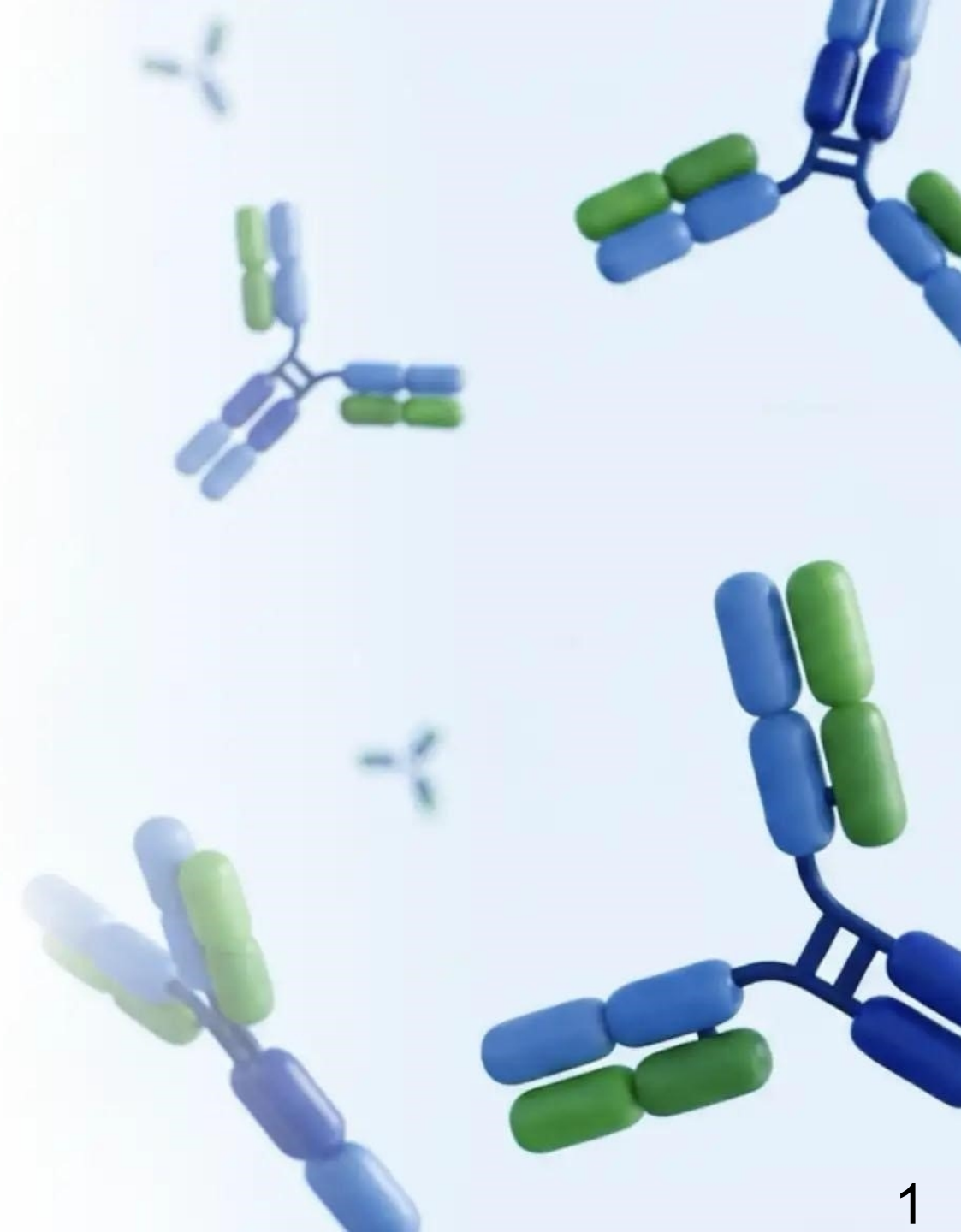




From Bispecific to Trispecific Antibodies: Reimagining the Next Generation of ADCs

Bonnie J. Hammer, Ph.D.

17th World ADC Conference, San Diego
October 2026



Novel Monoclonal, Bispecific, and Trispecific Antibodies: Discovered, Optimized, and Ready for the Clinic



Why Invenra?

Innovative

Science-first mentality | 10+ years
multispecific expertise

Proven

30+ partners | 2 clinical-stage

Easy

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

1

**Best
multispecifics
start with
quality mAbs**

Accelerated 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
unrivalled
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

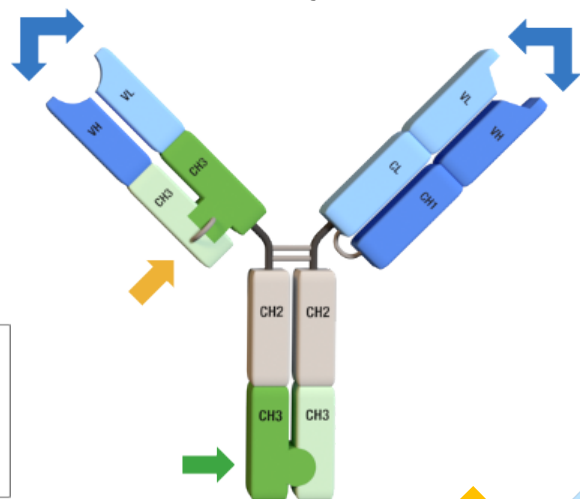
Support advanced therapeutics: ADCs, next generation Immuno-
Oncology & Cell Engagers



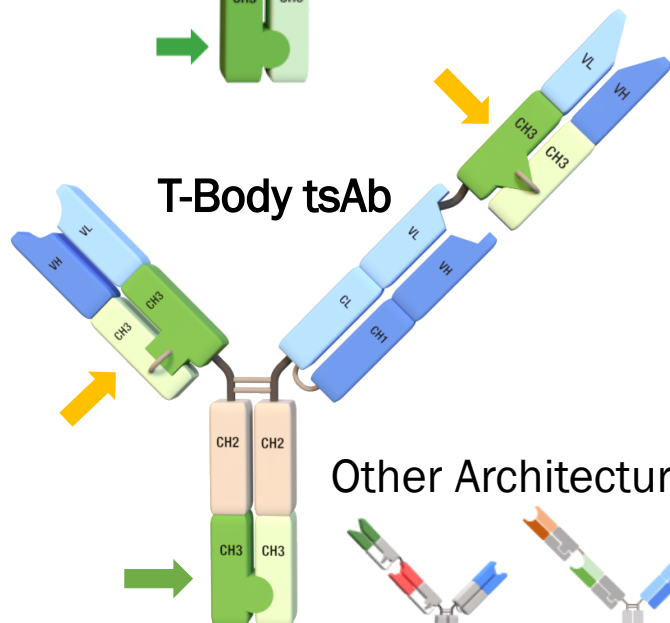
Invenra's B-Body[®] Bispecific and T-Body[™] Trispecific Platforms: Robust Solutions for Multispecific Antibody Development



B-Body bsAb



T-Body tsAb



Other Architectures:



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 and Light Chain Inversions In Fab Arms

- Robust expression yields
- Efficient purification
- “Plug & Play” variable domains
- Supports both kappa and lambda light chains

Benefits

B-Body Bispecific and T-Body Trispecific 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

+ more

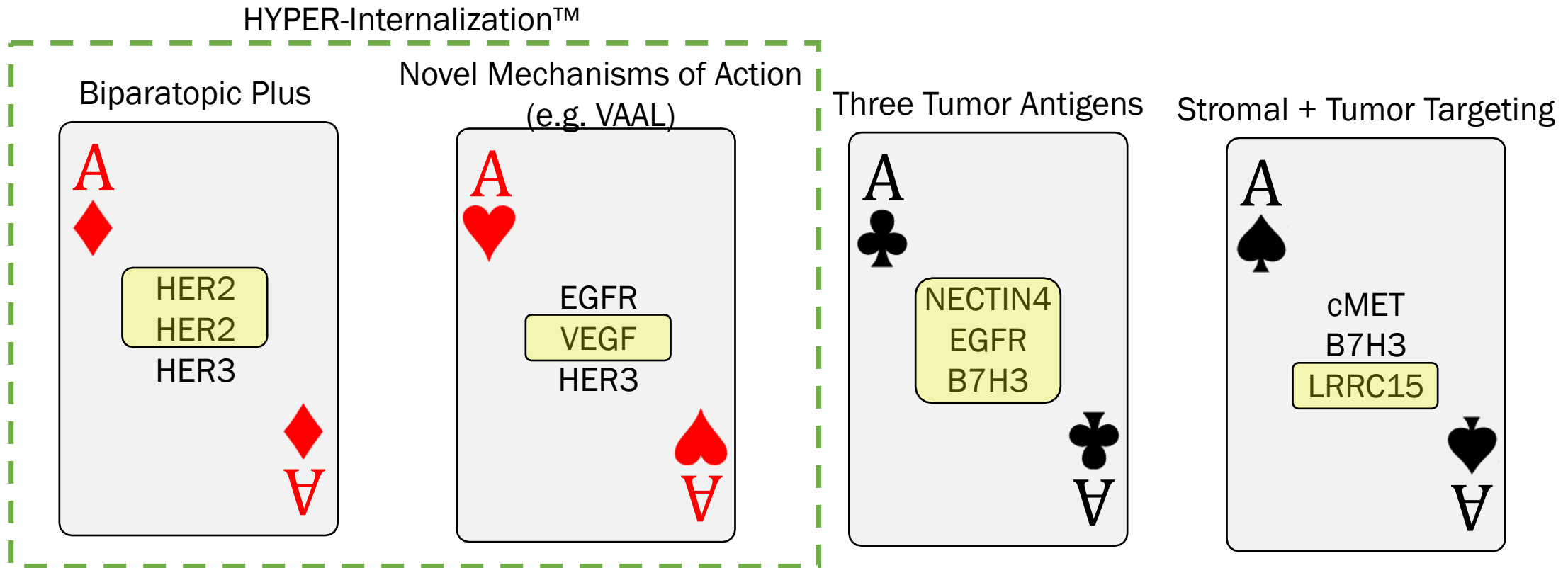


Why Trispecific (TsAb) ADCs?

- **More Cancer Indications Covered**
 - Targeting multiple targets increases the number of cancers that are likely to respond
- **Broader Patient Coverage within a Cancer Indication**
 - Targeting multiple targets increases the number of patients that are likely to respond in an indication
- **Better Tumor Control**
 - Targeting multiple targets limits the tumors escape routes and attacks a larger portion of a heterogenous tumor
- **More MOAs Available**
 - Increased Internalization—greater ADC delivery into cell
 - Biparatopic Plus
 - VAAL—VEGF Associated Avidity Lock
 - Stroma and Tumor Targeting

Trispecific Platforms: 52 Views of Cancer—4 Suits with Different MOAs

Example “cards” from the platform deck



Conventional ADCs deliver too little payload - and toxicity limits the dose



THE EXPOSURE BOTTLENECK

<1%

of injected ADC dose binds to tumor cells

Even less is internalized by cancer cells

1

DELIVERY IS RESTRICTED

Antigen heterogeneity and tumor stroma restrict delivery

2

DURABILITY ERODES

Alternative pathways and cancer cells with low-antigen densities drive escape

3

DOSE IS CAPPED

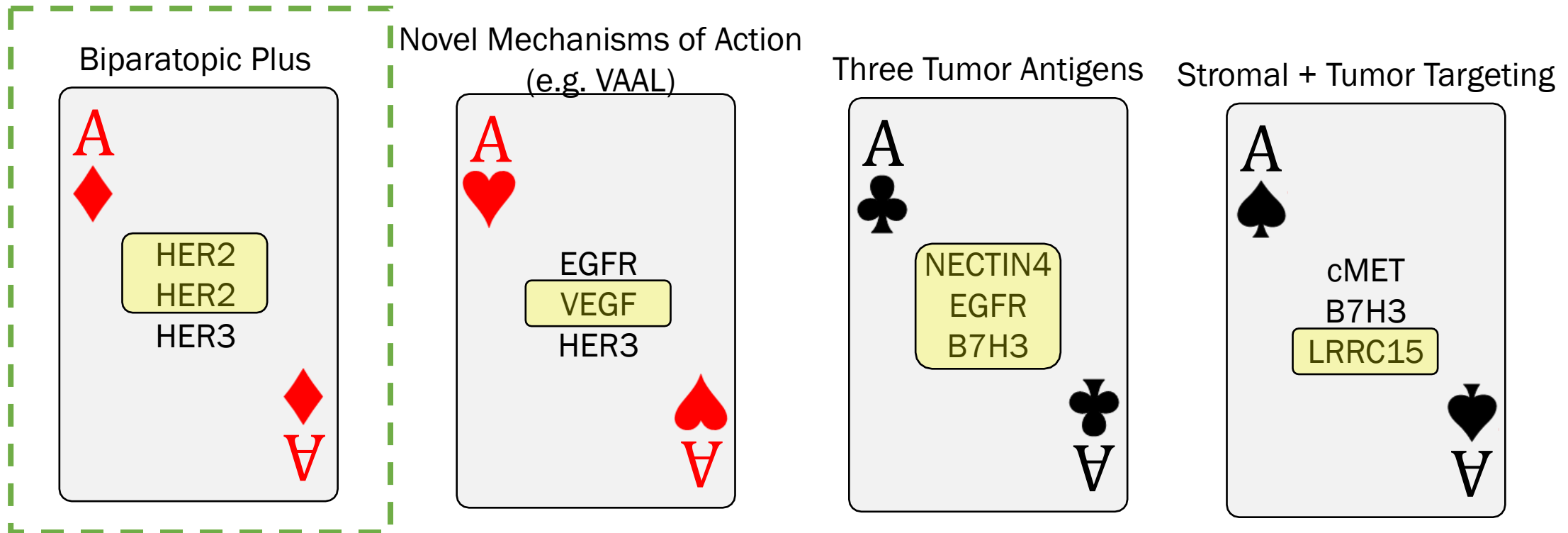
Normal-tissue expression of certain targets further narrows the therapeutic window

RESULT

Insufficient tumor payload • short durability • constrained dosing

Trispecific Platforms: 52 Views of Cancer—4 Suits with Different MOAs

Example “cards” from the platform deck



Why HER2 x HER2 x HER3



Biparatopic HER2 binding drives superior internalization and payload delivery compared to any monospecific or bispecific agent.

- Simultaneous engagement of Domain IV (trastuzumab epitope) and Domain II (pertuzumab epitope)
 - Induces receptor cross-linking,
 - accelerated lysosomal trafficking
 - Increased internalization rate
- HER3 arm extends killing reach into HER2-low and HER3-high tumor populations.

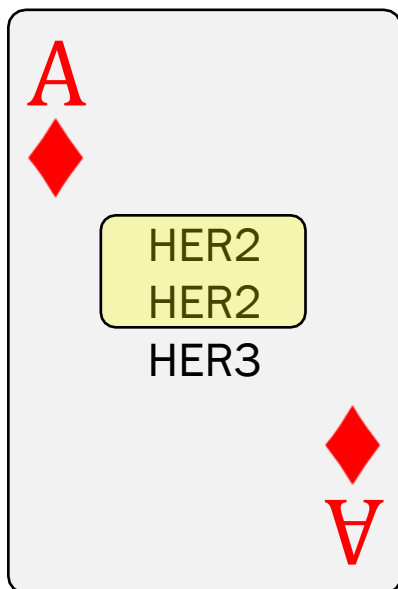
The only architecture that closes all three oncogenic signaling gaps simultaneously.

- Only a trispecific simultaneously blocks:
 - HER2 homodimerization
 - HER2:HER3 heterodimerization
 - NRG1 driven HER3 signaling

Preemptive resistance prevention against the primary escape mechanism.

- HER3 upregulation is the dominant acquired resistance mechanism to both T-DM1 and T-DXd
- Co-engaging HER3 from the first dose preempts this escape route before it develops
- No existing bispecific or biparatopic competitor can replicate this triple blockade

Biparatopic Plus



HER2 x HER2 x HER3 T-Body Trispecific Platform Performance

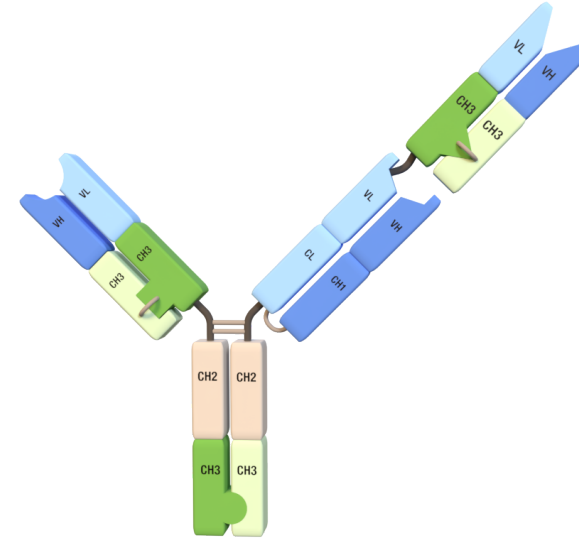
Manufacturing-Ready Trispecific Platform

Developability Excellence

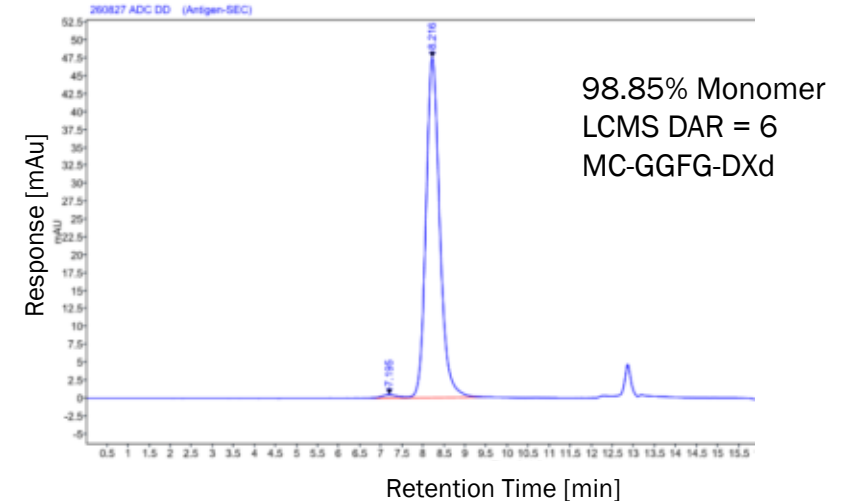
- IgG-like CHO transient yields (up to 1.5 g/L)
- Stable CHO pools in progress (1 g/L)
- Concentrated up to 100 mg/mL
- >95% purity by SEC
- Protein A + IEX compatible
- hFcRn Tg32 mouse PK ($t_{1/2}$ 8.8 days)

ADC-Compatible

- Disulfide conjugation validated
- Max DAR=6 for standard trivalent T-Body trispecific

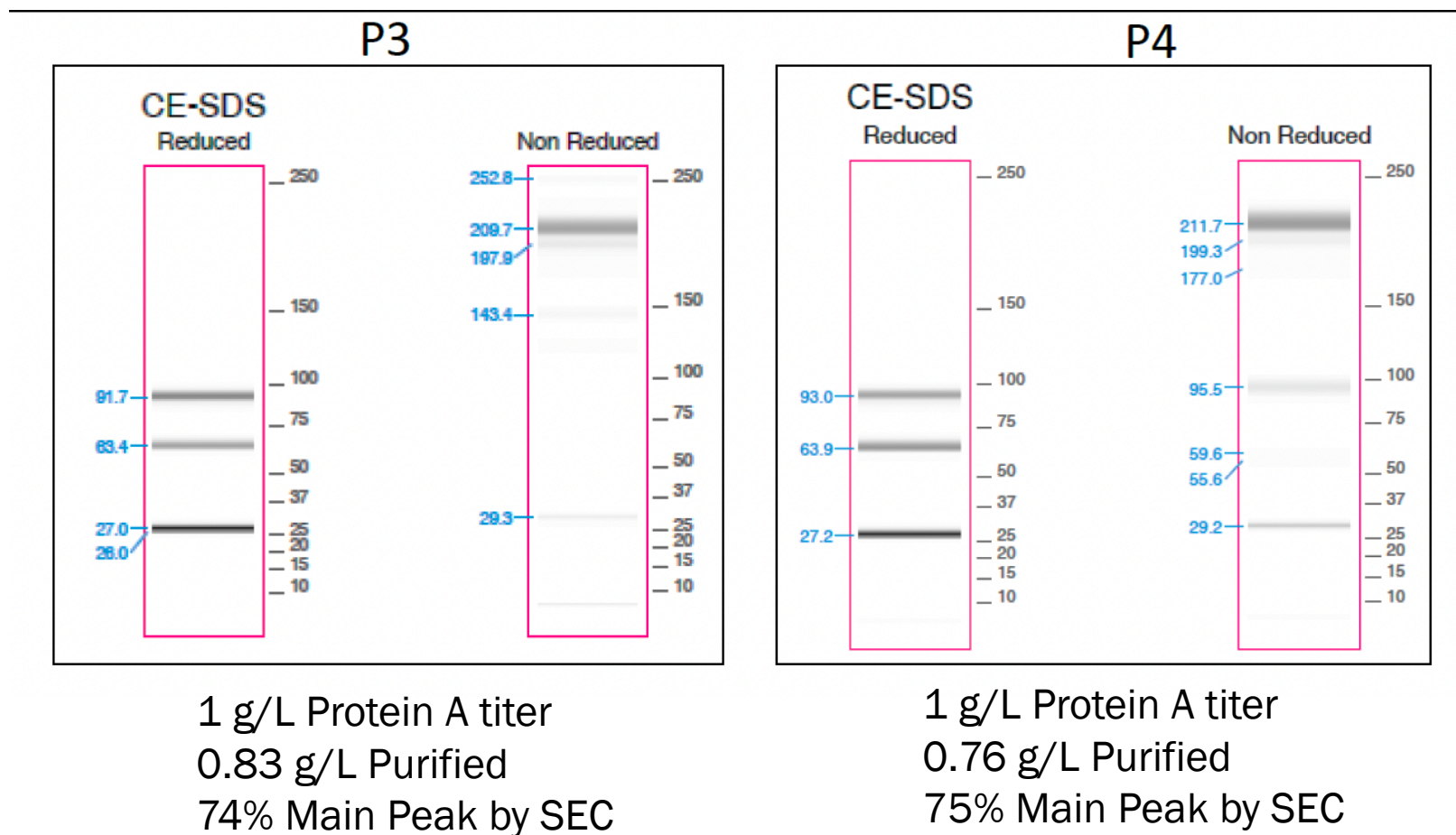


SEC Profile of HER2 x HER2 x HER3 ADC



Stable CHO Cell Line Production in Progress

CE of 2 Different **Stable Pools** After Single Step Protein A Purification of HER2 x HER2 x HER3

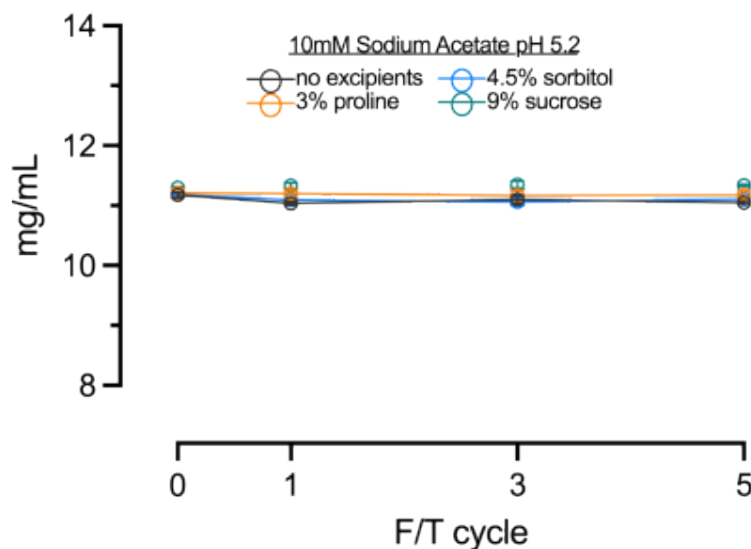


HER2 x HER2 x HER3 Developability

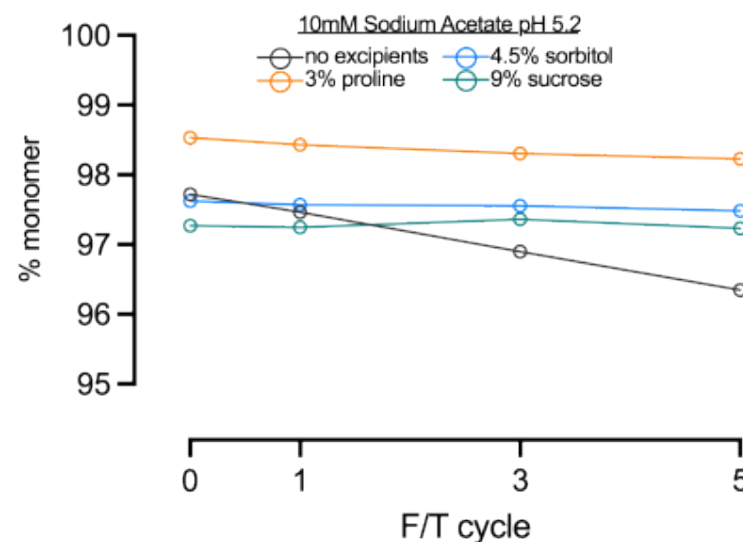
Formulation 10 mM Sodium Acetate pH 5.2	Tm1 (°C)	Tagg (°C)	Diffusion Interaction Parameter (mL/g)
No Excipients	63.0	74.4	21.67
+ 3% proline	63.0	64.2	30.54
+ 4.5% sorbitol	63.9	73.0	15.01
+ 2.9% sucrose	63.0	73.1	17.33

Stability with F/T Cycles

Concentration Stability

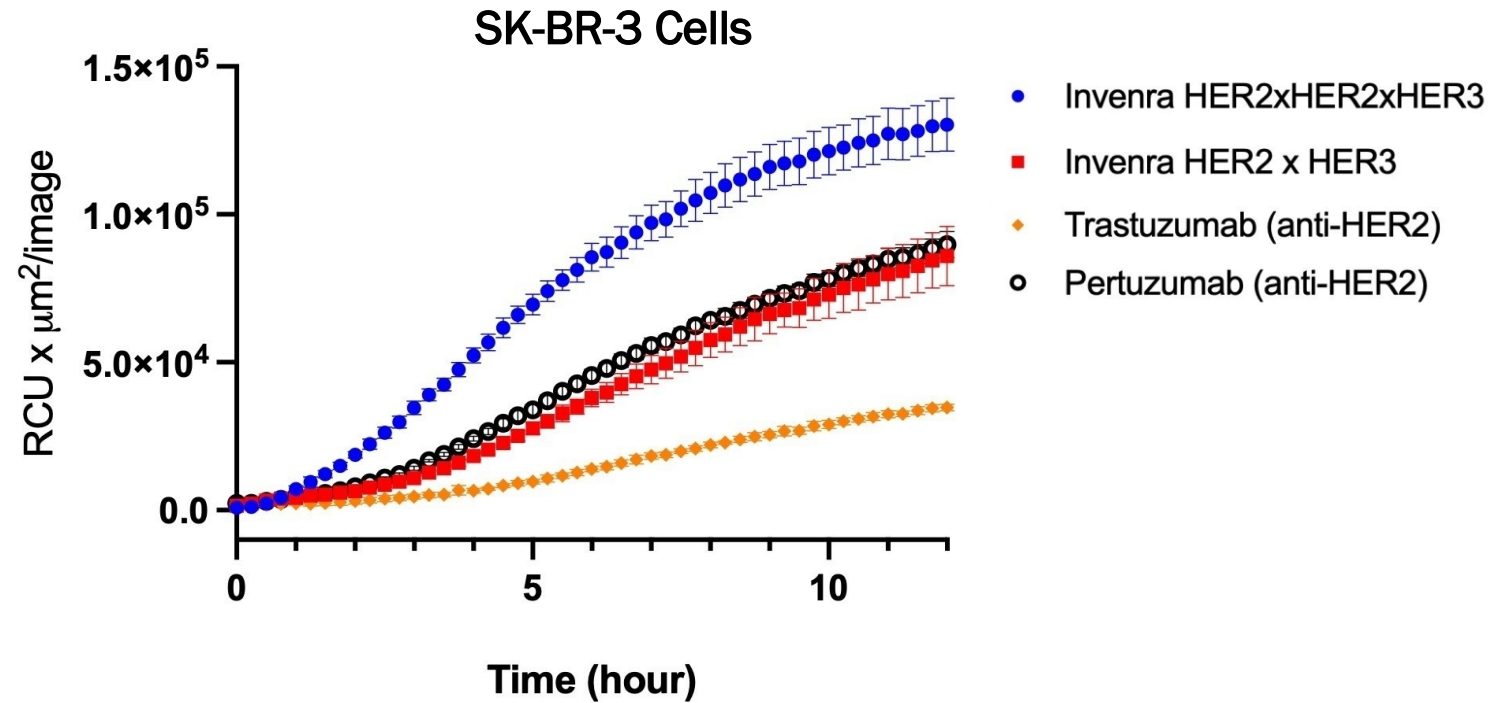


% Monomer



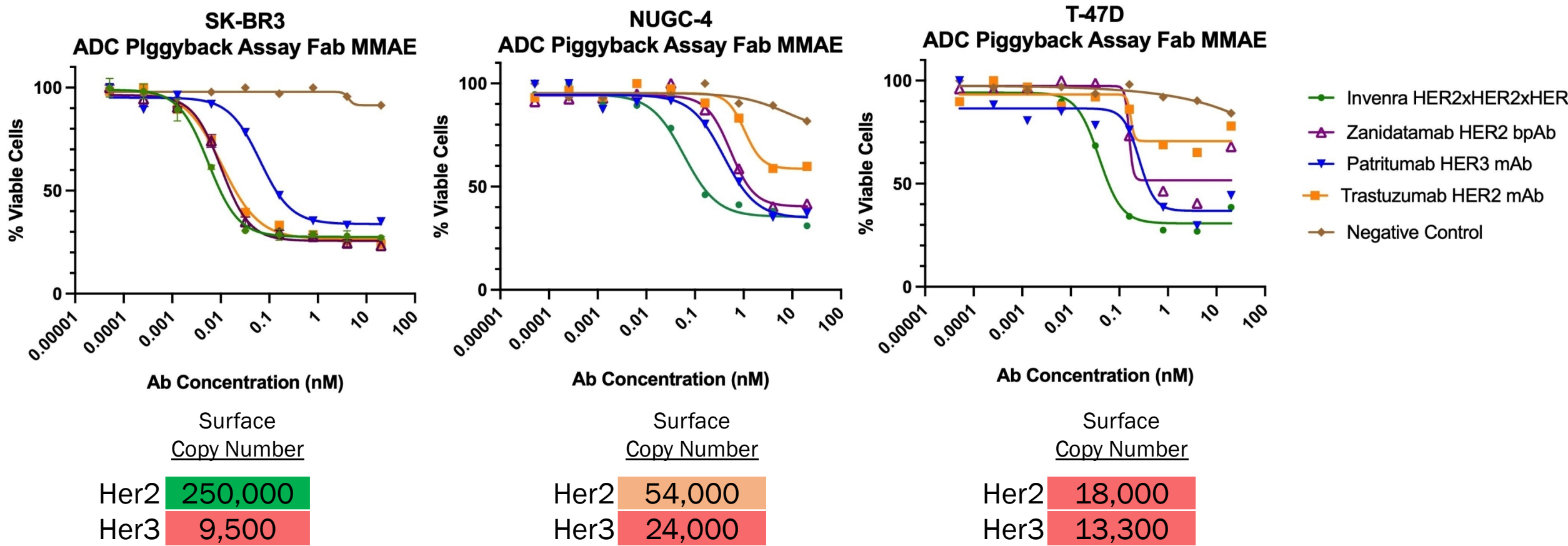
Increased Internalization with Biparatopic Antibodies

Invenra's HYPER-Internalization HER2 x HER2 x HER3 Internalization



Invenra's T-Body biparatopic-plus trispecific antibody internalizes faster than the monoclonal or bispecific antibodies alone

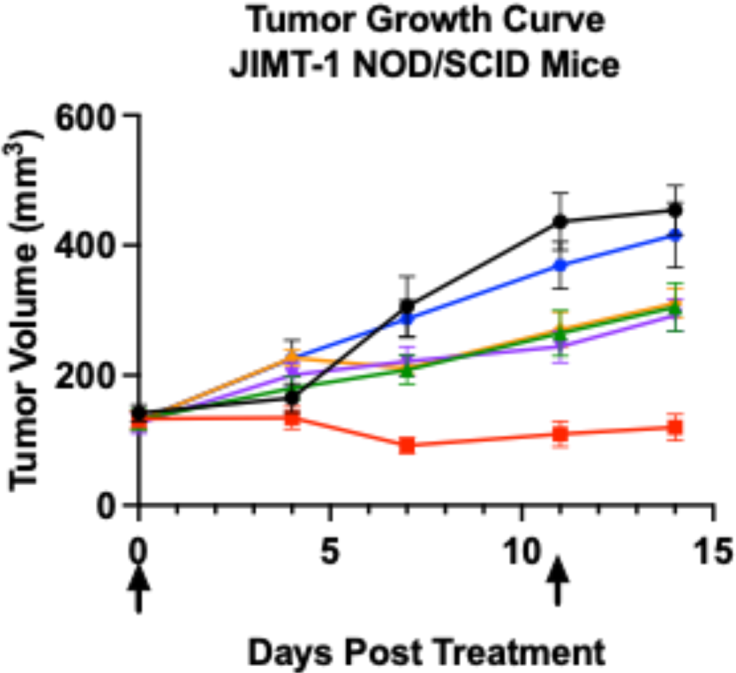
HER2 x HER2 x HER3(Biparatopic-Plus Trispecific) ADC Piggyback Data (Fab MMAE)



Invenra's T-Body biparatopic-plus trispecific outperforms HER2 and HER3 mAbs as well as a HER2 biparatopic

In Vivo Efficacy (In Progress)

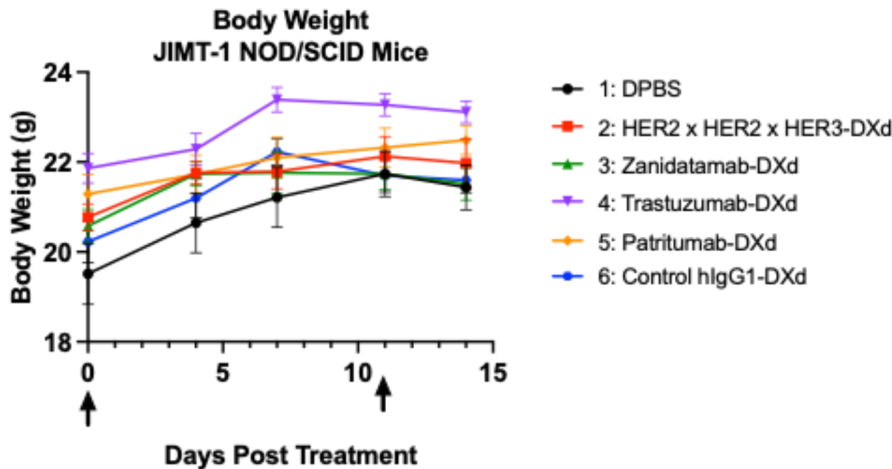
HER2 x HER2 x HER3 ADC



- MC-GGFG-DXD
- 1: DPBS
 - 2: HER2 x HER2 x HER3-DXd DAR6
 - 3: Zanidatamab-DXd DAR4
 - 4: Trastuzumab-DXd DAR8
 - 5: Patritumab-DXd DAR8
 - 6: Control hlgG1-DXd DAR8



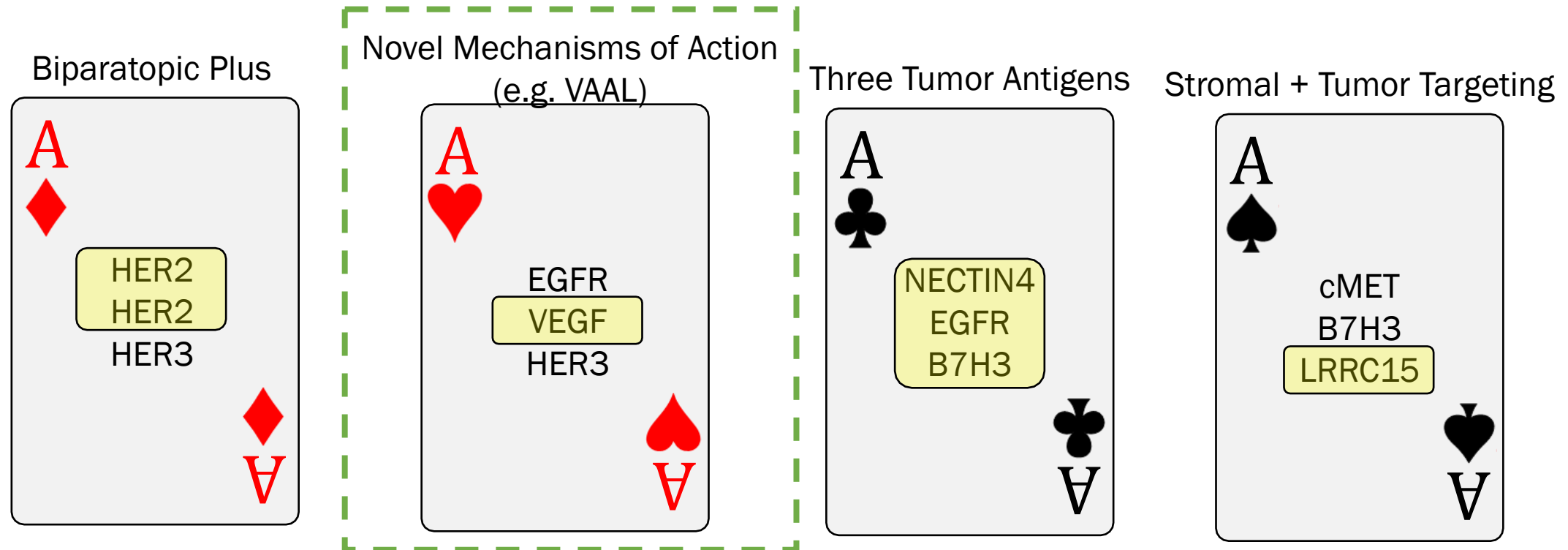
Molar equivalent dosing normalized to a 5 mg/kg dose for the control IgG1



HER2 x HER2 x HER3 tsAb ADC exhibits superior efficacy to a HER2 mAb ADC, a HER3 mAb ADC, and a HER2 biparatopic ADC.

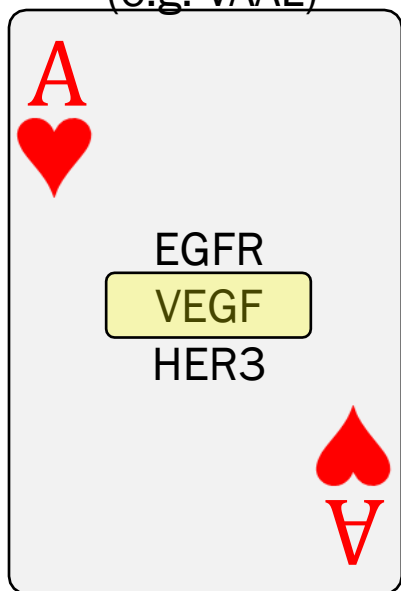
Trispecific Platforms: 52 Views of Cancer—4 Suits with Different MOAs

Example “cards” from the platform deck



♥ Why EGFR x VEGF x HER3

Novel Mechanisms of Action
(e.g. VAAL)



- **Solve the normal tissue toxicity problem inherent to EGFR- and HER3-directed therapy**
 - EGFR and HER3 are expressed on normal skin, GI, and kidney tissue, making high affinity monospecific ADCs inherently dose limited
- **Address the primary and dominant resistance axis in EGFR-driven cancers**
 - HER3 upregulation is the leading acquired resistance mechanism to EGFR TKIs and ADCs; co-engaging both targets from first dose pre-empts this escape route before it develops
- **Clinically validated target trio with an unmet need for a conditional-activation approach**
 - Izalontamab brengitecan (BL-B01D1), a first-in-class EGFR×HER3 bispecific ADC with FDA Breakthrough Therapy Designation, achieved a 66% ORR (confirmed 56%) in TKI-pretreated EGFR-mutant NSCLC (WCLC 2025), validating the target combination
 - The VAAL third arm delivers conditional tumor selectivity no bispecific can replicate

VAAL – VEGF Activated Avidity Lock



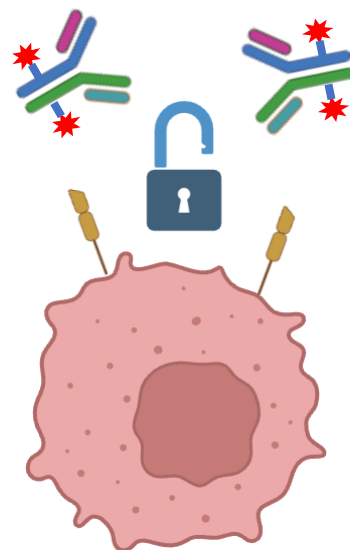
No VEGF = No avid binding.

A low monovalent affinity for the TAA arm

- No significant engagement of the target
- No internalization

Low VEGF Outside TME

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



With VEGF = VEGF Activated Avidity Lock

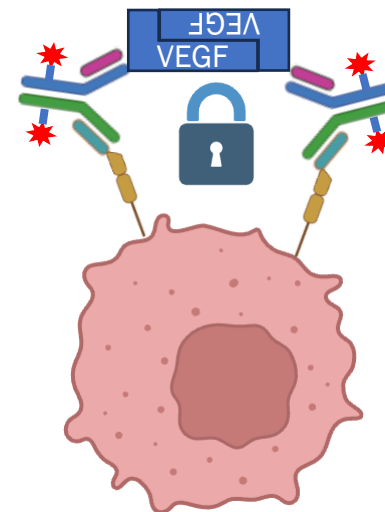
VEGF homodimer cross-links two antibodies

- Avidity increases K_d
- Tumor-binding arms now active
- Induced internalization.

High VEGF Within TME

VEGF homodimer bridges 2 antibodies, resulting in cluster formation and an avidity jump. **Increases tumor selectivity**

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

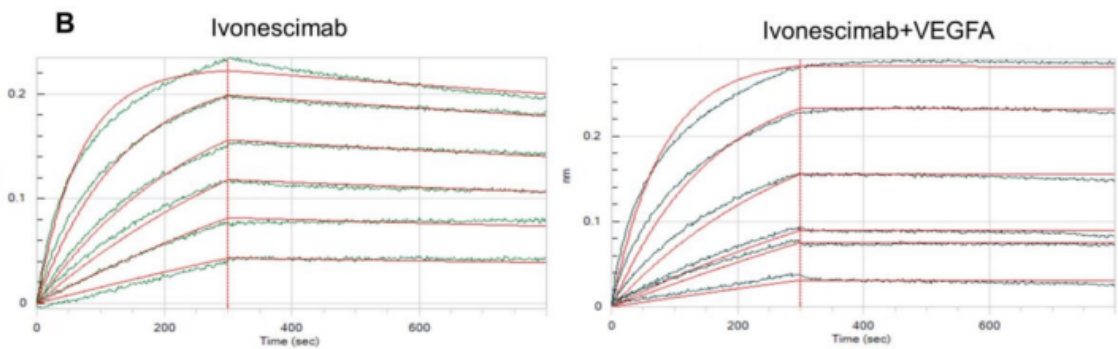


↓ On-target off-tumor risk

VEGF Driven Avidity Enhancement Examples



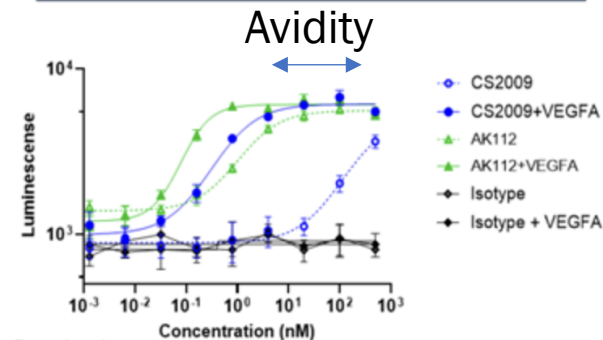
Akeso
Ivonescimab PD-1/VEGF



Slower dissociation rate of PD1 in the presence of VEGF

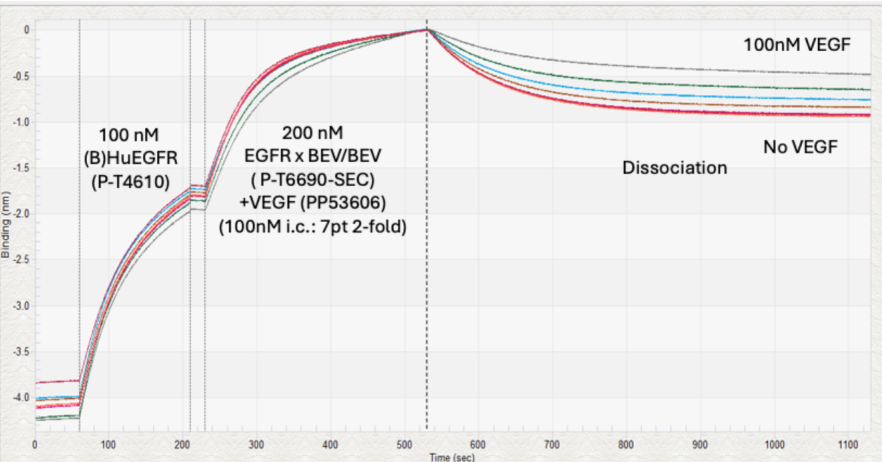
CStone
CS2009 PD-1/VEGF/CTLA-4

PD-1 reporter Assay with PD-L1 APC



Lower EC50 in the presence of VEGF

Invenra
T6690 EGFR/VEGF



Increasing concentrations of VEGF

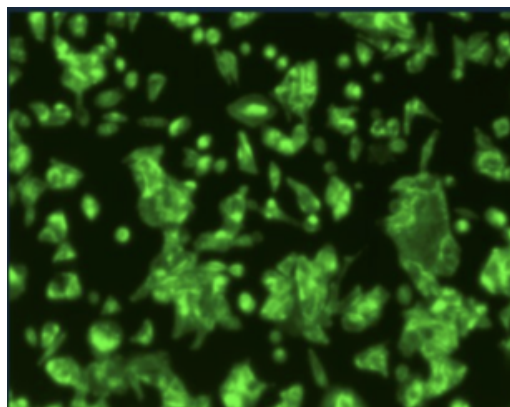
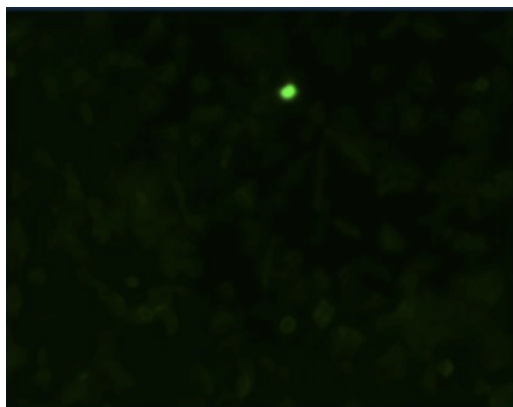
Slower dissociation rate of EGFR in the presence of VEGF

VAAL - VEGF Activated Avidity Lock

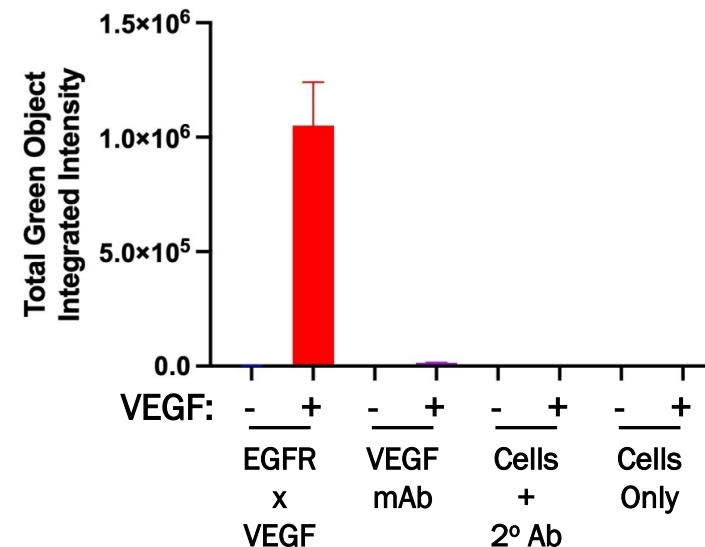
(-) VEGF

(+) VEGF

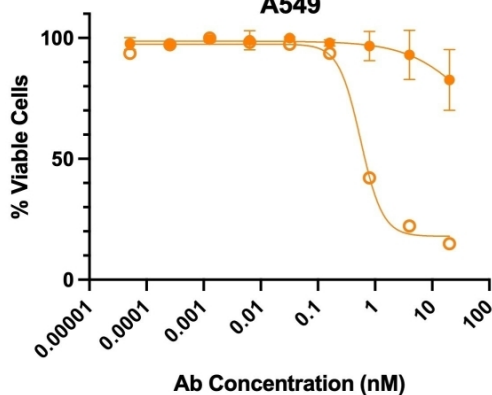
EGFRxVEGF bsAb



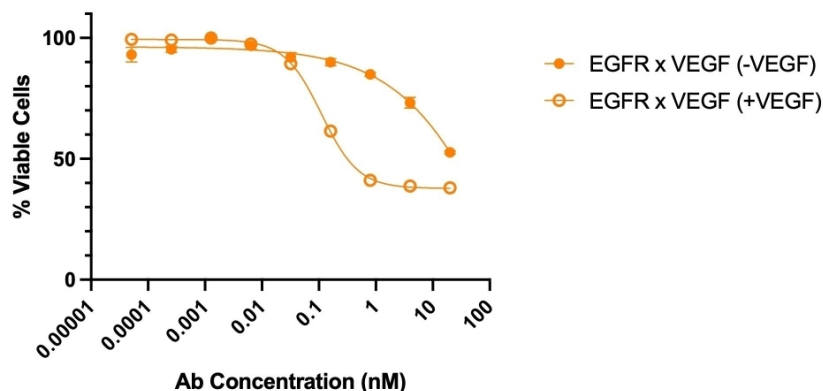
Overall Green Fluorescence - A-549



Piggyback ADC
fAb-Anti-hFc-cl-MMAE
A549



Piggyback ADC
fAb-Anti-hFc-cl-MMAE
NCI-H1975

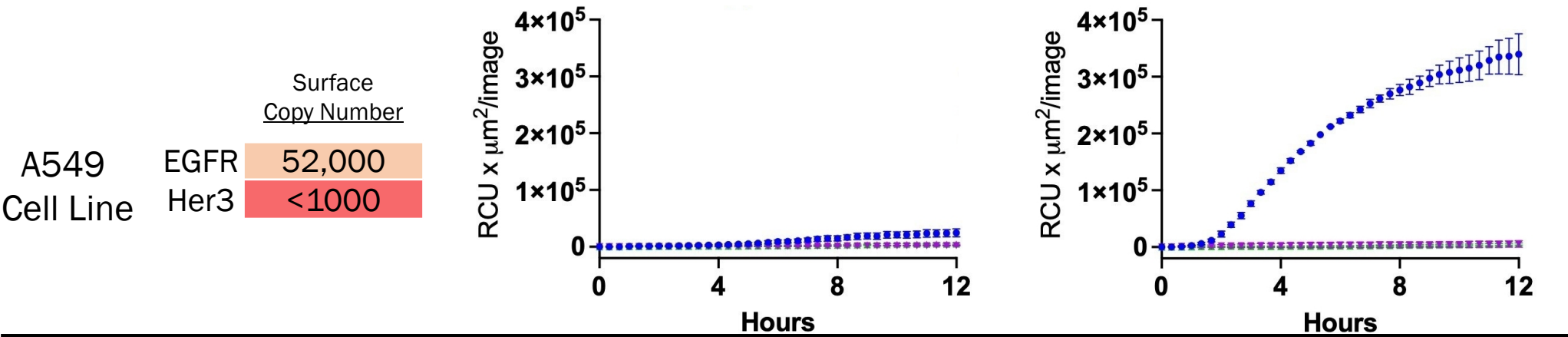


- A549 tumor cells expressing EGFR (~52,000 copies/cell) were incubated with EGFR x VEGF bispecific antibodies in the presence or absence of VEGF for 6 hrs
- Cells were fixed, permeabilized and stained with a secondary antibody
- The EGFR binder arm is low affinity and doesn't strongly engage EGFR on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

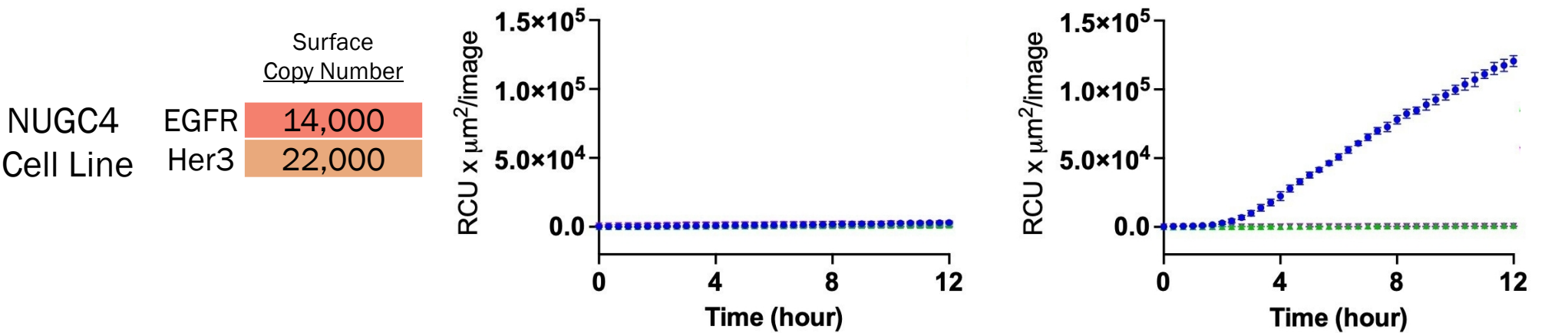
EGFR Surface Copy #~52,000 EGFR Surface Copy #~32,000

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

Triggered Internalization with VEGF TsAb (EGFR x VEGF x HER3)

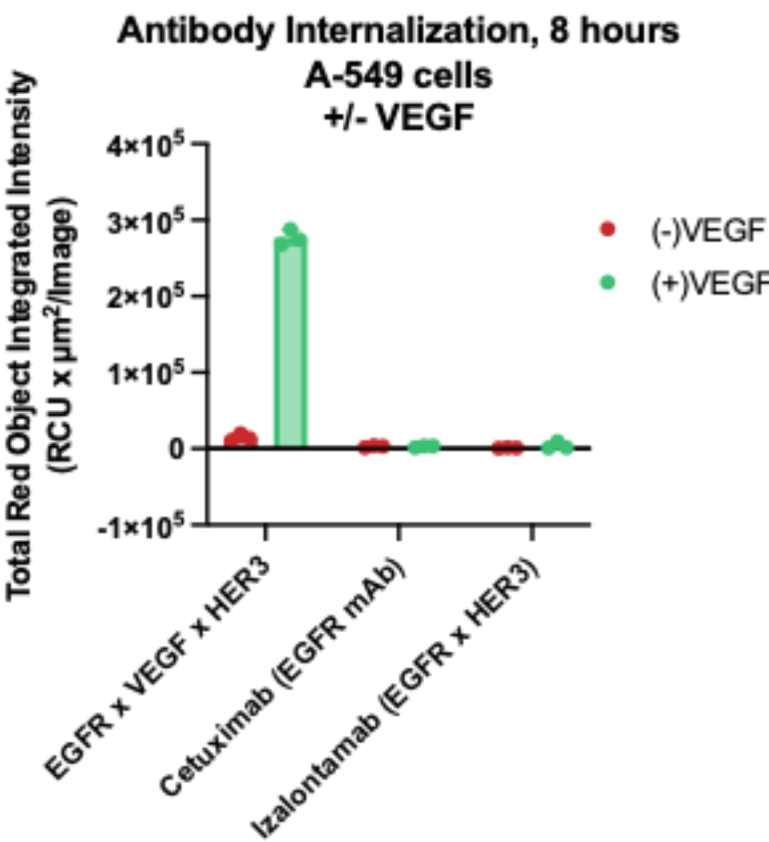
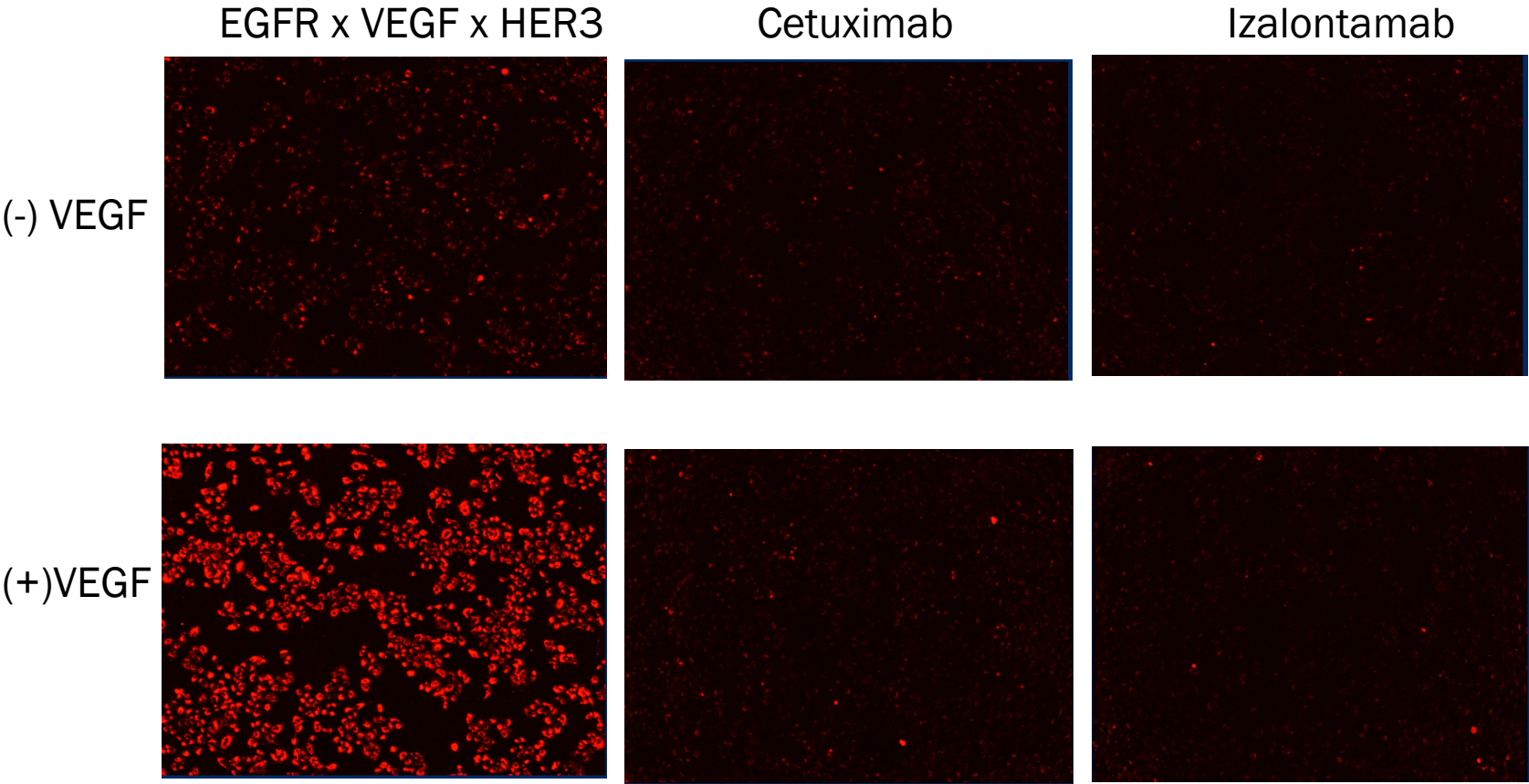


- EGFR x VEGF x HER3
- ▲ Cetuximab (EGFR mAb)
- ▼ Izalontamab (EGFR x HER3)



Internalization of trispecific antibody
Only when VEGF is present

FabFluor Internalization of T-Body TsAb (EGFR x VEGF x HER3)

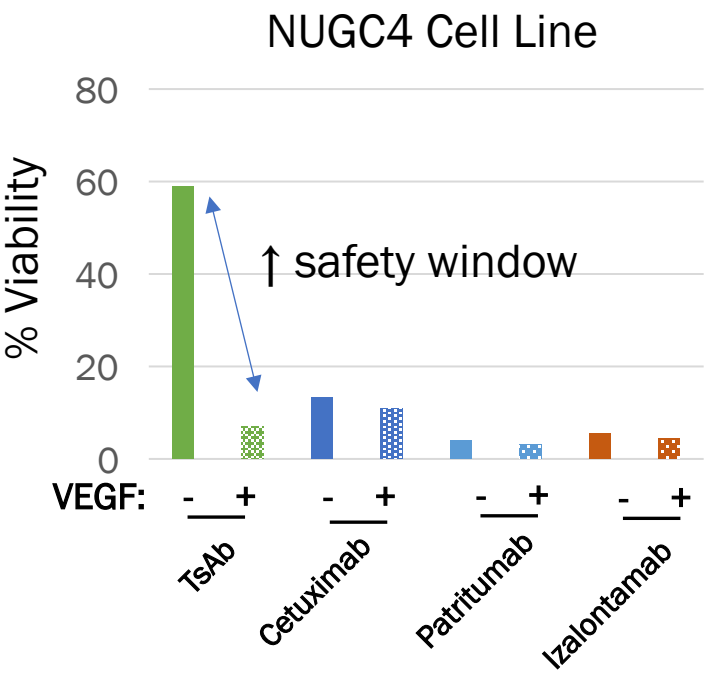
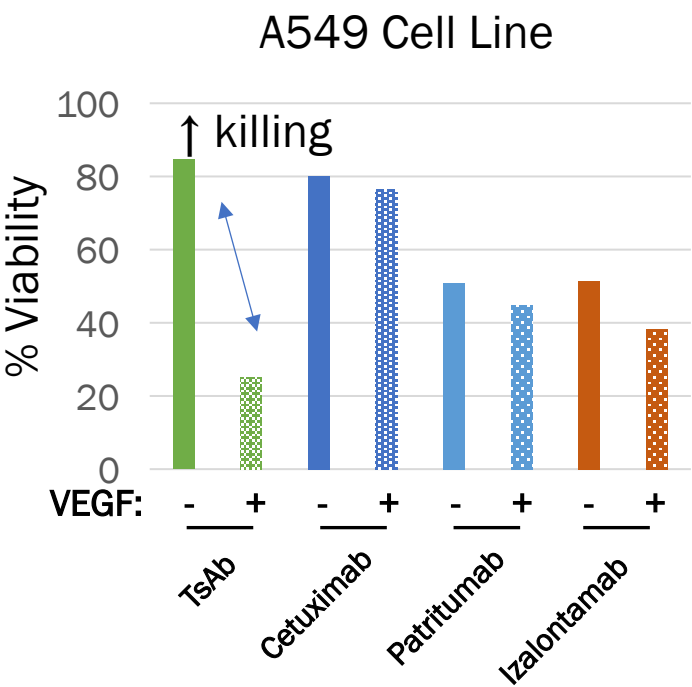


Piggyback ADC Assay with Fab MMAE

EGFR x HER3 x VEGF



4 nM antibody + MMAE Fab 5 days



VEGF binding arm increases cell killing in vitro

VEGF binding arm leads to improved safety window in vitro

Surface Copy Number

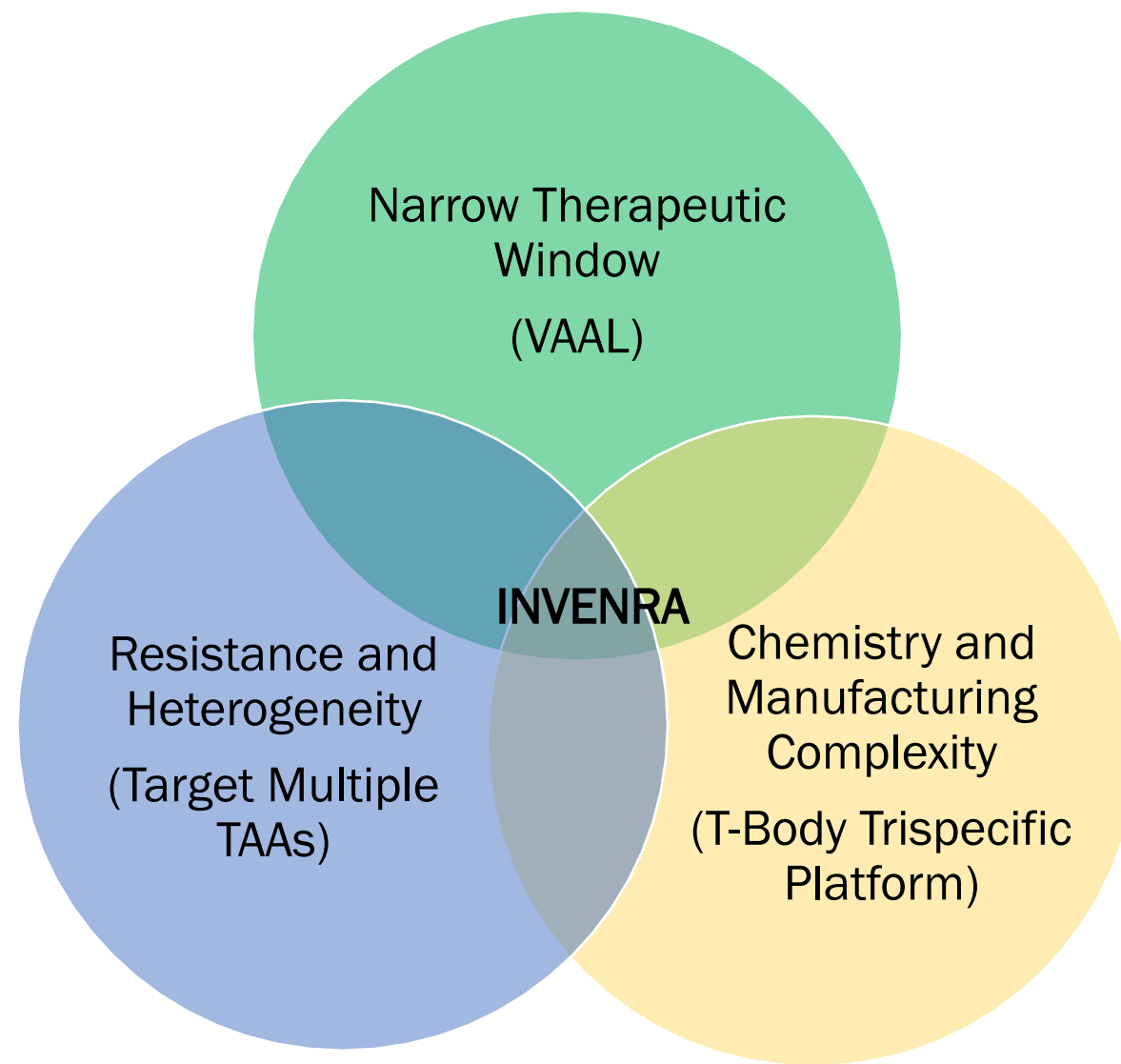
	A549	NUGC4
EGFR	52,000	14,000
Her3	<1000	22,000

ADC Challenges

Advancing next-generation ADCs requires addressing three interconnected challenges

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-plus antibodies and VAAL can increase internalization
- **Dense Stroma Limiting Access to Tumor**—target stroma as well as tumor with an “or” gate.



Summary

- HER2 x HER2 x HER3
 - Transient CHO expression of 1.5 g/L protein A titer
 - Stable CHO pool in progress 1 g/L protein A titer
 - Excellent stability indicators
 - Concentration up to 100 mg/mL
 - F/T stability
 - Excellent Diffusion Interaction Parameter in multiple buffers
 - Good mouse PK
 - Improved internalization and in vitro killing over HER2 or HER3 mAbs (piggyback ADC)
 - Proven cysteine conjugation to uniform DAR6
 - Good in vivo efficacy data showing superiority to T-DXd, patritumab-DXd, and zanidatimab-DXd.
- EGFR x HER3 x VEGF
 - Demonstrated triggered internalization in vitro
 - Improved safety window in in vitro assays
 - Next steps: in vivo efficacy

Invenra's Multispecific Antibody Platform Technologies

Platform Innovation: Proprietary B-Body® bispecific and T-Body™ trispecific platforms enable rapid generation of highly developable multispecific constructs

Technical Performance: Industry-leading expression yields (up to 11 g/L for bispecifics) with CMC-ready formats and sub-Q compatibility

Development Timeline: Accelerated discovery timelines - bispecific leads generated in 4 months, B-Body bispecific constructs from existing mAb sequences in 4 weeks

Discovery & Development Programs: Portfolio includes 30+ active programs with 2 antibody constructs advancing to clinical development through partner programs

Manufacturability: Standard downstream processing compatibility with robust chain pairing and assembly for complex multispecific formats



Read the stories of
52 Views of Cancer

Three Antibody Platforms - Three Access Points



	Antibodies	B-Body® Bispecifics	T-Body™ Trispecifics
Discovery	Custom mAb Discovery Target-to-lead generation using Invenra's proprietary display platforms Platform-Enabled Service	Custom BsAb Discovery Tailored dual-targeting antibodies for specific tumor biology Platform-Enabled Service • Twist Partnership	Custom TsAb Discovery Bespoke trispecifics from target-to-lead generation Strategic Collaboration
Express	Rapid mAb Expression Production of mAb controls to support multispecific programs Platform-Enabled Service	Rapid Bispecific Prototyping Fast-track bispecific development from validated antibodies Platform-Enabled Service • Twist Partnership	Trispecific Prototyping Rapid trispecific testing of partner mAbs, leveraging platform expertise Strategic Collaboration
Assets	Off-the-Shelf mAbs Pre-developed antibodies ready for immediate licensing (Coming soon) Platform-Enabled Service	Bispecific Catalog On demand bispecifics generated using Invenra's catalog of mAbs (Coming soon) Platform-Enabled Service	Trispecific Catalog ADCs T Cell Engagers Others (Coming soon) Strategic Collaboration

Visit us at Booth 35 to Learn More