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An Integrin-Targeting Peptide for Enhanced Lysosomal Delivery of Antibody-Drug Conjugates

Stanford researchers have developed a modular bioconjugation platform that improves the potency and selectivity of antibody-drug conjugates (ADCs) by enhancing their lysosomal internalization. The method attaches a cancer-selective, integrin-binding peptide directly onto a native monoclonal antibody using site-specific click chemistry that re-bridges the antibody's existing disulfide bonds, without requiring any protein engineering.

Internalization followed by lysosomal degradation is a rate-limiting step for most ADCs, and insufficient internalization is a major contributor to the narrow therapeutic windows that leads to clinical trial failure. Prior strategies to enhance internalization have relied on bispecific antibody scaffolds requiring more complex assembly, or on targeting constitutively expressed internalizing receptors that are not cancer-selective and risk off-tumor toxicity. By instead conjugating a well-characterized, cancer-selective integrin-binding peptide alongside the cytotoxic payload, this platform increases antibody internalization 200–900%, substantially higher than previously reported peptide-based strategies. Across multiple antibody/target/cell-line combinations (including HER2, EGFR, and CA9), the resulting constructs showed approximately 10-fold greater tumor cell killing than the corresponding conventional ADC, with minimal cytotoxicity from the targeting peptide alone. The strategy is modular and antibody-agnostic, suggesting broad applicability across existing and future ADC programs.

Stage of Development
Research - *in vitro* and *in vivo* data

Applications

- Enhancing the potency and therapeutic window of antibody-drug conjugates (ADCs) in oncology
- Retrofitting existing ADC programs to improve lysosomal internalization without antibody re-engineering
- Development of next-generation ADCs against solid tumor targets, including HER2, EGFR, and CA9

Advantages

- Compatible with native monoclonal antibodies via site-specific click chemistry — no protein engineering required
- Increases lysosomal internalization 200–900%, substantially exceeding prior peptide-based internalization strategies
- ~10-fold greater tumor cell killing than conventional ADCs across multiple antibody/target combinations, with minimal off-target cytotoxicity
- Cancer-selective targeting peptide avoids the off-tumor toxicity risk of constitutively expressed internalizing receptors used in prior approaches
- Modular, antibody-agnostic platform generalizable across ADC programs
- Produces stable, homogeneous conjugates via well-established pyridazinedione bioconjugation chemistry

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