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

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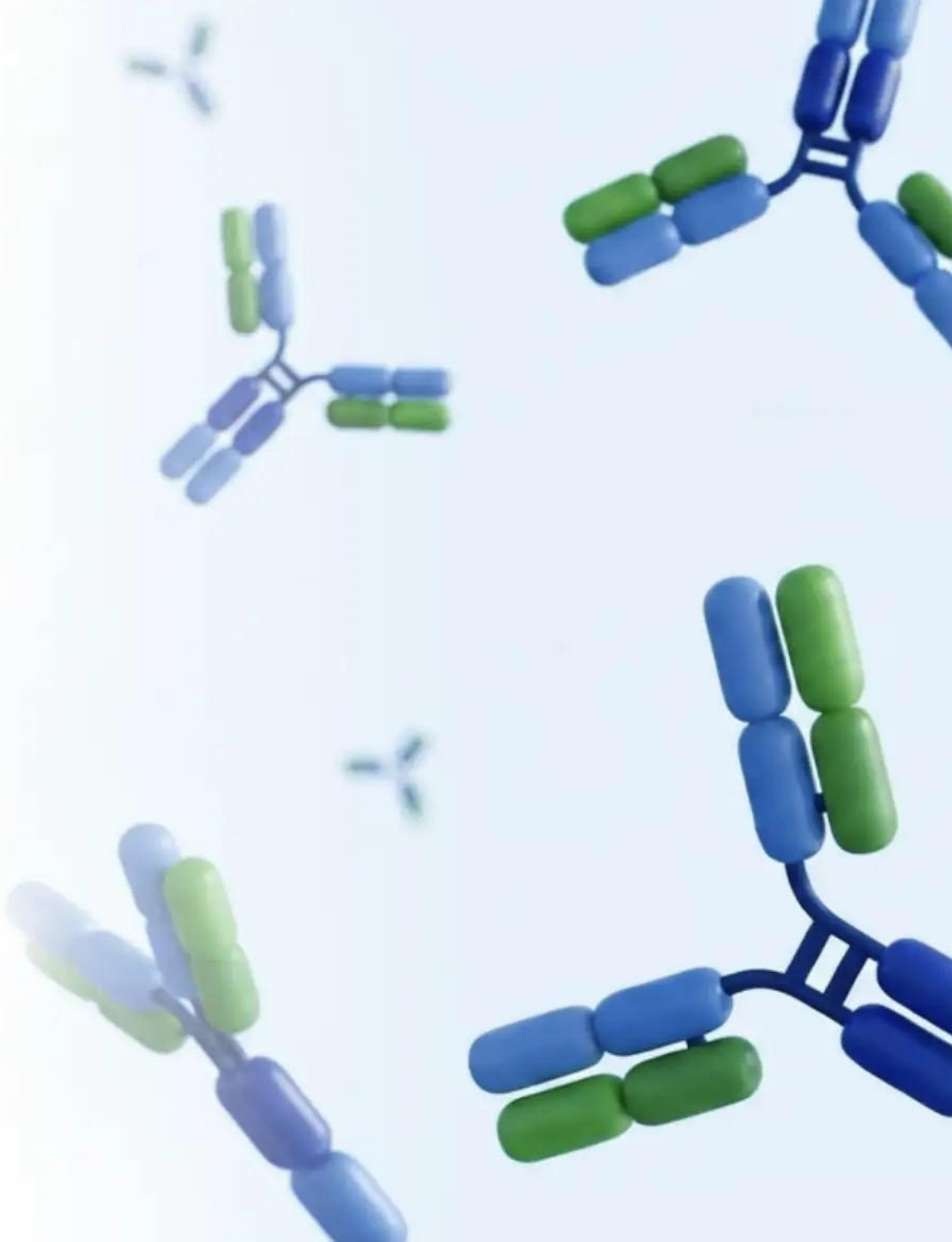
17th World ADC Conference, San Diego
October 2026



Confidential

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

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Why Invenra?

Innovative

Science–first mentality | 10+ years multispecific expertise

Proven

30+ partners | 2 clinical-stage

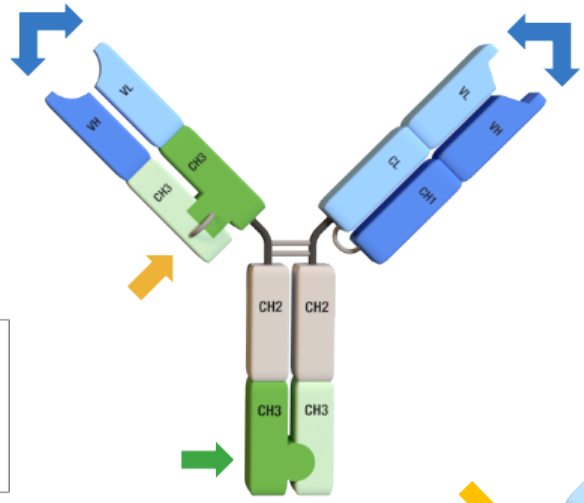
Easy

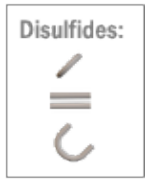
Flexible and transparent business terms from fee-for-service to strategic collaboration

		Accelerated timelines with transparent pricing and terms
1	Best multispecifics start with quality mAbs	>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

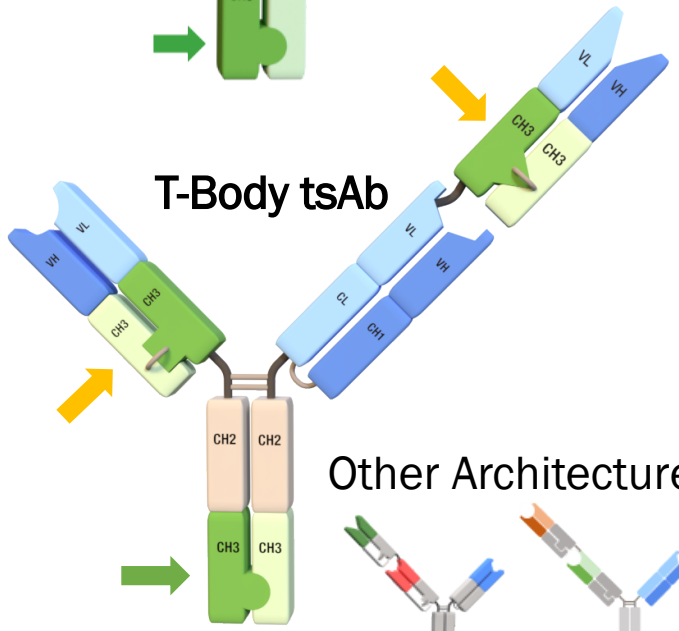
Invenra's B-Body® Bispecific and T-Body™ Trispecific Platforms: Robust Solutions for Multispecific Antibody Development

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

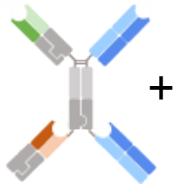
Fab Arms: Proprietary CH3 Domain Pairs

- 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



+ more

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

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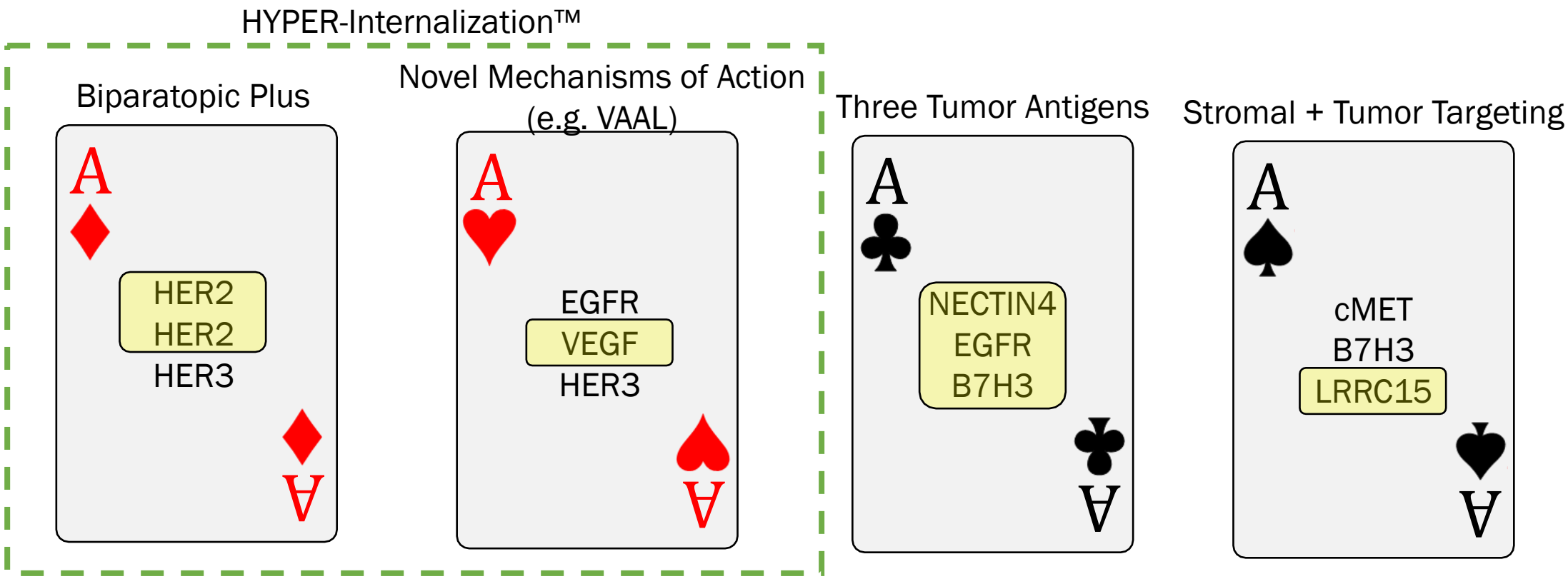
Why Trispecific (TsAb) ADCs?

- **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

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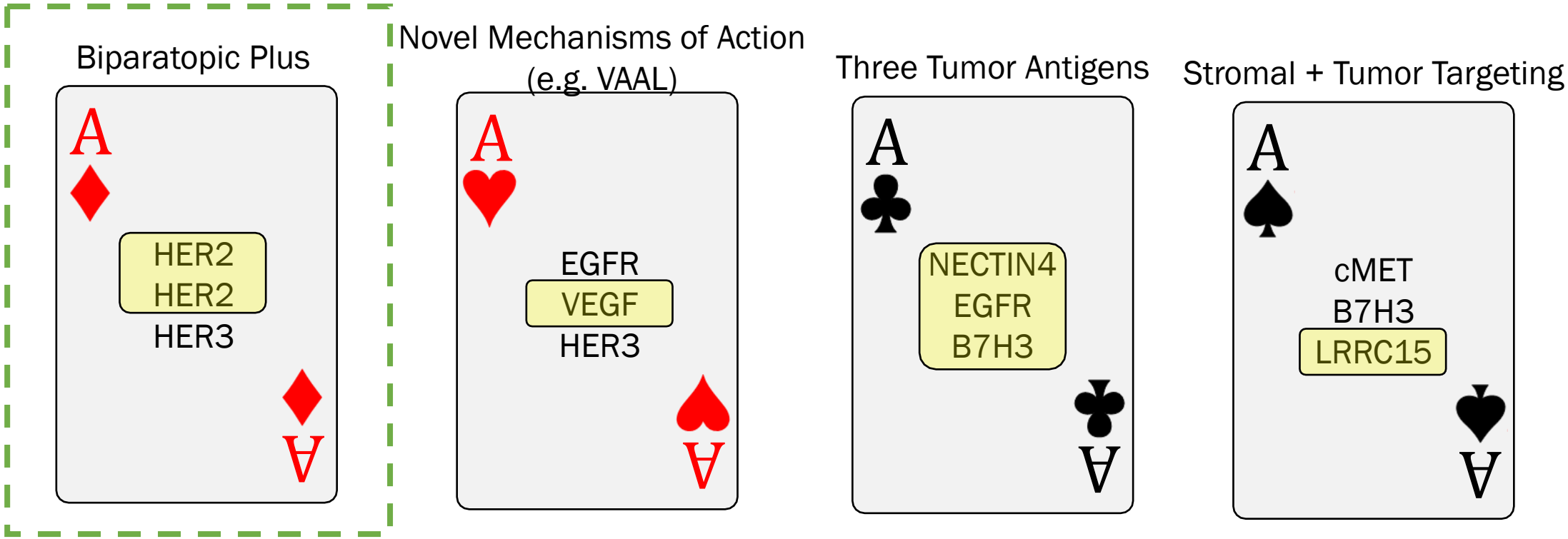
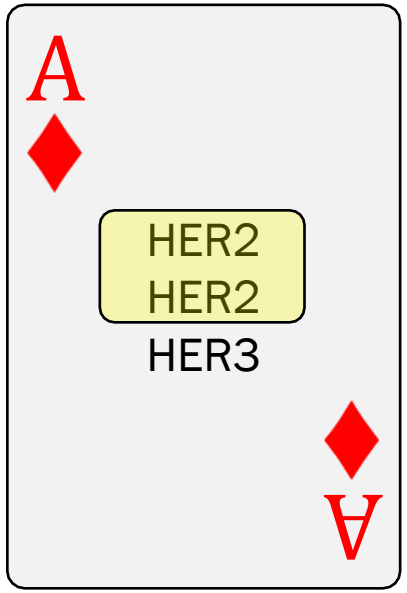


Why HER2 x HER2 x HER3

Biparatopic Plus



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

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HER2 x HER2 x HER3
T-Body Trispecific Platform Performance

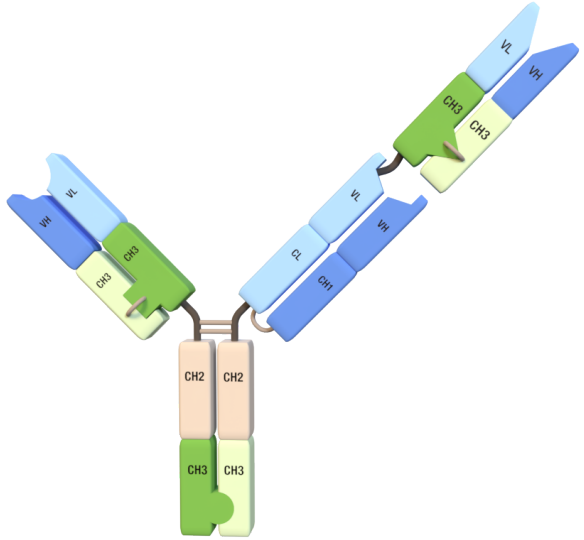
Manufacturing-Ready Trispecific Platform

Developability Excellence

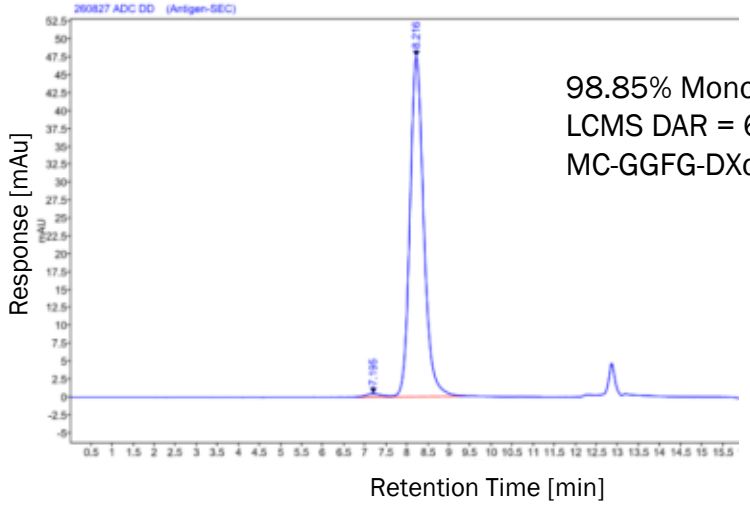
- IgG-like CHO transient yields (up to 1.5 g/L)
- Stable CHO pools in progress (1 g/L)
- Concentrated up to 100 mg/mL
- >95% purity by SEC
- Protein A + IEX compatible
- hFcRn Tg32 mouse PK (t½ 8.8 days)

ADC-Compatible

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



SEC Profile of HER2 x HER2 x HER3 ADC



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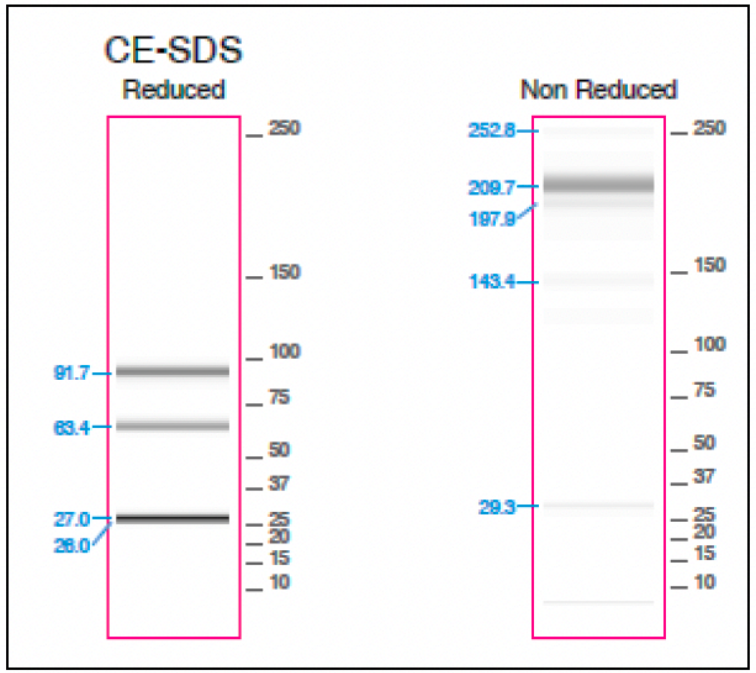
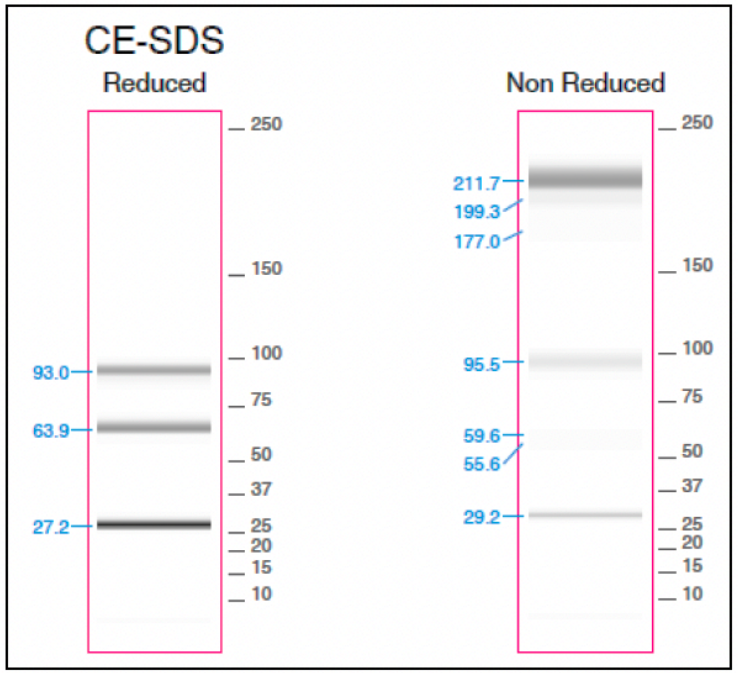
Stable CHO Cell Line Production in Progress

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



1 g/L Protein A titer
0.83 g/L Purified
74% Main Peak by SEC



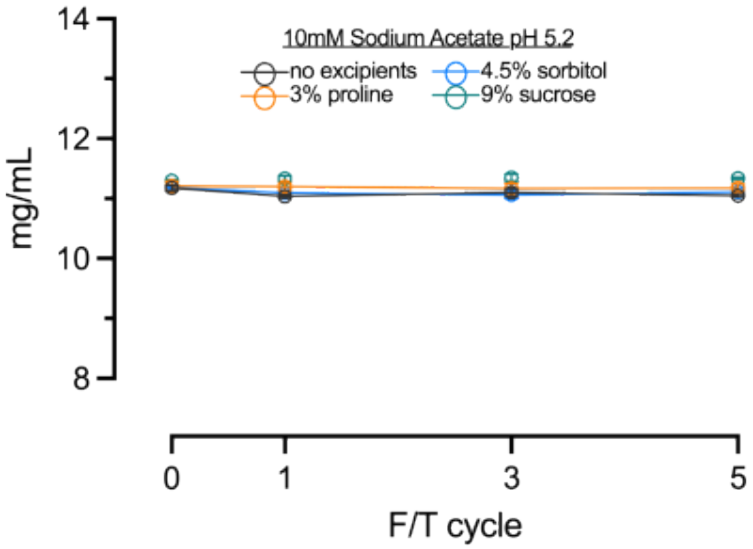
1 g/L Protein A titer
0.76 g/L Purified
75% Main Peak by SEC

HER2 x HER2 x HER3 Developability

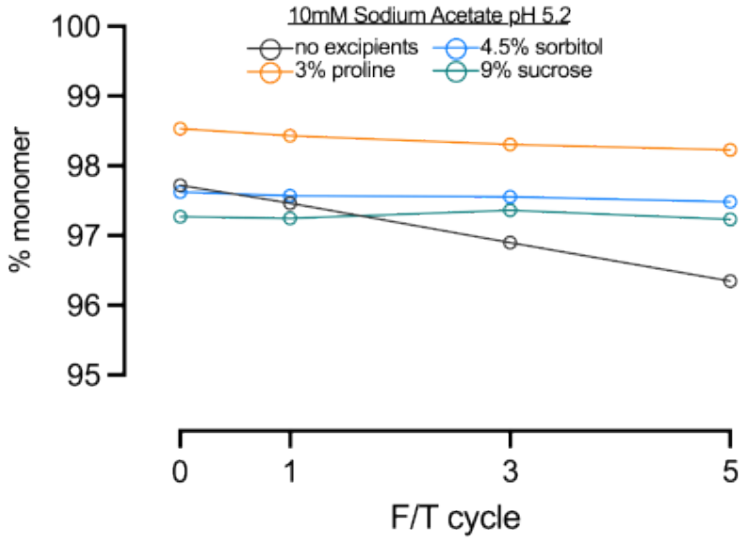
Formulation 10 mM Sodium Acetate pH 5.2	Tm1 (ºC)	Tagg (ºC)	Diffusion Interaction Parameter (mL/g)
No Excipients	63.0	74.4	21.67
+ 3% proline	63.0	64.2	30.54
+ 4.5% sorbitol	63.9	73.0	15.01
+ 2.9%sucrose	63.0	73.1	17.33

Stability with F/T Cycles

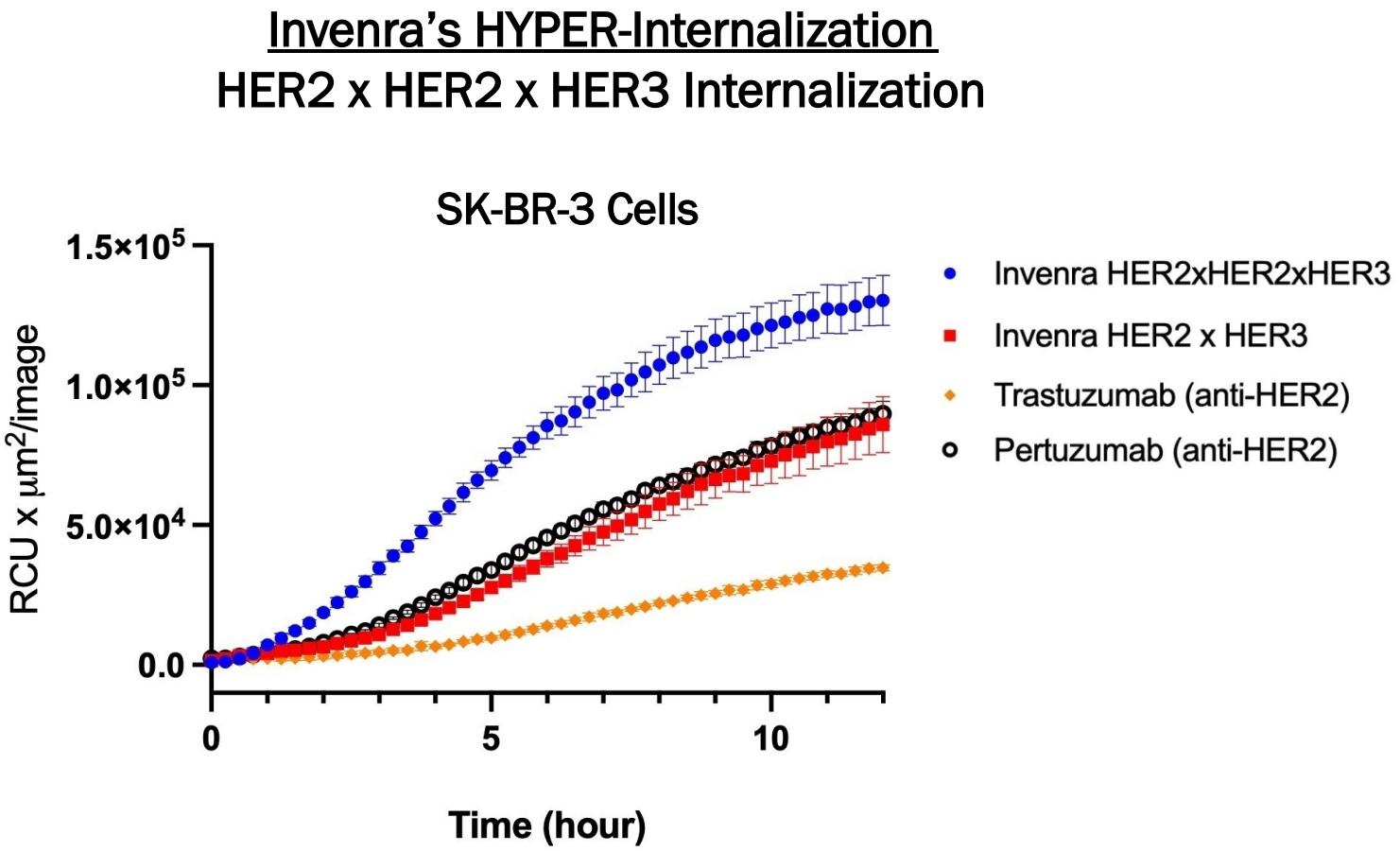
Concentration Stability



% Monomer



Increased Internalization with Biparatopic Antibodies



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

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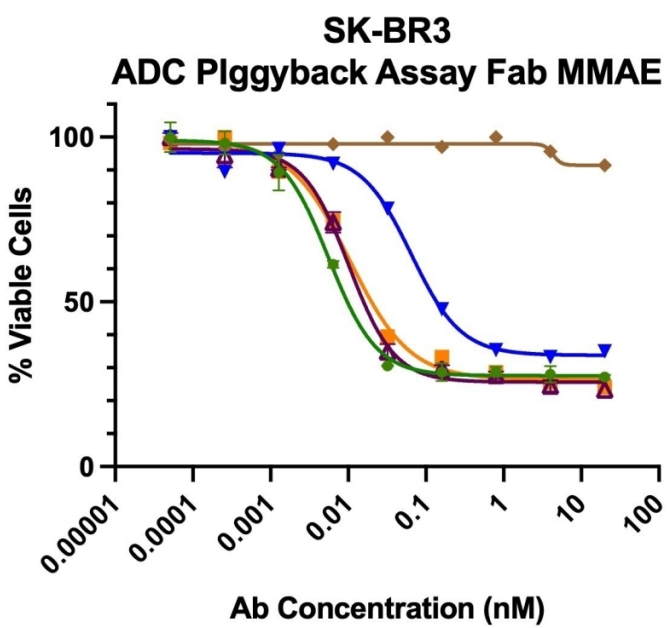
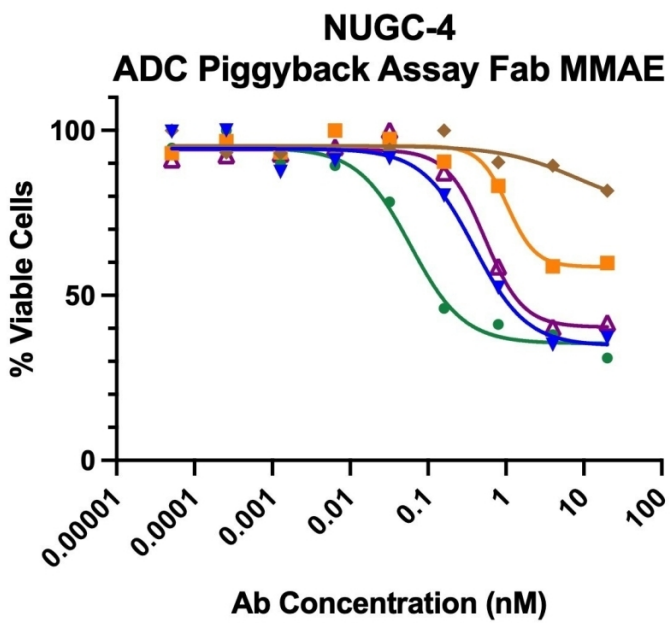
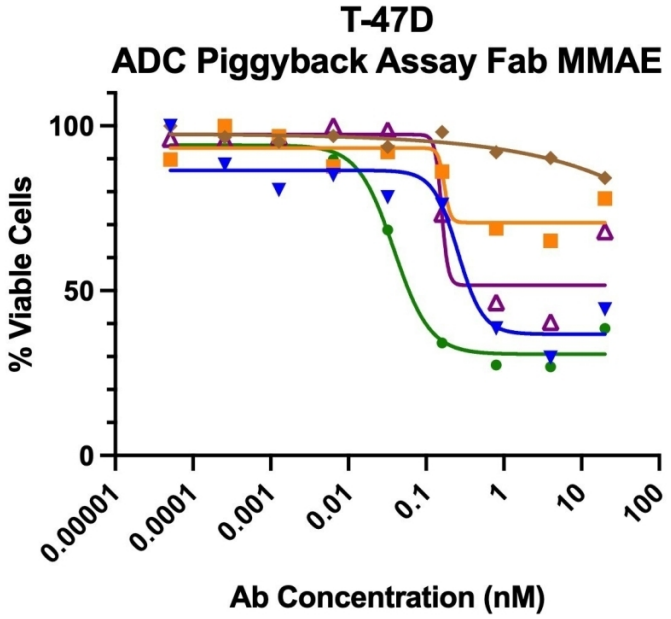
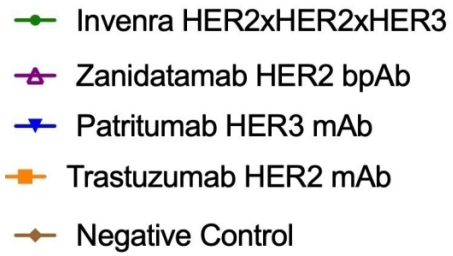
HER2 x HER2 x HER3(Biparatopic-Plus Trispecific) ADC Piggyback Data (Fab MMAE)









	Surface Copy Number
Her2	250,000
Her3	9,500

	Surface Copy Number
Her2	54,000
Her3	24,000

	Surface Copy Number
Her2	18,000
Her3	13,300

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

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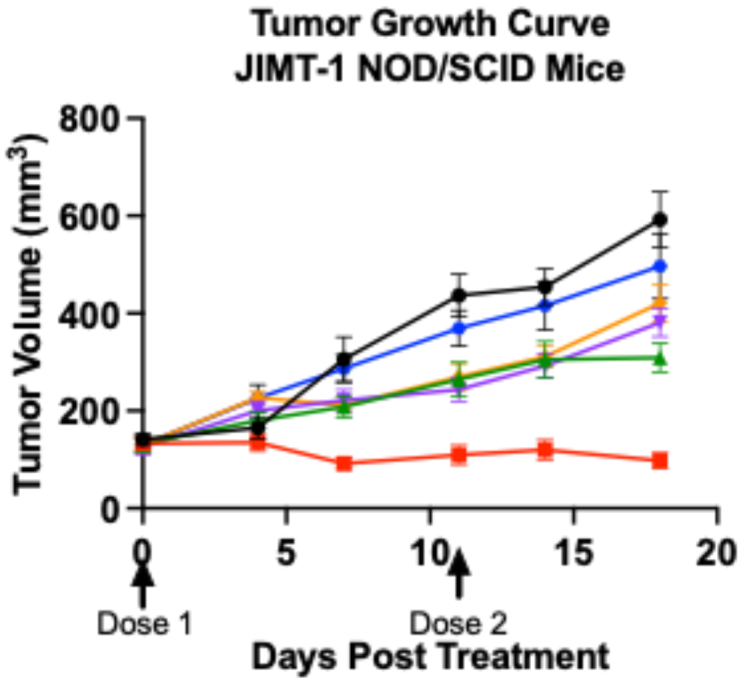
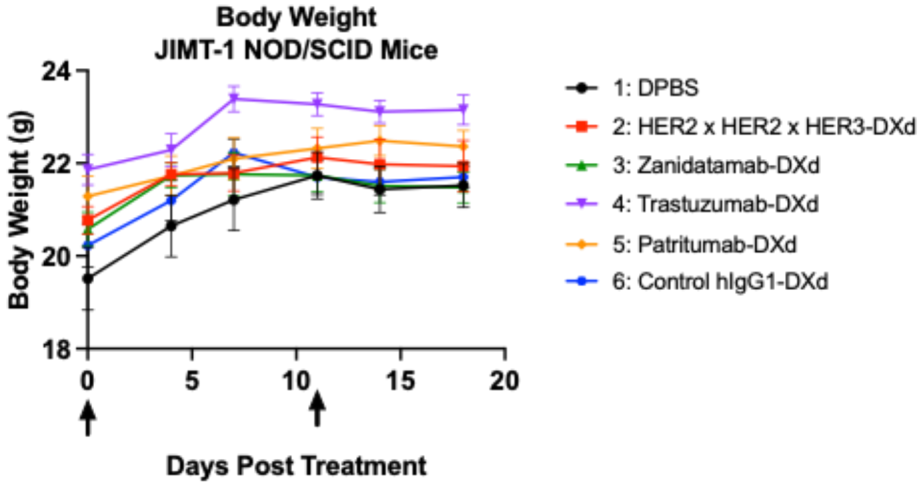
In Vivo Efficacy (In Progress)
HER2 x HER2 x HER3 ADC



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 hIgG1-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.

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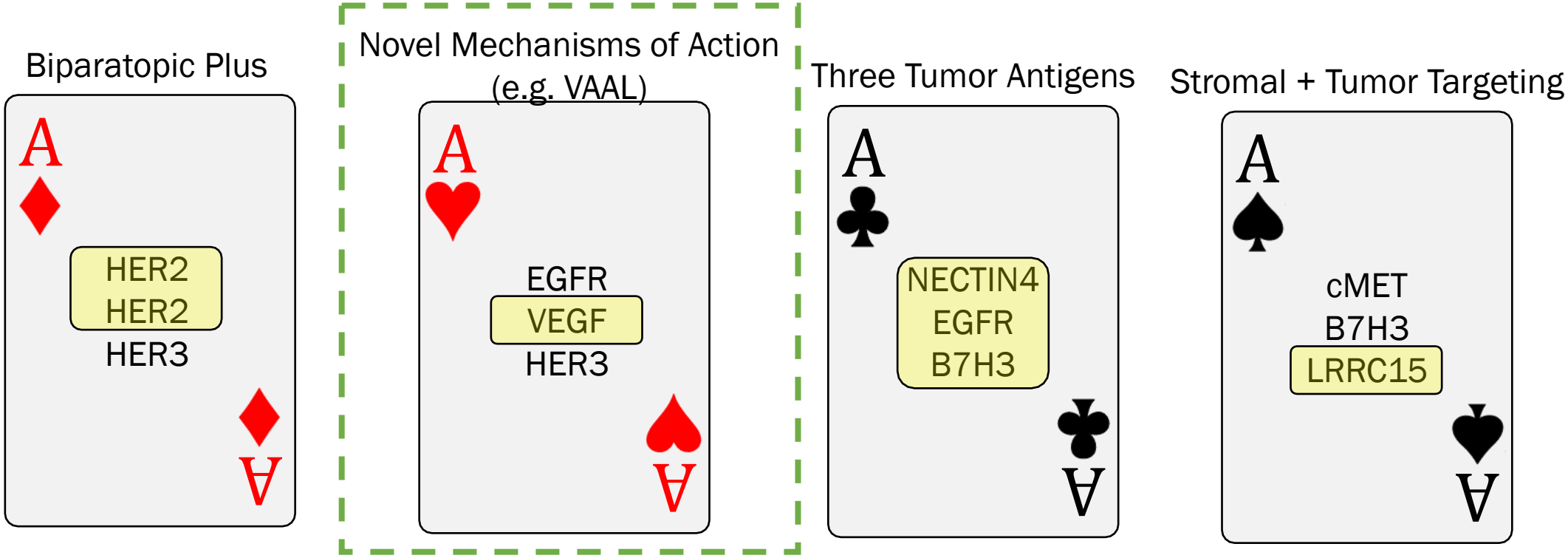
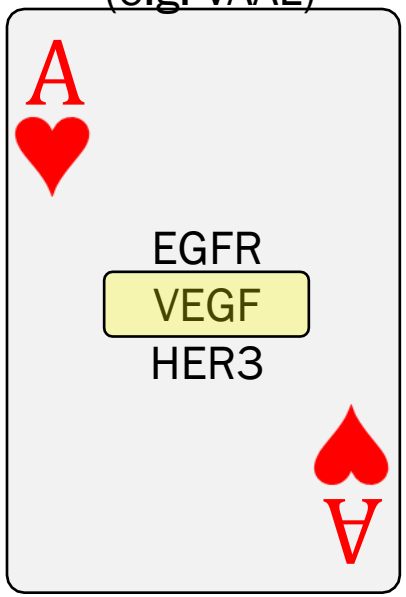
Trispecific Platforms:
52 Views of Cancer—4 Suits with Different MOAs

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.

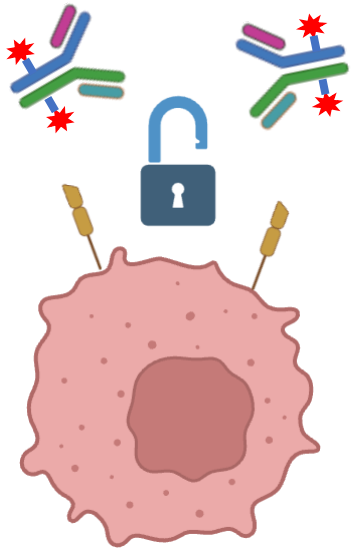
A low monovalent affinity for the TAA arm
- No significant engagement of the target
- No internalization

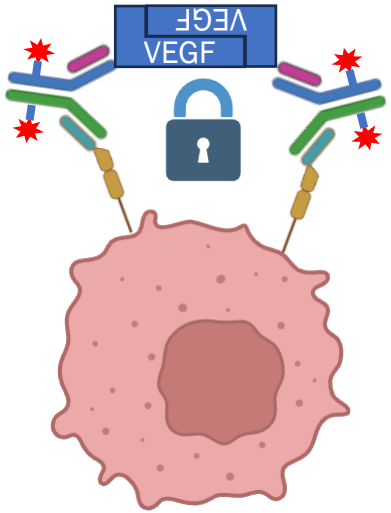
With VEGF = VEGF Activated Avidity Lock

VEGF homodimer cross-links two antibodies
- Avidity increases Kd
- Tumor-binding arms now active
- Induced internalization.

Low VEGF Outside TME

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





High VEGF Within TME

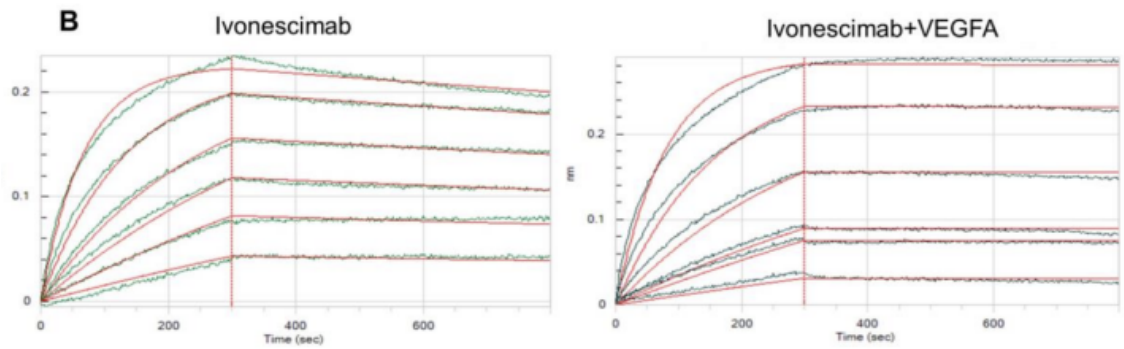
VEGF homodimer bridges 2 antibodies, resulting in cluster formation and an avidity jump. **Increases tumor selectivity**

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

↓ On-target off-tumor risk

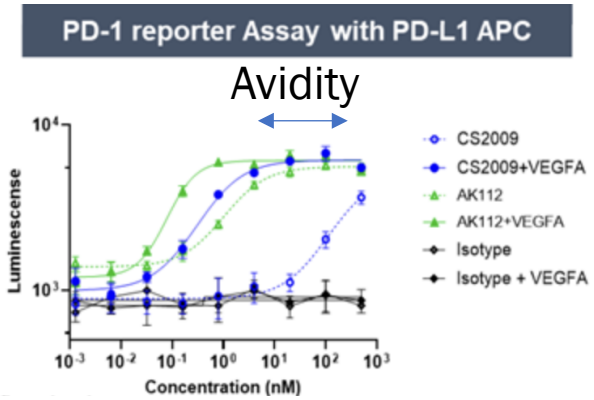
VEGF Driven Avidity Enhancement Examples

Akeso
Ivonescimab PD-1/VEGF



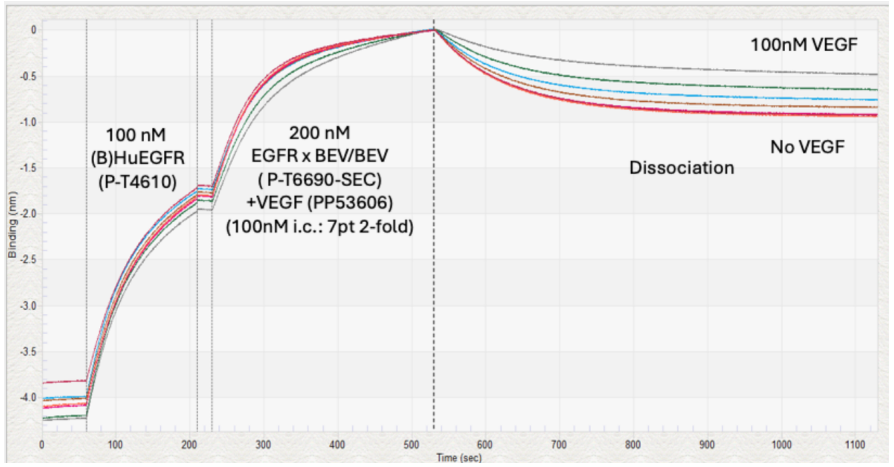
Slower dissociation rate of PD1 in the presence of VEGF

CStone
CS2009 PD-1/VEGF/CTLA-4



Lower EC50 in the presence of VEGF

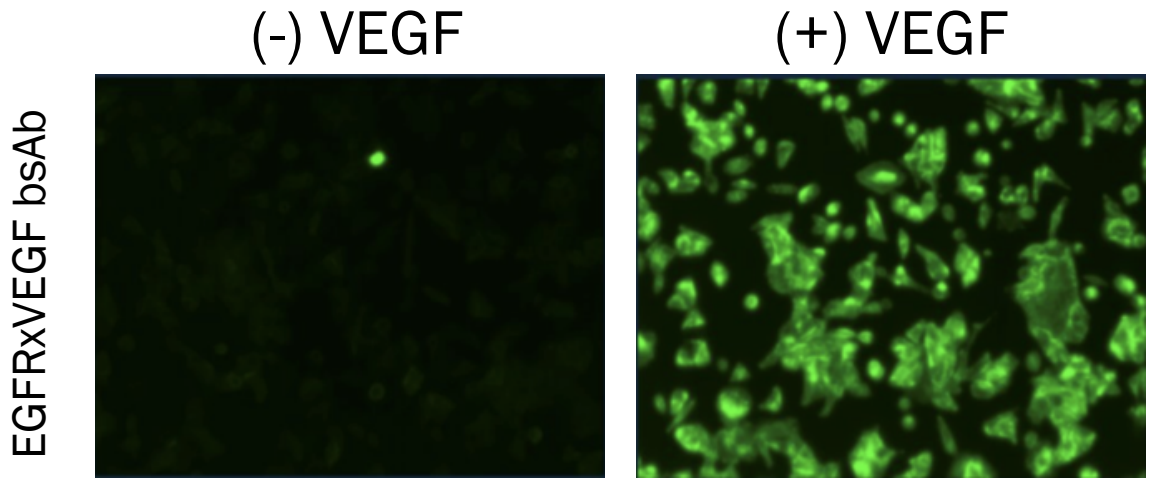
Invenra
T6690 EGFR/VEGF

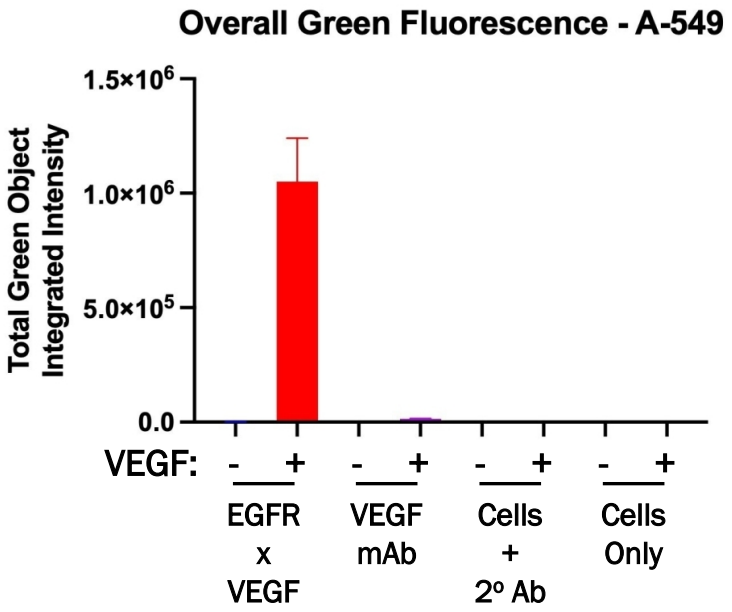


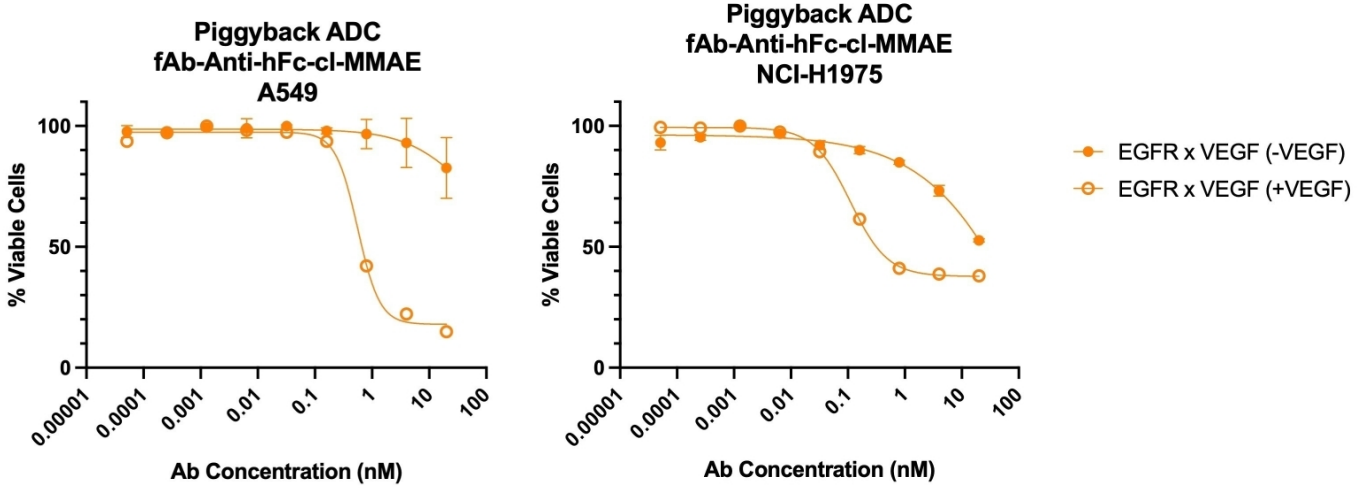
Increasing concentrations of VEGF

Slower dissociation rate of EGFR in the presence of VEGF

VAAL - VEGF Activated Avidity Lock







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

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

- 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

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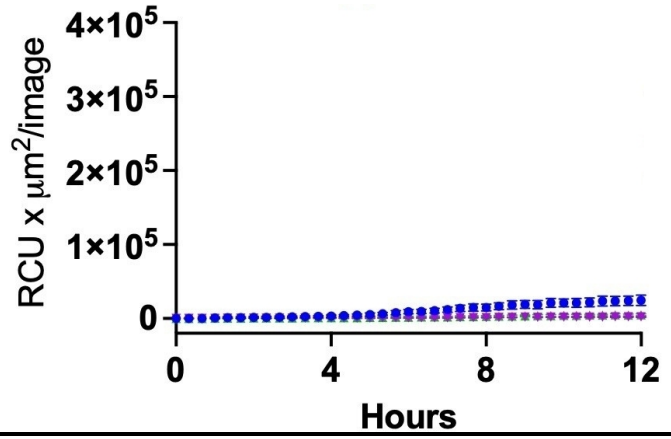
Triggered Internalization with VEGF TsAb (EGFR x VEGF x HER3)

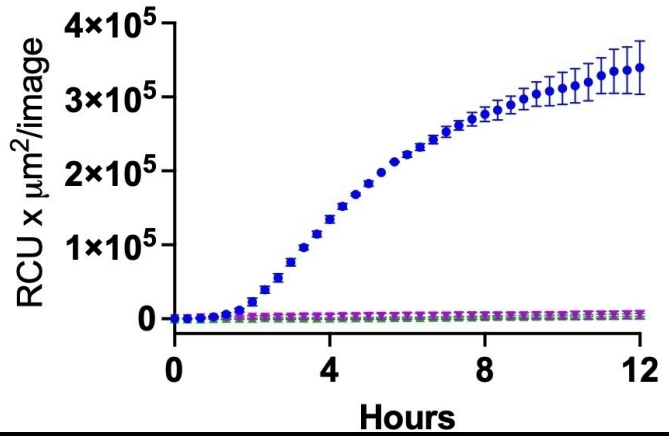
(-) VEGF

(+) VEGF

A549 Cell Line

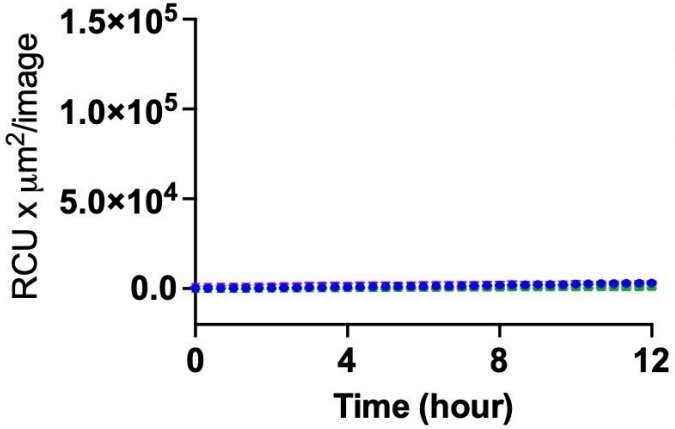
	Surface Copy Number
EGFR	52,000
Her3	<1000

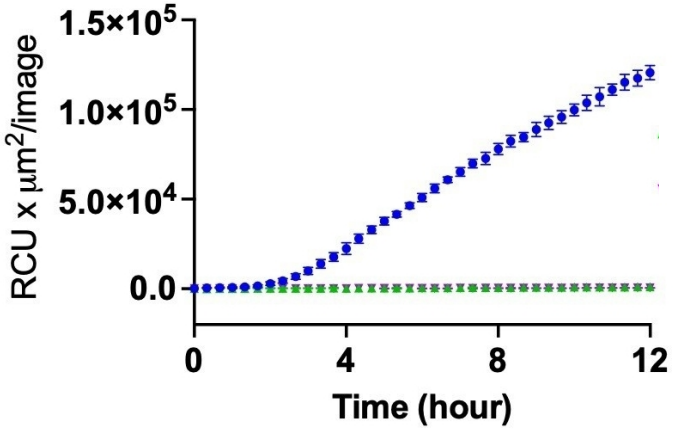




NUGC4 Cell Line

	Surface Copy Number
EGFR	14,000
Her3	22,000





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

Internalization of trispecific antibody
Only when VEGF is present

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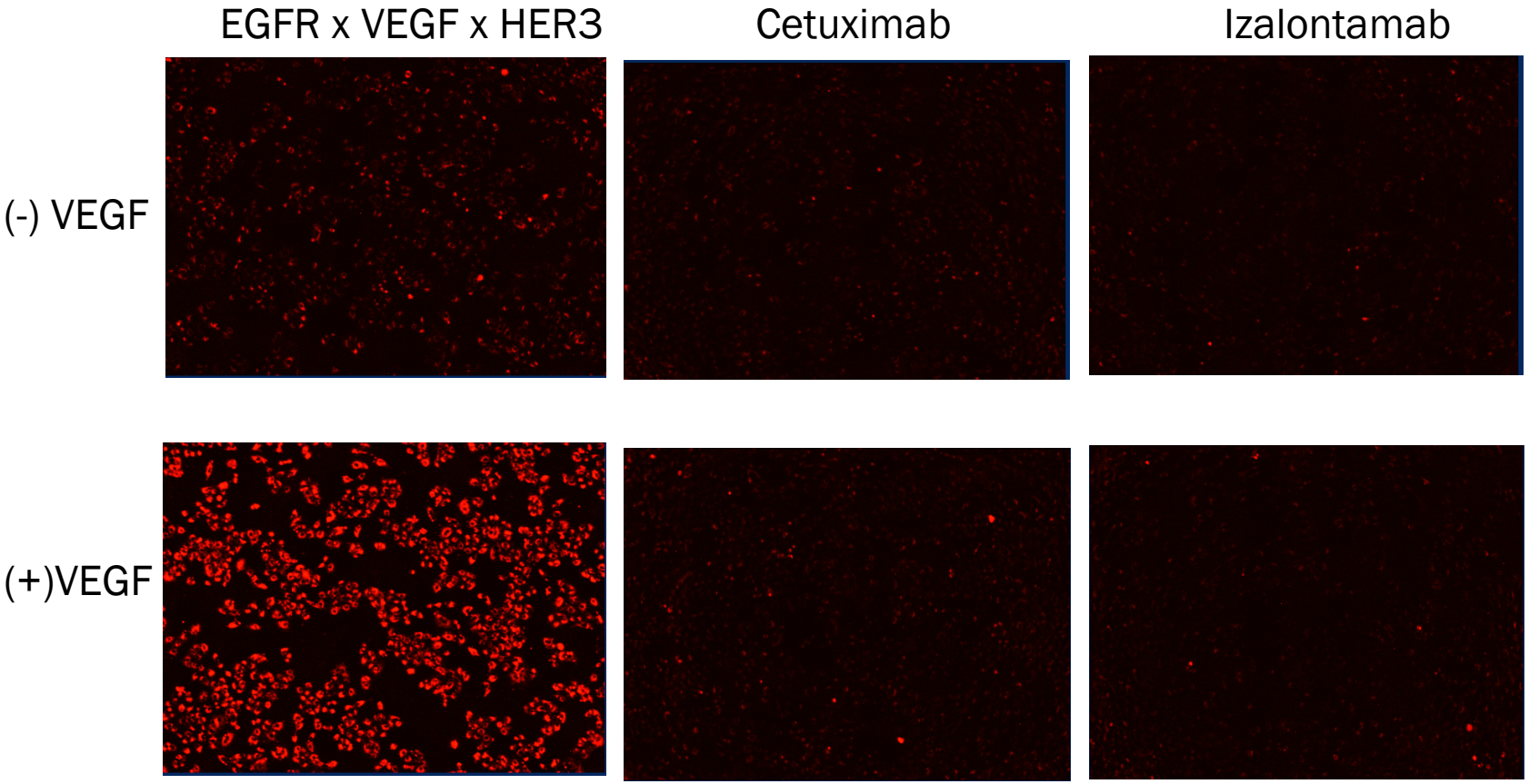
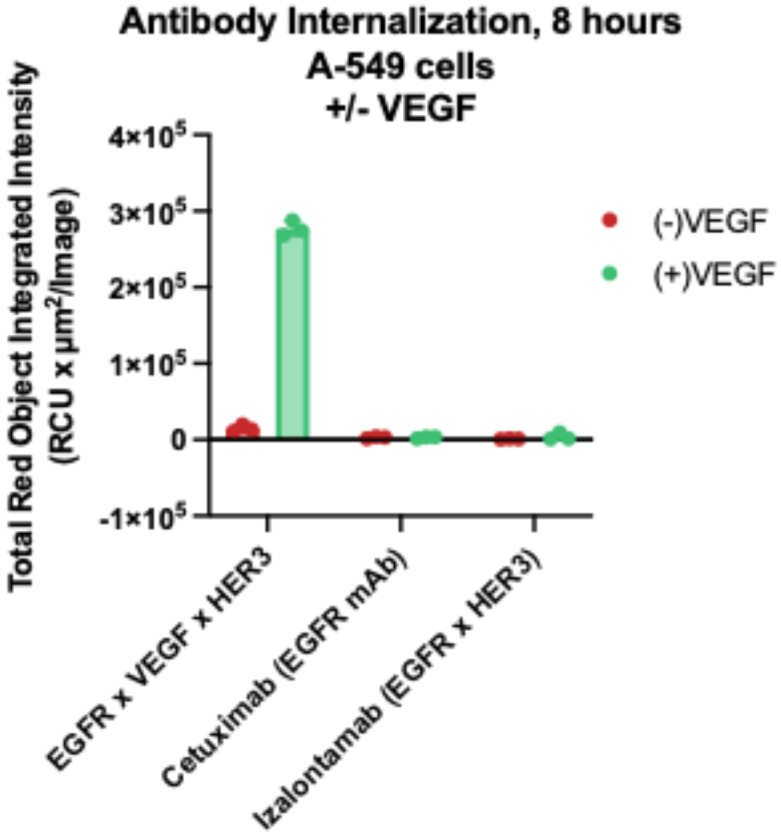
FabFluor Internalization of T-Body TsAb (EGFR x VEGF x HER3)





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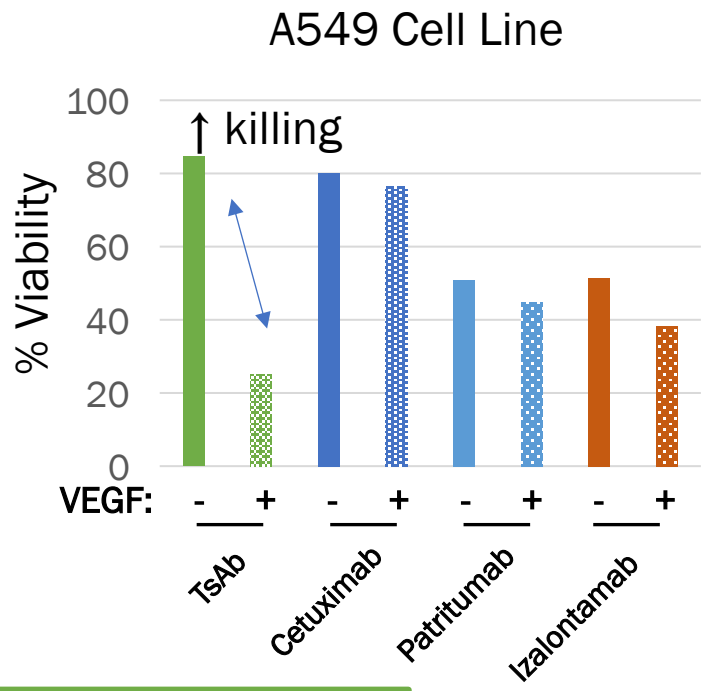
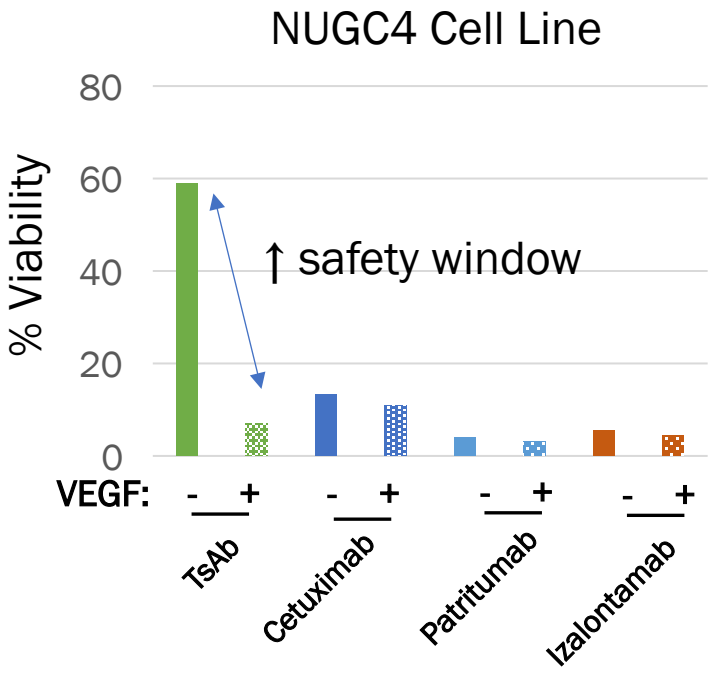
Piggyback ADC Assay with Fab MMAE
EGFR x HER3 x VEGF

4 nM antibody + MMAE Fab 5 days





VEGF binding arm increases cell killing in vitro

Surface Copy Number

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

VEGF binding arm leads to improved safety window in vitro

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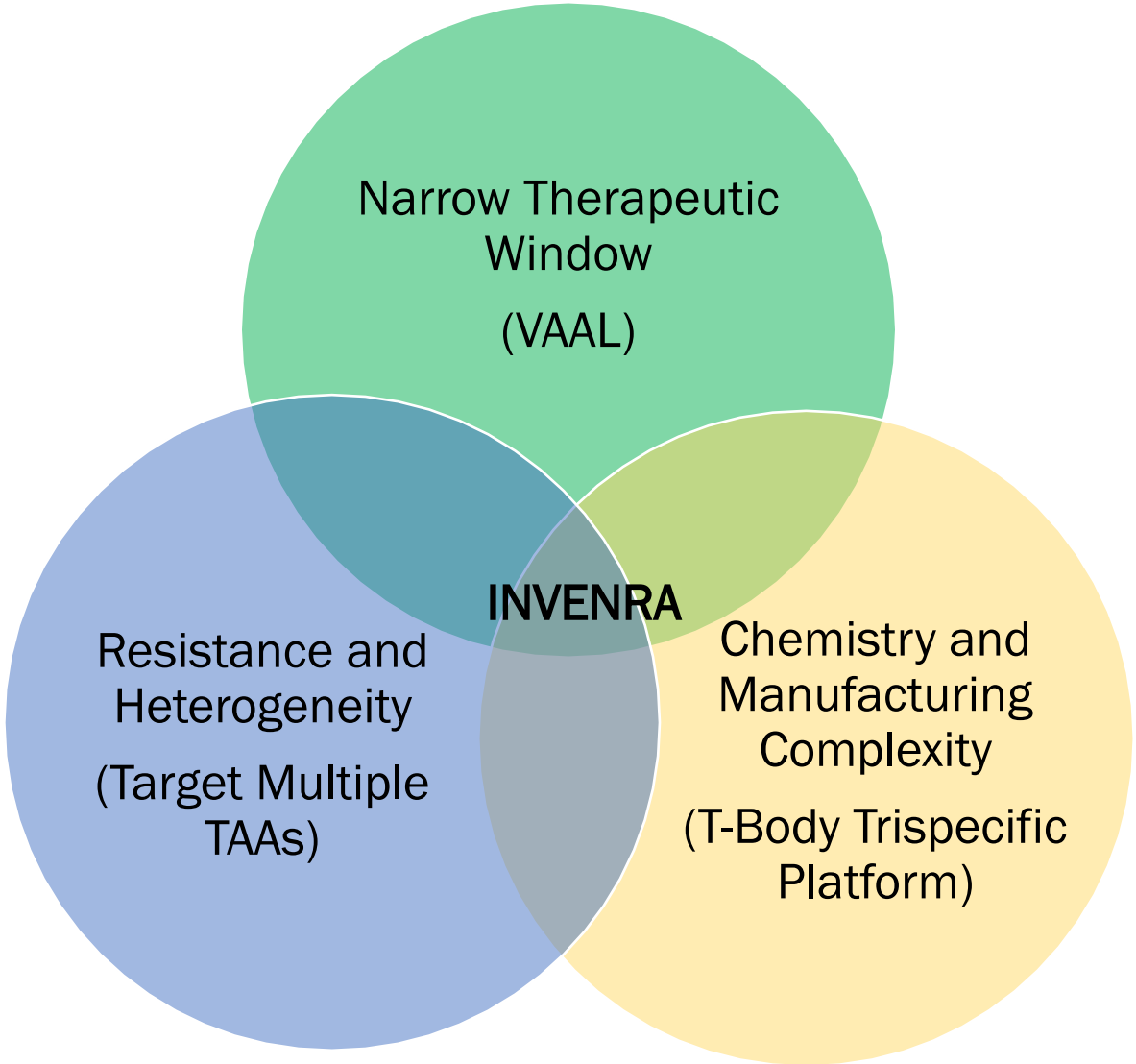
ADC Challenges

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.



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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

invenra

	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

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