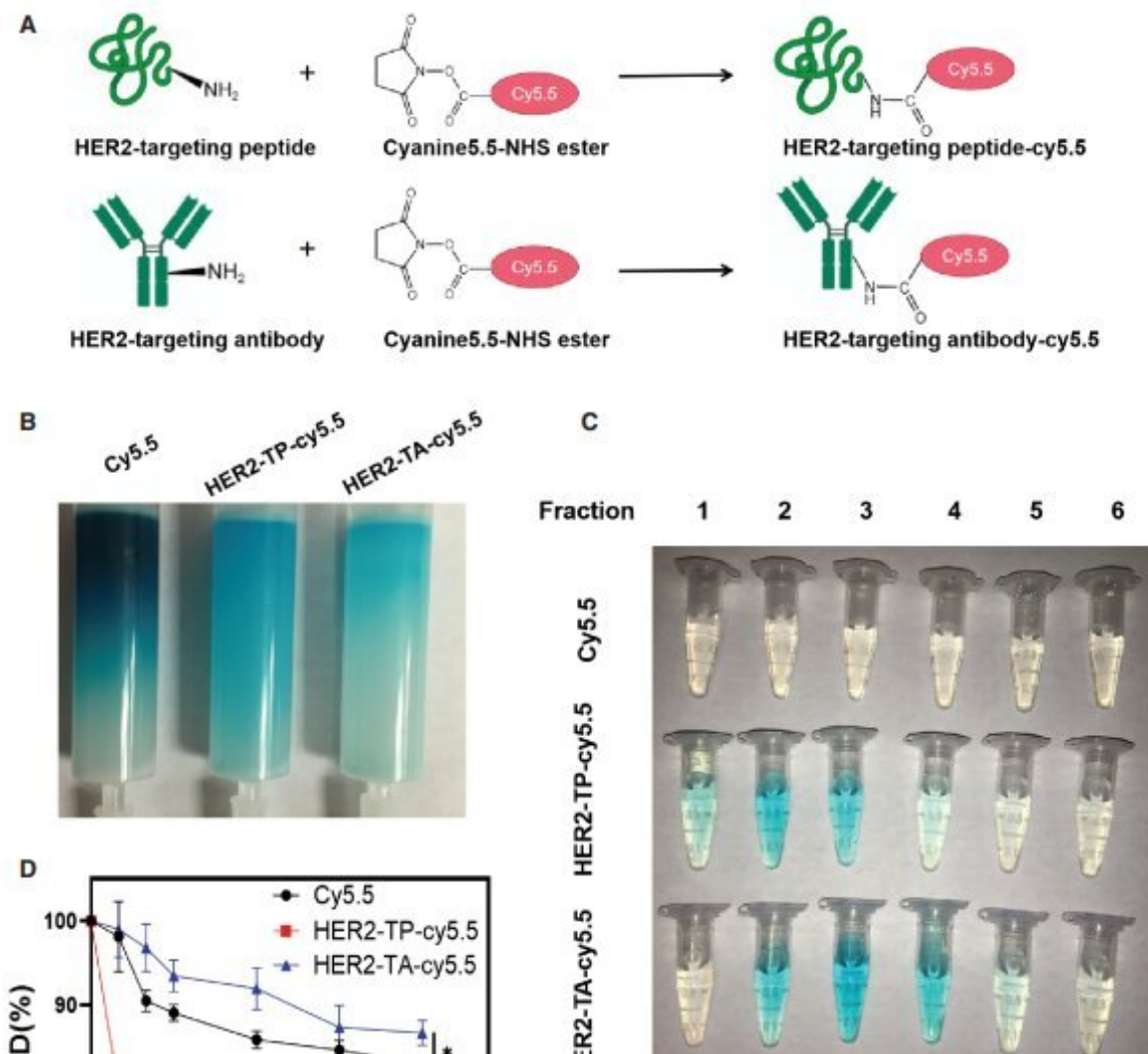


# A HER2-targeting peptide drug conjugate with better penetrability for effective breast cancer therapy

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Schematic diagram and pharmacokinetics of HER2-TP-cy5.5 and HER-TA-

cy5.5 conjugate synthesis. (A) Schematic representation of the utilization of HER2-targeting peptide/antibody and Cyanine5.5-NHS ester (Cy5.5) to form conjugates. (B) Purification of the conjugates, (C) Collection of the purified components. (D) The circulation time of free Cy5.5 and Cy5.5-labeled peptide/antibody after intravenous injection in mice via the tail vein. mean $\pm$ SD; n=3; \*p *BIO Integration* (2023). DOI: 10.15212/bioi-2023-0006

Antibody-drug conjugates (ADCs) have advantages including target specificity, wide therapeutic index and prolonged circulation half-life. A key limitation of ADCs, however, is the large size (~150 kDa), which markedly slows diffusion through the interstitium of solid tumors and prevents efficient penetration.

To address the size issue of ADCs in targeted [drug delivery](#), the authors of an article published in *BIO Integration* developed a HER2-targeting peptide-mertansine [conjugate](#) (HER2-TPMC) and conducted a head-to-head comparison with HER2-targeting antibody-mertansine conjugate (HER2-TAMC) as a possible alternative for high-penetration breast cancer therapeutics.

As expected, a pharmacokinetic (PK) assay revealed that HER2-TP had lower levels persisting in the circulation after 1 hour (~75%) compared to 85% of HER2-targeting antibody (HER2-TA). The cellular cytotoxic effect of HER2-TPMC was similar to HER2-TAMC in the HER2+ BT474 breast cancer cell line, thus demonstrating similar bioactivity of both conjugates. HER2-TPMC not only revealed higher uptake and specificity in in vitro 3D spheroid cultures compared to the parental drug, mertansine, but HER2-TPMC also had a significant retention in the spheroids.

This finding was in stark contrast to HER2-TAMC, a large-sized

conjugate which was not able to penetrate the spheroid barrier, thus resulting minimal penetration. In vivo tumoral uptake in a BT474 orthotopic model indicated increased tumor uptake and penetration of HER2-TP compared to parental drug and HER2-TAMC.

The authors successfully developed a HER2-targeting peptide-mertansine conjugate with specific cellular uptake that resulted in longer retention times in vitro and in vivo. HER2-TPMC (~5 kDa in size) exhibited rapid tissue penetration and enhanced tumoral uptake and retention in vitro and in vivo. Therefore, HER2-TPMC is a reasonable alternative for HER2-positive cancer chemotherapeutics.

**More information:** Yixia Liang et al, HER2-targeting Peptide Drug Conjugate with Better Penetrability for Effective Breast Cancer Therapy, *BIO Integration* (2023). [DOI: 10.15212/bioi-2023-0006](https://doi.org/10.15212/bioi-2023-0006)

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