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Defining the Ideal ADC Linker: Design Principles and Performance Traits

Jared Mattos, Principal Scientist – Bio Conjugation, April 2025

Introduction

Antibody-drug conjugates (ADCs) have emerged as a transformative class of therapeutics, bridging the specificity of monoclonal antibodies with the potency of cytotoxic drugs. Central to the efficacy and safety of these complex molecules is the linker—the molecular bridge that connects the antibody to its payload. A great ADC linker is not merely a passive connector; it is a highly engineered component that dictates how, when, and where the payload is released. This paper outlines the key characteristics of a successful ADC linker and explores how rational design impacts therapeutic outcomes.

1. Stability in Systemic Circulation

Once administered, an ADC may circulate for days or even weeks before reaching its target. This prolonged exposure to the bloodstream presents multiple opportunities for off-target interactions and premature payload release.

Key attributes:

- Resists degradation by plasma enzymes
- Prevents premature payload release
- Enhances half-life of the ADC

2. Tumor-Specific Payload Release

A crucial function of the linker is to ensure the payload is released only under tumor-specific conditions. The ideal linker responds to environmental cues unique to the tumor microenvironment.

Key release triggers:

- Acidic pH (endosomes/lysosomes)
- Reducing environment (intracellular glutathione levels)

- Tumor-specific enzymes (e.g., cathepsins, legumain)

3. Compatible with Payload & Antibody

An effective linker must maintain the functional integrity of both payload and antibody throughout development, storage, and *in vivo* circulation. Well-designed linker can be used to compensate for Payload compatibility issues and give new life to compound classes.

Key features:

- Chemically stable with both hydrophilic and hydrophobic payloads
- Maintains antibody integrity and binding affinity

4. Minimizes Off-Target Toxicity

The therapeutic window of ADCs is narrow, and off-target toxicity is a leading cause of clinical failure. Linkers play a pivotal role in reducing unintended interactions.

Safety enhancements:

- Prevents payload release in healthy tissues
- Minimizes systemic side effects through controlled activation
- Improve plasma stability
- Incorporate shielding groups or stealth motifs

5. Enables Consistent Drug-Antibody Ratio (DAR)

Homogeneity in DAR is vital for predictable pharmacokinetics (PK), efficacy, and safety. Advanced linker technologies can facilitate site-specific conjugation, producing uniform ADC populations.

Technological approaches:

- Site-specific conjugation (engineered cysteines, non-natural amino acids)
- Controlled reaction kinetics to limit DAR variability

6. Scalable for Manufacturing

A great linker is not only effective at small scale but also practical for clinical and commercial manufacturing.

Manufacturing attributes:

- Reproducible conjugation chemistry
- Compatible with GMP manufacturing conditions
- Cost-effective synthesis routes and raw materials

Conclusion

The chemical and biophysical properties of the linker play a crucial role in designing effective ADCs. As a central component of the molecule, the linker governs both pharmacological performance and manufacturability. The biophysical and biochemical stability of an ADC heavily depends on the chemical structure of its linker, which must be engineered to balance systemic stability with efficient intracellular payload release. This is especially critical when selecting between cleavable and non-cleavable linkers: cleavable linkers must remain stable in circulation but respond rapidly to intracellular cues, while non-cleavable linkers must allow the payload to retain cytotoxic activity even without cleavage.

Ultimately, the ideal linker is one that ensures ADC stability in the bloodstream, enables tumor-specific activation, preserves the functional integrity of its components, and supports consistent, scalable production. As the field advances, rational design of linker chemistry will continue to be a key driver in improving therapeutic outcomes and expanding the clinical impact of ADCs.

About the Author

Dr. Jared Mattos holds a Ph.D. in Chemistry from the Massachusetts Institute of Technology (MIT). He is an experienced chemist with expertise in antibiotic development and biotechnology. Dr. Mattos' specialization in bioconjugation includes the synthesis of payloads and linker-payloads, as well as the development of complex biomolecular conjugates and innovative linker-payload systems. His work while at Innovent Biologics pushed over twenty ADCs into preclinical development.

About Xcellon Biologics

Xcellon is a Maryland-based CDMO specializing in complex biologics, including ADCs, bispecific antibodies, and T-cell engagers. Our mission is to provide cutting-edge, cost-effective, and customized manufacturing solutions for complex biologics, fostering seamless collaboration with our partners to accelerate the delivery of transformative therapies to patients worldwide. We are committed to excellence, adaptability, and sustainability in every stage of biologics development and production.