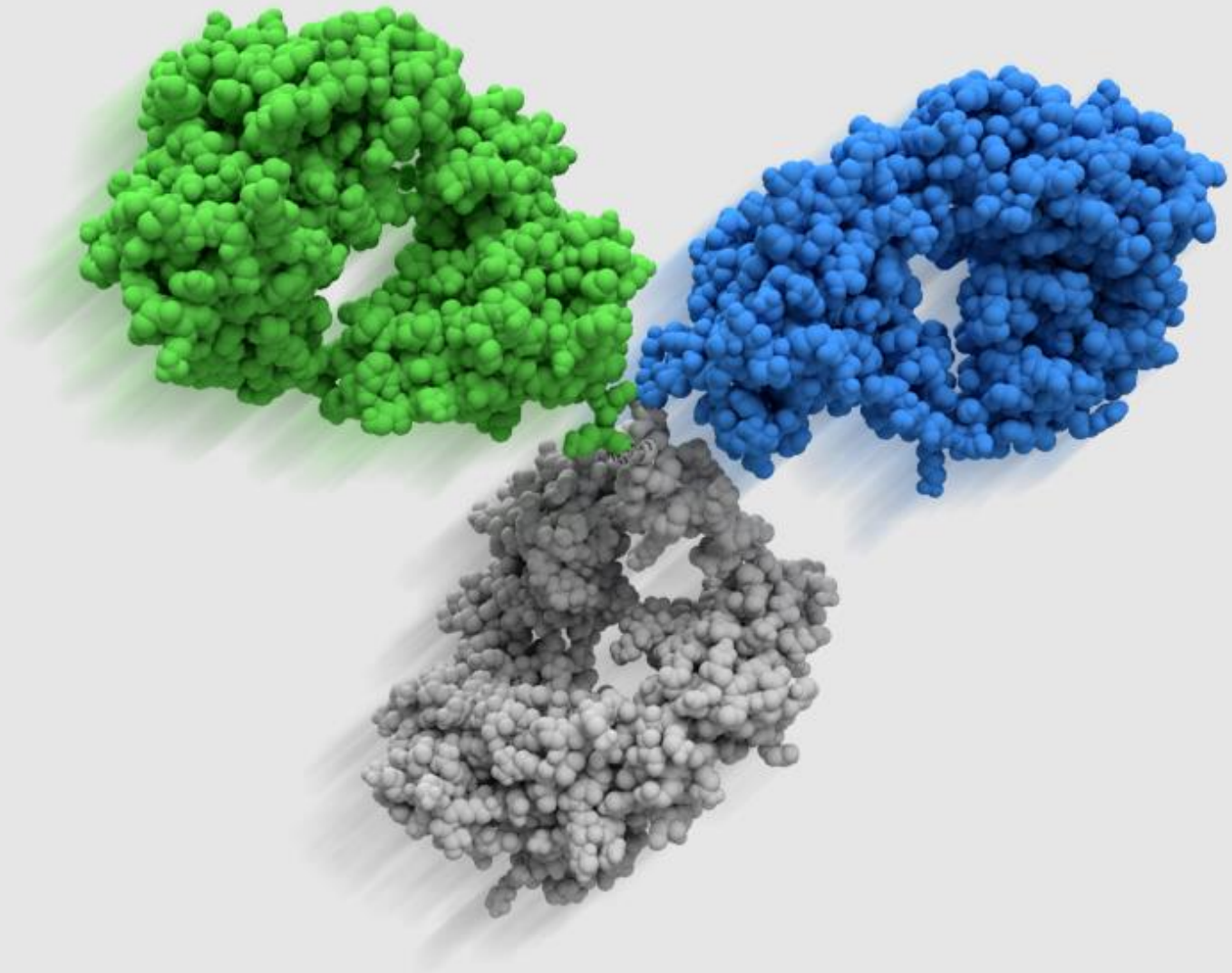
From Bi- to Trispecific Antibodies: Reimagining the Next Generation of ADCs



Bonnie Hammer, PhD
PEGS Conference

Contact: BD@Invenra.com
Nonconfidential

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 (2025)

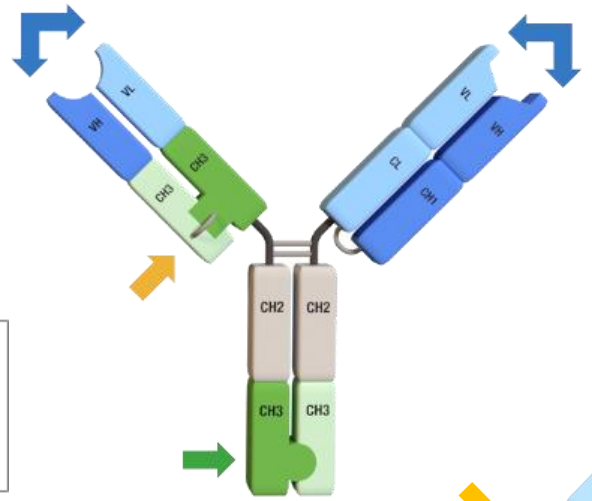
Easy

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

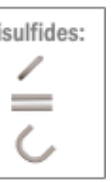
1	**Best multispecifics start with quality mAbs**	Accellerated timelines with transparent pricing and terms
		>30 diverse, optimized human libraries
		Achieve desired affinity, specificity, and functional profile goals
		Transfer easily to our multispecifics platforms
2	**B-Body® bispecific antibodies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

Invenra's B-Body® and T-Body™ Platforms: Robust Solutions for Multispecific Antibody Development

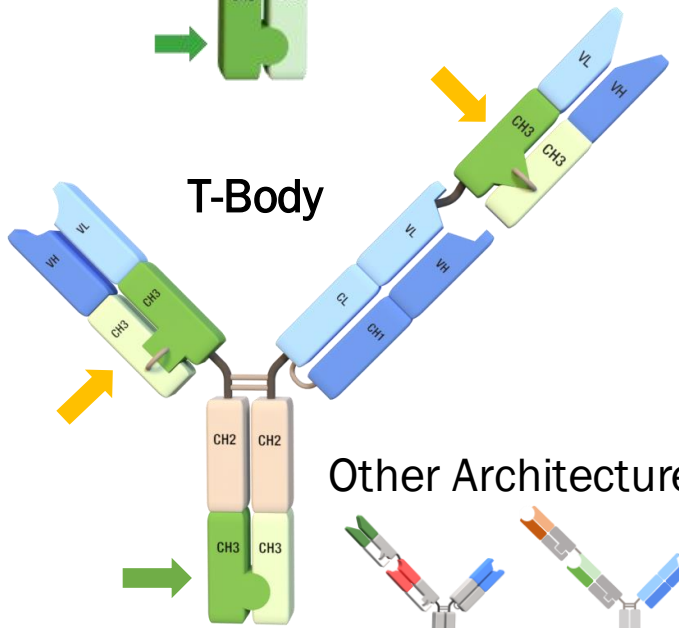
B-Body



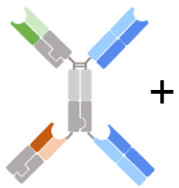
Disulfides:



T-Body



Other Architectures:



+ more

Engineering

Fc Region: Clinically Validated Knobs-into-Holes

- Drive heavy chain heterodimerization
- Compatible with standard Fc substitutions

Fab Arms: Proprietary CH3 Domain Pairs

- Substitutes for CH1/CL in two Fab Arms
- Solves light chain mispairing issue
- Natural asymmetry in isoelectric point

Proprietary Symmetrical Heavy & Light Chain Inversions in Fab Arms

- Robust expression yields
- Efficient purification
- "Plug & Play" variable domains

Benefits:

B-Body and T-Body Platforms provide a simple and accelerated path to Lead Candidates

- High stability, robust expression, mAb-like CMC
- Multiple formats: 1×1, 2×1, 2×2, trispecific
- Compatible with diverse mAbs & standard functional mutations
- Validated for conjugation
- Strong IP protection

Why Trispecific ADCs?

- Broader Patient Coverage within a Cancer Type
  - Targeting multiple targets increases the number of patients that are likely to respond in an indication
- More Cancers Types Covered
  - Targeting multiple targets increases the number of cancers that are likely to respond
- Better Tumor Control
  - Targeting multiple targets limits the tumors escape routes and attacks a larger portion of a heterogenous tumor
- More MOAs Available
  - VEGF Activated Avidity Lock (VAAL)
  - Biparatopic Plus
  - Stroma and Tumor

52 Programs. Four Mechanisms. One Deck.

Clubs: Three-TAA Targeting

Target three tumor associated antigens simultaneously and independently. Addresses heterogeneous tumors and reduces escape routes.

Spades: Stromal + Tumor Targeting

Deliver payload to the tumor microenvironment. Combines stromal + tumor antigens to penetrate stroma-dense cancers.

Diamonds: BP+ (Biparatopic-Plus)

Biparatopic binding drives >2× internalization, while the third arm addresses heterogeneity and blocks resistance. Not bispecific — three distinct specificities.

Hearts: Novel MOAs

Invenra's most differentiated mechanisms, exploring the full potential of trispecifcs to cure disease

Invenra is developing 52 T-Body ADCs programs across four strategic approaches to overcome resistance and improve tumor selectivity

52 Views of Cancer – 52 T-Body ADCs

Novel Mechanisms of Action
Ex. VEGF Activated Avidity Lock

12 More in Suit

Biparatopic Plus

12 More in Suit

Three Tumor Antigens

12 More in Suit

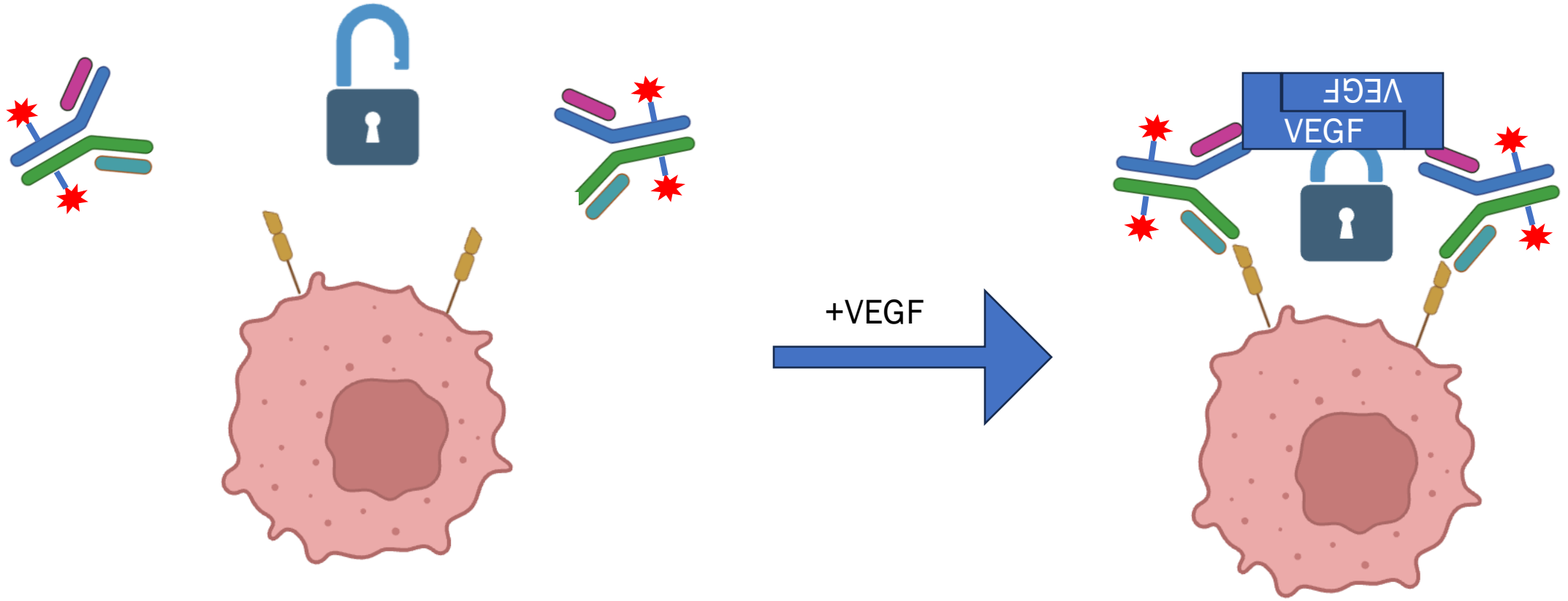
Stromal + Tumor Targeting

12 More in Suit

VAAL – VEGF Activated Avidity Lock

No VEGF=No avid binding. If affinity of TAA arm is weak, no significant engagement of target or internalization.

VAAL=VEGF Activated Activity Lock
Avid binding from VEGF mediated cross-linking
Cross-linking additionally leads to internalization.



❤️ VAAL – VEGF Activated Avidity Lock

🔴 Outside TME
Low VEGF

Tumor antigen binding arms have weak monovalent binding
Low VEGF ⟶ no clustering
Minimal off-tumor binding

On-target off-tumor risk ↓

Weak monovalent tumor antigen binding arms outside TME reduces on-target off-tumor tox **increasing the therapeutic window**

⚡ Activation Trigger
High VEGF in TME

⚡ VEGF Clustering
VEGF homodimer bridges two molecules
Avidity increases KD ~
Tumor binding arms now active

Ex. CS2009: 300 fold increase in PD1 reporter activity

VEGF homodimer bridges 2 antibodies ⟶ cluster formation ⟶ avidity jump.
Increases tumor selectivity

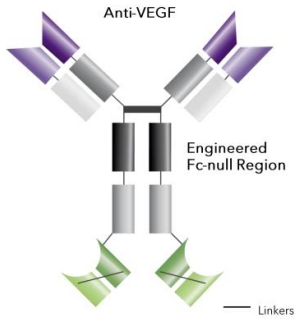
🎯 TME Triggered Internalization
Avid bivalent engagement of Tumor binding arms
ADC internalized, payload released
On-tumor selectivity preserved

Full ICD + ADCC activated

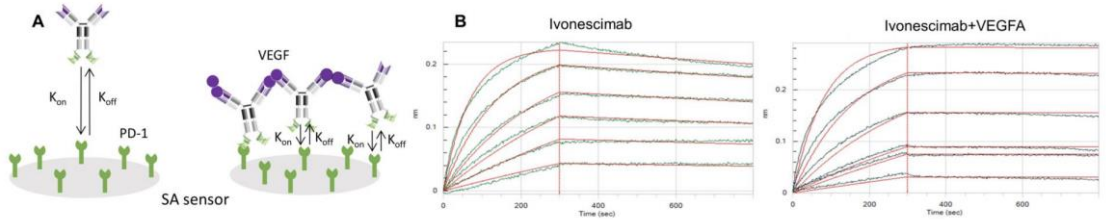
Converts tumor's own hypervascularization into ADC activation switch **increasing internalization**

VEGF Driven Avidity Enhancement Examples

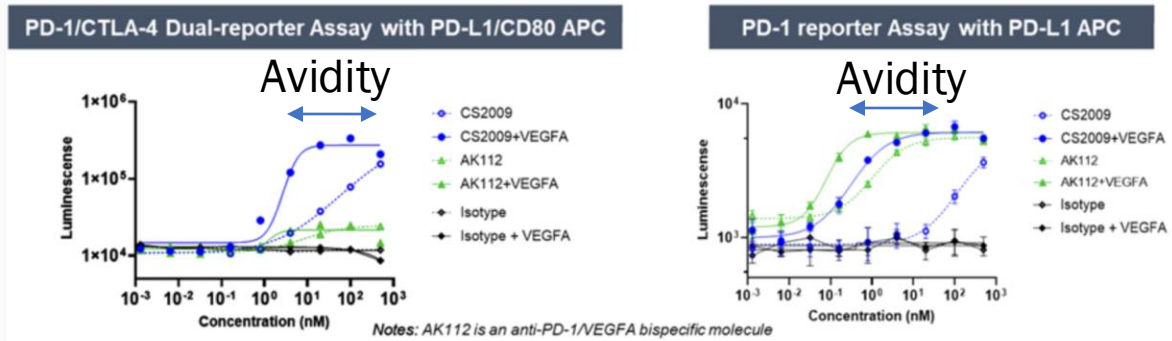
Akesobio
Ivonescimab PD-1/VEGF



CStone
CS2009 PD-1/VEGF/CTLA-4

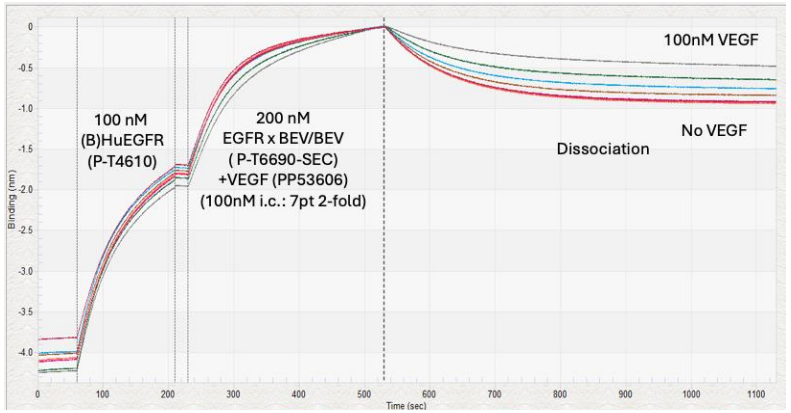


Fixed antigen	Antibody	VEGFA-his (nM)	K_D (M)	k_{on} (1/ms)	k_{dis} (1/s)
PD1-his, 200 nM	Ivonescimab	0	7.15E-10	2.94E+05	2.10E-04
	Ivonescimab + VEGF	50-1.56	3.83E-11	2.51E+05	9.62E-05



Notes: AK112 is an anti-PD-1/VEGFA bispecific molecule

Invenra Data—EGFR x VEGF



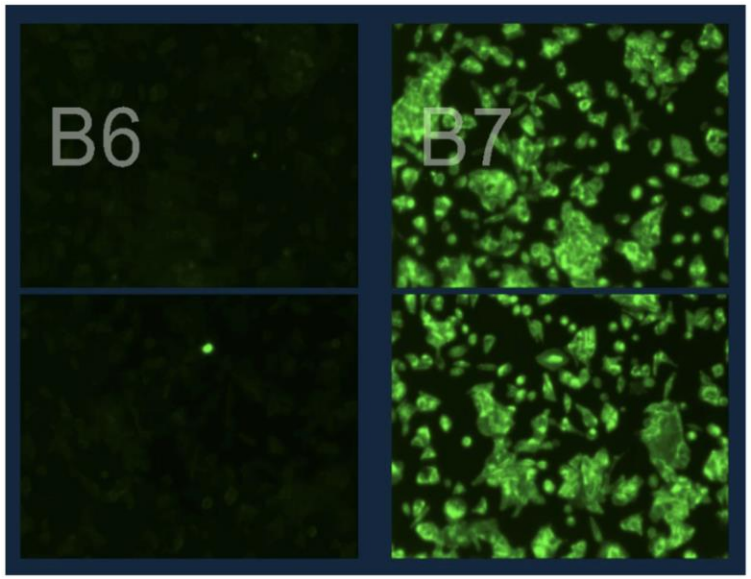
Increasing concentrations of VEGF

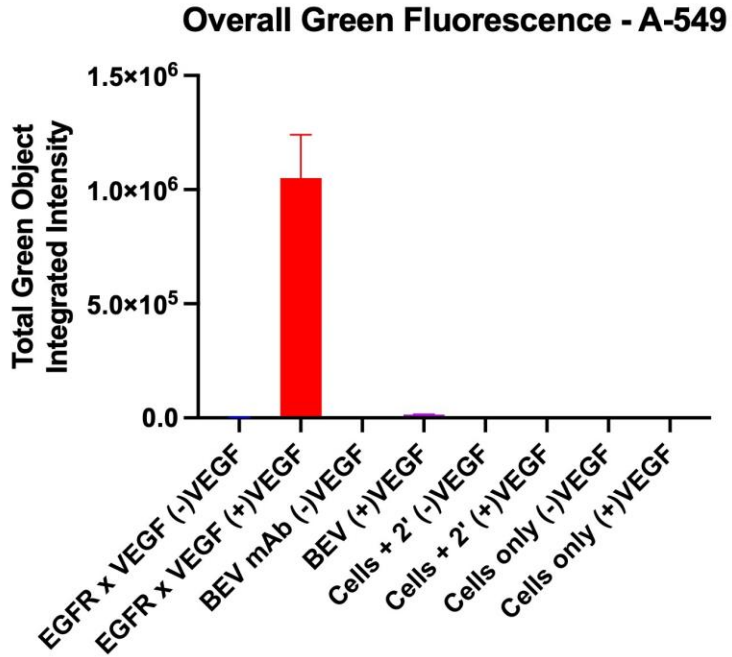
❤️ Further Implications of Clustering Through a VEGF Mechanism→ Making "Dirty" targets "Clean"

- Most ADC targets exhibit some degree of normal tissue expression.
- VEGF provides an avidity binding enhancement for bsAbs or tsAbs.
- Lower affinity Abs to the TAA can be utilized to reduce normal tissue binding in locations where VEGF is not present.

Target	Normal Tissue Expression
EGFR	Skin, GI tract, liver, kidney
TROP-2	Kidney, lung, liver, GI epithelium
B7-H3	Broadly expressed across many normal tissue
HER3	Skin, GI tract, reproductive tissues

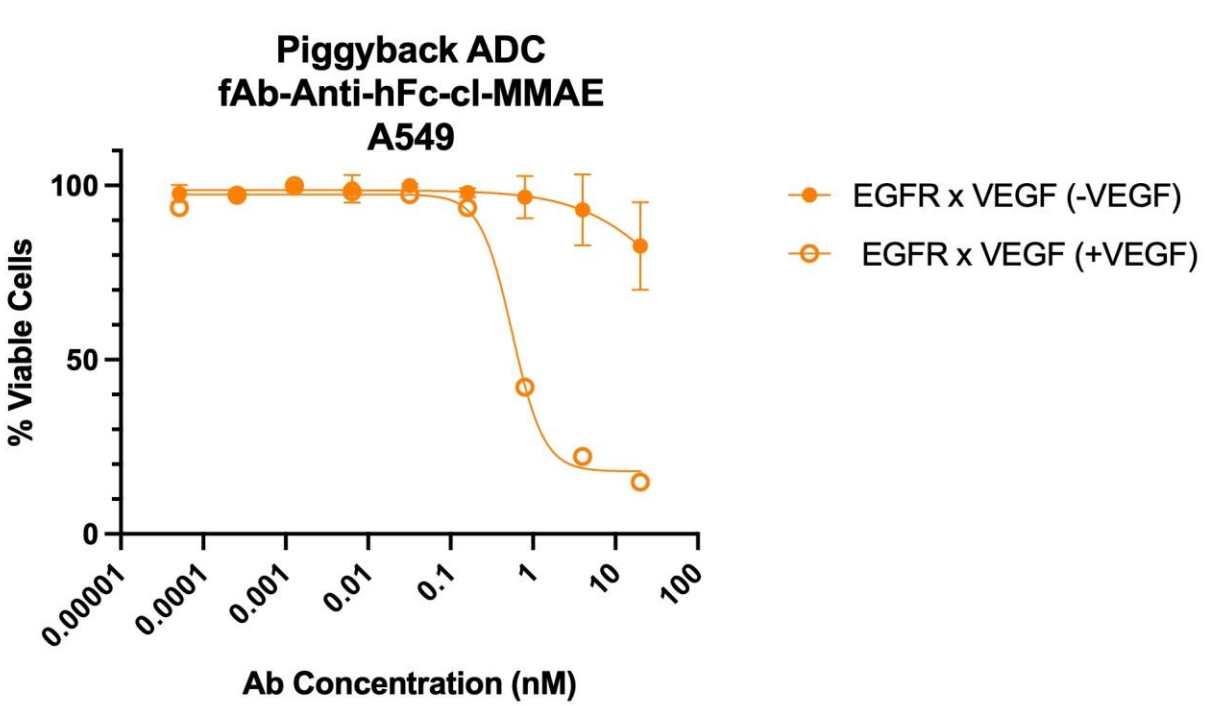
VAAL - VEGF Activated Avidity Lock



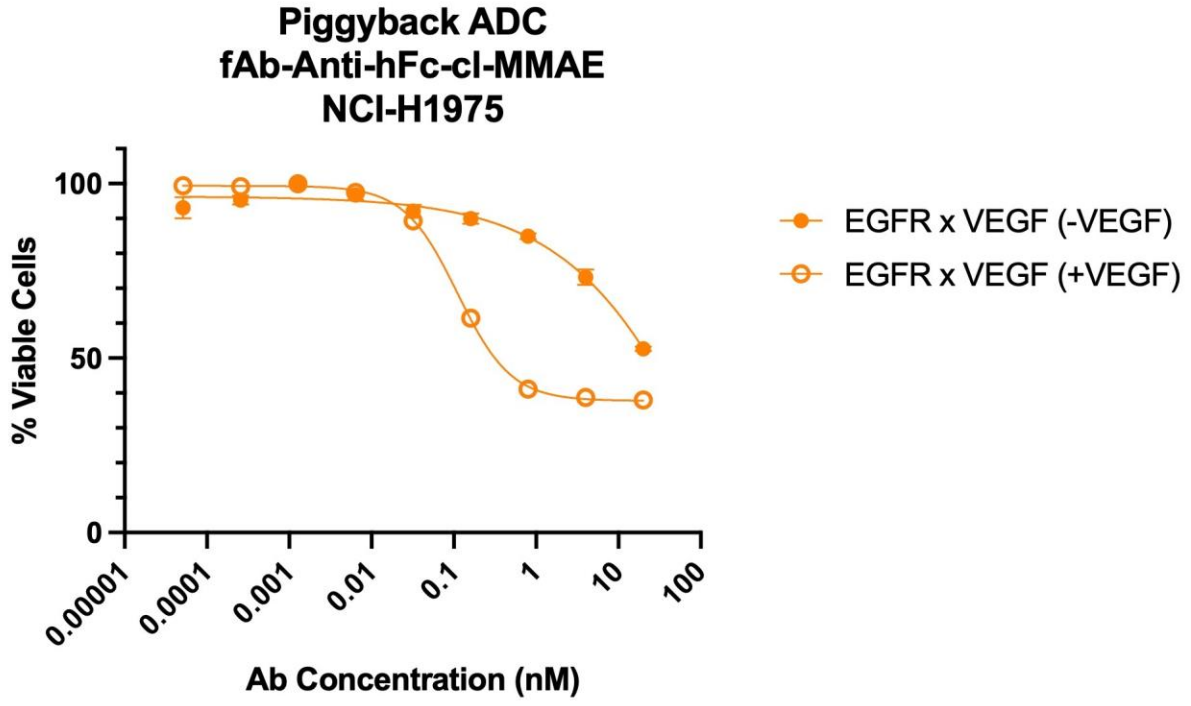


- A549 tumor cells expressing EGFR (~52,000 copies/cell) were incubated with EGFR x VEGF bispecific antibodies in the presence or absence of VEGF for 6 hrs
- Cells were fixed, permeabilized and stained with a secondary antibody
- The EGFR binder arm is low affinity and doesn't strongly engage EGFR on A549 cells without VEGF present
- When VEGF is present, strong binding and internalization is observed

❤️ Piggyback ADC Assay with Fab MMAE Secondary–bsAb



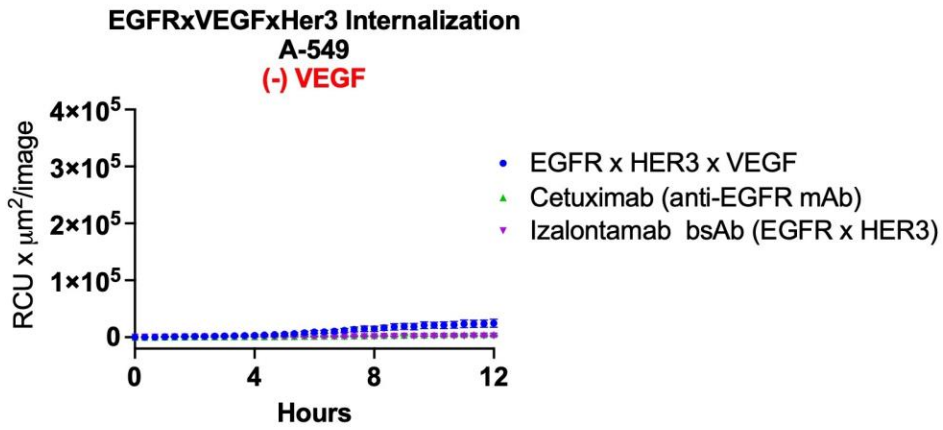
EGFR Surface Copy #~52,000

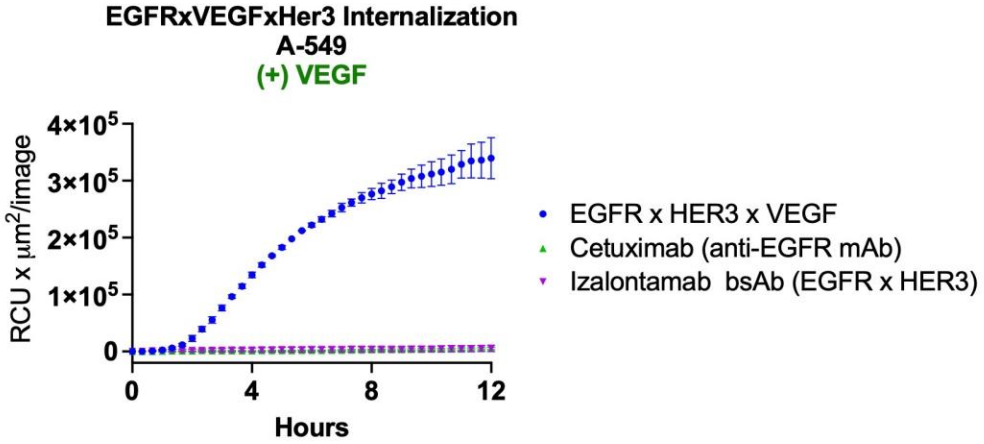


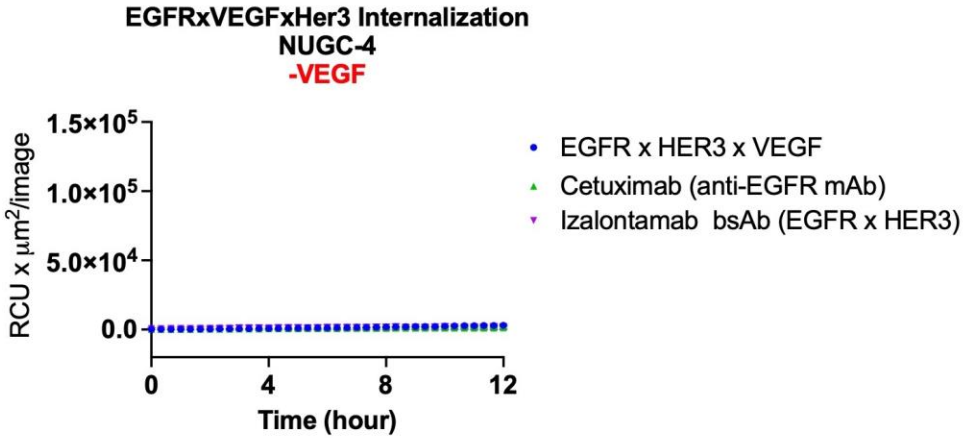
EGFR Surface Copy #~32,000

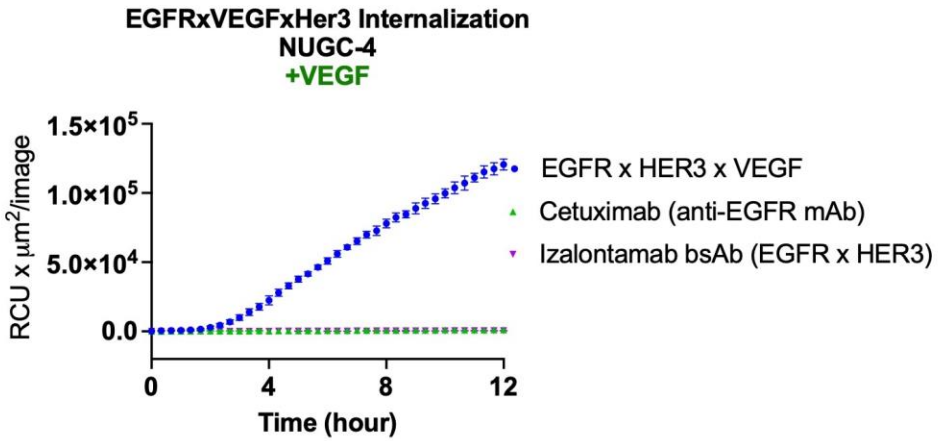
Large Differential in Killing in the Presence vs. Absence of VEGF

Triggered Internalization with VEGF



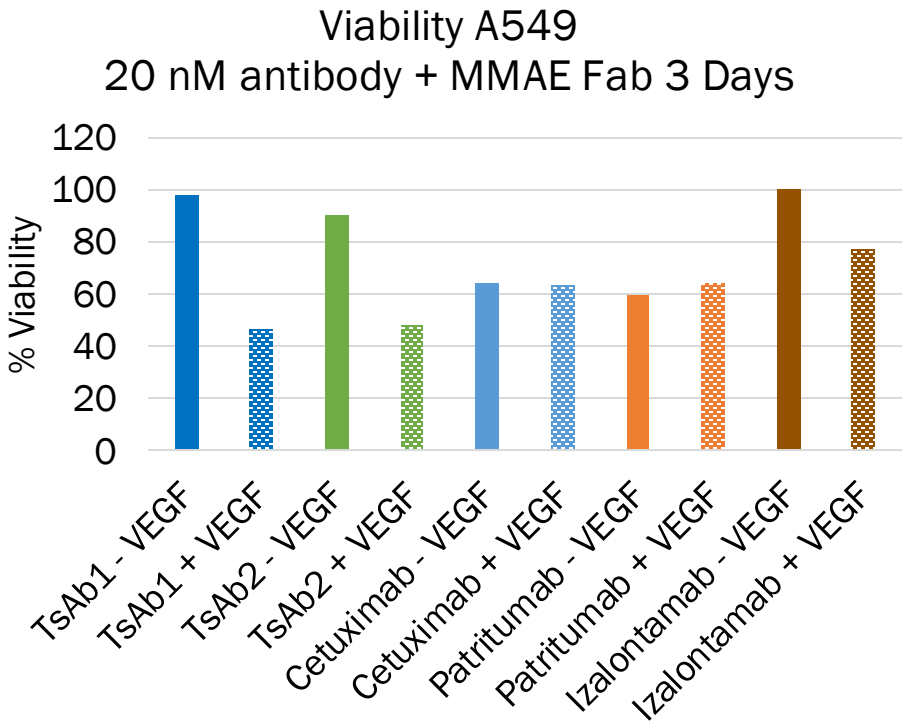




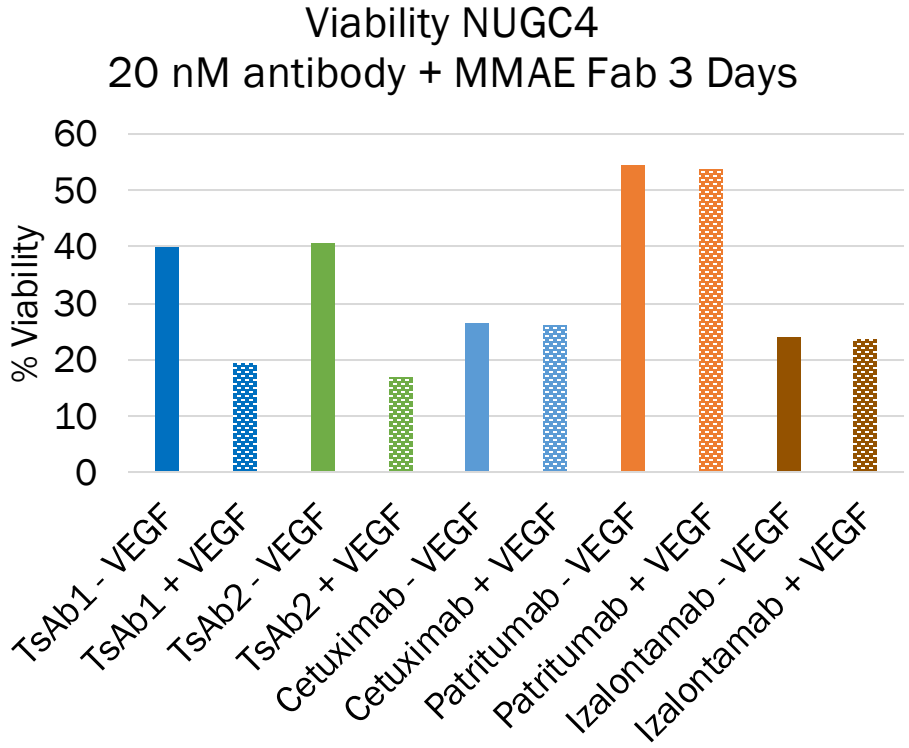


VEGF Triggers Internalization

❤️ Piggyback ADC Assay with Fab MMAE Secondary—EGFR x HER3 x VEGF



EGFR Surface Copy #~52,000
HER3 Surface Copy #<1000



EGFR Surface Copy #~14,000
HER3 Surface Copy #~22,000

Differential in Killing Between +/-VEGF for tsAbs

52 Views of Cancer – 52 T-Body ADCs

Novel Mechanisms of Action

12 More in Suit

Biparatopic Plus

12 More in Suit

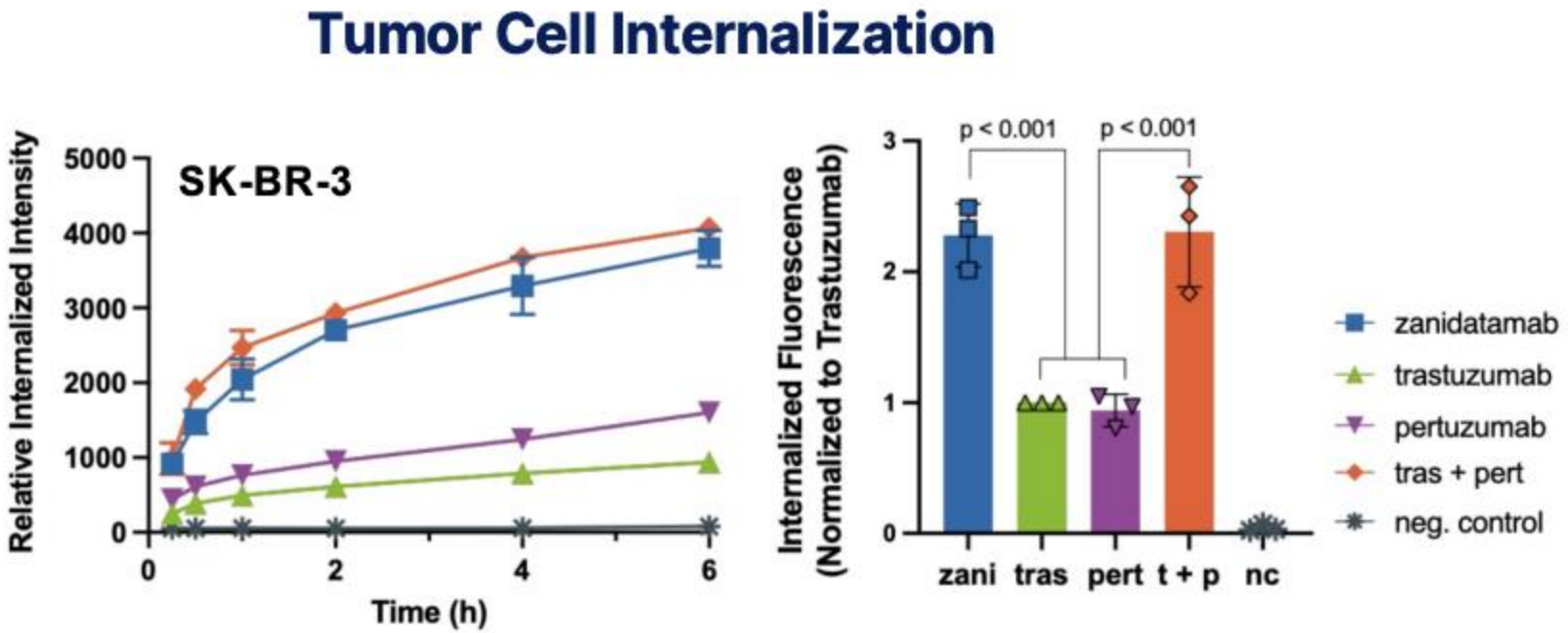
Three Tumor Antigens

12 More in Suit

Stromal + Tumor Targeting

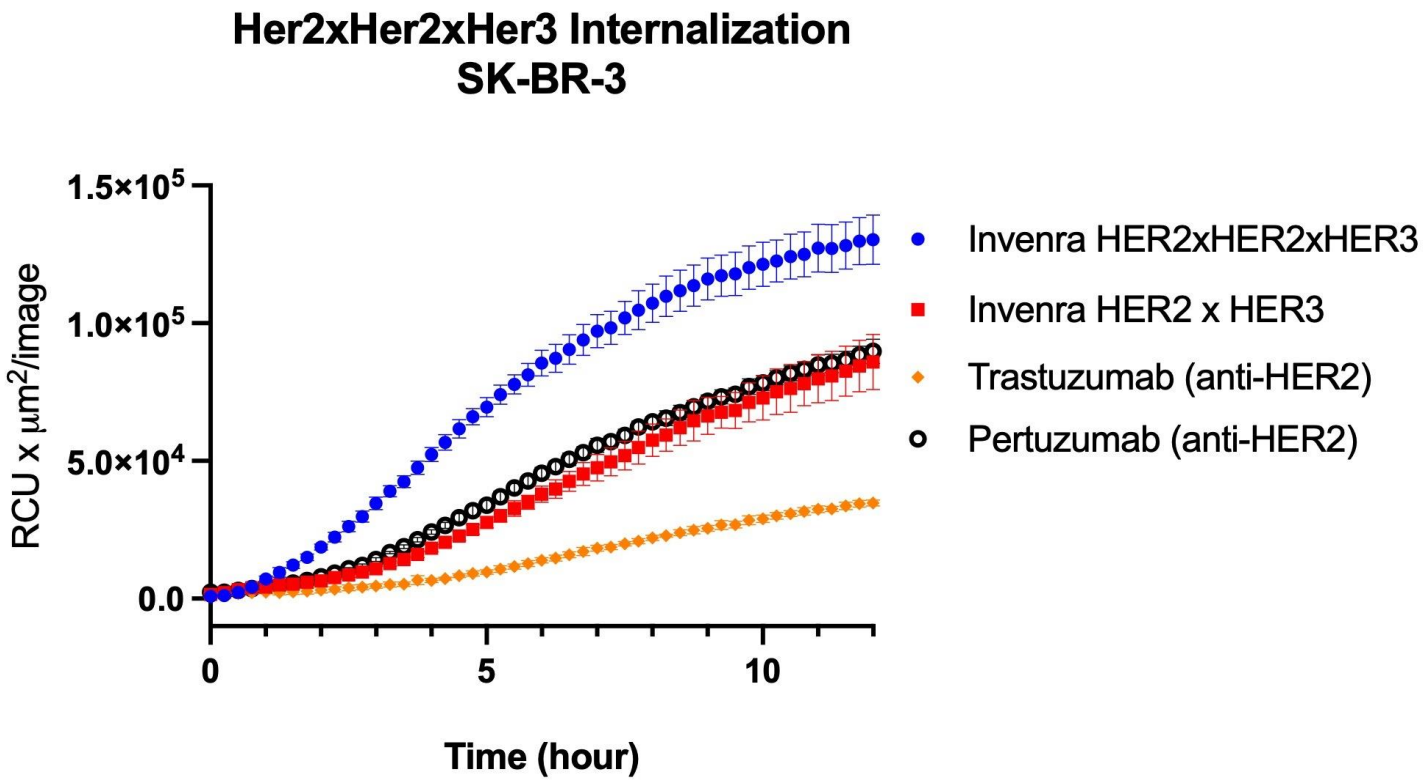
12 More in Suit

♦ Increased Internalization with bpAbs



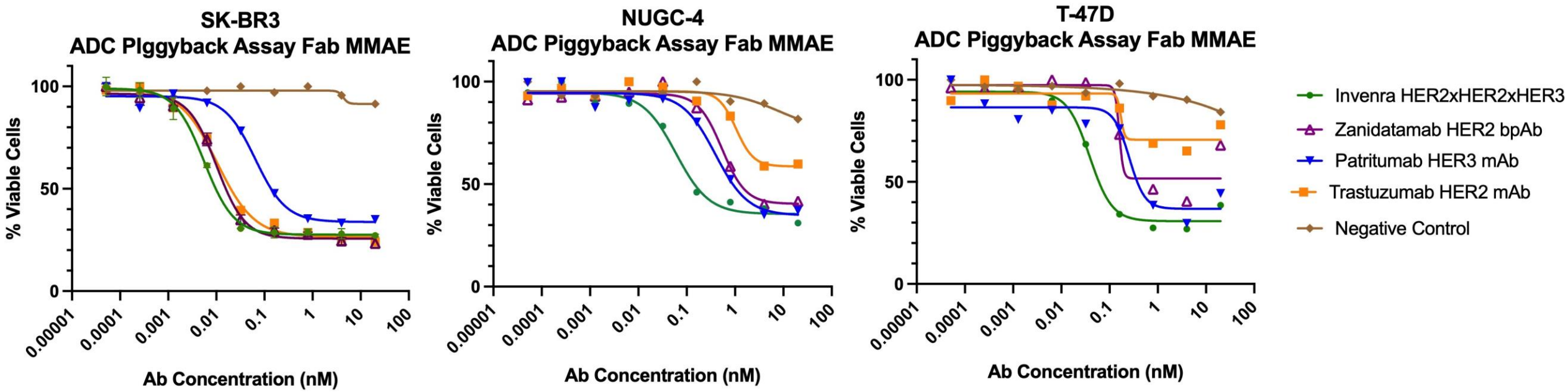
Zymeworks 2023 Presentation HER2

♦ Increased Internalization Rate with Biparatopic Plus (HER2 x HER2 x HER3)



Incucyte Fabflour pH Dye for Internalization

♦ HER2 x HER2 x HER3(Biparatopic Plus) ADC Piggyback Data (Fab MMAE)



Cell Line	HER2 Surface Copy #	HER3 Surface Copy #
SKBR3	250,000	9,500
NUGC-4	54,000	24,000
T-47D	18,000	13,300

52 Views of Cancer – 52 T-Body ADCs

Novel Mechanisms of Action

12 More in Suit

Biparatopic Plus

12 More in Suit

Three Tumor Antigens

12 More in Suit

Stromal + Tumor Targeting

12 More in Suit

Three Targets - One Safety Profile

01 Payload Drives MTD

FDA analysis: 8 vc-MMAE ADCs targeting different antigens all reached Phase II at 1.8–2.4 mg/kg. The antigen did not drive the MTD.

02 Bispecific ADC Data

Izalontamab brengitecan (EGFR×HER3) and JSKN016 (TROP2×HER3) show primarily payload-class toxicity. No additive toxicities from dual targeting.

03 Trispecific Edge

A third target arm captures heterogeneity and pre-empts resistance without altering the toxicity envelope.

Hypothesis Is Strongest When:

1. All three targets are tumor-restricted with limited normal tissue expression

2. DAR is equivalent to monospecific comparators (toxicity scales with total payload dose)

3. Trispecific scaffold maintains linker stability and favorable PK

Source: FDA IND Analysis (PMC), BMS/FDA BTD, Alphamab (JSKN016)

Clinical Evidence Supports the Hypothesis

Bispecific ADCs in the clinic show no additive toxicity from multi-targeting — validating the trispecific approach.

Izalontamab Brengitecan

EGFR × HER3 | Topo1i Payload

RP2D at 2.5 mg/kg with hematologic toxicities consistent with monospecific Topo1i ADCs (T-DXd, sacituzumab govitecan). No qualitatively new toxicity from bispecific format. FDA Breakthrough Therapy Designation, Aug 2025.

JSKN016

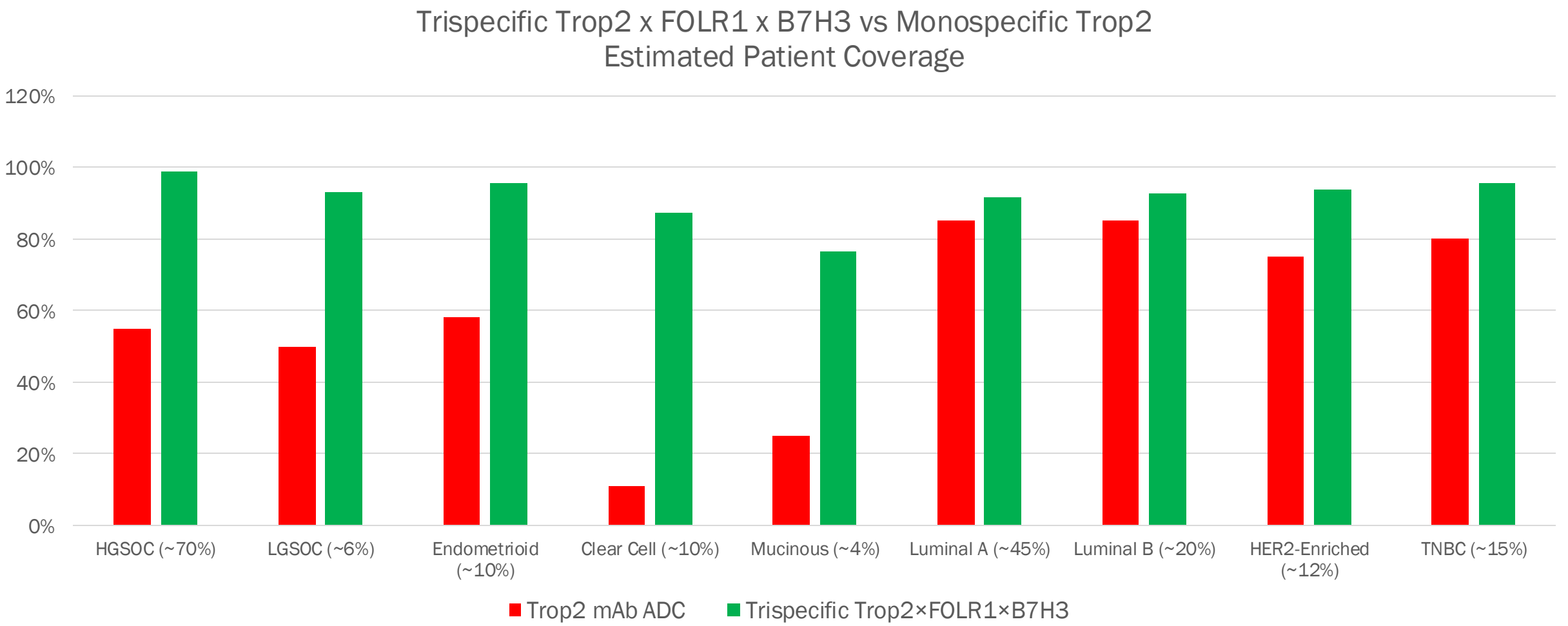
TROP2 × HER3 | Topo1i Payload

Phase I data showed manageable, predictable safety profile with class-consistent hematologic toxicities. RP2D confirmed; Phase III underway. No additive toxicity from dual-targeting format.

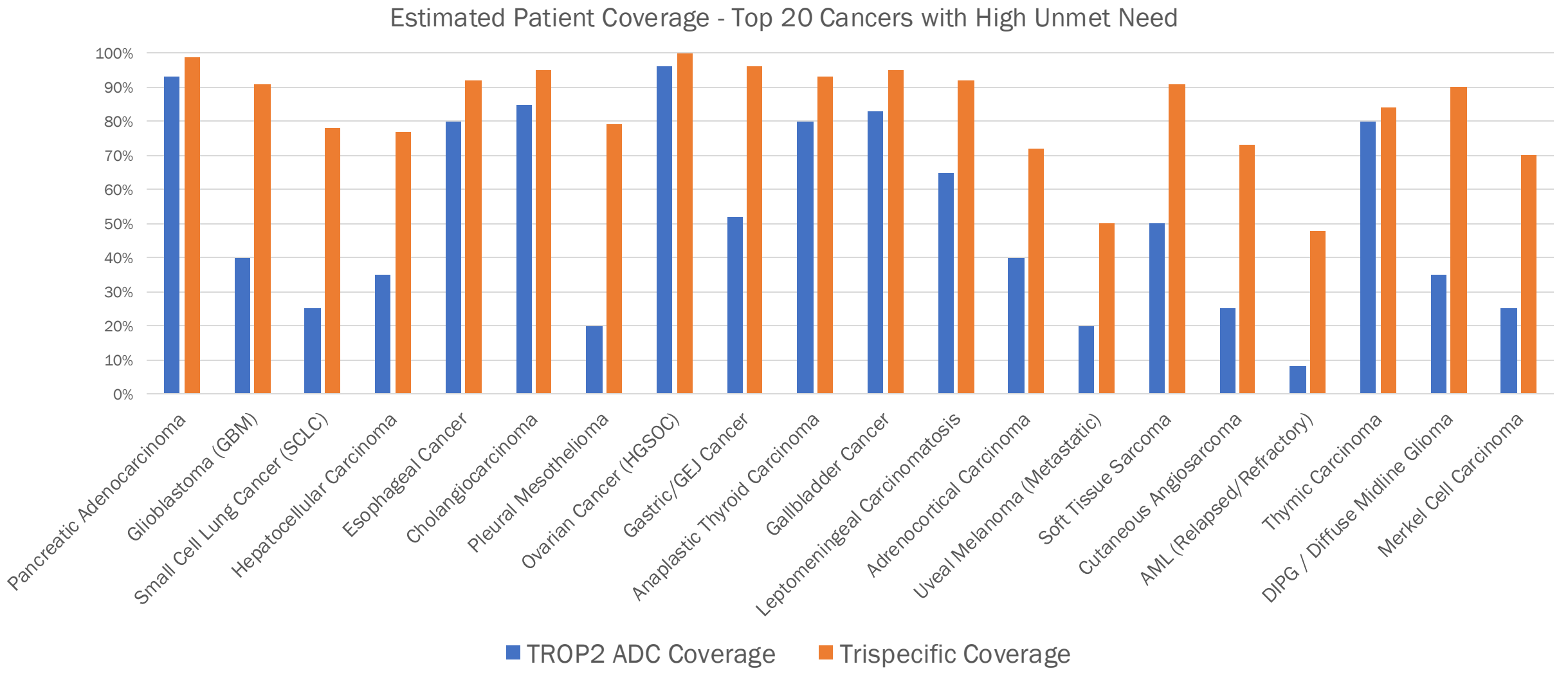
T-Body Platform Advantage: If bispecifics show no additive toxicity, well designed trispecifics should not either

Source: BMS/FDA BTD, Alphamab (JSKN016), PMC Review

Broader Coverage Within a Cancer Type: Ovarian and Breast Cancer Coverage



Potential for Multi-Cancer Coverage



Better Tumor Control with Trispecific Antibodies

- 1. Monospecific ADCs are vulnerable to antigen downregulation or outgrowth of clones that lack the antigen
- 2. Tumor heterogeneity of antigen expression is widespread and makes single-target therapies inherently incomplete
- 3. Multi-antigen engagement increases ADC avidity and internalization efficiency, delivering more payload per tumor cell.
- 4. Multi-target ADCs demonstrate broader and more durable tumor control *in vivo, including in drug-resistant cell populations that evade monospecific therapy.*

T-Body Platform Performance

Manufacturing-Ready Trispecific Platform

Expression Excellence

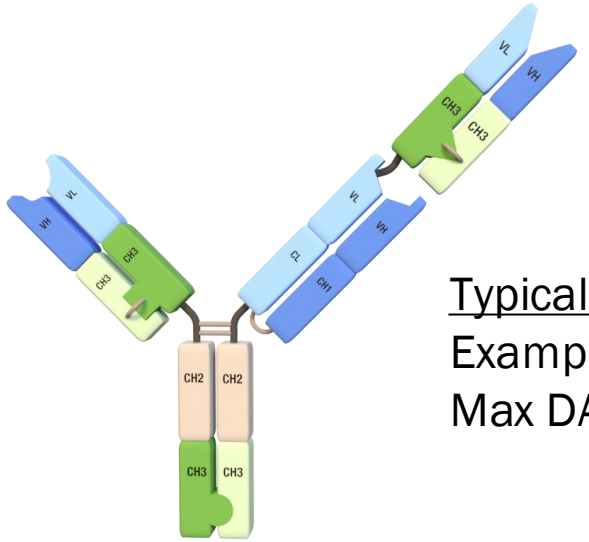
- IgG-like transient yields (300+ µg/mL)
- 90%+ single-step purity
- Protein A + IEX compatible
- Supports both kappa and lambda light chains

Proven Track Record

- Rapid prototyping enables 52 Views strategy
- Normal IgG-like PK in rats (t½ 6.6 days)

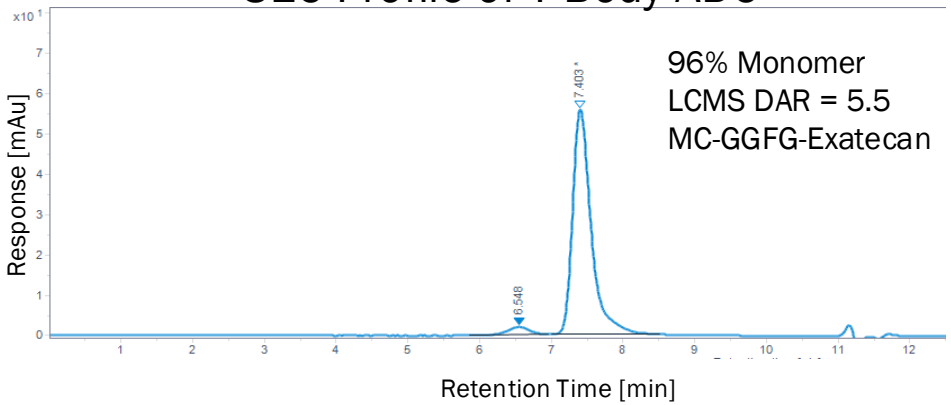
ADC-Compatible

- Validated by 3rd Party (Xcellon)
  - Conjugation stability validated
  - Disulfide conjugation by 3rd Party
- Compatible with standard Fc modifications

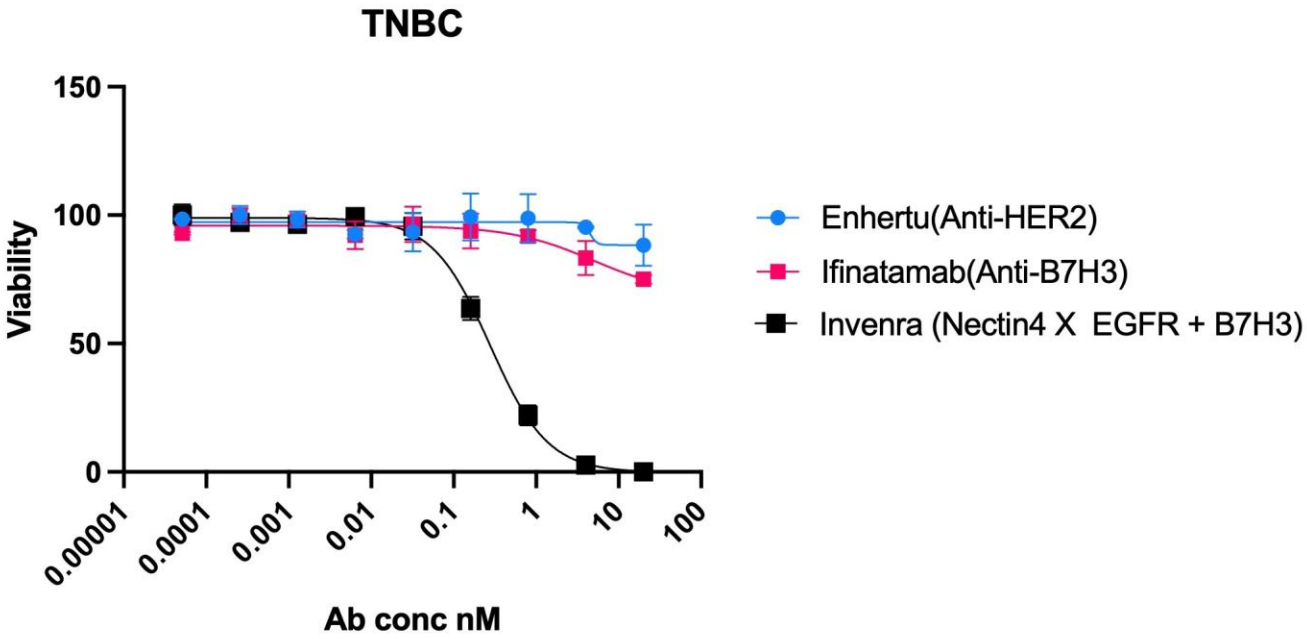


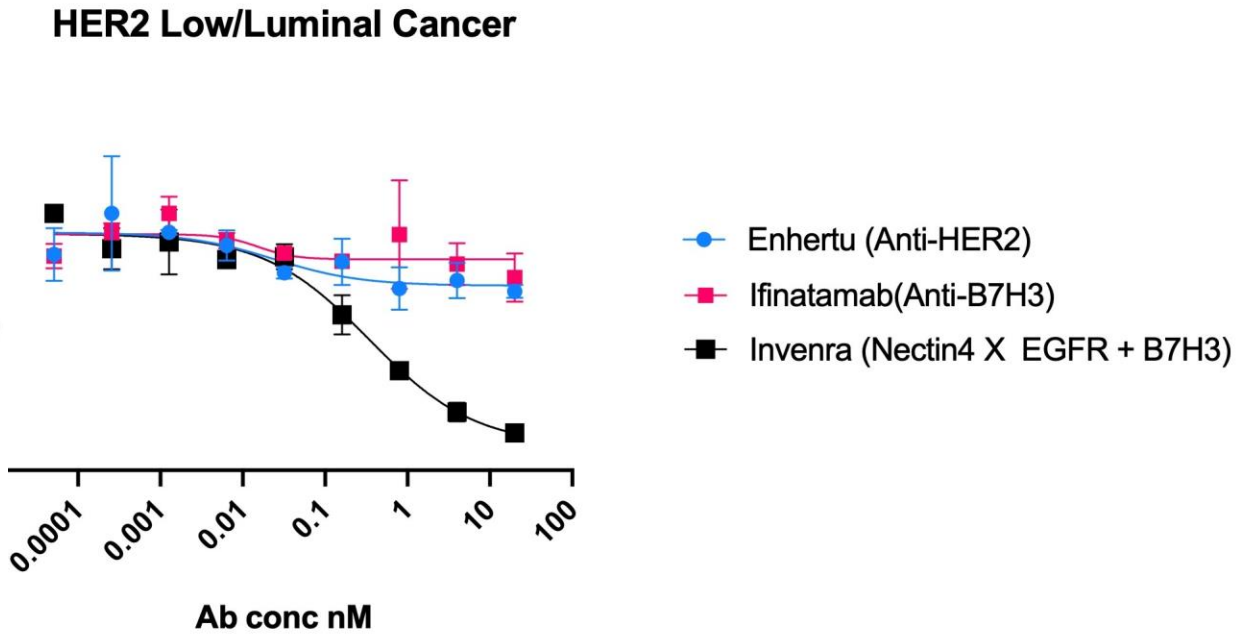
Typical T-Body ADC
Example using Cys-conjugation
Max DAR = 6

SEC Profile of T-Body ADC



Cytotoxicity Data for a T-Body Trispecific ADC for Breast Cancer





Invenra tsAb
DAR=5.56
% Monomer=95%
MC-GGFG-Exatecan

Enhertu Biosimilar
DAR=7.8
DXd

Infinatamab Biosimlar
DAR=3.7
DXd

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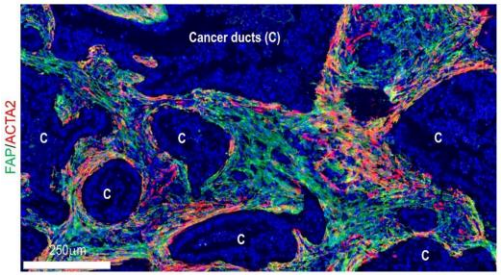
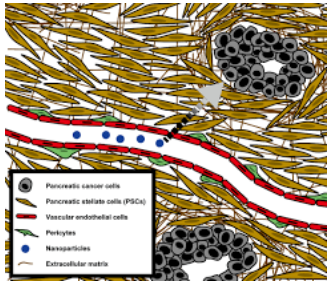
The Stromal Barrier Problem Example for PDAC

- Pancreatic ductal adenocarcinoma (PDAC) is characterized by a **dense desmoplastic stroma** that can constitute up to 90% of the tumor mass
- This stroma creates **elevated interstitial fluid pressure (IFP)**, compresses blood vessels, and limits convective and diffusive transport of drugs into tumor, severely impairing efficacy of conventional chemotherapy and antibody-based therapies
- CAFs drive **ECM deposition and immunosuppression** via TGF-β, CXCL12, and other signals, effectively excluding cytotoxic T cells and promoting an immune-cold tumor microenvironment



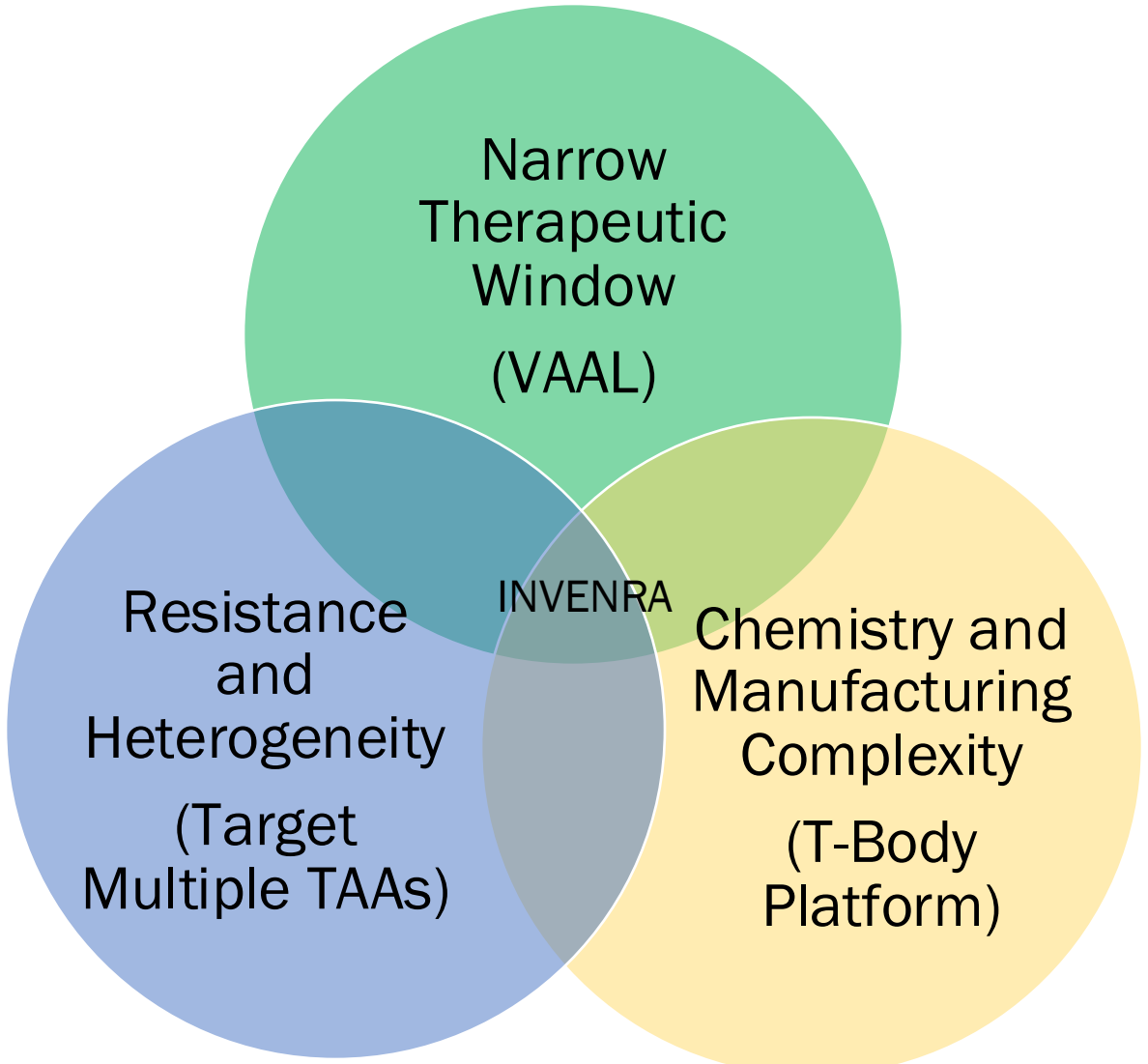


Addressing the Stromal Barrier Problem with a T-Body ADC Targeting Stroma and Tumor

- Perivascular concentration becomes an asset: CAFs and ECM components are **concentrated precisely where ADCs stall** — at the perivascular/stromal rim — so the stroma arm binds and internalizes drug right at the penetration bottleneck
- Stromal depletion opens conduits: CAF targeting disrupts the structural integrity of the desmoplastic matrix, mechanically creating channels through which subsequent drug (including freed payload via bystander effect) can penetrate tumor nests more deeply
- Self-amplifying mechanism: As stromal cells are eliminated, interstitial fluid pressure drops and vascular compression is relieved, improving perfusion and allowing even more ADC to enter — a positive feedback loop not present with monospecific tumor-targeting agents

ADC Challenges

Advancing next-generation ADCs requires addressing three interconnected challenges

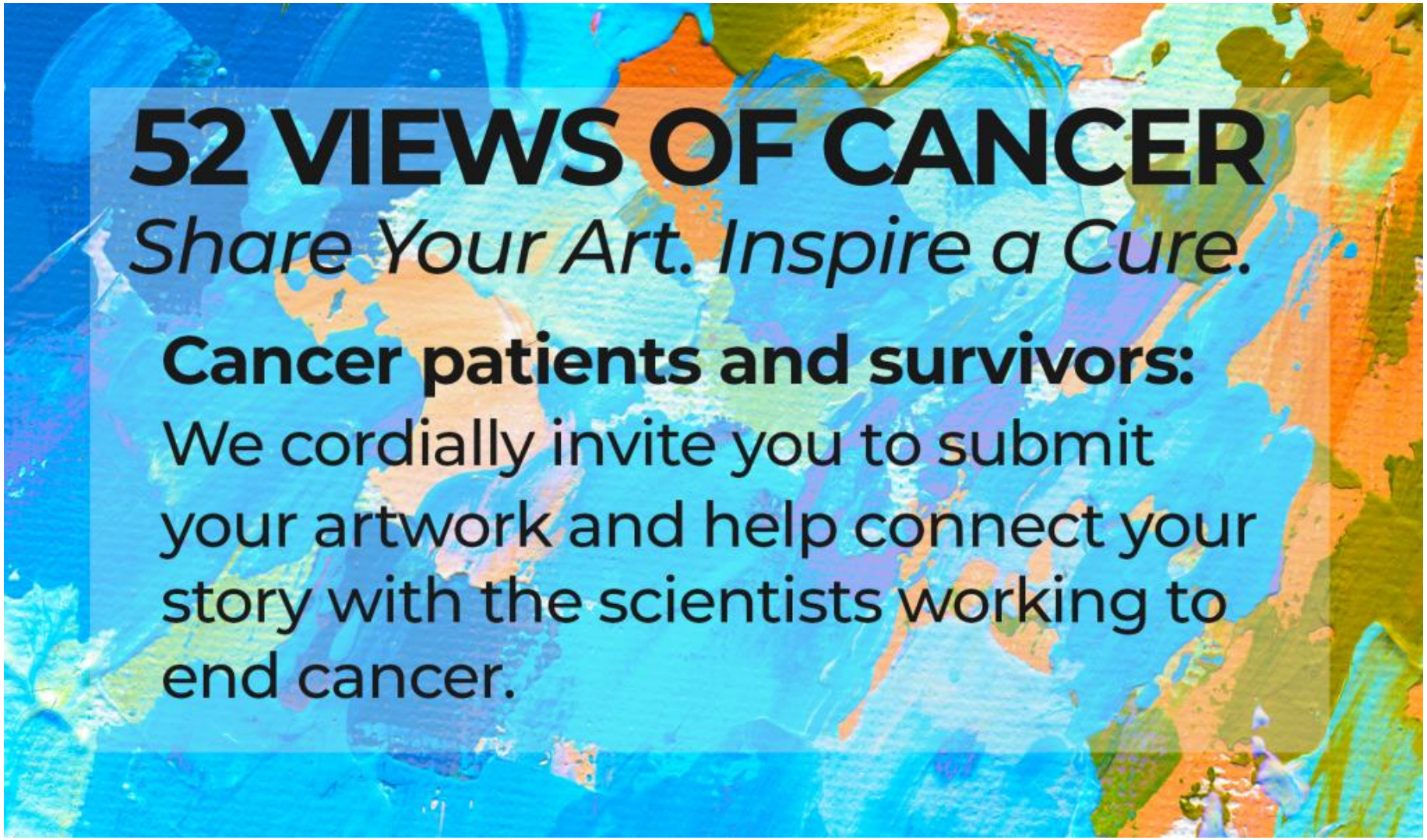


Summary

Trispecific ADCs can address multiple issues that limit traditional mAb ADCs:

- **Resistance and Heterogeneity**—simultaneously targeting multiple tumor associated antigens
- **Poor Normal to Tumor Expression Window**—use novel MOAs like VAAL to achieve conditional avid binding
- **Poor Internalization**—biparatopic + antibodies and VAAL can increase internalization
- **Dense Stroma Limiting Access to Tumor**–target stroma as well as tumor with an “or” gate.

52 Views of Cancer Initiative



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