Developing Robust and Scalable Processes to Expedite the Development and Manufacturing of ADCs

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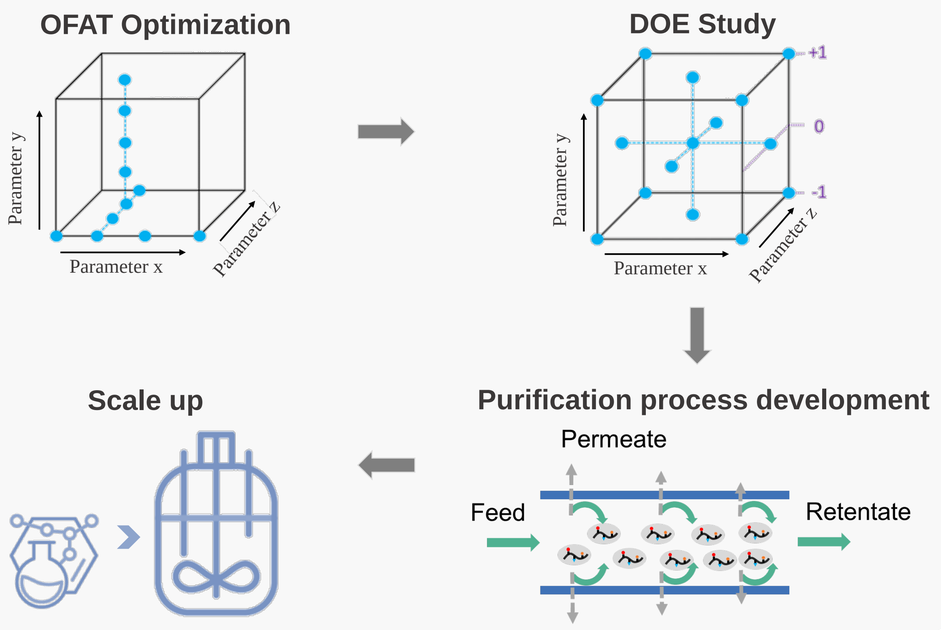
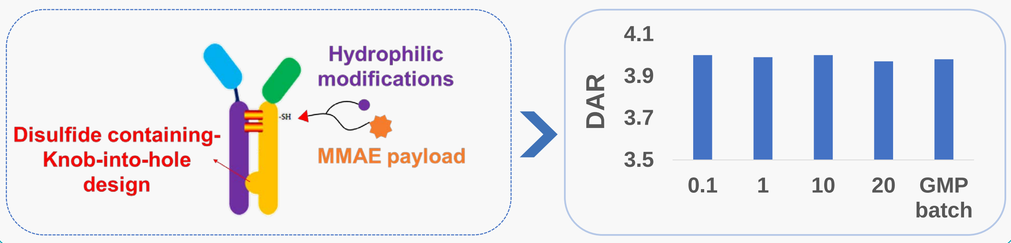
Introduction

Along with a vast number of ADC candidates advance to clinical stages, the needs for a streamlined and robust conjugation process to handle different designs of ADC molecules have become more prominent. However, significant challenges posed by the inherent properties of ADC, for example highly heterogeneous, prone to be aggregated, difficult in impurity removal and maintaining batch-to-batch consistency, still exist and would take a great deal of efforts & skills to tackle. As a global CDMO organization, AsymBio provides end-to-end ADC development solutions to help address those CMC challenges. In this poster, we presented several case studies to highlight our efforts in addressing those challenges in ADC conjugation and purification process development. Our strategy includes comprehensive OFAT and DOE optimization of conjugation parameters, proven TFF and chromatography process and robust process scale-up scheme. It enables the accelerated development of robust and scalable conjugation processes, minimizing the risk in future ADC manufacturing.



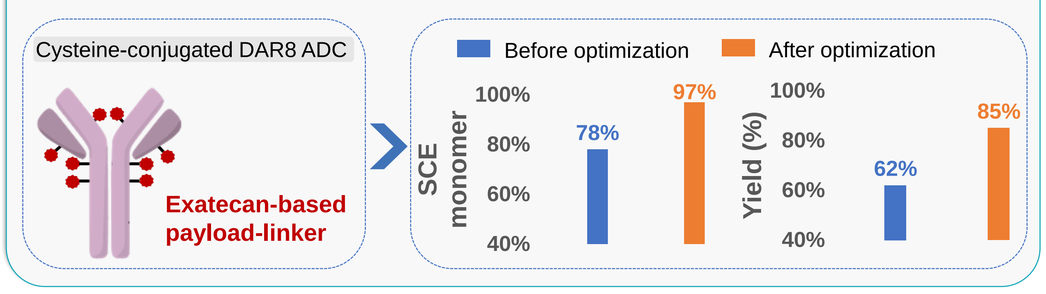
Case Study I: Process Optimization for More Reproducible & Homogeneous ADCs

This case shows a bispecific nanobody drug conjugate with a targeted DAR value of 4. The payload is MMAE and the linker contains a branched hydrophilic moiety as an added modification to the molecule design. The BsAb bears a disulfide-containing knob-into-hole structure, which results in additional needs to control unintended Cys-conjugation. We systematically optimized the reduction and conjugation process parameters to generate DAR 4 species accounting for greater than 98%, and the DAR value remains highly consistent at different synthesis scales.



Case Study II: Optimization to Minimize the Level of ADC Aggregation

In this case, the molecule is designed as a cysteine-conjugated DAR8 ADC. The hydrophobicity from the exatecan-based payload-linker in this ADC causes ADC aggregation in conjugation process, resulting in low yield. We optimized the process by adjusting the reaction parameters, utilizing solubilizing reagents to improve the solubility of the payload-linker and ADC molecules. After optimization, the ADC monomer ratio (measured by SEC) and the reaction yield were significantly improved.



Case Study III: Optimization on the Removal of Unconjugated Drug Related Species

It is common practice to incorporate a hydrophilic moiety in linkers to maintain a balance between the hydrophobicity of the payload, including options like PEG, sugar, PSAR, etc. Occasionally, enhanced payload-linker combinations demonstrate excellent compatibility during conjugation but cannot be efficiently eliminated through conventional TFF processes. In this case, activated charcoal filtration is utilized for removing residual unconjugated (free) drugs, providing comparable efficacy to chromatography but at a lower cost.

Activated charcoal filters **Small scale:** **Large scale:**

	Modes of Operations		
	Circulation (3 batch volumes)	Circulation (10 batch volumes)	Filtration
Residual Free Drug Post Operation (μM)	0.10	0.06	0.08
ADC Recovery (%)	85.7	82.1	73.4

Case Study IV: Robust Scale-up Strategy

AsymBio has established a comprehensive scale-up strategy by focusing on key process parameters. To ensure successful manufacturing, we confirm and lock the process parameters by performing a test run at 20-50 g scale. In addition, a 2-5 g scale of use test run using the same grade of materials as those used in manufacturing production is also carried out prior to the initiation of real manufacturing process.

Process Parameter Types	Examples of Process Parameters	Scale-up Strategy
Volume Dependent	PL/Reducing Reagent Feeding Speed	Maintain the Same Feeding Speed
Volume Independent	mAb Concentration, pH, Equivalent of PL/Reducing Reagent, Reaction Time, Temperature	Optimizing the Operation Space
Nonlinear Parameters	Agitation Speed	Mixing study at different scales

Process Development → **Process Scale-up** → **Process lock run** → **Use Test** → **Tech Transfer to MFG Dept** → **Manufacturing**

Conclusion

Case studies showcase the capability of AsymBio's bioconjugation platforms in addressing process development challenges such as ADC heterogeneity, aggregation, impurity removal and batch-to-batch inconsistency. Our well-developed conjugation process platforms are flexible to handle different ADC molecule designs and offer a solid foundation to support the process development and process transfer for pre-IND, IND and BLA projects. The conjugation process development can be expedited with a compressed timeline, typically 2-3 months, for an IND project. Under the strict compliance to EHS regulation on OEB5 level materials, we aim to safely and efficiently deliver consistent and scalable bioconjugation processes for all our clients.

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