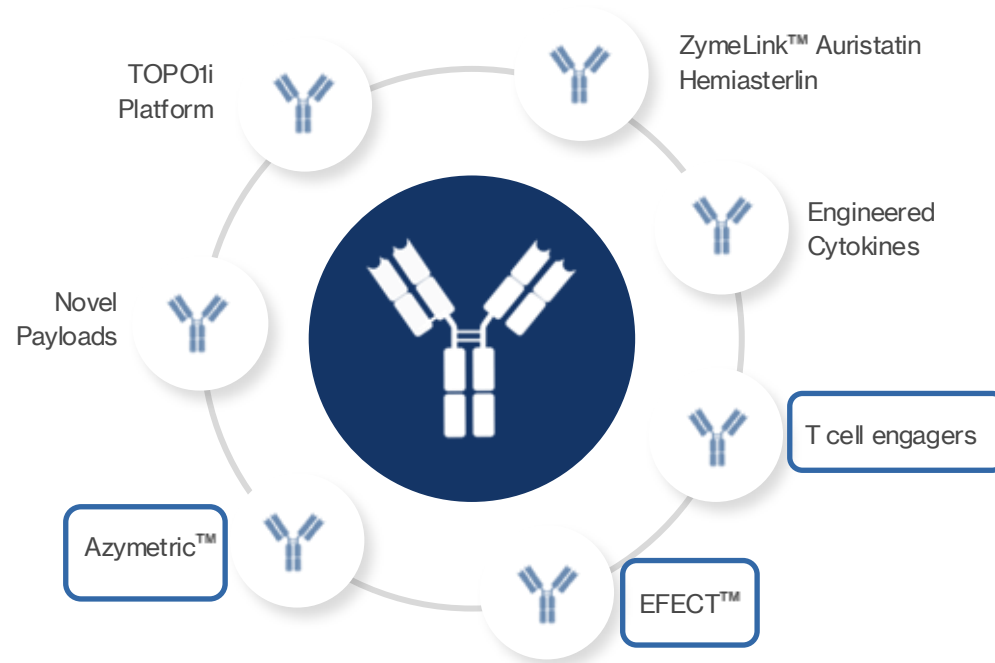
**MAY 13, 2026**

Nasdaq: ZYME | [zymeworks.com](https://zymeworks.com)

# 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



**Biparatopic Antibodies**



**ADCs**

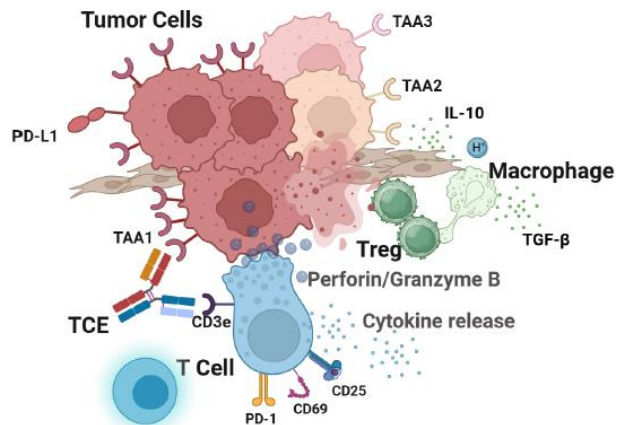


**TCEs**

# 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

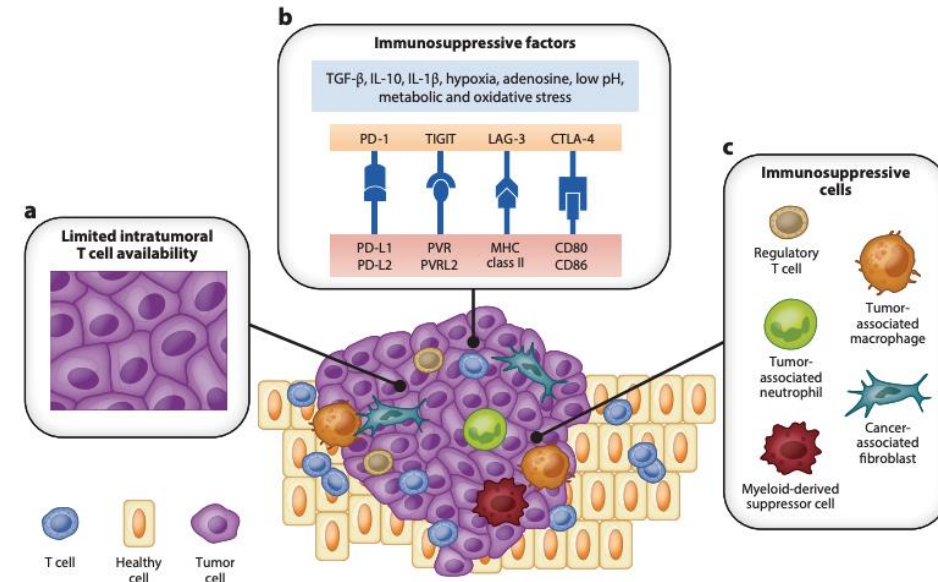
**Solution 1:**  
Target selection and molecular design



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

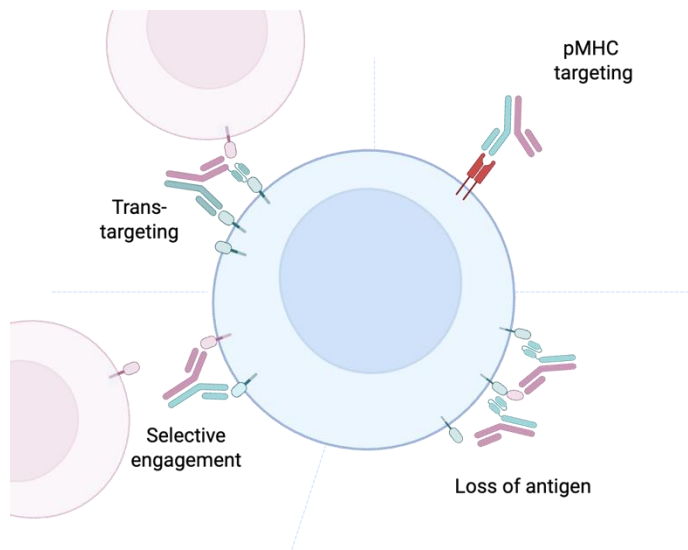


Arvedson T et al Ann Rev Cancer Biol 2022

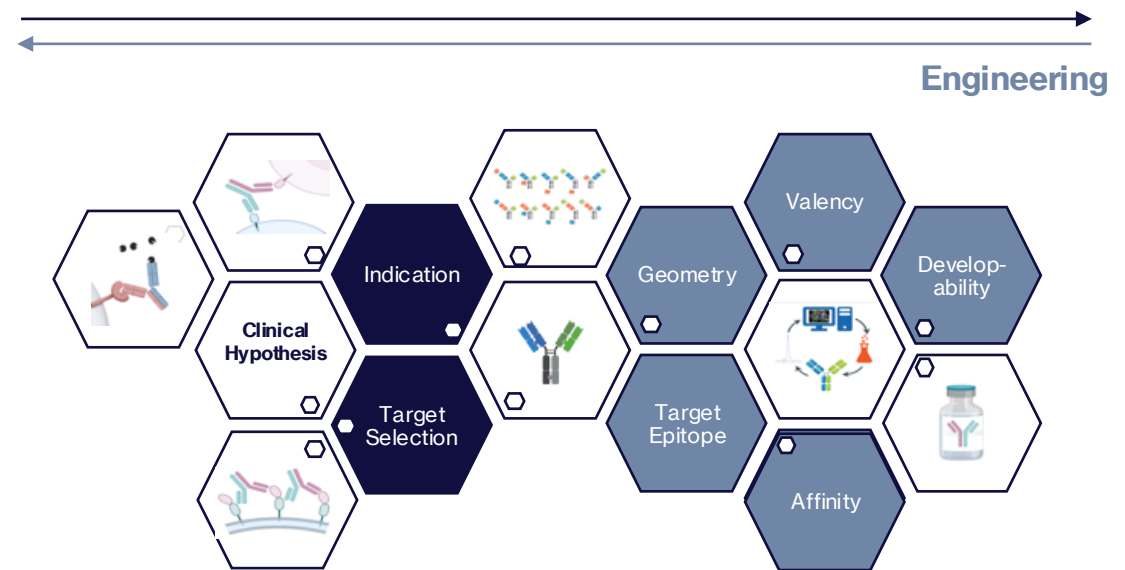
# Multispecific Antibody Development Requires Optimization Of Multiple Parameters To Engineer The Desired Biology

Understanding the interplay of antibody geometry with optimal paratope affinity, valency, and target epitope is critical to identifying best-in-class multispecific antibody therapeutics

## Clinical Hypothesis and Mechanisms of Action



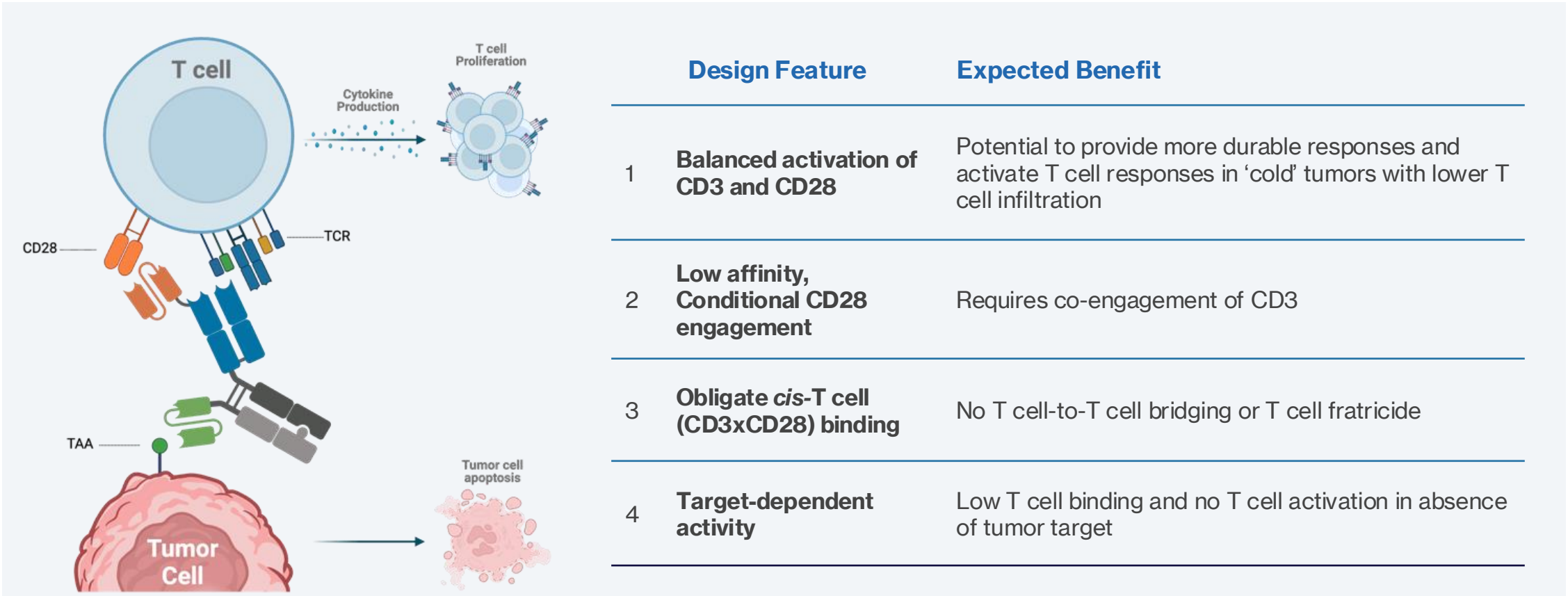
## Biology



Zymeworks' Azymetric™ platform enables the development of multispecific antibodies with high flexibility and manufacturability

# Trispecific T-Cell Engagers

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



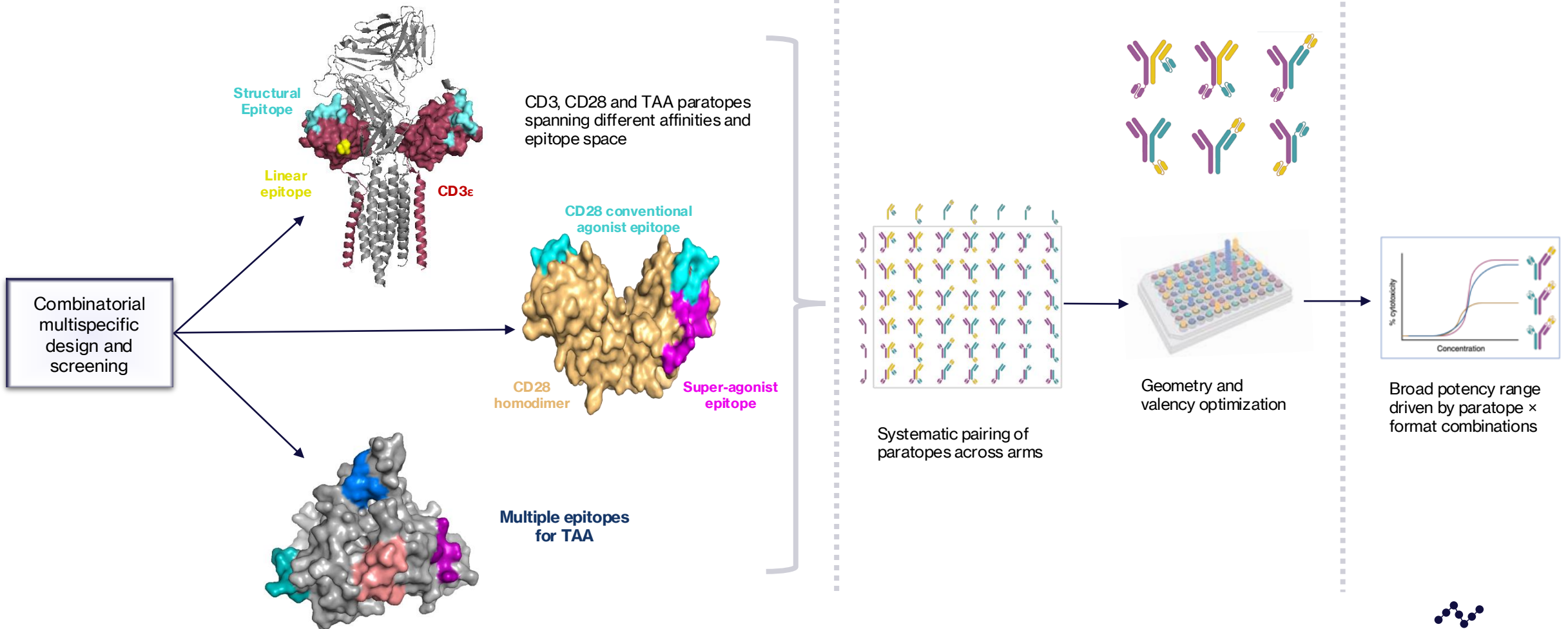
CRS: Cytokine release syndrome; irAEs: immune-related adverse events

# Extensive Paratope And Format Exploration Enables Discovery Of Best TriTCEs

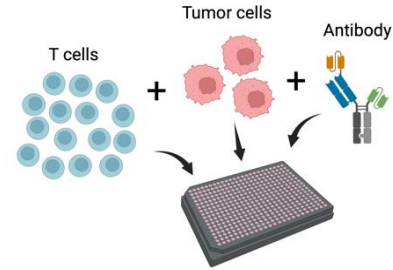
## Selection of Diverse Paratopes and Affinities

## Combinatorial Assembly And Format Screening

## Functional Screening

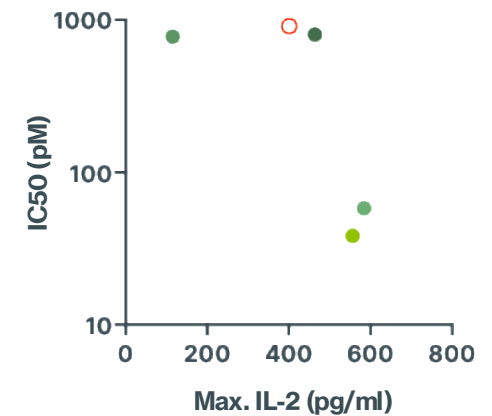
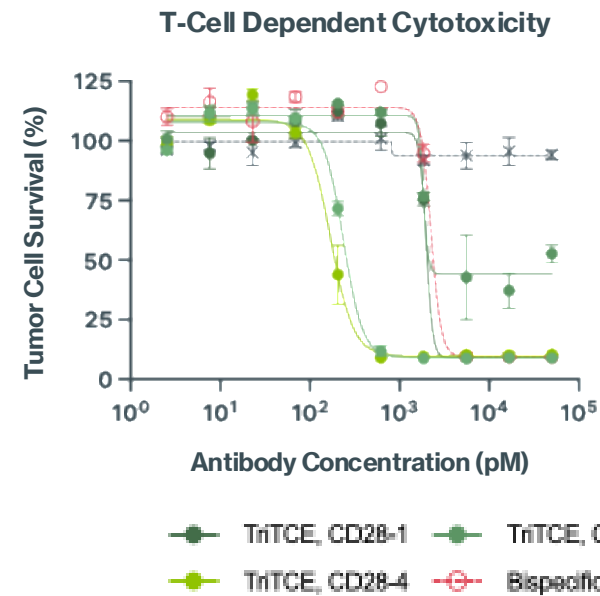
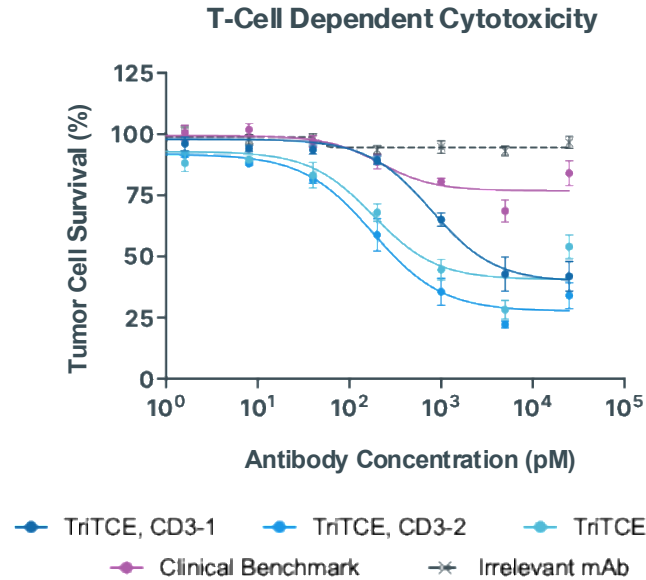
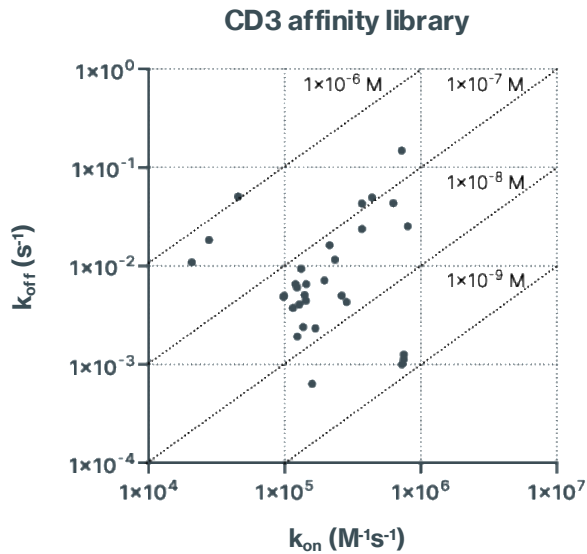


# Optimizing CD3 And CD28 Affinities For Best Trispecific TCEs



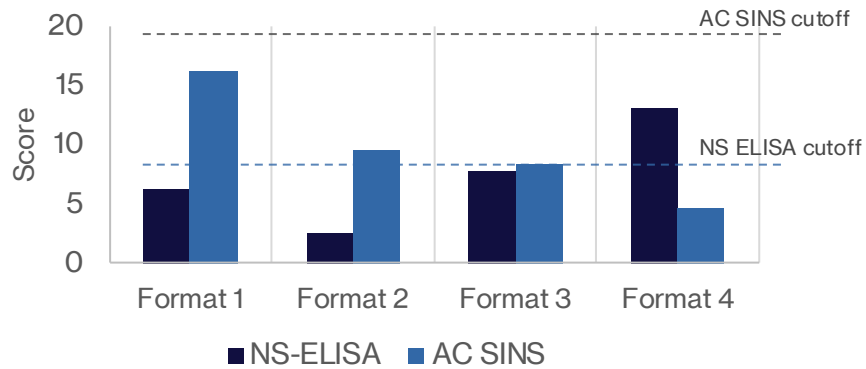
Fine-tuning CD3 kinetics

Fine-tuning CD28 co-stimulation

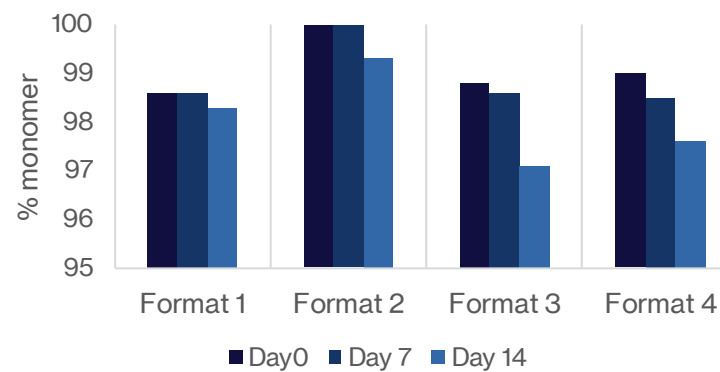


# Multispecific Antibodies Must be Engineered For Optimal Activity And Developability

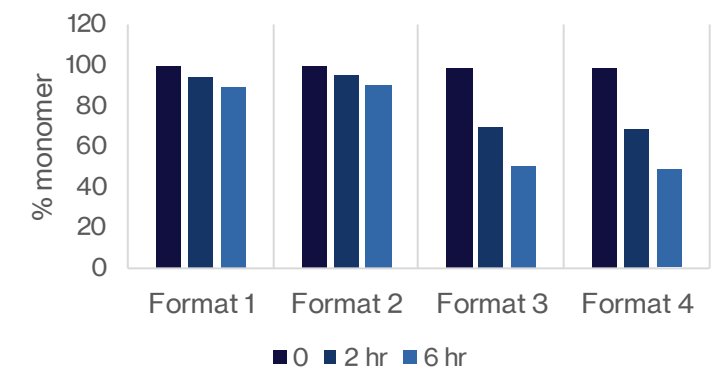
## Non-specific Interactions



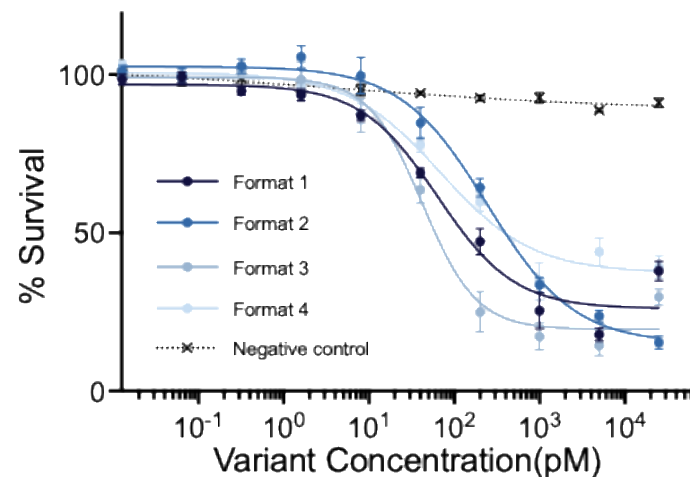
## Accelerated Stability (T°C)



## Accelerated Stability (pH)



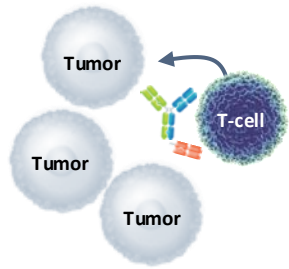
## T-cell Dependent Cytotoxicity



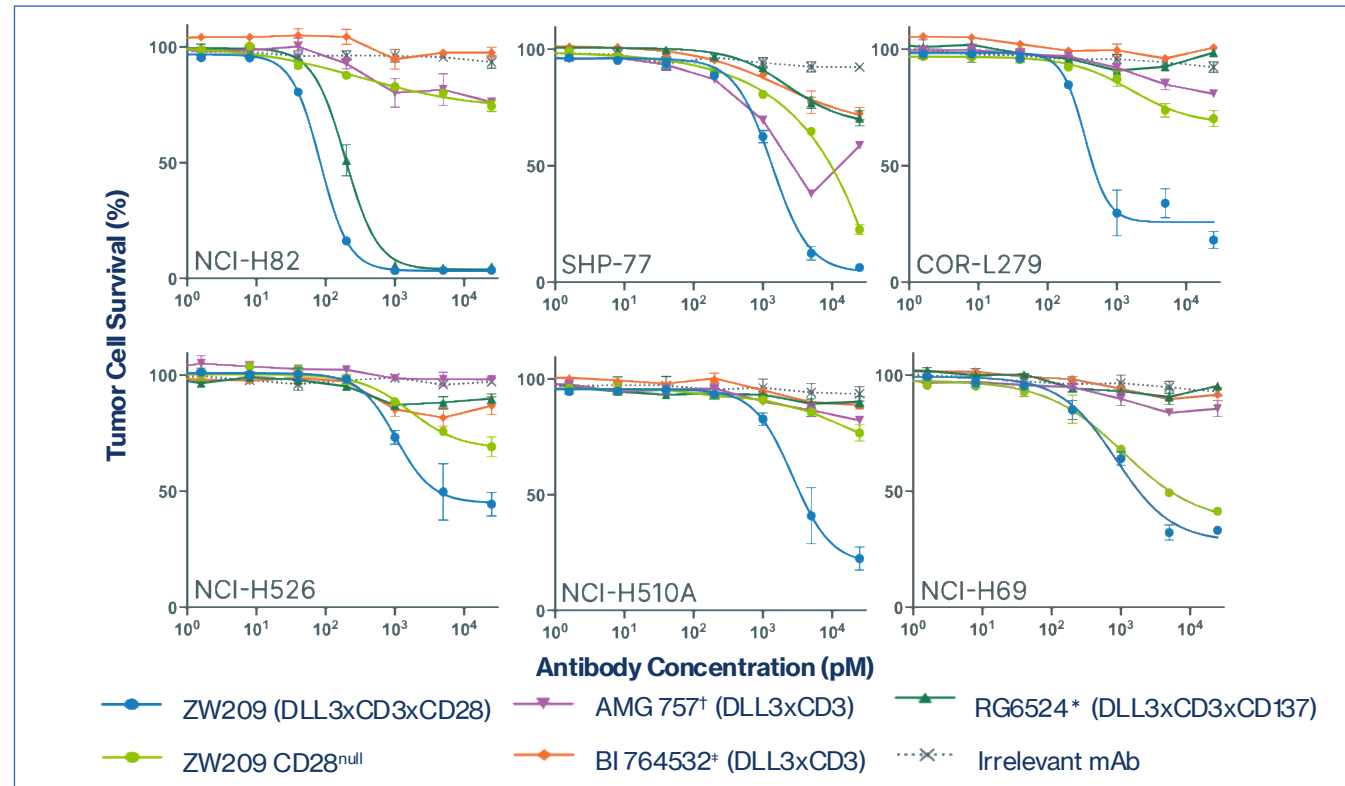
- Engineering liabilities out of paratopes and selecting the right format is key to making robust multispecific therapeutics.
- Potency is key for T cell engagers, but the developability profile will indicate how easily it can be manufactured.

# A DLL3-Targeted TCE with Co-Stimulation

# 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.

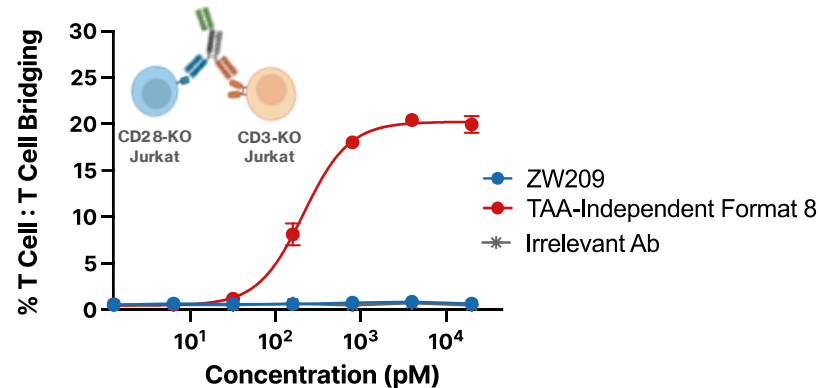
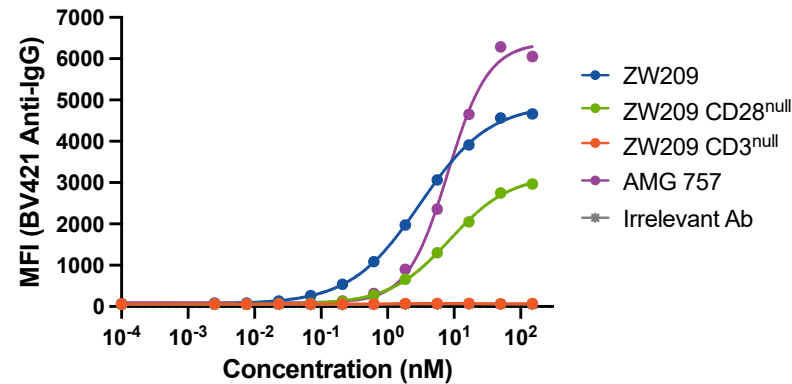
# ZW209: DLL3 x CD3 x CD28 Trispecific T Cell Engager Designed For Treatment Of Small Cell Lung Cancer

ZW209 design facilitates desirable T cell engagement

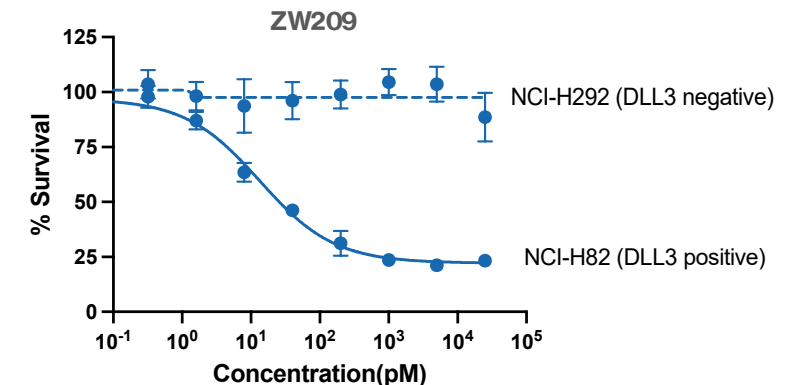
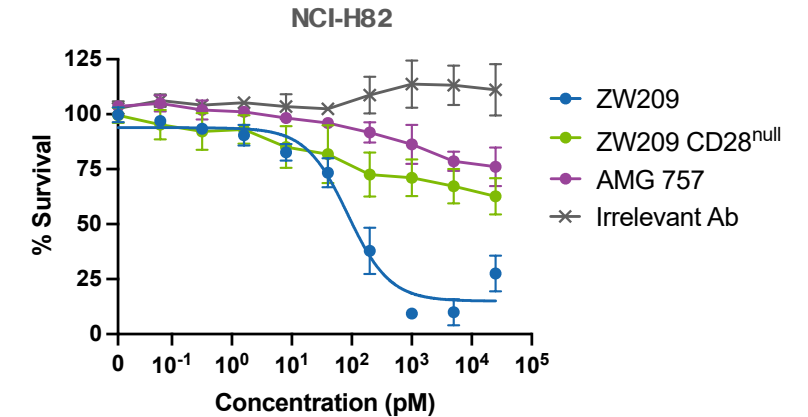
## Design Feature

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

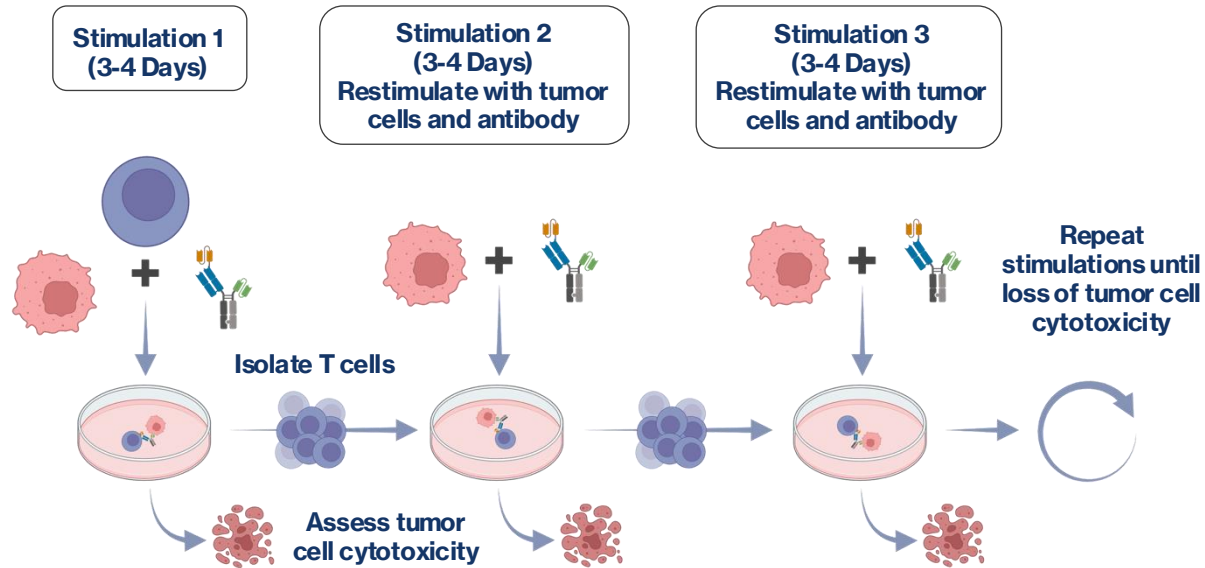
**Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate Cis Binding**



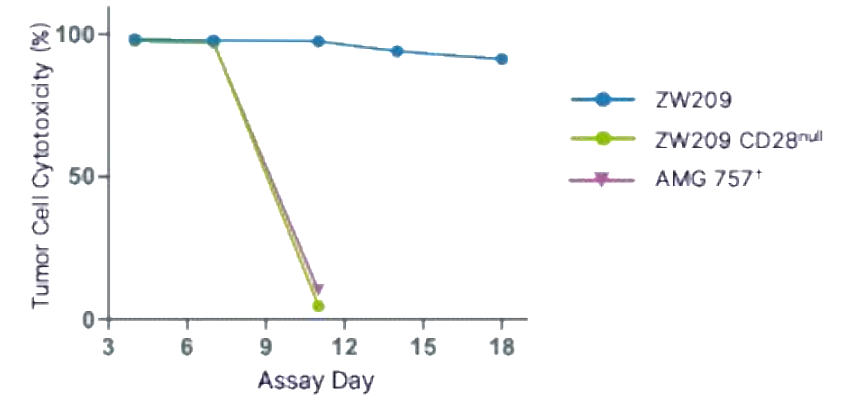
**Improved Cytotoxicity Over Bispecifics in Low E:T Conditions**



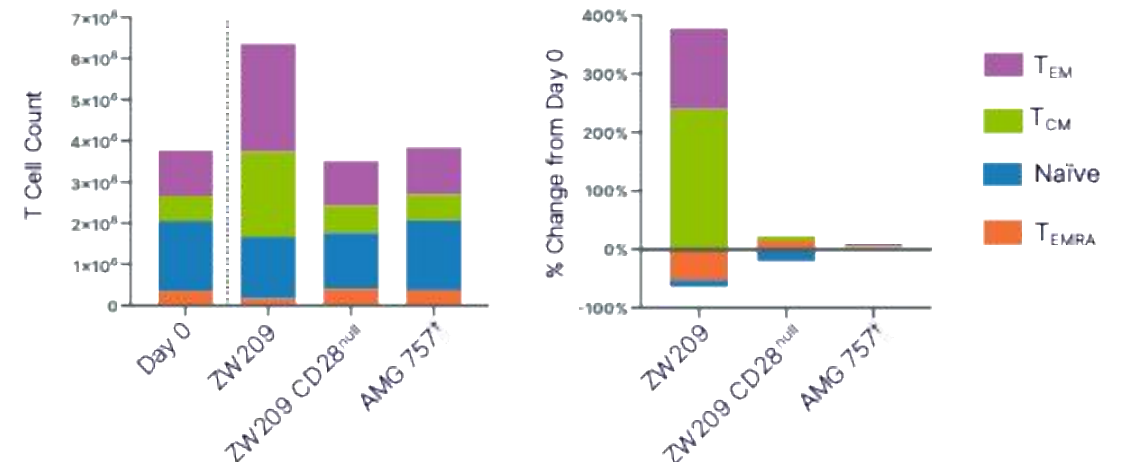
# ZW209 Demonstrates Prolonged T cell Cytotoxicity In Repeat Challenge Assay



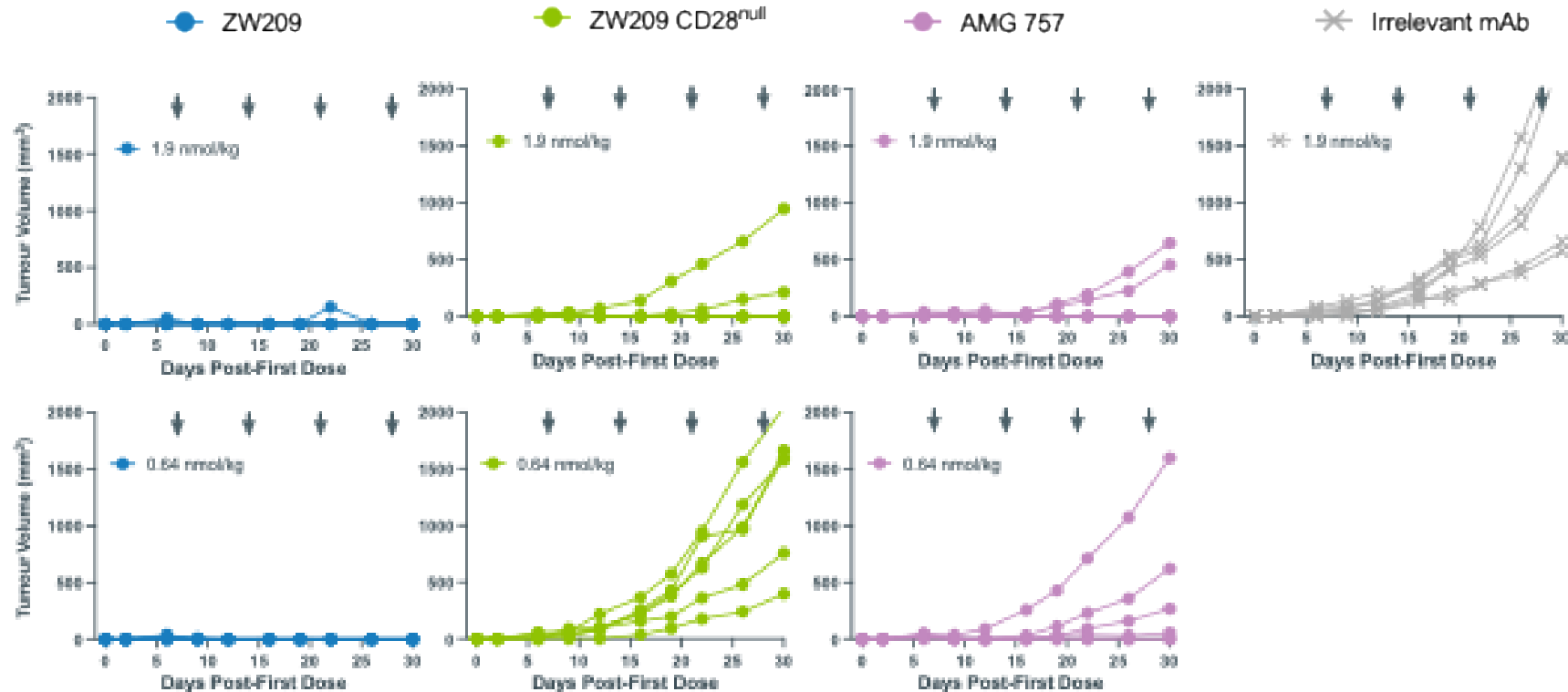
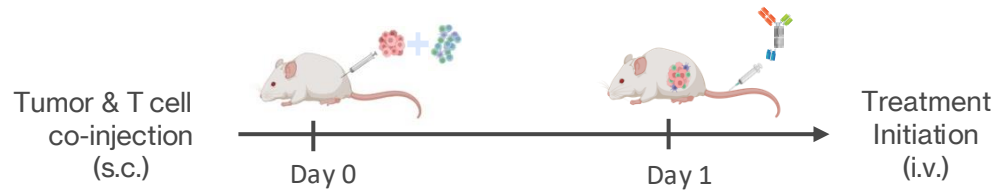
Sustained cytotoxicity relative to bispecific TCEs



Expanded of effector memory (T<sub>EM</sub>) and central memory (T<sub>CM</sub>) T cell populations after 2<sup>nd</sup> stimulation (Day 7)



# ZW209 Mediates Enhanced Antitumor Activity Compared To Bispecific And Benchmark Antibody

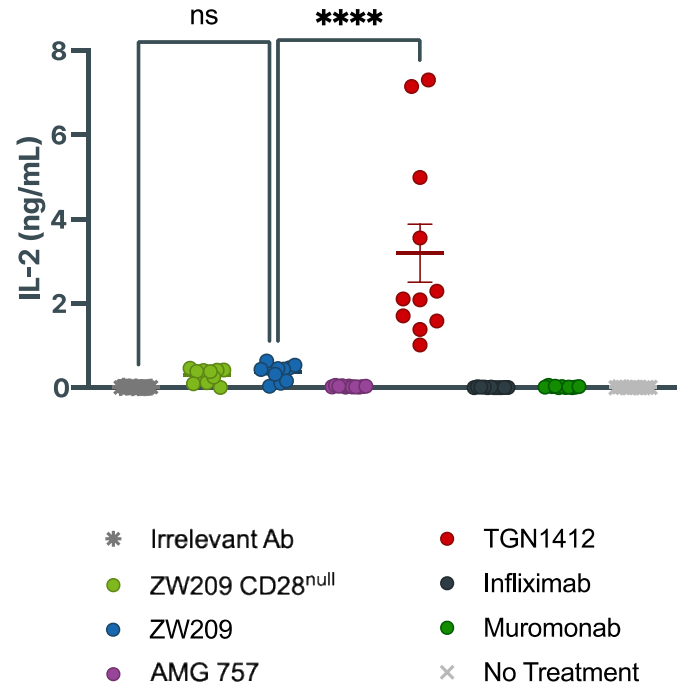


ZW209 shows superior anti-tumor activity compared to the bispecific and benchmark antibody in NCI-H82 admixture xenograft model

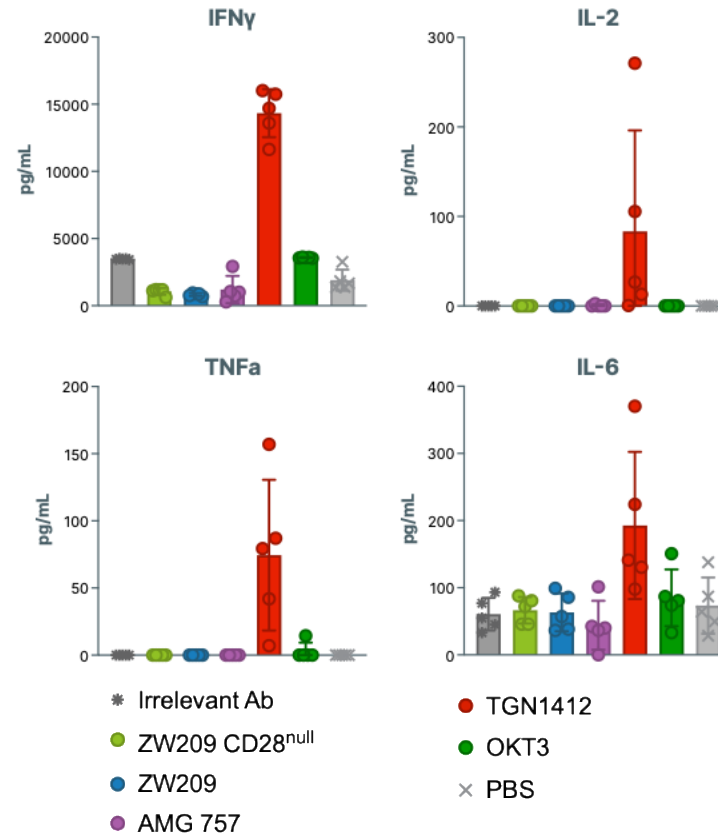
# ZW209 Has A Favorable Safety Profile *In Vitro* And In Animal Studies

## No Cytokine Activation With PBMCs Alone

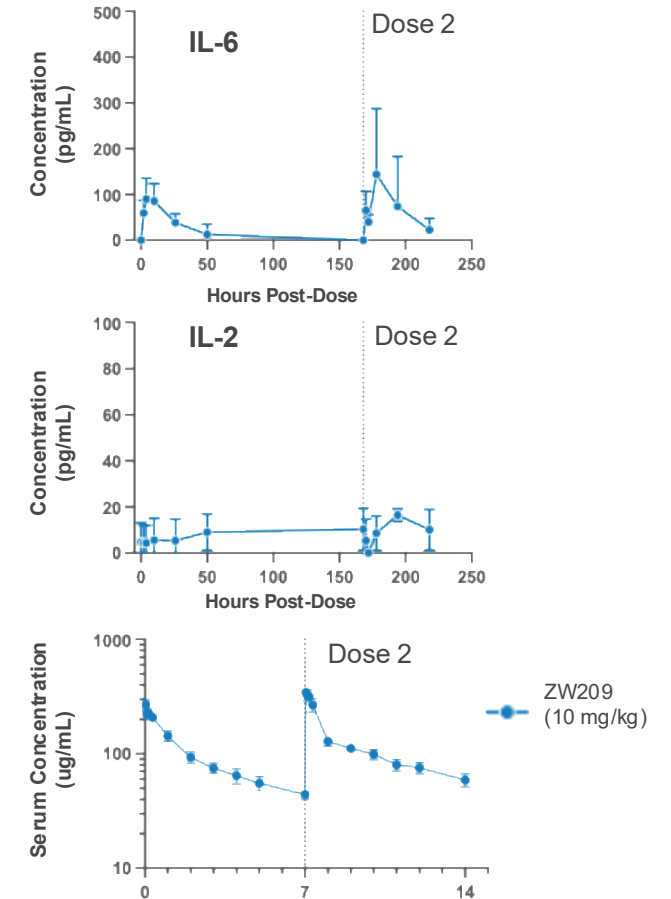
### Solid-Phase Cytokine Release Assay



## Induces Minimal Systemic Cytokine In Humanized Mouse CRS Model



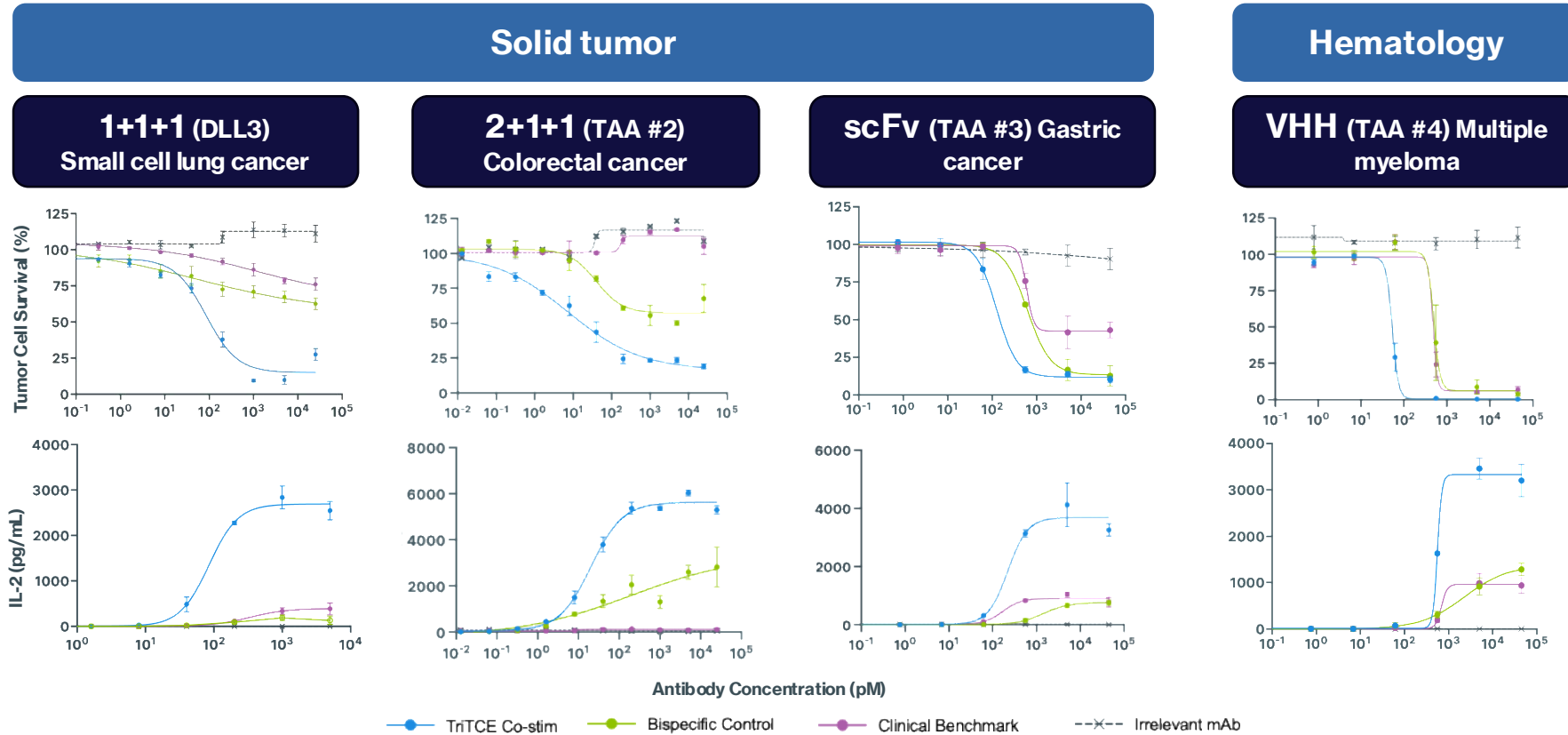
## Well-Tolerated In Cynomolgus Monkeys



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

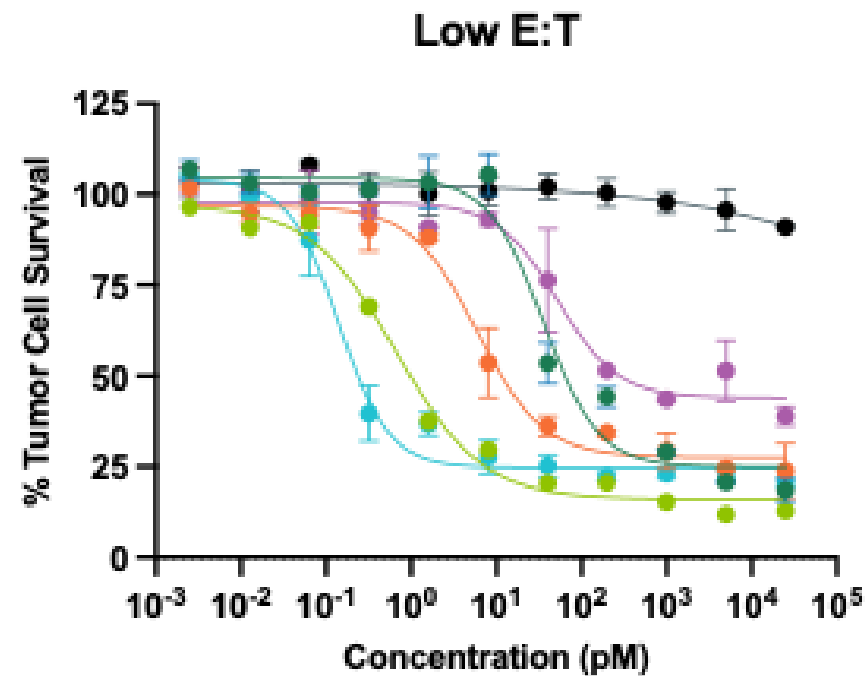
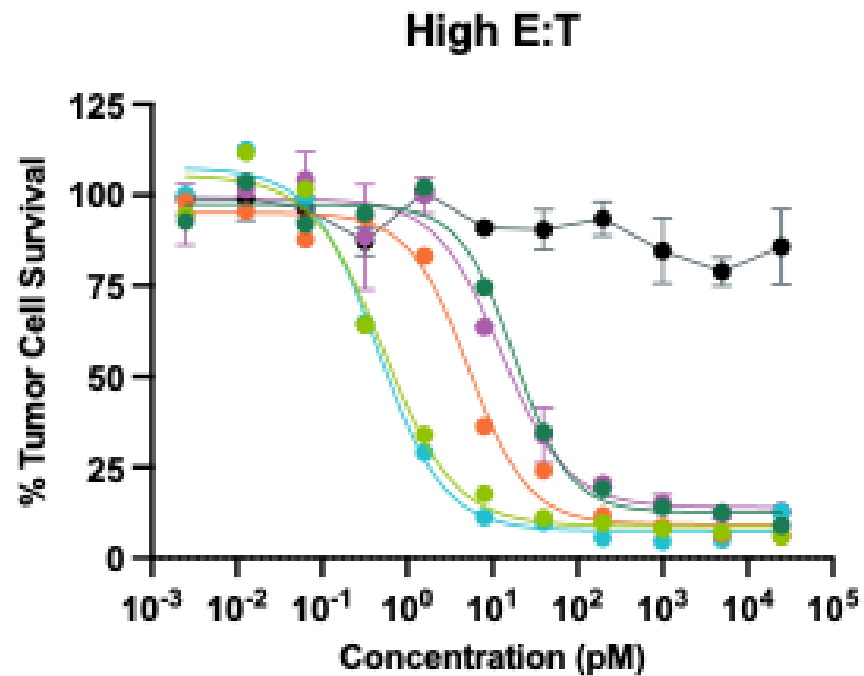
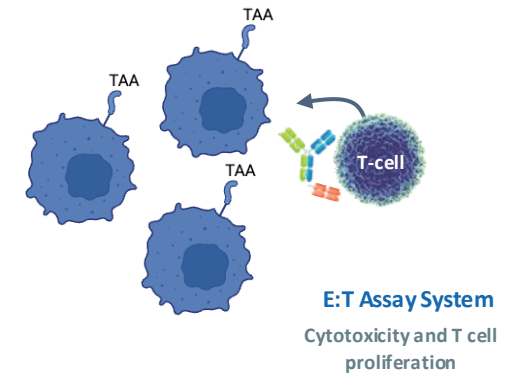
# **A Co-Stim Story For Many Indications And Targets**

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



Optimal format and valency changes based on target and indication

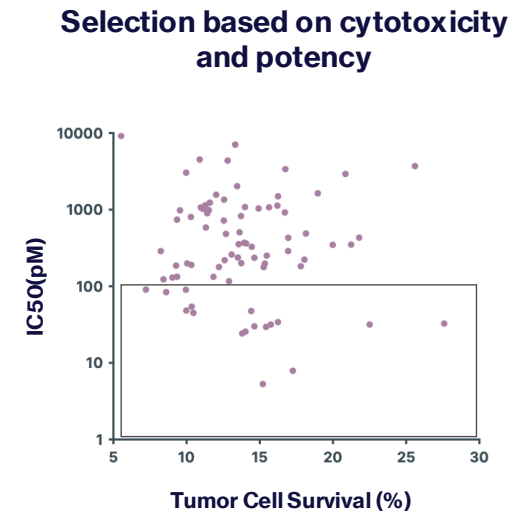
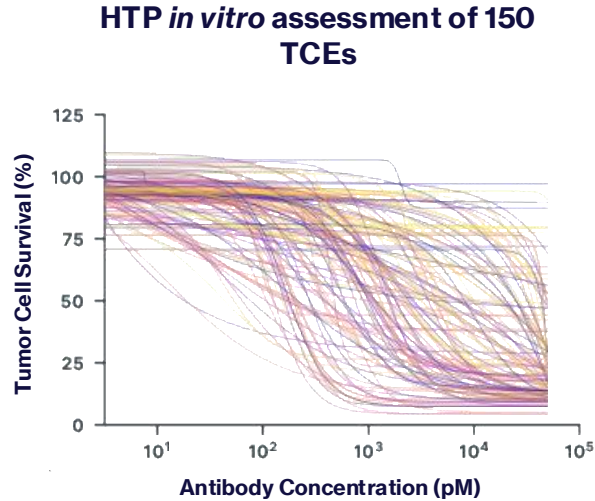
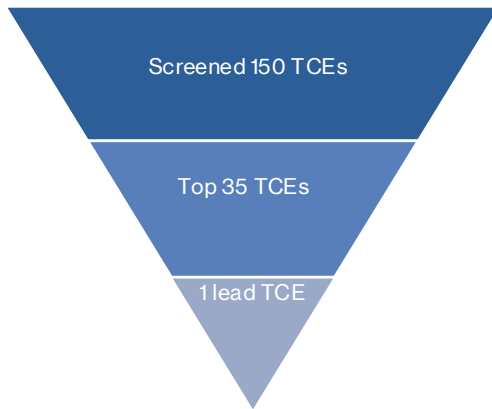
# Format Can Completely Change The Activity of A T cell Engager



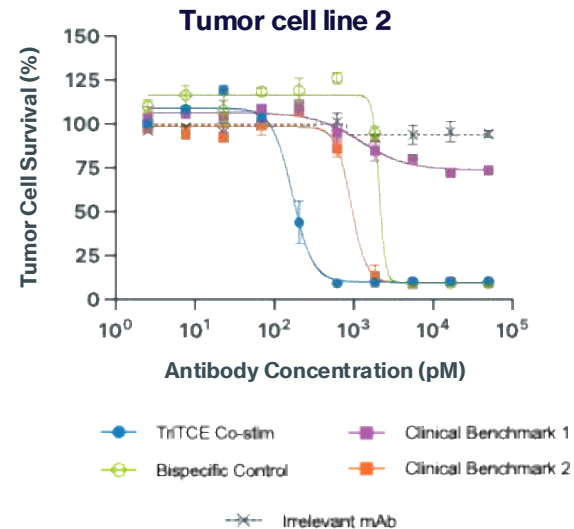
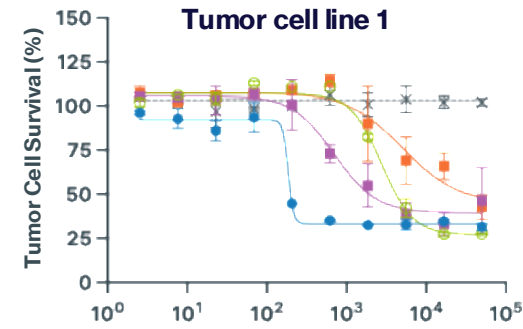
- Format 1
- Format 2
- Format 3
- Format 4
- Benchmark
- Negative control

# Targeting Peptide-MHC Using TriTCE Co-Stim Platform

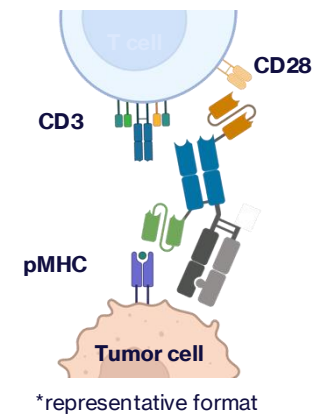
## pMHC TriTCE Screening Funnel



## Lead TCE selection



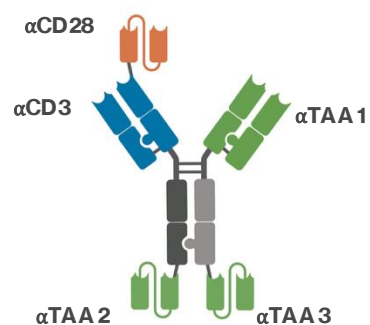
## Identification of Lead $\alpha$ pMHC TriTCE format\*



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

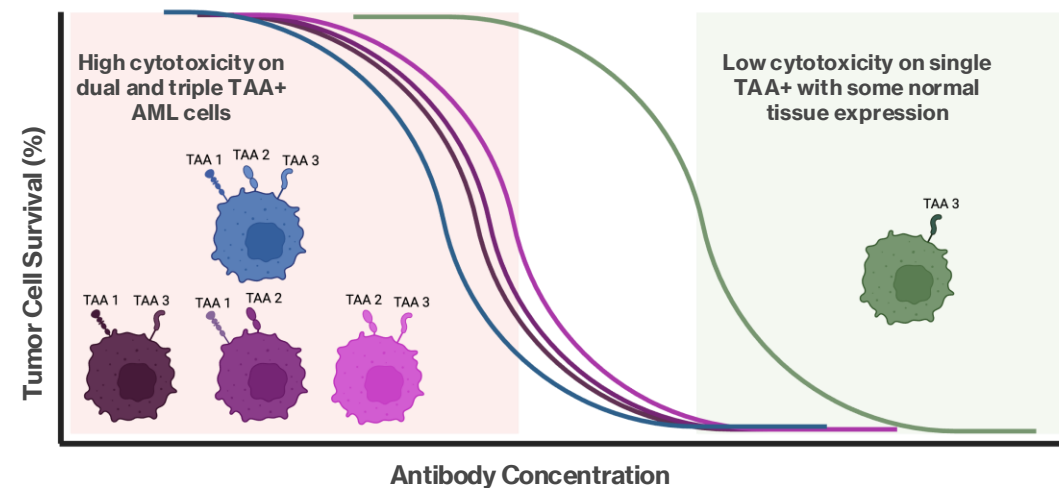
Biological Challenge	Limitation of Mono-antigen Targeted Therapies
Heterogeneous intertumoral antigen expression	Antigen escape
Lack of a clean single target between AML blast, LSCs and healthy cells	Narrow therapeutic window

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



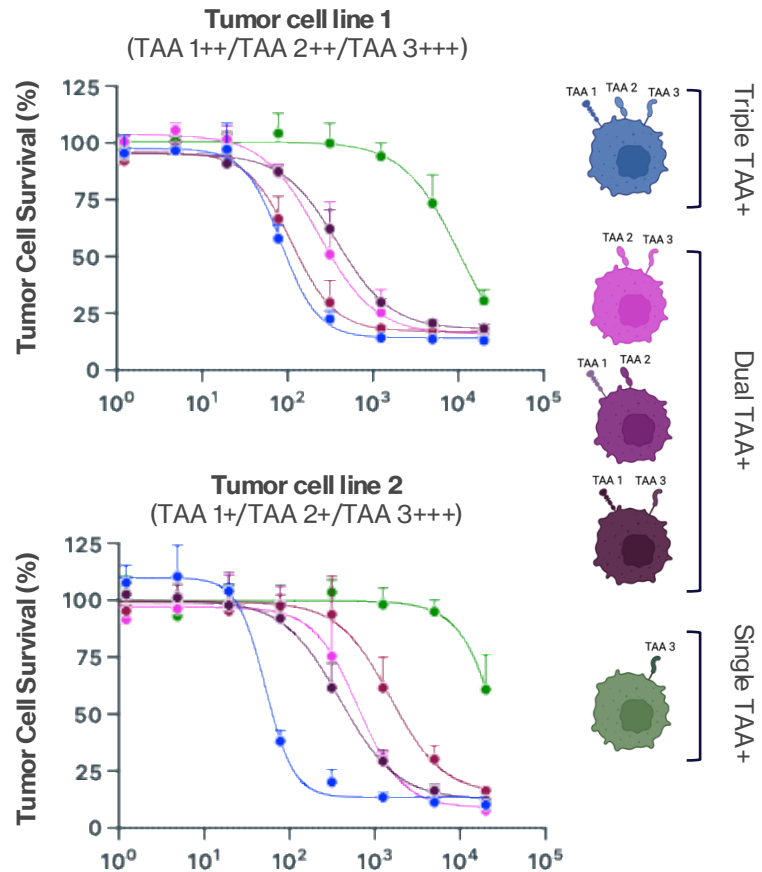
\*representative format

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	✗

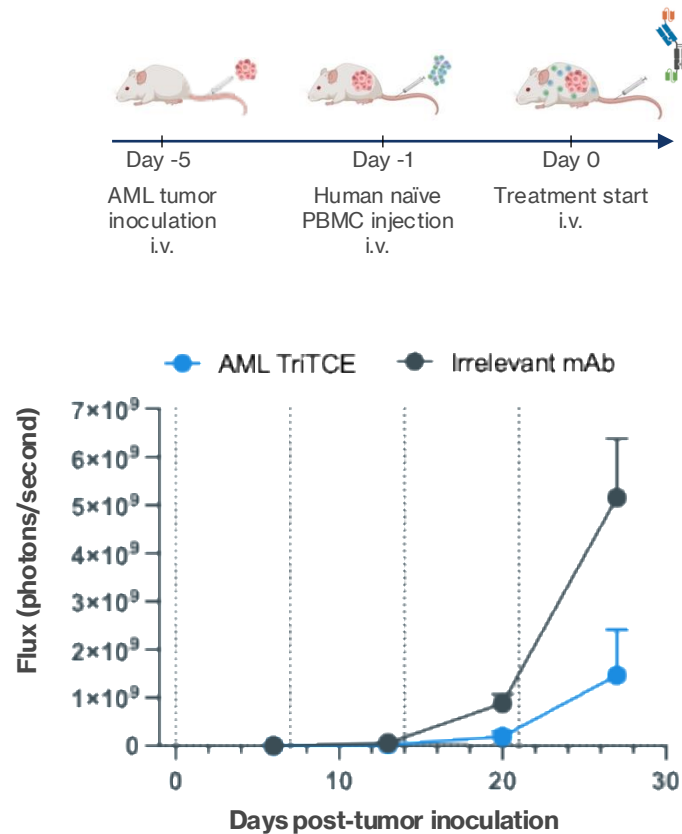


# Logic-Gated TriTCE Co-Stim Platform Can Overcome Antigen Escape In Acute Myeloid Leukemia

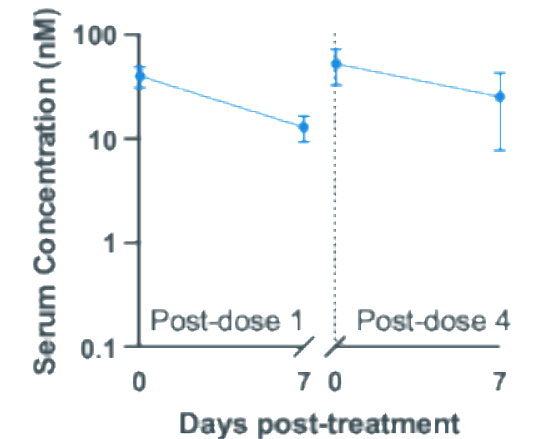
Lead logic-gated TriTCE demonstrates desired TAA-selective cytotoxicity



*In vivo* anti-tumor activity of AML TriTCE in disseminated AML xenograft model (TAA 1+/TAA 2+/TAA 3++)

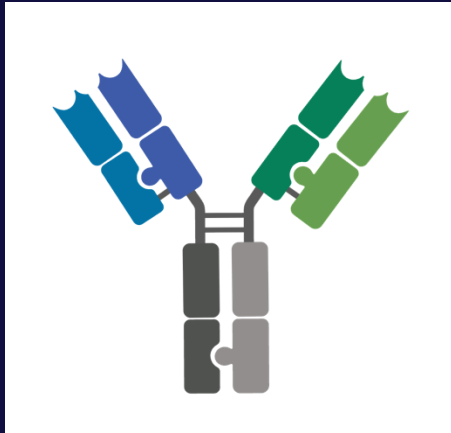


Antibody-like serum PK of AML TriTCE



# Summary

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**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

# Acknowledgments

## Multispecific Antibody Therapeutic Department

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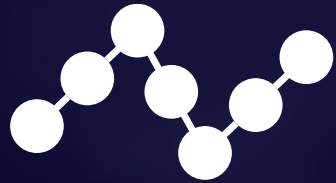
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Richard Kunze  
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**National Research Council (NRC) Canada**

Health and Human Therapeutics department





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