Overcoming limitations of current antibody-drug conjugates (ADCs) by a novel linker technology

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Introduction

Antibody-drug conjugates (ADC) enable the targeted delivery of cytotoxic drugs. A critical and challenging step of the ADC generation is the drug attachment to the antibody. Currently, various conjugation methods are used that either result in a broad and inhomogeneous drug distribution or in a precisely defined antibody-to-drug ratio (DAR) using site-specific conjugation approaches. However, most common site-specific payload conjugation technologies either 1) require antibody and/or cell line engineering efforts 2) use linkers with limited solubility (suboptimal for hydrophobic payloads) or 3) deploy unstable chemistry for payload-linkage. Together, these limitations lead to a challenging ADC manufacturing process and premature termination of clinical programs due to limited ADC efficacy and/or high toxicity. We here introduce a novel and versatile ADC-linker technology that aims to address the points and enables the following:

- ADC generation within 48 hours
- Site-specific drug attachment to native Abs “off-the-shelf”, no engineering
- Abs retain native glycosylation pattern and amino acid sequence
- LINKER® synthesized within 48 hours by CRO
- Enzyme available to produce clinical grade ADC
- Highly stable ADCs with favorable physicochemical properties
- Drug-to-antibody ratios (DAR) of 2 and 4 possible
- Various chemistries tested: Azide, thiol or combinations thereof
- Various payloads tested (toxins, dyes, metal chelators…), also combinations are possible
- Various ADCs are possible
- ADCs remain stable in different biological matrices
- ADCs are stable in human serum in multiple tumor models

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Araris ADCs show superior in vitro cytotoxicity

Trastuzumab-Amanitin ADCs (DAR2): Comparison of Araris Linker Technology vs THIOMAB™ conjugation technology. Cytotoxicity assay on HER2-overexpressing cell lines. Data generated in collaboration with Heidelberg Pharma.

Araris ADCs show superior anti-tumor efficacy in vitro

Therapeutic treatment in HER2+ tumors: comparison Araris-Amanitin ADC vs THIOMAB™-Amanitin. Mice were treated with one injection 2 or 6 mg/kg (JIMT-1) and 3 mg/kg (NCI-N87) ADCs on day 0. Data generated in collaboration with Heidelberg Pharma.

Conclusion & Contact

We introduced a novel propriety antibody-conjugation technology that allows for site-specific payload attachment to a single residue within the heavy chain of native IgG-antibodies. With our technology, no antibody engineering is necessary and the light chain is unaffected under the conditions used. The presented results indicate that our linker technology a) allows for fast (within 48 h) and straightforward manufacturing of ADCs using different payloads without protein engineering efforts, b) results in ADCs with favorable biophysical properties and c) enables the generation of highly potent and stable, thus safer, next generation ADCs. Further we have data showing that Fc-gamma receptor and FcRn binding is retained upon linker conjugation. Importantly, our ADCs showed superior efficacy in different tumor animal models as compared to control THIOMAB™ ADCs. For further information, please contact: pspsycher@ararisbiotech.com