Invenra's B-Body® and T-Body™ Platforms: Rapid, Comprehensive Screening for Optimal Multispecific ADC Development

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Abstract

Invenra's proprietary B-Body and T-Body multispecific platforms were built for rapid, in-format discovery as well as for streamlined manufacturing. These platforms provide a rapid screening system to empirically identify optimal target combinations for bispecific and trispecific ADCs. We describe the generation of a 12x12 matrix of bispecific B-Body antibodies targeting 6 antigens to identify optimal pairs for multispecific ADCs for breast cancer. This approach demonstrates the potential of our dual-platform strategy to advance next-generation ADC development for more effective cancer therapeutics.

Key Questions for Multispecific ADCs:

1. How does target expression influence the selection of target combinations?
2. How might various target combinations perform against heterogeneous or relapsed/refractory tumors?
3. Can a variety of cancer subtypes be effectively targeted with a single multispecific ADC?

Breast Cancer Facts and Figures:

- Breast cancer is the most common cancer diagnosed among women in the United States.
- 1 in 8 women in the US will develop breast cancer in their lifetime.

- Breast cancer is the 2nd leading cause of death from cancer among women.
- Triple negative breast cancer accounts for 10-15% of all breast cancer diagnoses in the U.S.

Sources: Breast Cancer Facts & Figure 2024-2025, American Cancer Society
National Breast Cancer Foundation, Inc.

Challenges and Opportunities for the Treatment of Breast Cancer

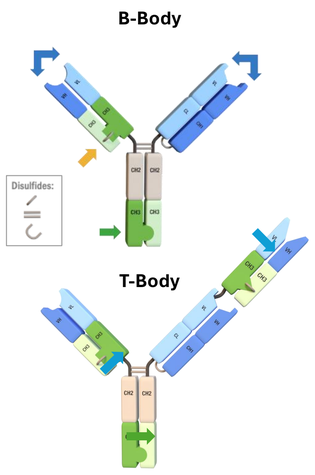
Challenges for Breast Cancer ADCs

- Suboptimal efficacy & safety profile of many monospecific ADCs
- Tumors are heterogeneous
- Many tumors develop resistance leading to relapse
- Difficult-to-treat subtypes such as TNBC

Opportunities for Multispecifics

- Enhance tumor-targeting and overcome tumor resistance, improving efficacy & safety
- Allow targeting of complementary pathways in cancer signaling and progression
- Allow targeting of molecules involved in immune modulation—potential added antitumor activity beyond just cytotoxic drug delivery

The B-Body® Bispecific and T-Body™ Trispecific Platforms



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

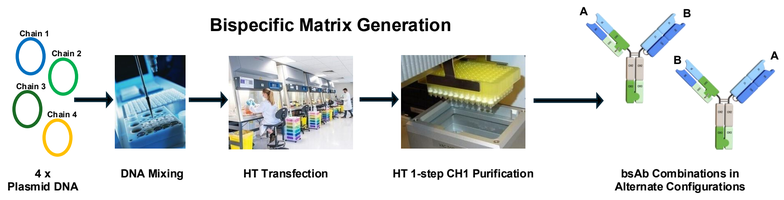
Proprietary Symmetrical Heavy & Light Chain Inversions in Fab Arms

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

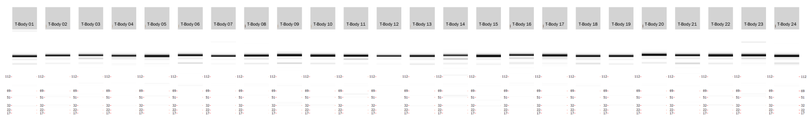
B-Body and T-Body Platforms provide a simple and accelerated path to Lead Candidates

- 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

High Throughput "Plug & Play" Screening with the B-Body Platform



T-Body Platform Enables Exploration of Target Combinations from a Bispecific Matrix



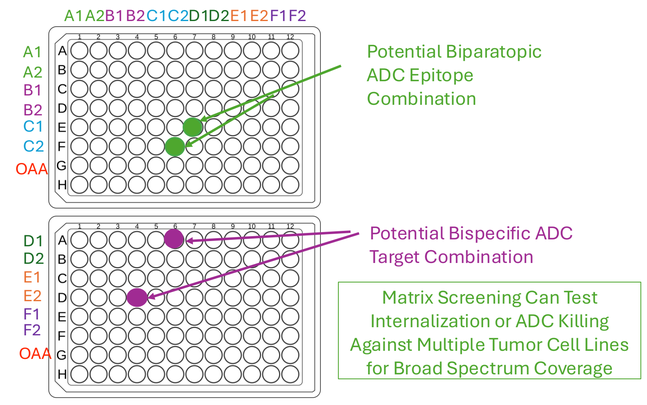
T-Body Matrix Expression Results

- 5 Chain transient transfection into CHO cells
- Expression followed by CH1 purification yields range from 70-340 mg/L
- Non-reducing CE-SDS of proteins post CH1 purification showed purities ranging from 75 to 95%.

Multispecific ADC Proof of Concept:

Objective:	Demonstrate multispecific screening capabilities for ADCs
Set Up:	12x12 matrix (6 targets) screened against 3 breast cancer cell lines of different subtypes with varying target expression levels
Materials:	1-step purified B-Body bispecifics expressed in HEK cells
Assays:	Piggyback ADC killing (MMAE toxin) and developability assays
Results:	Top B-Body bispecific pairing informed selection of T-Body trispecific pairings

12x12 Matrix B-Body Screening to Inform Optimal Bispecific Target Pairs and Top Targets for Trispecifics



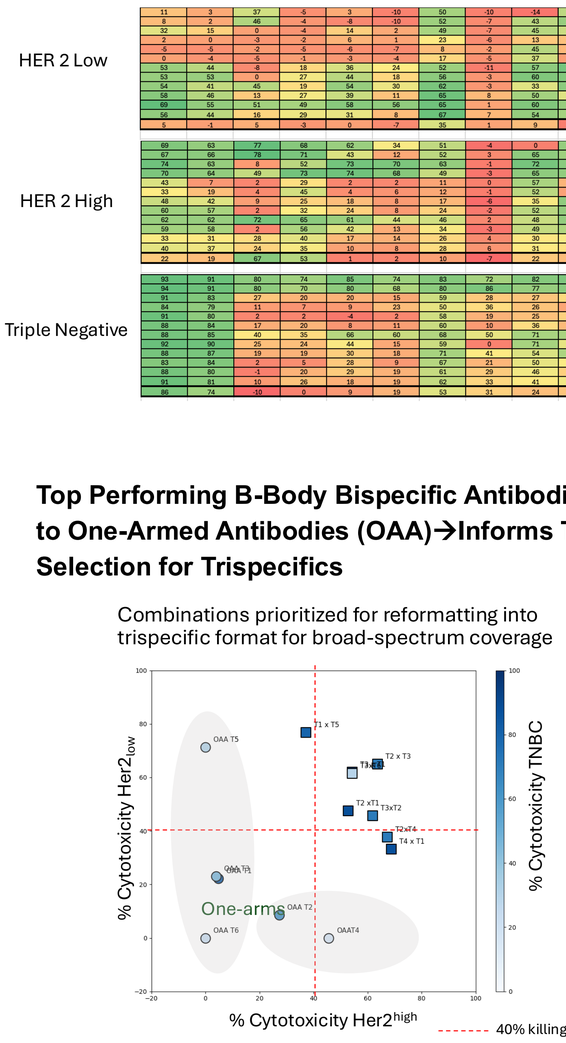
Matrix Screening of Antibodies to Multiple Target Epitopes
Unique Targets (ABCDEF) & Unique Epitopes (1-2)

3 Breast Cancer Cell Lines Used for ADC Screening

Cell Line	Target A	Target B	Target C	Target D	Target E	Target F
TNBC						
Her2 High						
Her2 Low						

Expression
High
Medium
Low

Heat Maps of Cytotoxicity Across 3 Breast Cancer Cell Lines for B-Body® Bispecific Matrix in Piggyback ADC Assay



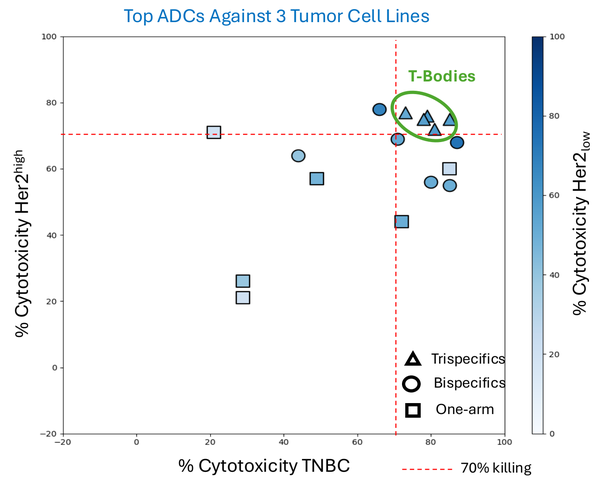
Top Performing B-Body Bispecific Antibodies Compared to One-Armed Antibodies (OAA)→Informs Target Selection for Trispecifics

Combinations prioritized for reformatting into trispecific format for broad-spectrum coverage

Cytotoxicity Observed for One-Armed Antibodies Compared to Top Bispecific Antibodies Against 3 Different Breast Cancer Cell Lines in a Piggyback ADC Assay

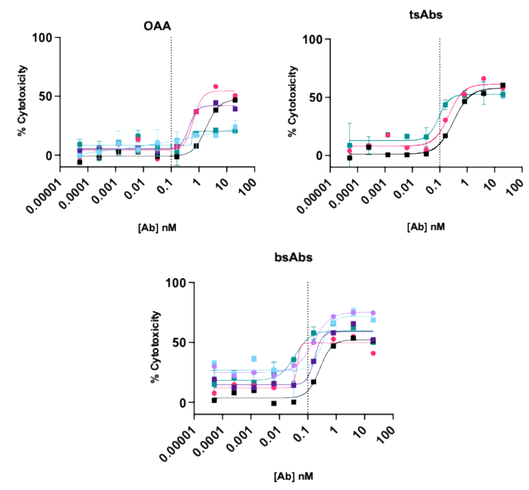
	HER2 High	HER2 Low	TNBC
OAA T1	22.27	4.75	85.81
OAA T2	8.65	27.3	63.81
OAA T3	23.11	3.89	47.23
OAAT4	0	45.51	17.88
OAA T5	71.34	-5.2	31.97
OAA T6	0	0	24.73
T3 x T1	61.97	54.33	87.89
T2 x T3	64.97	63.6	70.84
T1 x T5	76.78	37.14	79.72
T4 x T1	33.18	68.72	87.84
T2 x T1	47.57	52.78	87.92
T3 x T2	45.73	61.82	71.23
T2 x T4	37.73	67.22	71.37
T3 x T6	61.43	54.28	29.93

Identification of Top Multispecific ADCs



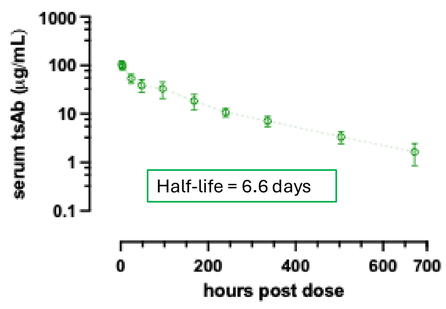
T-Body™ trispecific antibodies exhibit robust killing in piggyback ADC assays against 3 different cell lines

Dose Response Curves for Top OAA, bsAbs, and tsAbs



Example dose response curves for one-armed antibodies (OAA), B-Body ® bispecific antibodies (bsAbs), and T-Body ™ trispecific antibodies (tsAbs) in a piggyback ADC assay using MMAE toxin.

T-Body Trispecific Has IgG-Like PK in Rats



t1/2 (h)	158.83
Tmax (h)	2
Cmax (µg/ml)	104.84
AUC 0-t (ug/ml*h)	9651.04
Cl_obs (ml/h/kg)	0.499

A T-Body trispecific antibody was dosed in rats at 5 mg/kg for assessment of PK properties. The T-Body trispecific exhibited a standard, IgG-like PK profile in rats.

Summary:

Invenra's B-Body® and T-Body™ platforms enable direct comparison of multispecific formats to identify lead candidates

Bispecific and trispecific ADCs were more efficient at killing the three tumor cell lines than monospecific ADCs.

Trispecific ADCs were more efficient at killing the three tumor cell lines than bispecific ADCs

Trispecific ADCs are hypothesized to be more effective in heterogeneous tumors and in refractory/relapsed tumors where protein expression of a target may be downregulated, shed, or lost.

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