Guide-effector bsADCs: Driving co-endocytosis for enhanced payload delivery

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BACKGROUND

- Many tumor-associated antigens show low internalization, limiting ADC efficacy.
- Bispecific antibodies (BsAbs) can simultaneously engage two receptors to enhance internalization via co-endocytosis.
- By pairing a rapidly internalizing receptor (guide) with a poorly internalizing receptor (effector), BsAbs enhance intracellular trafficking and payload delivery.

OBJECTIVE

- To define co-endocytosis as a mechanistic strategy by which guide–effector bispecific antibodies enhance internalization and intracellular payload delivery relative to monospecific formats.

METHODS

- A201 and BsAb-293 are Bispecific antibodies HER2×TROP2 and cMET×HER3 were engineered, expressed in ExpiCHO cells, and purified by Protein A affinity chromatography.
- OBI-201 is a next-generation bsADC that co-targets HER2 and TROP2, leveraging A201 site-specific glycan conjugation and a hydrophilic linker technology, with Exatecan in drug-to-antibody ratio (DAR) of 4.
- Binding affinity was evaluated by ELISA and cell-binding assays across tumor cell lines with varying HER2/TROP2 or cMET/HER3 expression.
- Real-time Internalization was monitored at 37 °C using Cytation 5 imaging with a pH-sensitive dye, where fluorescence increased upon lysosomal trafficking.

RESULTS

Figure 1. BsAb cMET×HER3 targets both HER3 and cMET

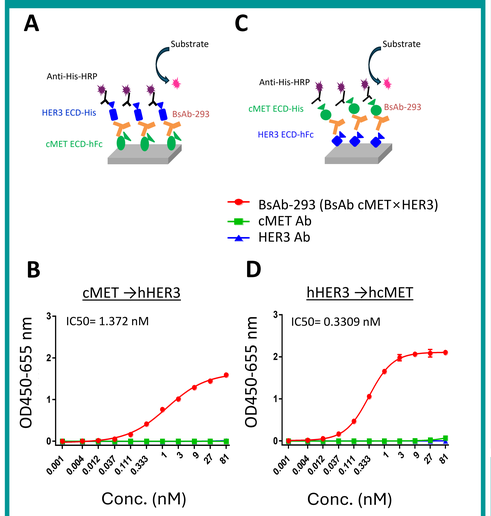


Figure 2. BsAb cMET×HER3 engages both HER3- and cMET-expressing cancer cell lines

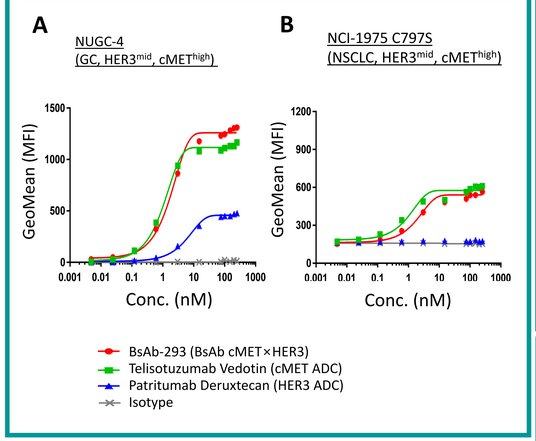
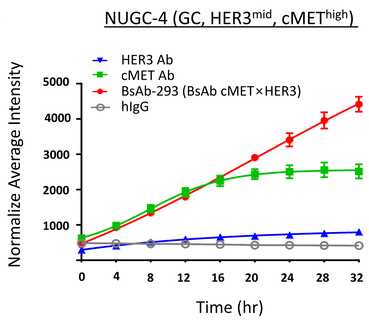


Figure 3. BsAb-293 drives efficient internalization via guide-effector co-endocytosis



B

Name	Maximum Average Intensity
Isotype	415
HER3 Ab	808
cMET Ab	2518
BsAb-293	**4419**

Data represent the signal intensity measured at 32 hours in NUGC-4 gastric cancer cell line.

Figure 4. Fast-internalizing cMET enables co-endocytosis of HER3 and enhances lysosomal trafficking

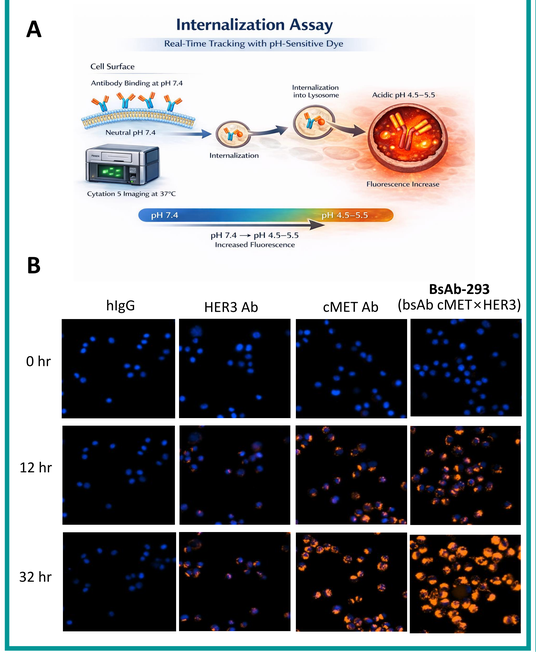
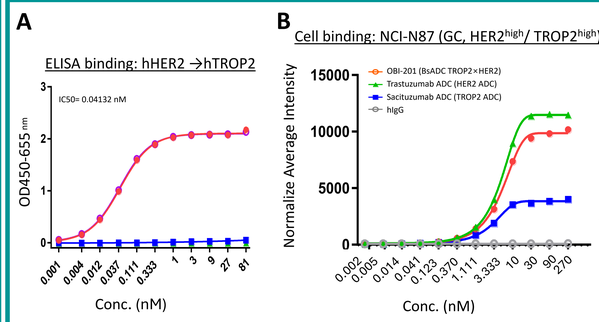


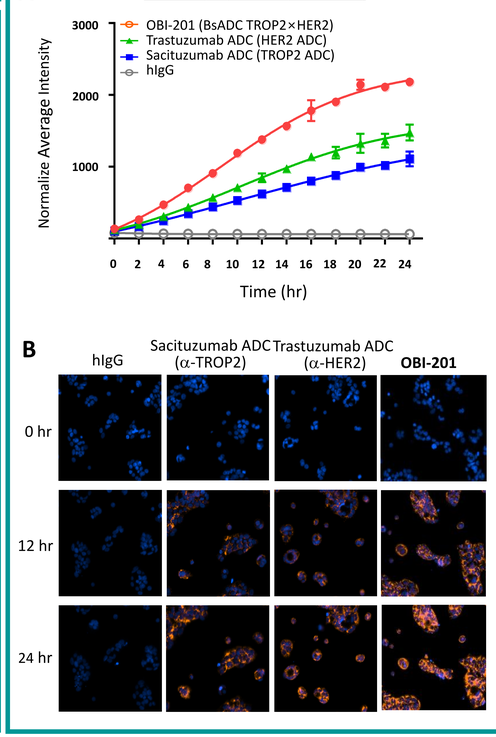
Figure 5. OBI-201 demonstrates high-affinity, dual target binding to HER2 and TROP2 in ELISA and cell binding



C

Name	NCI-N87 (GC, HER2high/ TROP2high) EC50 (nM)
OBI-201 (BsADC TROP2×HER2)	5.498
Trastuzumab ADC (HER2 ADC)	4.917
Sacituzumab ADC (TROP2 ADC)	3.266
hIgG	-

Figure 6. OBI-201 enhances lysosomal trafficking and intracellular payload delivery



C

Name	Maximum Average Intensity
OBI-201 (BsADC TROP2×HER2)	**2020.9**
Trastuzumab ADC (HER2 ADC)	1459.4
Sacituzumab ADC (TROP2 ADC)	1148.3
hIgG	59.5

Data represent the signal intensity measured at 24 hours in NCI-N87 gastric cancer cell line.

CONCLUSIONS

- Overcoming Resistance: Traditional ADCs often exhibit limited efficacy due to insufficient target internalization and heterogeneous antigen expression across tumor cells. This new mechanism bypasses those hurdles.
- Guide–Effector Co-endocytosis: This is a "buddy system" strategy. One antibody arm (the guide) targets a rapidly internalizing protein to "pull" the other arm (the effector, carrying the drug payload) into the cell, even if the effector's target usually stays on the surface.

DISCLOSURE
This study was funded by OBI Pharma, Inc. All authors are employees of OBI Pharma, Inc.

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