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Making a Meaningful Difference

On a mission to improve the standard of care for difficult-to-treat diseases

Next Generation Trispecific T Cell Engagers (TriTCE) Designed to Improve Treatment Responses in Oncology

Genevieve Desjardins, PhD
Principal Scientist, Multispecific Antibody Therapeutics

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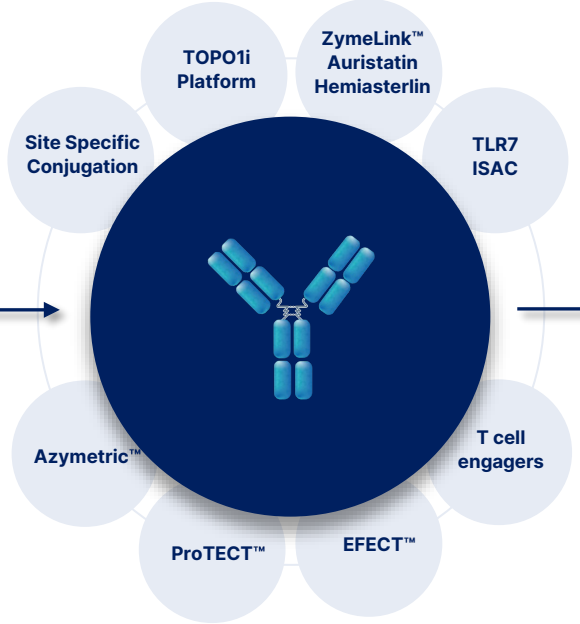
ADC and Multispecific Modalities Driving Our Pipeline

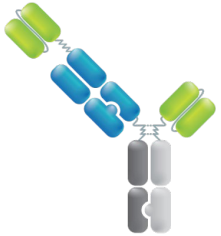
Select Difficult-to-Treat Cancers & Target

Design with Complementary Technology



Optionality with Two Foundational Fit-for-Purpose Modalities

Antibody-Drug Conjugates
Customization:
- Antibody properties
- Antibody format
- Payload
- DAR



Multispecifics
Customization:
- Multiple MOA in single molecule
- Synergistic biology
- Precision targeting through multivalency

5 **New** INDs expected by 2026

ADC: antibody-drug conjugate; DAR: drug to antibody ratio; IND: investigational new drug (application); ISAC: immune stimulating antibody conjugate; MOA: mechanism of action; TOPO1i: topoisomerase-1 inhibitor; TLR7: toll-like receptor 7.

Differentiated Development of Multispecific Antibody Therapeutics

Versatile multispecific antibody therapeutics enhancing potency and precision with proven track record and robust clinical pipeline

Program	Potential Indication	Target(s)	Preclinical / Phase 1 / Phase 2 / Pivotal	Collaboration Partners
Zanidatamab Bispecific	BTC	HER2 x HER2	HERIZON-BTC-302	Jazz Pharmaceuticals, BeiGene
	GEA	HER2 x HER2	HERIZON-GEA-01	Jazz Pharmaceuticals, BeiGene
	BC	HER2 x HER2	EMPOWHER-BC-303[1]	Jazz Pharmaceuticals, BeiGene
	BC and other solid tumors	HER2 x HER2	8+ ongoing Phase 1 and Phase 2 trials (view)	Jazz Pharmaceuticals, BeiGene
ZW171 Bispecific T Cell Engager	OVCA, NSCLC and other MSLN-expressing cancers	MSLN x CD3 (2+1)	Expected IND filing in 2024	
TriTCE Co-Stimulatory Trispecific T Cell Engager	Under active evaluation	TAA x CD3 x CD28	Pilot toxicology studies	
TriTCE Checkpoint Inhibition Trispecific T Cell Engager	Under active evaluation	TAA x PD-L1 x CD3	Pilot toxicology studies	
Selected Partnered Programs				
JNJ-78278343 Bispecific	Castration-Resistant Prostate Cancer	CD3 x KLK2	Azymetric™ | EFECT™	Johnson & Johnson Innovation

BC: breast cancer; BTC: biliary tract cancers; CD3: cluster of differentiation 3 protein complex and T cell co-receptor; CD28: cluster of differentiation 28; CLDN: claudin; GEA: gastroesophageal adenocarcinoma; HER2: human epidermal growth factor receptor 2; KLK2: kallikrein-related peptidase 2; MSLN: mesothelin; NSCLC: non-small cell lung cancer; OVCA: ovarian cancer; PD-L1: programmed cell death ligand 1; TAA: tumor associated antigen; TriTCE: trispecific T cell engager.
1. Trial initiation expected in the second half of 2024.

Next Generation CD28 Co-Stimulatory Trispecific T cell Engager

Designed to provide more durable responses in solid tumors and superior activity in ‘cold’ tumors

Therapeutic Rationale

Next Gen TriTCE Co-stim can provide increased T cell fitness, activation, and proliferation via tumor-dependent T cell co-stimulation

Product Differentiation

Novel approach of modular geometry and avidity screening of trispecifics to optimize T cell activation by Signal 1 and Signal 2

TriTCE Co-stim show superior anti-tumor activity to bispecific benchmarks and exhibit no activation of T cells in absence of tumor cells

Recent Milestones

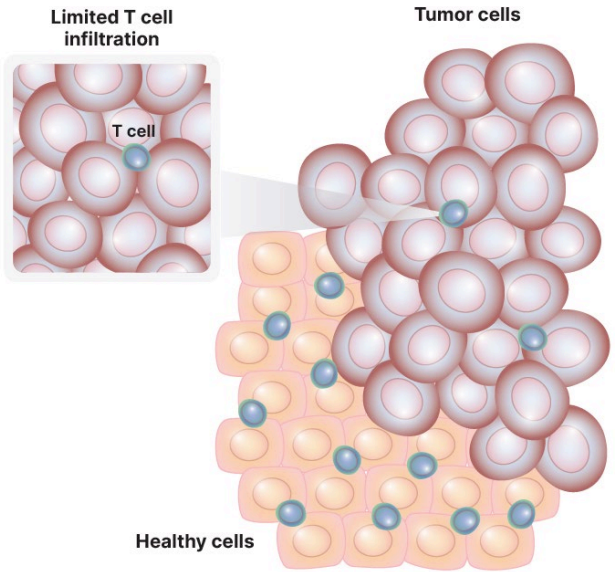
Pilot toxicology studies and PK analyses with lead CLDN18.2 TriTCE Co-stim

Expand utility to additional tumor targets

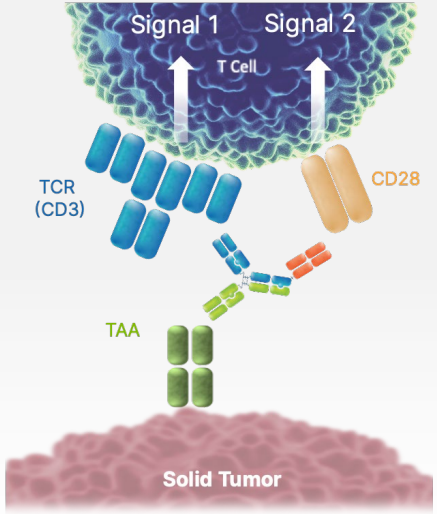
DLL3: delta-like ligand 3; PK: pharmacokinetics; TriTCE Co-Stim: Co-stimulatory trispecific T cell engager.

Trispecific Co-Stimulatory T Cell Engagers To Overcome Lack of Efficacy and Durability of Responses in Solid Tumors

Low T cell infiltration and T cell anergy remain challenges in the treatment of solid tumors



Zymeworks Trispecific Co-Stimulatory Program



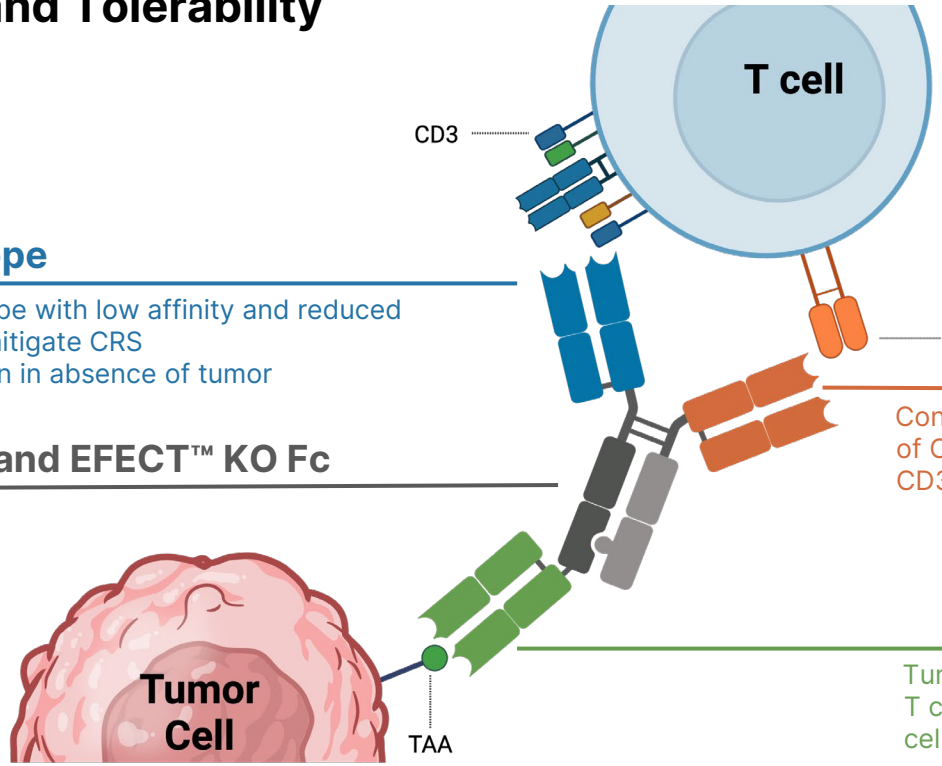
Provides Signal 1 (CD3) and Signal 2 (CD28) in one molecule to **increase T cell activation and proliferation**

Engineered to balance signal 1 and 2 for optimized **TAA-dependent T cell activation** and expansion

TriTCE Co-stim have the potential to provide an **effective and durable antitumor response** in patients with poorly infiltrated tumors.

TCR: T cell receptor.
Arvedson T et al Ann Rev Cancer Biol 2022.

TriTCE Co-Stim Engineered for Enhanced T Cell Functionality, Antitumor Activity and Tolerability



αCD3 Paratope

Novel CD3 paratope with low affinity and reduced T cell binding to mitigate CRS
No T cell activation in absence of tumor

Azymetric™ and EFECT™ KO Fc

αCD28 Paratope

Conditional CD28 binding, requiring co-engagement of CD3, and exhibiting obligate cis-binding with CD3, reducing the risk of T cell-mediated fratricide

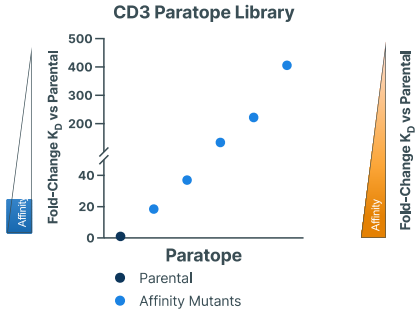
αTAA Paratope

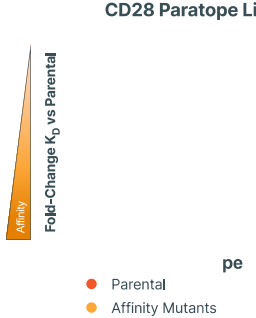
Tumor–targeting paratope drives target-dependent T cell responses, mitigating the risk of peripheral T cell activation

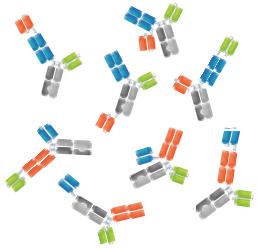
T cell engager antibody design is critical to elicit **optimal T cell synapse formation** and to the **widened therapeutic index**

CRS: cytokine release syndrome; KO Fc: knocked out fragment crystallizable region of antibody (Fc).

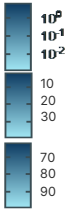
Lead TriTCE Co-Stim Selected Following Extensive Format Screening for Potent, Target-Dependent T Cell Activation

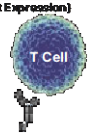
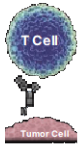






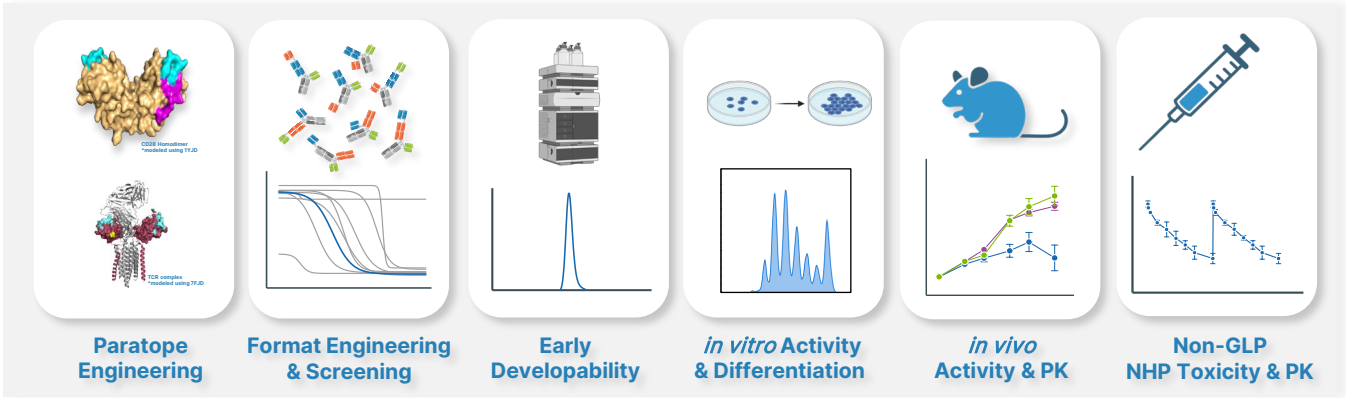
Antibody Format	1	2	3	4	5	6	7	8	9	10
Target-Dependent?	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗
Potency (IC_{50}; pM)										
Yield (mg/L)										
Thermal Stability (T_m; °C)										

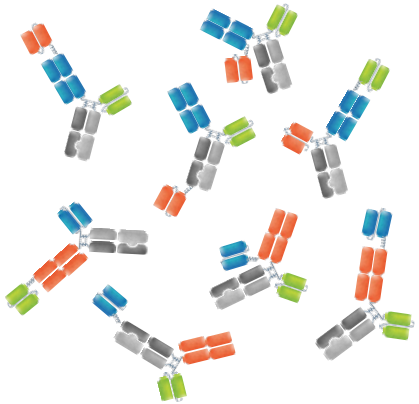


	Desired	Not Desired
	Lead TriTCE	Target-Independent TriTCE Co-Stim
Periphery (No Target Expression) 	✓ No T Cell Activation ✓ No Loss of T cell Viability	✗ T cell Activation ✗ Loss of T cell Viability
Tumor (Target Expression) 	✓ Cytotoxicity of Target Cells ✓ T Cell Activation	✓ Cytotoxicity of Target Cells ✓ T Cell Activation

Newhook L et al, Abstract #1372 presented at SITC 2023.

Lead Molecules Identified Using a Validated Workflow





αTAA x αCD3 x αCD28

TriTCE Co-Stim Lead Format Selection

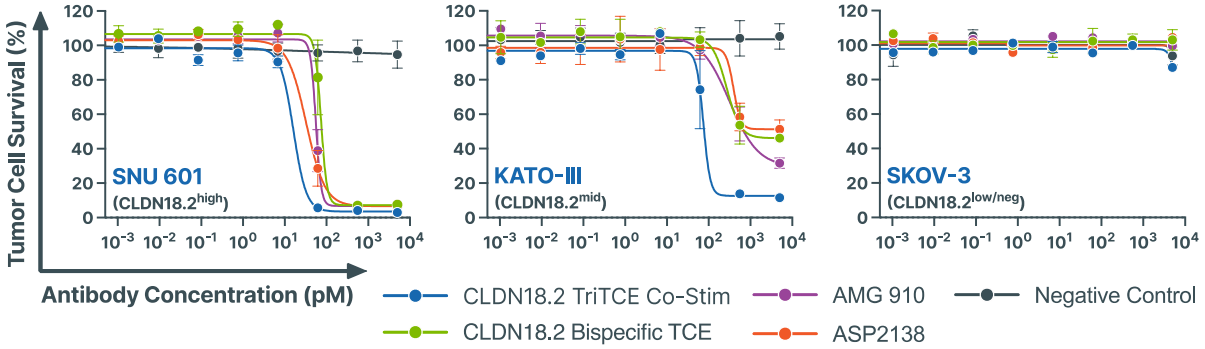
In vitro screening identified TriTCE Co-stim molecules with **enhanced TAA-dependent anti-tumor activity compared to a bispecific TCE**, and transferability across TAA targets

Evaluated with 3 targets including CLDN18.2 and DLL3

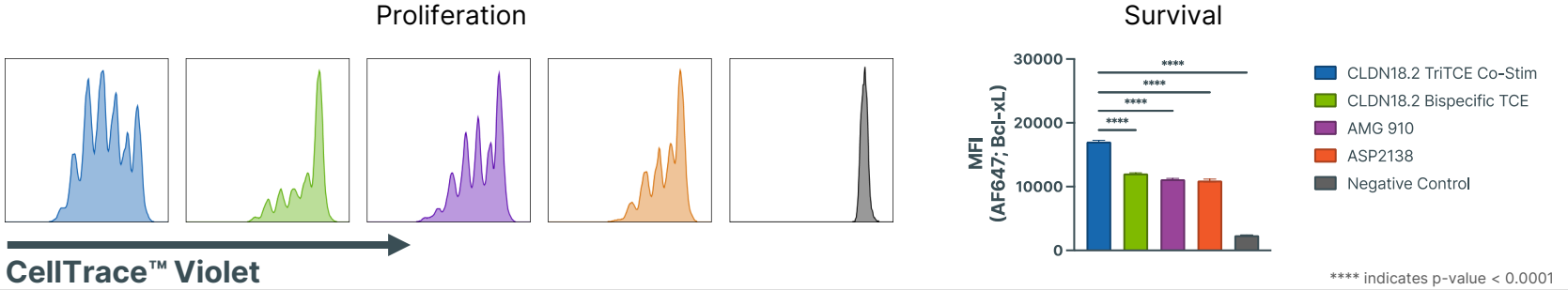
GLP: good laboratory practice; NHP: non-human primate.
Newhook L et al., Abstract #6719 presented at AACR Annual Meeting 2024.

CLDN18.2 TriTCE Co-Stim Enhances T Cell Responses and Antitumor Activity

Enhanced Cytotoxicity at Low E:T



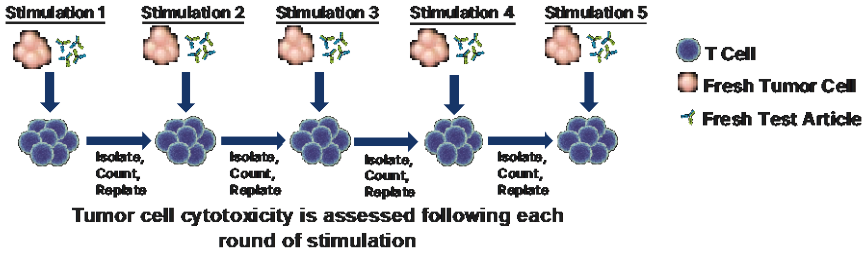
Improved T Cell Proliferation and Survival



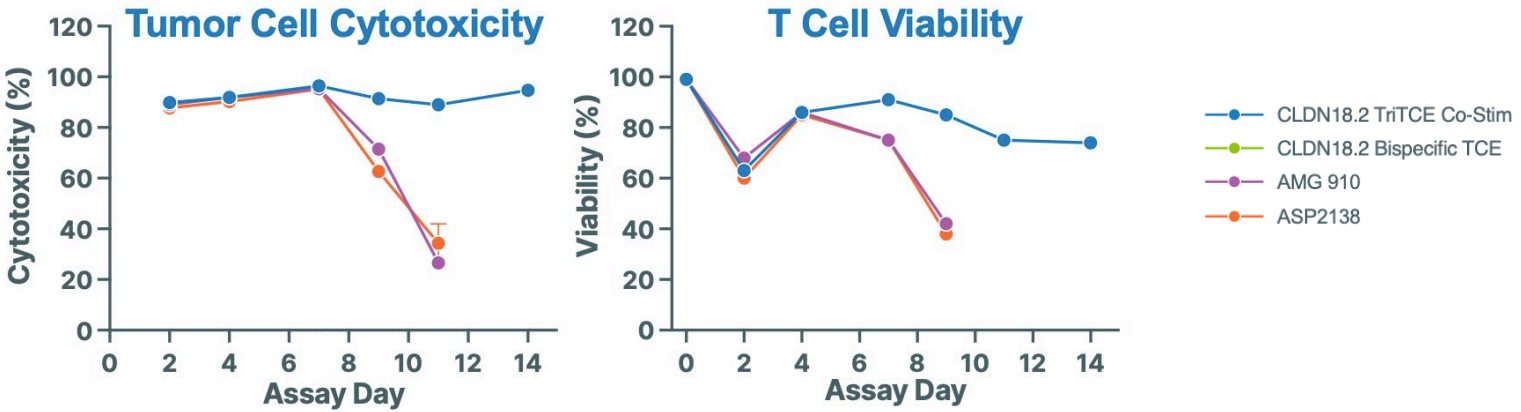
E:T: effector-to-target cell ratio.
Newhook L et al., Abstract #6719 presented at AACR Annual Meeting 2024.

TriTCE Co-Stim Results in Enhanced T Cell Fitness and Increased Durability of Antitumor Responses

Sustained Tumor Cell Cytotoxicity Over Repeated T Cell Simulation and Tumor Cell Challenge



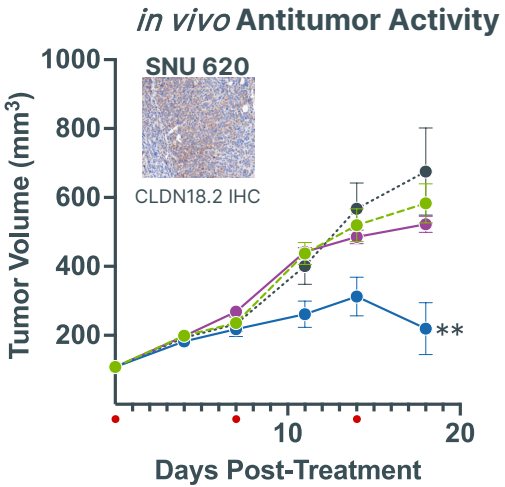
CD28 co-stimulation mediates sustained T cell activity *in vitro* relative to bispecific TCE



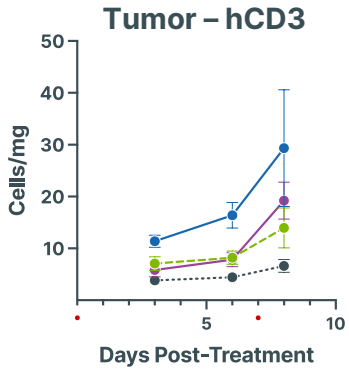
Adapted from Newhook L et al., Abstract #6719 presented at AACR Annual Meeting 2024.

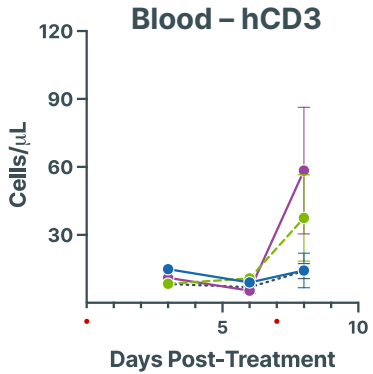
CLDN18.2 TriTCE Co-Stim Mediates Enhanced Antitumor Activity and Increases Activated Intratumoral T Cells *in vivo*

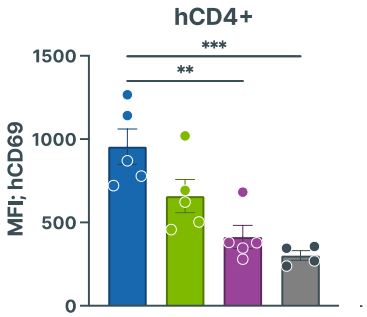
Greater Antitumor Activity and Increased Activated T cell Infiltration in Tumor But Not in Blood

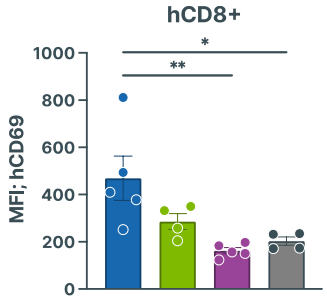


Test articles dosed at 0.01 mg/kg





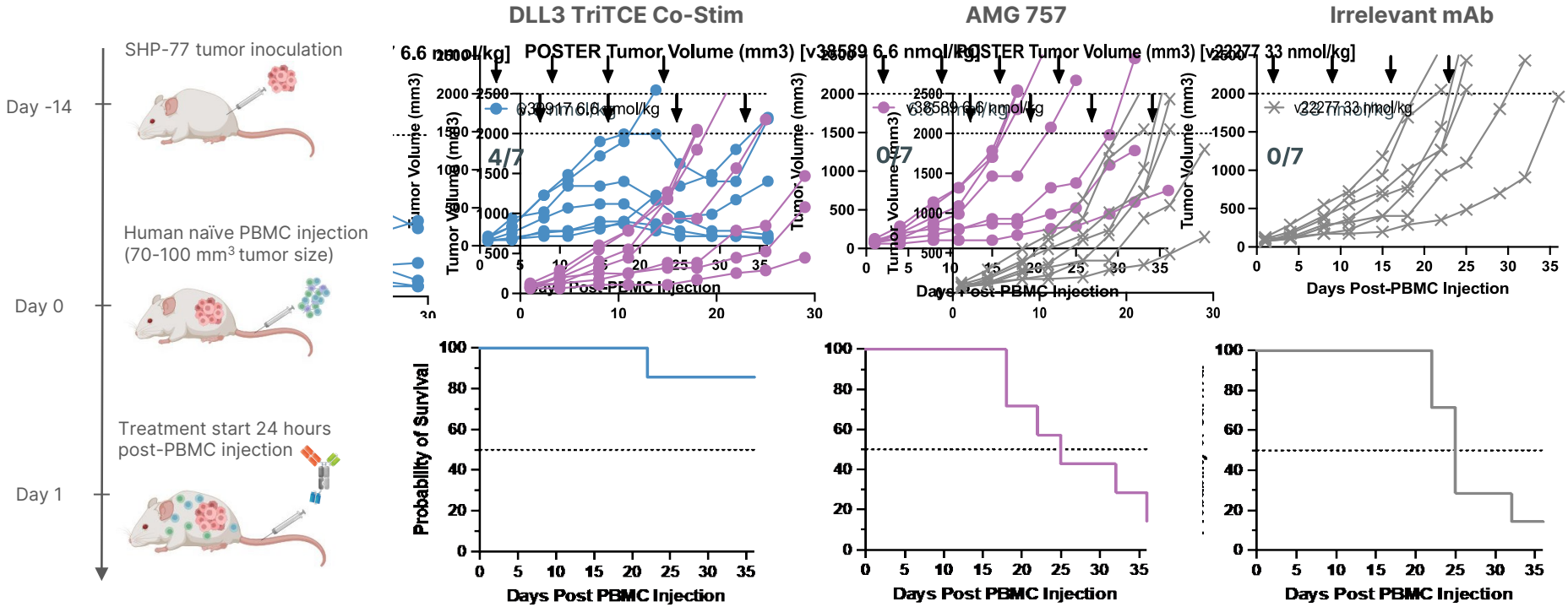




* indicates p-value < 0.05; ** p≤0.01, *** p<0.001

Newhook L et al., Abstract #1372 presented at SITC 2023.

DLL3 TriTCE Co-Stim Mediates Superior *in vivo* Antitumor Activity in an Established SCLC Humanized Xenograft Model

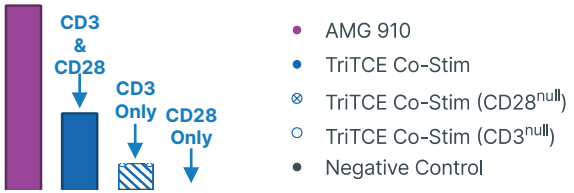


PBMC: peripheral blood mononuclear cells.
Repenning P et al., Abstract #6716 Presented at AACR Annual Meeting 2024.

CLDN18.2 TriTCE Co-Stim Exhibits Optimal Engagement of T Cells

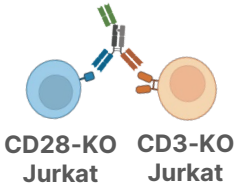
Conditional Binding of CD28, Requiring Co-engagement of CD3

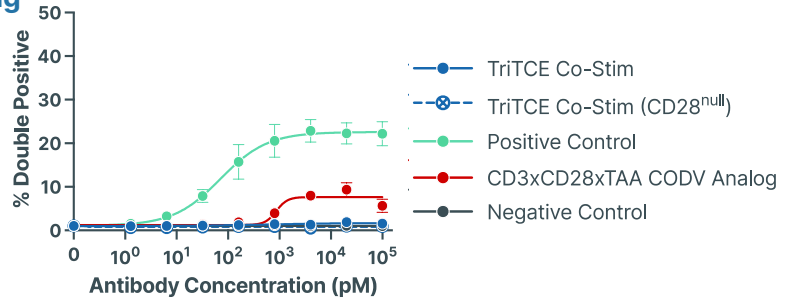
T Cell Binding



Obligate *cis* Binding of CD3 and CD28 on T Cells

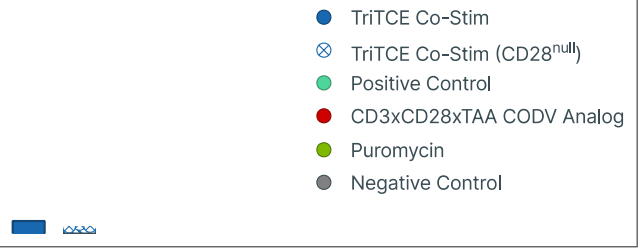
T Cell: T cell Bridging





No Reduction of T Cell Viability

T Cell Monoculture Viability



** indicates p-value < 0.01, **** p<0.0001

- TriTCE Co-Stim does not mediate T cell: T cell bridging
  - Cell bridging by immune cell-engaging antibodies has the potential to mediate effector cell fratricide, ultimately depleting cells required for therapeutic efficacy (Wang et al., 2018).

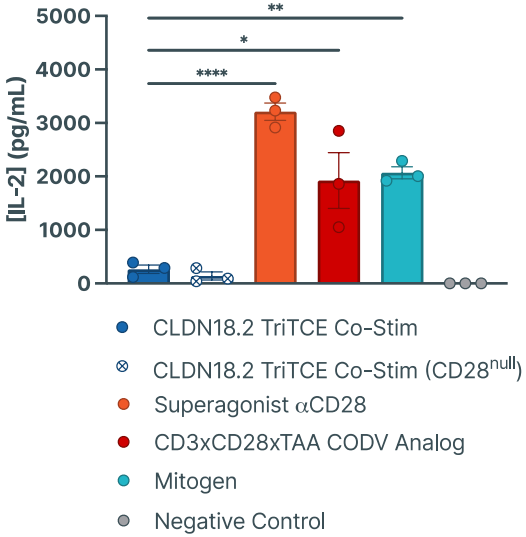
Newhook L et al., Abstract #6719 presented at AACR Annual Meeting 2024.

CLDN18.2 TriTCE Co-Stim Has Favorable Safety Profile in Preclinical Studies

No cytokine release observed using *in vitro* or *in vivo* models of CRS

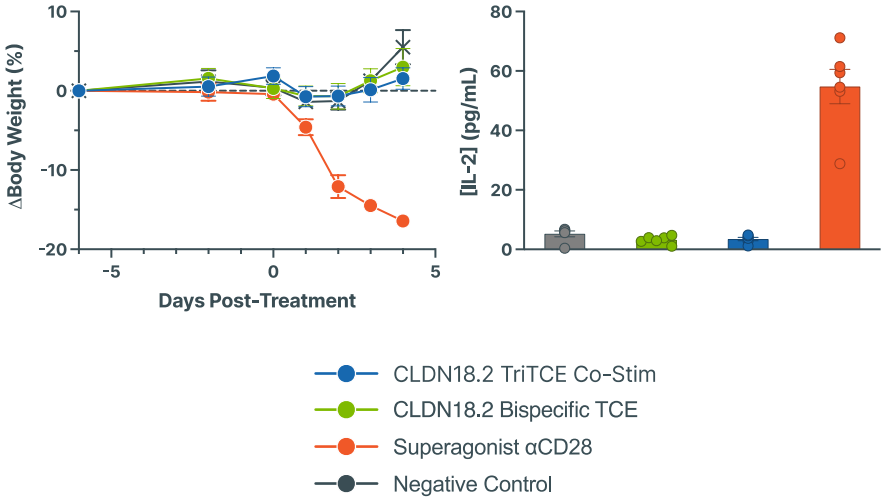
No Cytokine Release *in vitro* with Human PBMC Only

Solid-Phase Cytokine Release Assay



No Body Weigh Loss or Systemic Cytokine Release *in vivo*

Humanized Mouse CRS Model

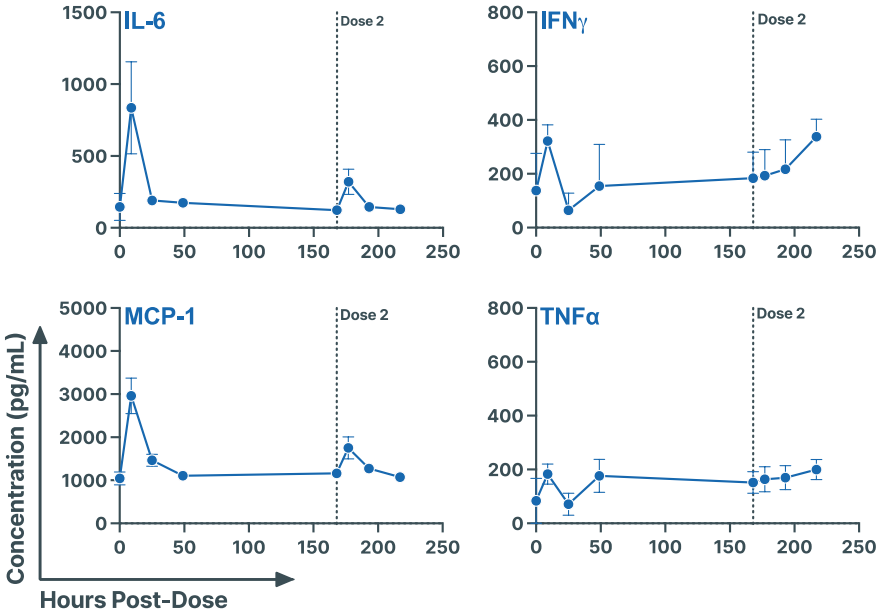


* indicates p-value < 0.05; ** p≤0.01, **** p<0.0001

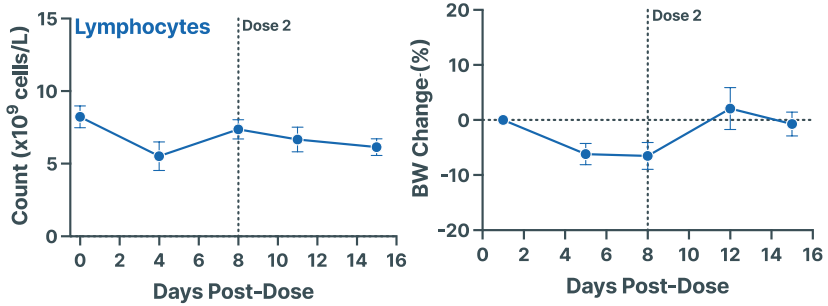
Newhook L et al., Abstract #1372 presented at SITC 2023.

CLDN18.2 TriTCE Co-Stim is Well-Tolerated in Cynomolgus Monkeys

Transient, Minor Increase in Serum Cytokine Post-Dosing



Transient, Minor Decrease in Lymphocyte Count and Body Weight Post-Dosing



Surrogate TriTCE Co-Stim*- 3 mg/kg

- Toxicology findings were mild and associated with the known mechanism of action of TCEs
- No histopathological changes observed in the stomach, where CLDN18.2 is expressed (Türeci et al., 2011)

*Surrogate TriTCE Co-Stim exhibited ~10-fold increased cytotoxic potency vs. lead TriTCE Co-Stim and ~15-fold reduced cytotoxic potency vs. AMG 910 in cynomolgus T cell-dependent cytotoxicity assays *in vitro*. AMG 910 dosed up to 0.03 mg/kg in a one-month, repeat dose NHP toxicology study (Bialis et al, 2020).

Newhook L et al., Abstract #6719 presented at AACR Annual Meeting 2024.

Summary

1. Next generation multispecific T cell engagers with additional modalities can address existing challenges limiting the efficacy of TCE in solid tumors.
2. TriTCE Co-stim approach results in differentiated antitumor activity in low E:T settings and has potential to improve outcome for patients, especially those with poorly infiltrated tumors, by increasing the depth and durability of response.
3. Demonstrated *in vitro* and *in vivo* activity across multiple programs, including CLDN 18.2 and DLL3 targeted TriTCE, with a favorable safety profile.

Newhook L et al., Abstract #6719 presented at AACR Annual Meeting 2024.
Repenning P et al., Abstract #6716 Presented at AACR Annual Meeting 2024.

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