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Making a Meaningful Difference

Developing novel medicines for patients with difficult-to-treat cancers and other serious diseases

Engineering Trispecific T-cell Engagers to Address Biological Challenges in the Treatment of Solid Tumors

Nina Weisser, Director, Multispecific Antibody Therapeutics

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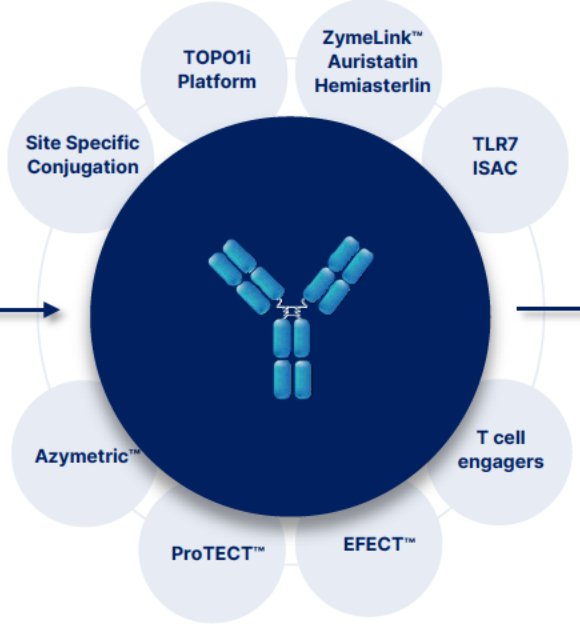
ADC and Multispecific Modalities Driving Our Pipeline

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

Goal of 5 **New** INDs by 2027

DAR: drug to antibody ratio; ISAC: immune stimulating antibody conjugate; MOA: mechanism of action

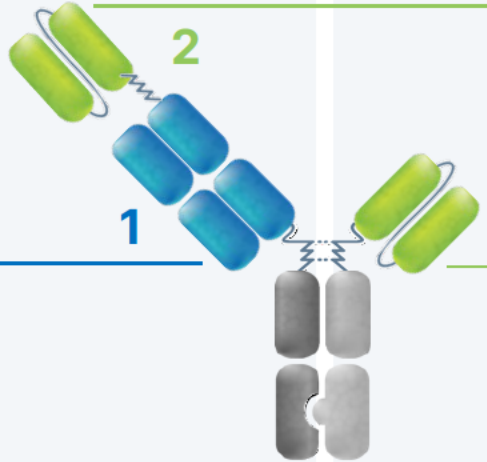
Multispecific Antibody Therapeutic (MSAT) Program

Multispecific Antibody Therapeutics Development

Comprehensive Engineering Solutions Applied to Optimize Fit for Purpose Therapeutics

Anti-CD3 paratope
- Affinity
- Epitope
- Stability
- Format

1

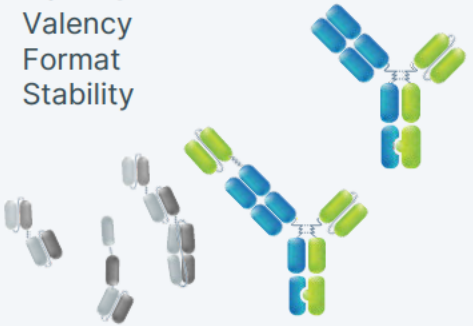


e.g. ZW171

Anti-TAA paratope
- Affinity
- Epitope
- Valency
- Stability
- Format

3

Antibody Format and Geometry
- Half life
- Valency
- Format
- Stability

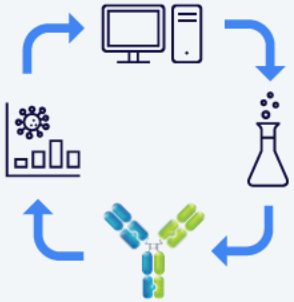


T cell engager antibody design is critical for a **widened therapeutic index** and **optimal T cell synapse formation**

TAA: tumor associated antigen; TCE: t cell engager

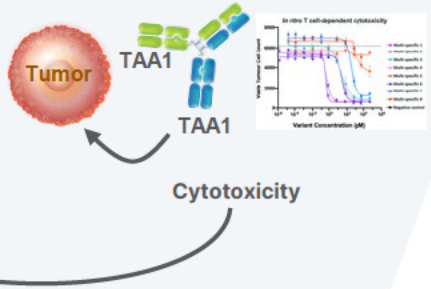
Core Competency of Protein Engineering and Flexibility of Azymetric™ Platform Enables Screening of Multiple Parameters in Parallel

Paratope screening & optimization, *in silico* affinity engineering



Generate panel of extensively engineered antibodies: valency, geometry & affinity

In vitro & *in vivo* biophysical and functional characterization of multispecific antibodies



Single lead optimized to:

- Target TAA over-expressing cells
- Improve T cell responses
- Maximize therapeutic index
- Modulate cytokine release

- Core competency of protein engineering harnessed to engineer and optimize multiple parameters in silico
- Flexibility of Azymetric™ platform enabled extensive screening of antibodies based on valency, geometry, and affinity

TAA: tumor associated antigen

Differentiated Development of Multispecific Antibody Therapeutics

Versatile multispecific antibody therapeutics optimizing 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-01			Jazz Pharmaceuticals, BeiGene
	GEA	HER2 x HER2		HERIZON-GEA-01			Jazz Pharmaceuticals, BeiGene
	BC and other solid tumors	HER2 x HER2		8+ ongoing Phase 1 & Phase 2 trials (view)			Jazz Pharmaceuticals, BeiGene
ZW171 Bispecific T-Cell Engager	Pancreatic, OVCA, CRC	MSLN x CD3 (2+1)	On track for IND filing in 2024				
TriTCE Co-Stimulatory Trispecific T cell engager	Under active evaluation	CLDN18.2 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
Undisclosed Bispecific	Oncology	Undisclosed	Azymetric™ | EFECT™				Bristol Myers Squibb[1]

[1]Original Agreement with Celgene (now a Bristol-Myers Squibb company).
BTC: biliary tract cancer; CLDN: claudin; CRC: colorectal cancer, GEA: gastroesophageal adenocarcinoma; HER2: human epidermal growth factor 2; IND: investigational new drug; BC: breast cancer; MSLN: mesothelin; OVCA: ovarian cancer; TAA: tumor associated antigen; TriTCE: trispecific t-cell engager

ZW171
MSLN x CD3 Multispecific

A bispecific T-cell engager on track for IND filing in 2024

Design
Optimized 2+1 avidity driven geometry incorporating novel low affinity CD3 binder to direct T-cell targeting of MSLN expressing tumors

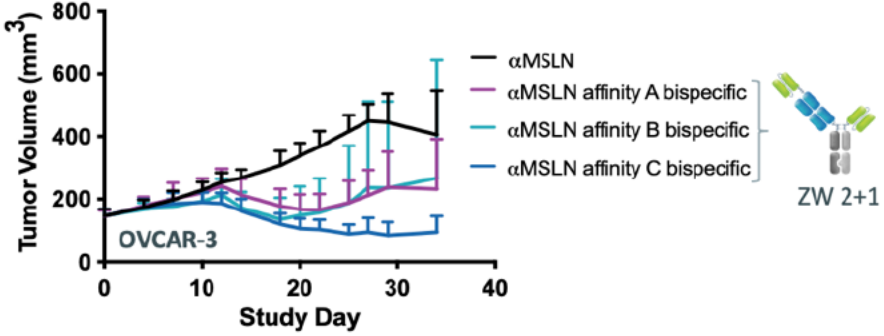
Mechanism
Engages immune system via MSLN-dependent T-cell activation to direct efficient tumor killing with limited cytokine release

Profile
Enhanced anti-tumor activity and safety profile in preclinical models supports opportunity to overcome clinical limitations of prior MSLN-directed therapies

IND: investigational new drug; MSLN: mesothelin; scFV: single-chain variable fragment
1. Afacan N et al., Abstract #2942 presented at AACR 2023

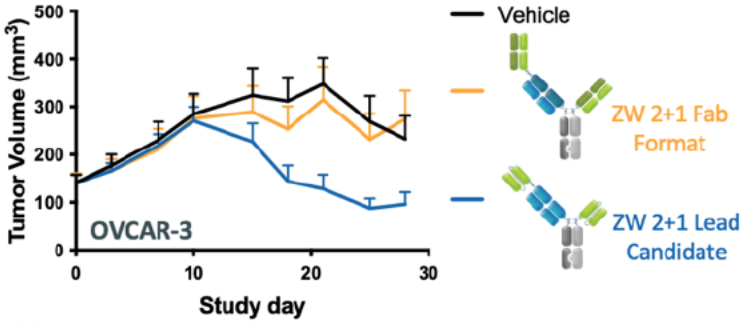
ZW171 Lead Candidate Confirmed through Format and Affinity Screening In Vivo

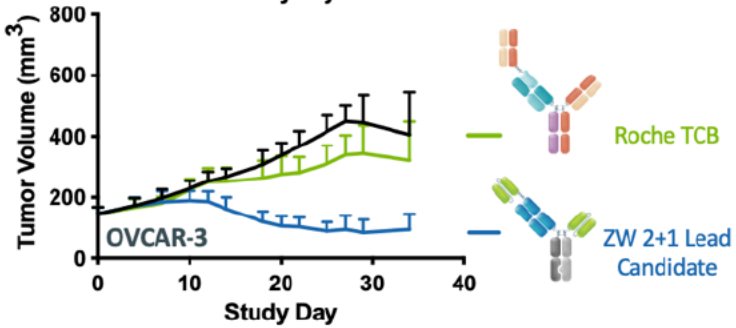
Anti-MSLN Paratope Affinity is Critical



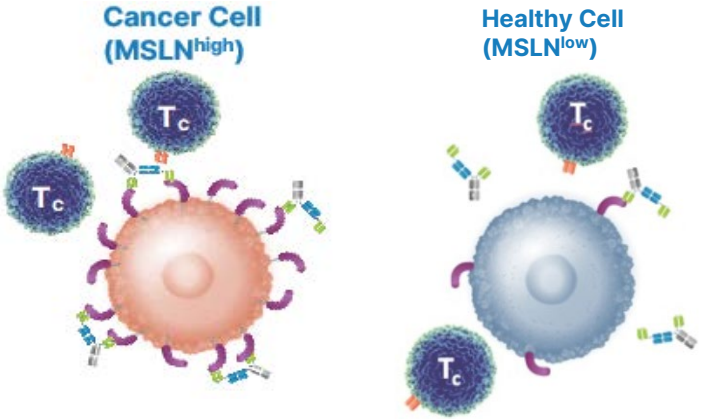
In vivo anti-tumor activity evaluated with established tumor models that have reduced sensitivity compared to co-implantation (tumor + PBMC) models

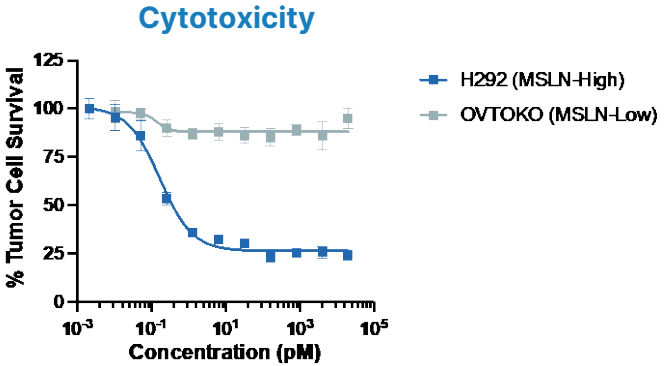
2 + 1 Geometry is Critical

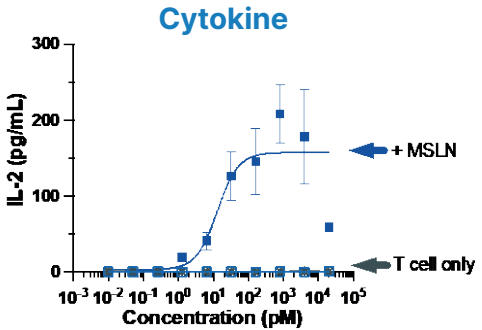


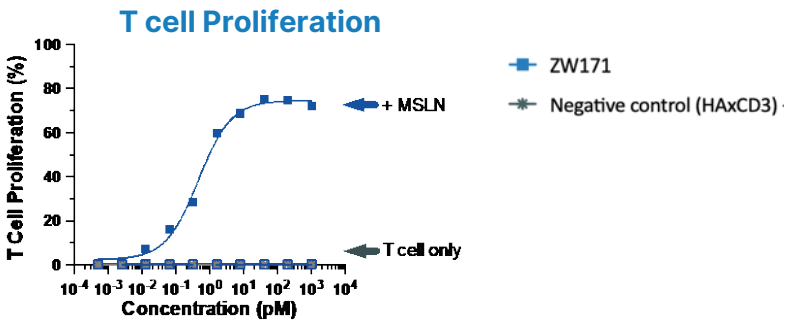


ZW171 Induces Potent MSLN-Dependent Cytotoxicity and T Cell Activation





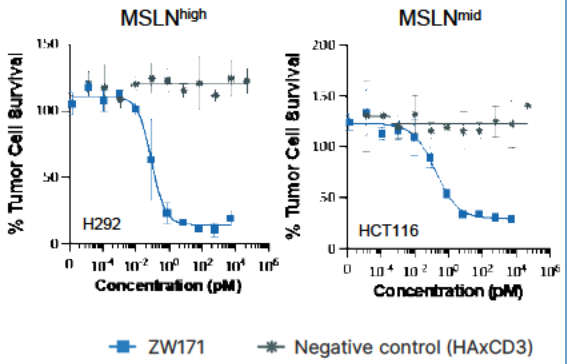




ZW171: MSLN x CD3 T Cell Engaging Multispecific Designed to Expand the Therapeutic Window

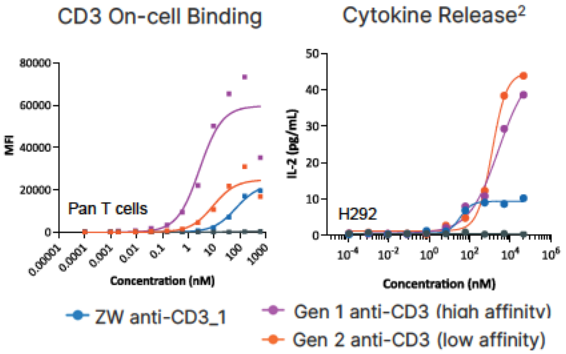
Engineered with 2+1 Format
Facilitates Avidity-Driven Binding[1]

Tumor Cell Cytotoxicity in Mid–to-High Expressing MSLN Models[1]



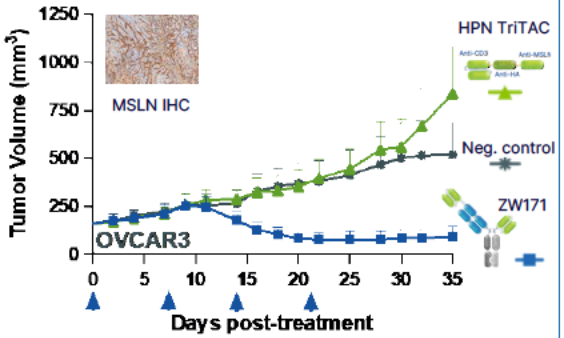
Novel CD3 Paratope with Enhanced Safety

Proprietary CD3 engager has low affinity CD3 binding and cytokine release[1]



Pilot NHP toxicology data shows ZW171 is well-tolerated up to 30 mg/kg[1]

Differentiated by Greater Anti-Tumor Activity
in MSLN-Expressing Tumor Models[1]



OVCAR-3 tumor engrafted mice were humanized with donor PBMC (3 donors) and dosed i.v. QW x4 with ZW171 or i.p. daily x 18 with HPN triTAC. Neg control (HAxCD3)

bsAb: bispecific antibody; Gen: generation; MSLN: mesothelin

1. Afacan N et al., Abstract #2942 presented at AACR 2023 2. Cytokine release from T cell dependent cytotoxicity assay with pan T cells and H292 tumor cells at 5:1 E:T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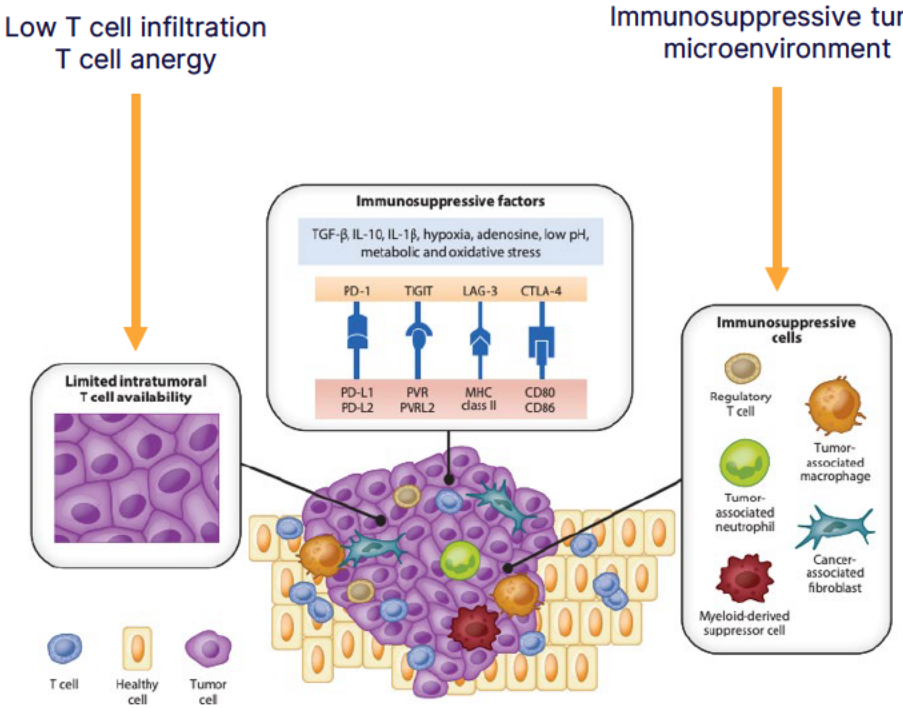
Multispecific Antibody Therapeutic Development
Beyond Bispecific TCE
TriTCE to Address Biological Challenges in the Treatment of Solid Tumors

Challenges Remain: Solid Tumors Present Obstacles not Found in Blood Cancers



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Zymeworks Multispecific T Cell Engager Strategy: Utilizing Azymetric™ to Build Differentiated & Next Generation Multispecific T Cell Engagers

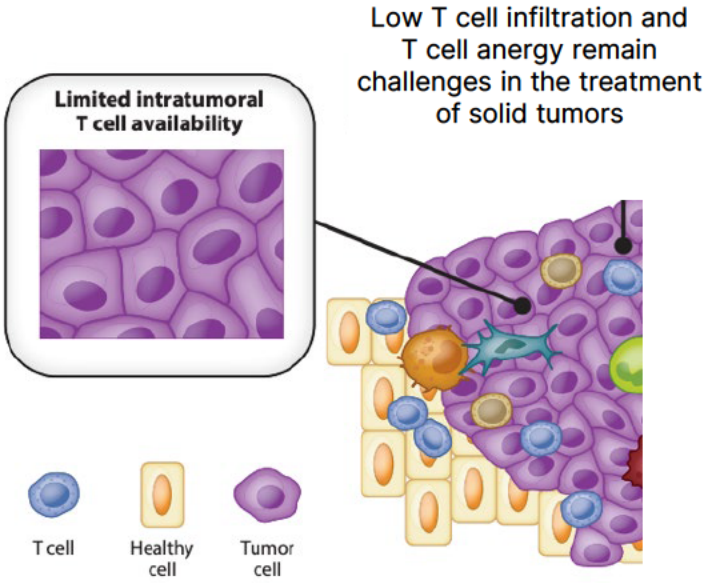
Biological Problem	Zymeworks Solution
Limited T cell intratumoral availability and T cell anergy in solid tumors	**TriTCE Co-stimulation** Increase T cell fitness, activation and proliferation via tumor-dependent T cell co-stimulation
Immunosuppressive tumor microenvironment limiting T cell responses in solid tumors	**TriTCE Checkpoint Inhibitor** Increase T cell responses through simultaneous checkpoint blockade and avidity-driven binding

CRS: cytokine release syndrome; TCE: t cell engager

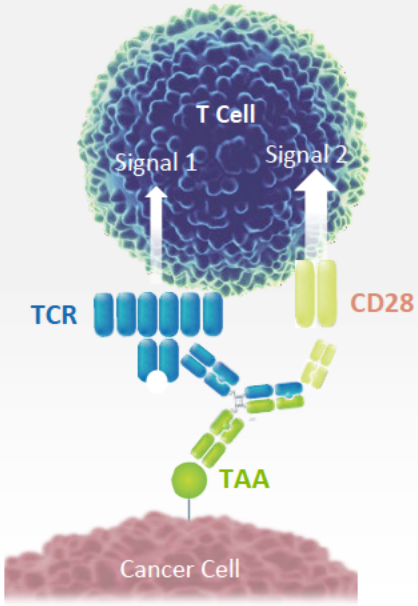
Multispecific Antibody Therapeutic Development

TriTCE Co-stimulatory Therapeutic Program

Zymeworks Trispecific Co-stimulatory T Cell Engagers: Overcoming Lack of Efficacy and Durability of Responses in Solid Tumors by Optimization of Signal 1 and 2



Zymeworks Trispecific Co-stimulatory Program



Provides Signal 1 (CD3) and Signal 2 (CD28) in one molecule

Engineered to balance signal 1 and 2 for optimized T cell activation and expansion

TriTCE Co-stim have the potential to provide more durable responses and re-invigorate 'cold' tumors with lower T cell infiltration

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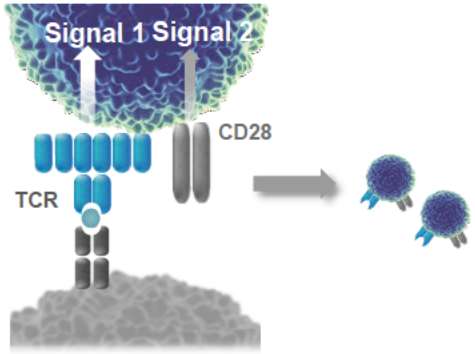
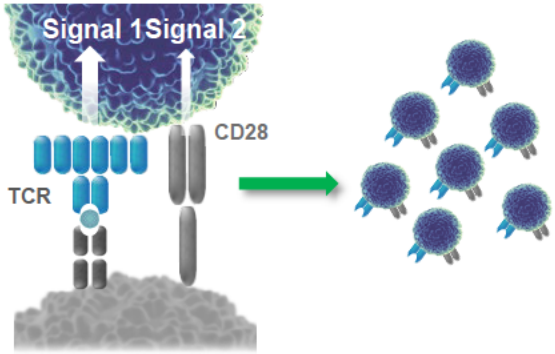
Balance of T Cell Activation by Signal 1 and Signal 2 Critical to Achieve Optimal T Cell Activation and Prevent Severe Adverse Events

No signal 2 → T cell anergy and limited T cell proliferation

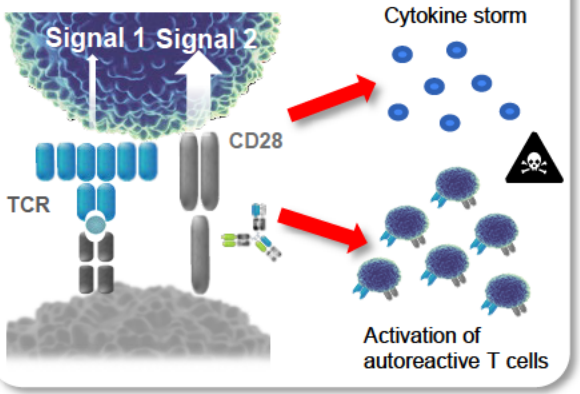


T cell anergy, reduced T cell activation and proliferation

Optimal Signal 1 and Signal 2 → T cell activation and proliferation



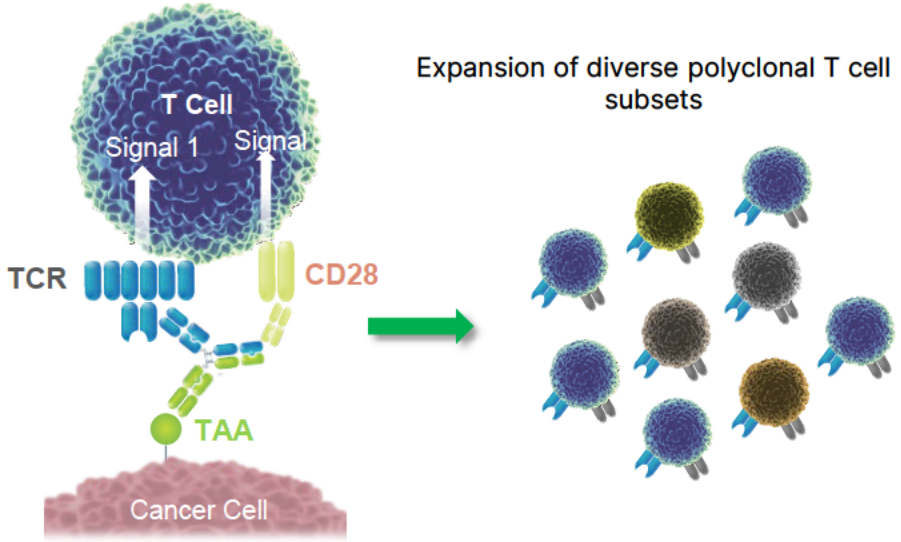
Strong T cell (CD28) activation can induce cytokine storm and immune-related adverse events



T cell overactivation potential toxicities

Optimal signal strength for T cell activation:

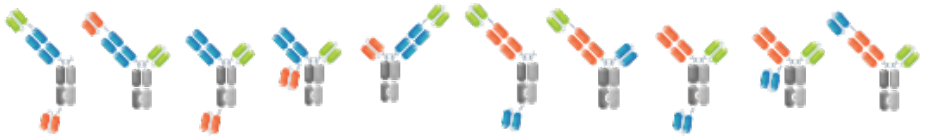
Zymeworks TriTCE Co-stim: TAA-Dependent T Cell Activation and Conditional CD28 Co-stimulation

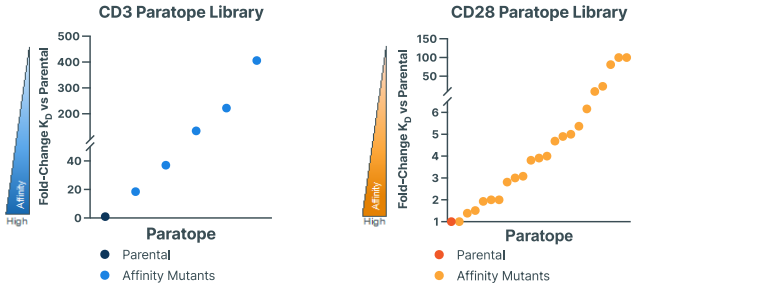


Design Criteria

- ✓ Trispecific that provides Signal 1 and 2 in one molecule
- ✓ Optimized αCD3 and αCD28 affinities and formats to enhance T cell activation and expansion
- ✓ Conditional CD28 co-stimulation, dependent on CD3 engagement and TAA expression
- ✓ Target-dependent T cell activation, no T cell activity in the absence of target antigen
- ✓ Enhanced antitumor activity and CD28-dependent functionality compared to CD3xTAA bispecific

Engineering and Screening Approaches Enable Identification of Optimal Format and Paratope Affinities for Robust 'Signal 1' + 'Signal 2' T Cell Activation and Synapse Formation



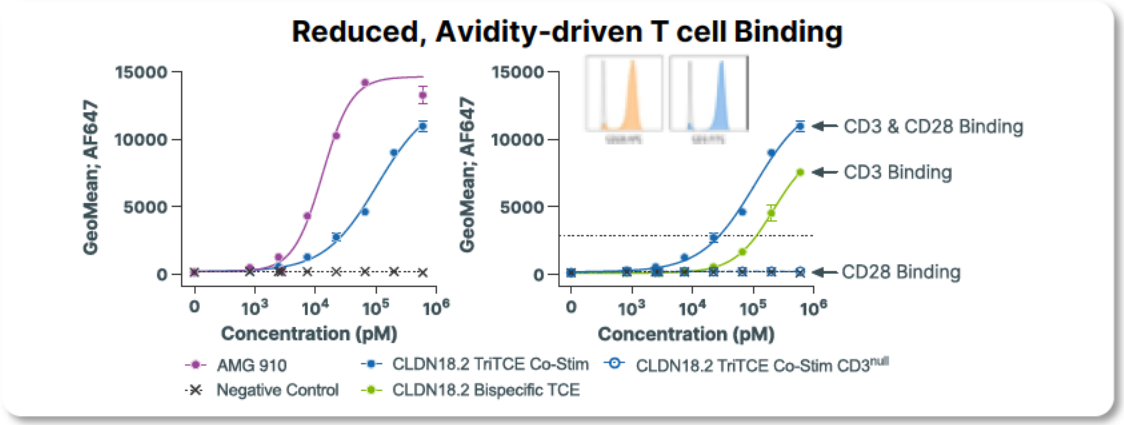


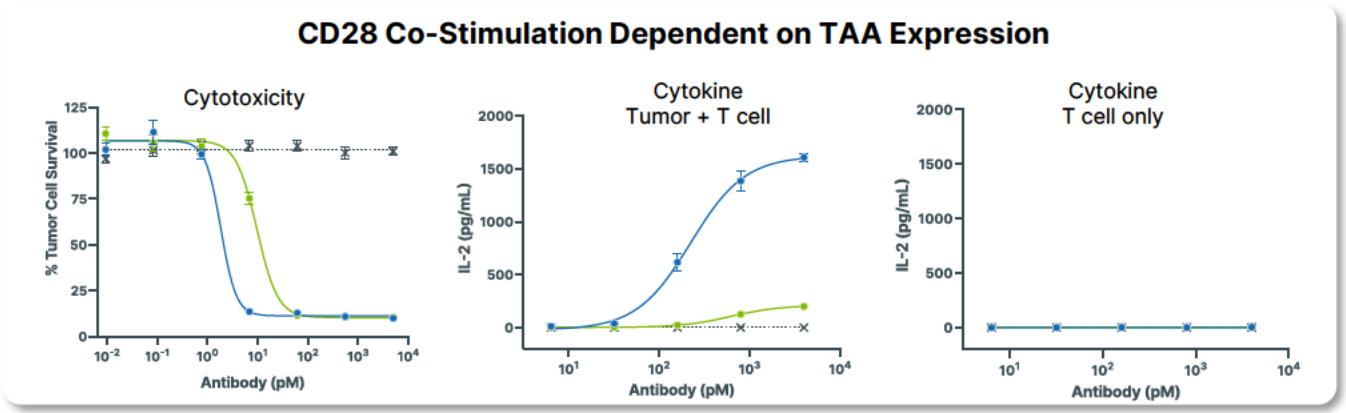
Antibody Format	1	2	3	4	5	6	7	8	9	10
IC50 (pM)										
TAA-Dependent?	✓	✓	✓	x	✓	✓	x	x	x	x

10^{0}
10^{-1}
10^{-2}

- **Engineering solutions employed to optimize signal strength** for T cell activation and anti-tumor activity, including modifications paratope affinities and antibody format geometries
- 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

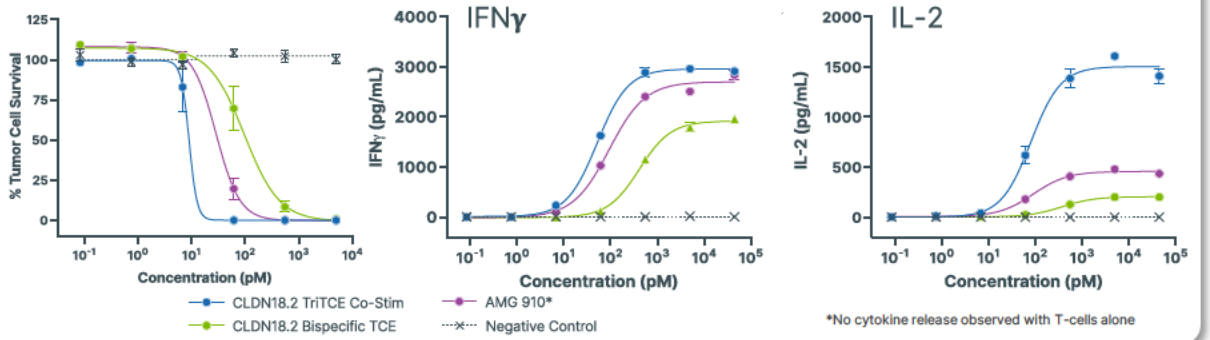
CLDN18.2 TriTCE Co-stim Mediate Conditional CD28 Co-stimulation Dependent on CD3 Engagement and TAA Expression



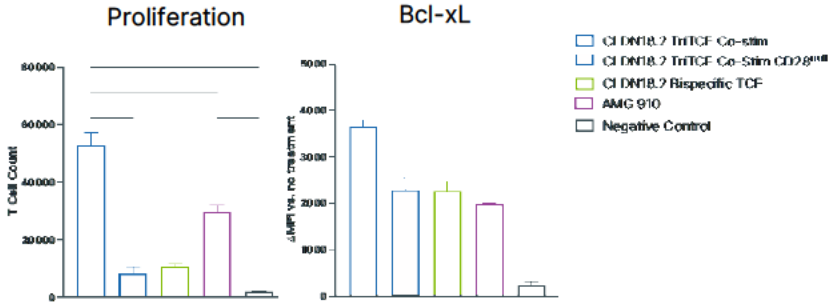


TriTCE Co-stim Enhance T Cell Responses at Low Effector to Target Cell Ratios

Enhanced Cytotoxicity and CD28-Dependent Cytokine Activity* at Low E:T



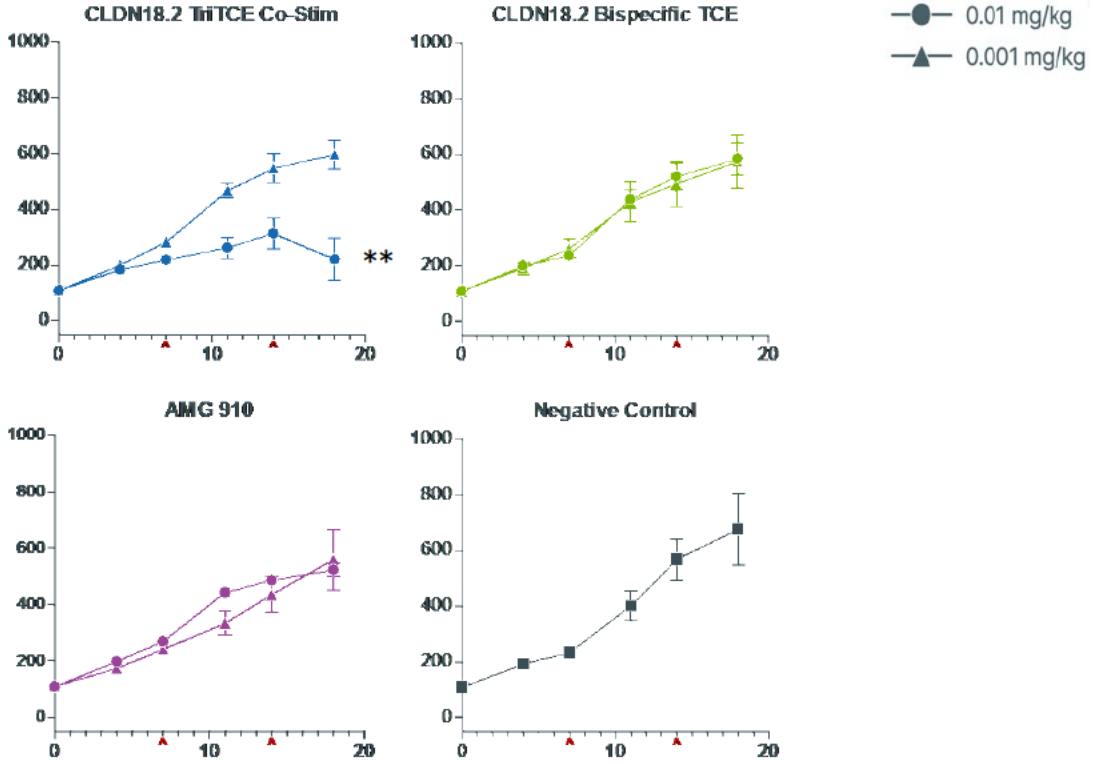
Improved T cell Proliferation and Survival



CLDN18.2 TriTCE Molecule Show Greater Anti-tumor Activity Compared to Bispecific TCE

CLDN18.2+
Tumor engraftment

huPBMC
engraftment



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

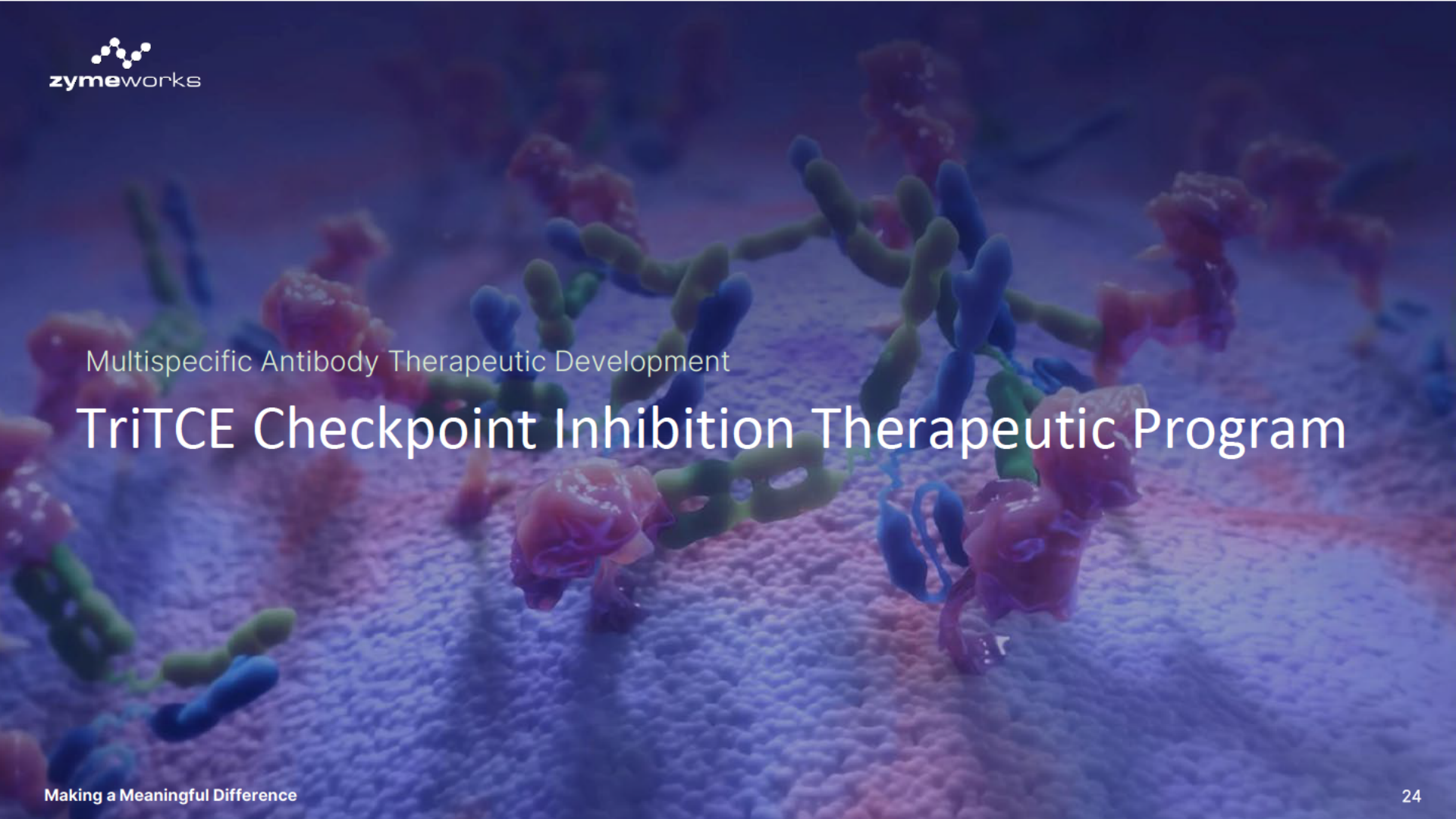
Next Milestones

Additional mechanistic and safety data to be presented at SITC 2023, Abstract #1372

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

Expand utility to additional tumor targets

TCE: t cell engager; TriTCE Co-Stim: Co-stimulatory trispecific TCEs; PK: pharmacokinetics

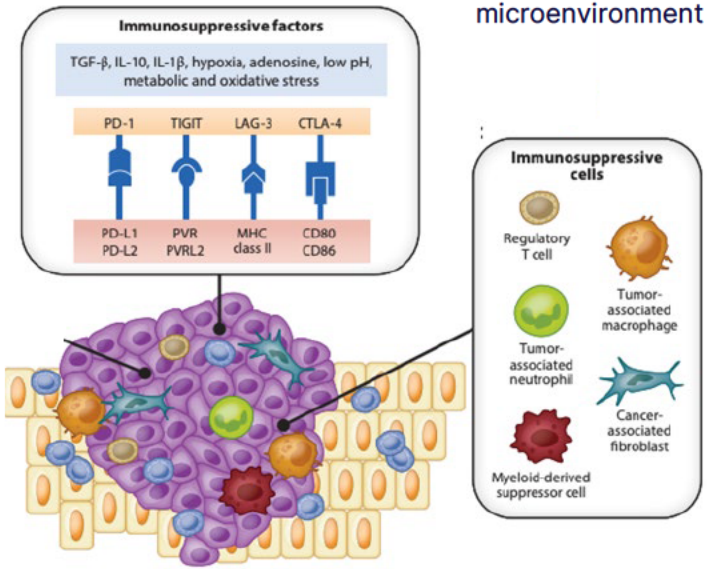


Multispecific Antibody Therapeutic Development

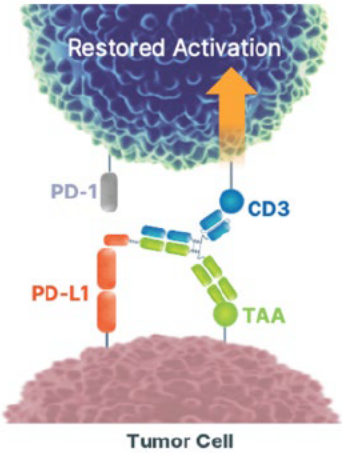
TriTCE Checkpoint Inhibition Therapeutic Program

Zymeworks Trispecific Checkpoint Inhibition: Integrated Checkpoint Inhibition (CPI) for the Treatment of Solid Tumors

Immunosuppressive tumor microenvironment



Zymeworks Trispecific Checkpoint Inhibition (CPI) Program



Trispecific with integrated CD3 and PD-L1 engagement (engineered PD1 domain)

Engineered for enhanced activity in TAA⁺PDL1⁺ tumors with multiple MOA

TriTCE CPI have the potential to enhance T cell responses in immunosuppressed and exhausted T cell microenvironments

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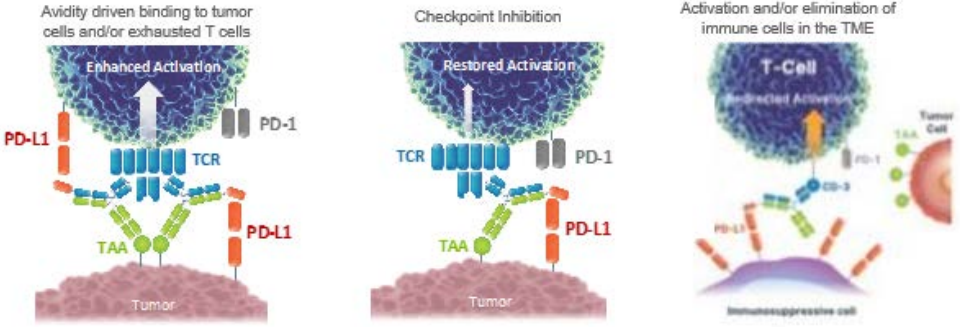
TriTCE CPI: Next Generation Trispecific T Cell Engagers (TriTCE) with Integrated Checkpoint Inhibition (CPI) for the Treatment of Solid Tumors

Proposed mechanisms of action for TriTCE CPI therapeutics

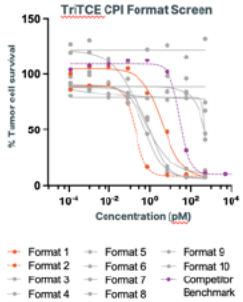


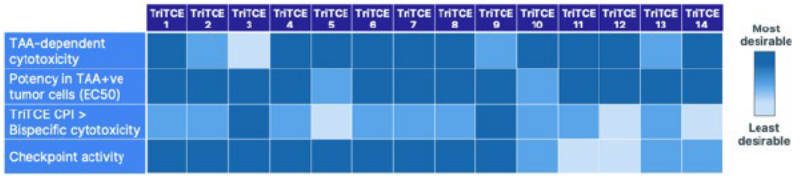
Improve T cell responses and anti-tumor activity in immunosuppressed solid tumors via concurrent T cell activation and checkpoint inhibition

Different TriTCE CPI geometries and PD-L1 affinities were screened for increased T cell-dependent cytotoxicity

Engineered PD1 domain library with various domain affinities

Panel of molecules including modifications PD1 domain affinities and antibody format geometries





In vitro screening identified TriTCE CPI molecules with enhanced TAA-dependent anti-tumor activity and CPI compared to a bispecific TCE

Poffenberger MC et al., TriTCE CPI, next generation trispecific T cell engagers with integrated checkpoint inhibition (CPI) for the treatment of solid tumors. Abstract #2982 presented at American Association for Cancer Research annual meeting 2023.

Next Generation PD1 Checkpoint Inhibition Trispecific T cell Engager

Designed to provide more durable responses in immunosuppressed solid tumors

Therapeutic Rationale

Next Gen TriTCE CPI can provide increased T cell responses in suppressive tumor microenvironments

Product Differentiation

Novel approach of modular geometry and avidity screening of trispecifics to optimize avidity-driven activity and checkpoint inhibition

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

Next Milestones

Additional mechanistic and safety data to be presented at SITC 2023, Abstract #4766

Pilot toxicology studies and PK analyses

Expand utility to additional tumor targets

TCE: t cell engager; TriTCE CPI: Checkpoint inhibition trispecific TCEs; PK: pharmacokinetics

Summary

- Protein engineering strengths and Azymetric™ platform enables comprehensive design and screening of multiple parameters in parallel
- ZW171 is a 2+1 bispecific TCE with a promising antitumor and safety profile and has the potential for first or best in class treatment for the treatment of MSLN expressing tumors
- TriTCE Co-stim molecule have differentiated antitumor activity in low E:T settings and have potential in improve responses in tumors with low T cell infiltration
- TriTCE CPI molecules have differentiated antitumor activity in $TAA^{+}PD\text{-}L1^{+}$ tumors and have potential to improve responses in immunosuppressed tumors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Thank you