Preclinical Discovery of ARX622, a Site-Specific TLR7-Agonist Antibody-Drug Conjugate

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Immune-Stimulatory ADCs (ISACs) Provide Targeted “Danger” Signals and Complement Multiple Established Treatment Modalities

The “Danger Hypothesis:” non-self + danger = immunity

“I would suggest that the criteria have to do with what is dangerous rather than what is ‘self’.”

Polly Matzinger

ISACs: Multiple Mechanistic Advantages

- Tumor-specific activity with systemic administration
- Broad “danger” signal induction (TNF/IL-6, IFNs, chemokines)
- APC maturation + polyclonal Ag presentation
- Complementary MOA to: ADCs, checkpoint blockade, others

New ISAC field can learn from decades of ADC experience
DAR Heterogeneity and Instability Can Limit the Potential of Traditional ADCs With Stochastic Conjugation

**Heterogeneous DAR Mixture:**
- Low DAR
- High DAR

**Labile Linker/Conjugations:**
- Toxicity Potential and Reduced Payload Delivery to TME

**Ambrx ADC and ISAC Focus:**
1. Homogenous DAR
2. Stable conjugation chemistry
3. Non-cleavable linker
4. Low payload cell-permeability
Ambrx ISAC Platform: Highly Stable and Homogenous via Site-Specific Conjugation and Optimized Linker Chemistry

Multi-Factor Optimization to Design Selective, Potent, and Stable ISACs

- **Antibody**: tumor-associated antigen (TAA) selection, epitope, Fc function
- **Payload**: target, potency, bioconjugation potential, cell permeability
  - **Ambrx**: novel TLR7 agonist (TLR7a) payloads have a range of potencies
  - Free drug-linker has low cell permeability
- **ISAC**: linker stability, DAR, and conjugation site
  - Site-specific conjugation enables high DAR homogeneity
  - Optimized conjugate site and stable linker chemistry
  - Drug-Linker hydrophilicity optimized for enhanced PK
ReCODE and EuCODE Platforms: An Expanded Genetic Code Incorporating Synthetic Amino Acids (SAAs)

- Orthogonal tRNA synthetase
- Unique Amber Codon in mRNA
- SAA incorporation site on protein

para-Acetyl-phenylalanine

1. Ambrx’s SAA: e.g., pAF
2. Orthogonal tRNA synthetase
3. Orthogonal tRNA
4. Unique Amber Codon in mRNA
5. SAA incorporation site on protein
Ambrx Site-Specific Conjugation Technology Facilitates Highly Homogenous ISAC Generation

- **Oxime conjugation chemistry**: homogenous, clinically validated stability (ARX788 and ARX517)
- Conjugation site optimized for pharmacologic and biophysical properties
- Focus on **non-cleavable linkers**

![Diagram](image)
Site-Specific ISAC Conjugates Display Increased Parental mAb-Like Thermal Stability vs. Cysteine Conjugates

Ambrx site-specific ISAC has a parental mAb-like CH2 transition temperature, unlike DAR-matched random Cys-conjugate ISAC
Same mAb, Same TLR7 Payload: Site-specific Conjugation Promotes Extended PK and Reduces Target-Independent Activity Compared to Cysteine Conjugate

Pharmacokinetics in Balb/c mice

Tumor cell + macrophage reporter co-culture

Site-specific conjugation facilitates extended PK and reduced off-target activity vs. Cys-conjugation
TLR7 Prioritized as Payload Target Due to Selective Expression and Type I IFN Induction

Guiducci et al, J Exp Med 2013

BioGPS.org, Primary Cell Atlas
Different Conjugation Sites and Payloads Yield a Panel of ISACs With Differential Biologic Activity

Same payload, different conjugation sites

Same conjugation site, different TLR7a payloads

Tumor Cells + TLR7 Reporter Cells → NF-κB Activation
ARX622- A HER2-Targeted, TLR7-Selective ISAC that Induces Conditional Immune Cell Activation

Ambrx Drug-Linker is a Novel TLR7-Selective Agonist

ARX622 Promotes Conditional Immune Activation in the Presence of HER2+ Tumor Cells

Positive Control
(TLR7=DSR-6434 / TLR8=R848)

Ambrx ISAC Drug-Linker
ARX622 Activates Multiple Anti-Tumor Immune Mechanisms: Robust Type I and Type III IFN Production

- **IFN-α2a**
- **IFN-β**
- **IFN-λ1 (IL-29)**

Cytokine Production Activation/Differentiation

Tumor Cells + PBMCs → Cytokine Production Activation/Differentiation
ARX622 Promotes Dose-Dependent Tumor Growth Inhibition in a Syngeneic Immunocompetent Model

- ARX622 showed dose-dependent tumor growth inhibition in immunocompetent mice
- No body weight loss or hypersensitivity upon repeated doses
ARX622 Promotes Tumor-Specific Proinflammatory Cytokine and Type I IFN Production

MC38-hHER2, Balb/c

+ test article

24h

Tumor cytokines
Serum cytokines

Tumor cytokines
Serum cytokines

TNF-α

IL-12p70

IFN-β

Concentration (pg/mL)

Concentration (pg/mL)

Concentration (pg/mL)

Vehicle
ARX622
HER2 mAb
Isotype ISAC

Vehicle
ARX622
HER2 mAb
Isotype ISAC

Vehicle
ARX622
HER2 mAb
Isotype ISAC
ARX622 Induces Long Term Protection Against HER2-Negative Tumor Variant Re-Challenge

ARX622-treated recipients are protected from HER2-positive and HER2-negative tumor growth
ARX622 Induces Complete Tumor Regression in the HER2-High SKOV3 CDX Model at Single Doses ≥ 0.3 mg/kg

- ISAC exhibited ~10x increased potency vs. MTI-based ADC
- Multiple ISAC mechanisms likely contribute to efficacy: cytostatic cytokines, ADCP, pDC cytotoxicity
Raising the Bar: Ambrx HER2 ISAC Promotes Regression of Large, Established SKOV3-scid Xenograft Tumors

Dose at: **200mm³**

**ARX622 displays anti-tumor activity in therapeutic setting**
Ambrx ISAC Reduces SKOV3 Tumor Growth in HER2 mAb and HER2-ADC Non-Responder Mice

ARX622 displays anti-tumor activity in HER2-targeted therapy non-responder mice
ARX622 + HER2-ADC Combination Induces Enhanced Tumor Growth Inhibition in the HER2-Low JIMT-1 CDX Model

JIMT-1 (HER2-Low)

CDX Summary: Pre-clinical support for monotherapy, combo with HER2-ADCs, and usage post-HER2-ADCs
ARX622 is Well-Tolerated in NHPs and Displays ~60x Pre-Clinical Therapeutic Index

NHP Study Summary: (repeat i.v. dosing)

- No mortality or moribundity
- No clinical signs
- No adverse histopathologic findings
- No adverse clinical chemistry or hematologic findings
- Pharmacodynamic Biomarkers: transient cytokine elevation

![Graph showing ARX622 Total Ab Plasma Concentration (ng/mL) over time]
Ambrx ISAC Platform is Engineered for Stability and Broad Danger Signal Induction, Facilitating an Encouraging Therapeutic Index and Robust Efficacy Profile

Pre-Clinical ARX622 Data Highlights

- Induction of broad danger signals: proinflammatory cytokines, Type I/III IFN, (APC maturation, ADCC enhancement not shown today)
- Repeat doses were well-tolerated in NHP
- Robust tumor growth inhibition in syngeneic tumor model with evidence of polyclonal immunologic memory
- Complete regression of large tumors with single-dose (including post-HER2-ADC treatment)
- Monotherapy efficacy in HER2-low setting
- Support for combination with HER2-ADCs