# Developability Assessment and Optimization of Antibodies and Antibody-derived Molecules at Early-Stage Discovery

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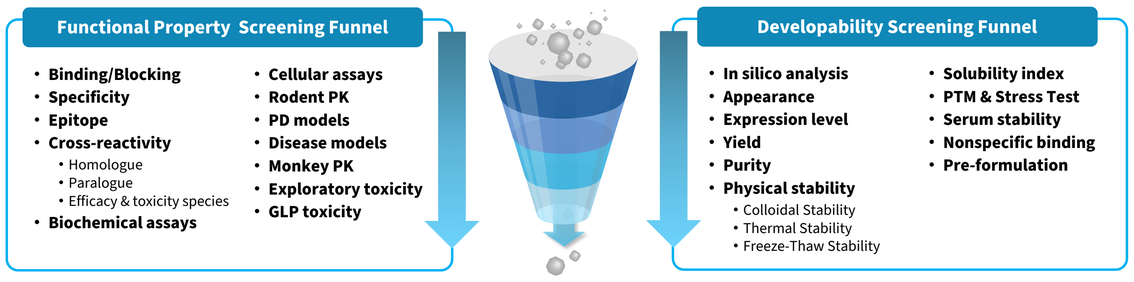
## Abstract

In order to lower risk of moving an antibody candidate with poor developability to the CMC development stage, the candidate's developability-related properties should be screened, assessed and optimized as early as possible. Assessment of developability at the early discovery stage should be performed in a rapid and high-throughput manner while consuming small amounts of testing materials. In addition to monoclonal antibodies, other antibody derivatives such as bispecific antibodies, multispecific antibodies, fusion proteins and antibody–drug conjugates, should also be assessed for developability. The criteria of developability are relative as expected clinical indication, dosage and administration route of the antibody could affect these criteria. Thus, we recommend a general developability screening process during the early discovery stage of antibody-derived therapeutics. Poor developability is detected on a functional antibody or antibody-derived molecule, the focus can be optimization of its developability and retaining of its functionality. Computational tools, combined with protein engineering and analytic methods, can be used for developability improvement. Some cases are shown here regarding significant improvement of stability, solubility, specificity, homogeneity and pharmacokinetics of antibody related candidates.

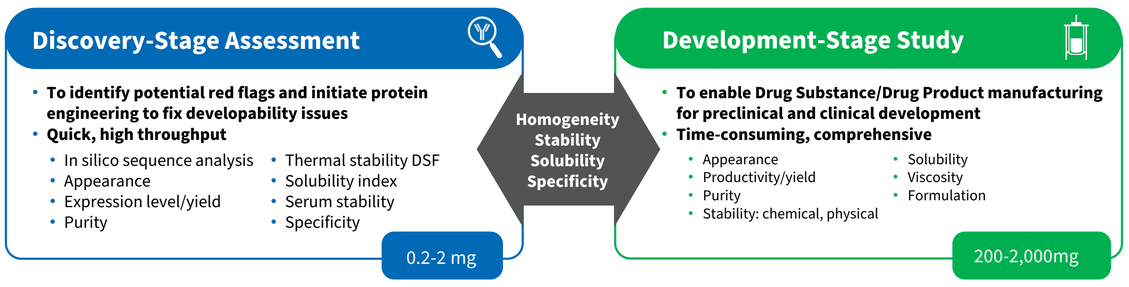
## Antibody Therapeutics: Two Screening Funnels in Parallel

**Fig 1.** Functional property and developability are two parallel screening criteria in discovery-stage.



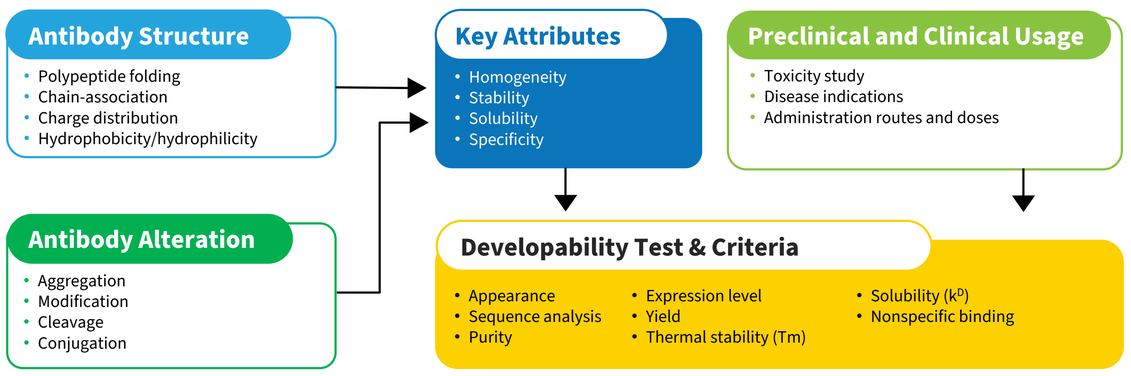

## Discovery-Stage Assessment vs. Development Stage Study

**Fig 2.** Developability assessment is a critical step that can reduce the CMC and clinical development risk.



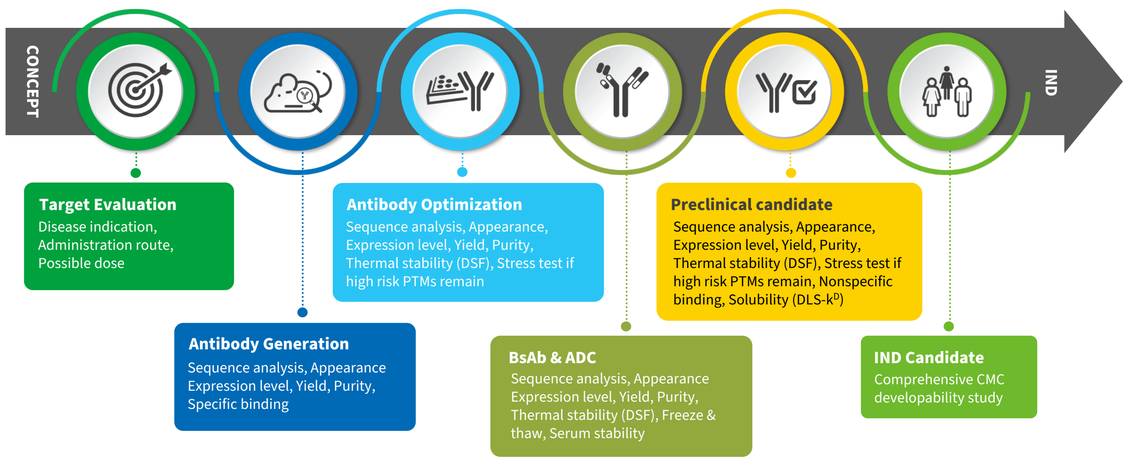

## Key Factors Affecting Developability Assessment

**Fig 3.** Four key attributes of developability - homogeneity, stability, solubility and specificity (or 1H3S) - are determined by antibody structure and alteration. These attributes and the usage of antibody candidates (indication, dose, delivery, ROA) are used to determine the eventual developability criteria.



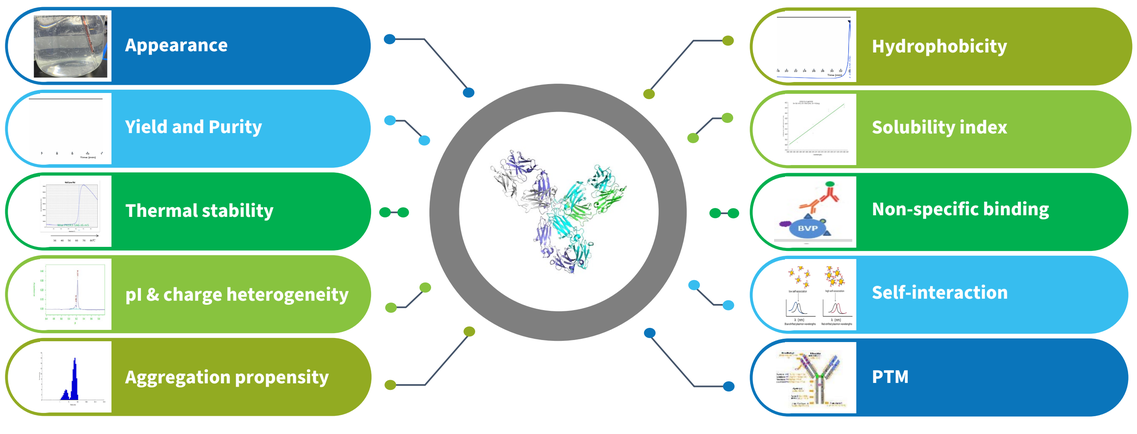

## Developability Assessment at Different Discovery Stages

**Fig 4.** Considerations for developability-related criteria are different across the various discovery and development stages.




## Experimental Tools for Developability Assessment

**Fig 5.** To identify potential developability red flags or issues during the discovery stage, a set of properties "1H3S" (Homogeneity, Stability, Solubility, Specificity) should be assessed by quick and high-throughput methods.




## Case Studies of Developability Assessment

**Fig 6.** Purity could have a significant impact on binding affinity in the antibody screening stage.

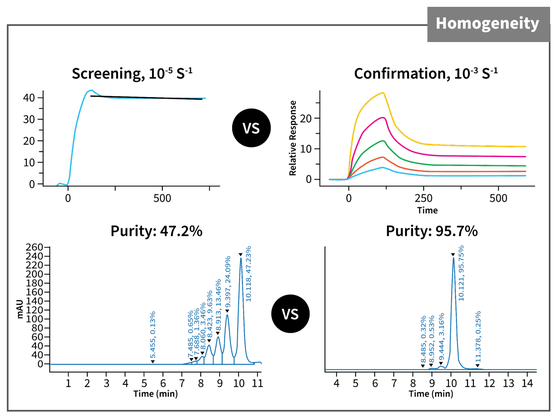



**Fig 7.** Thermal stability (Tm) could be improved through optimal humanization or affinity maturation.

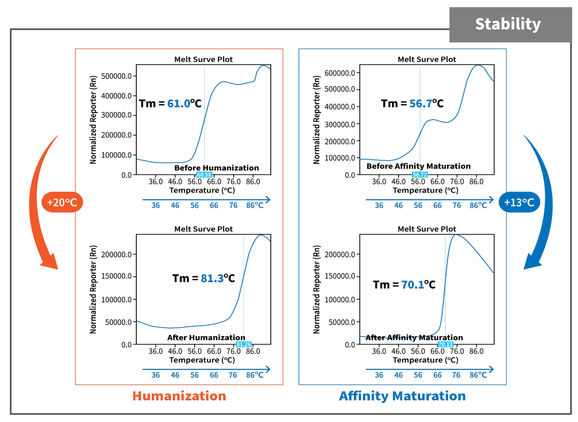



**Fig 8.** Solubility could be improved by optimizing formulation.

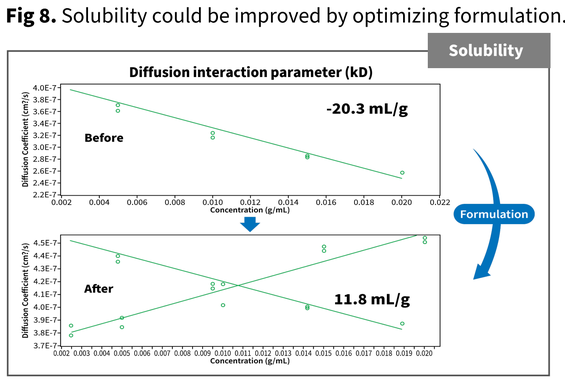
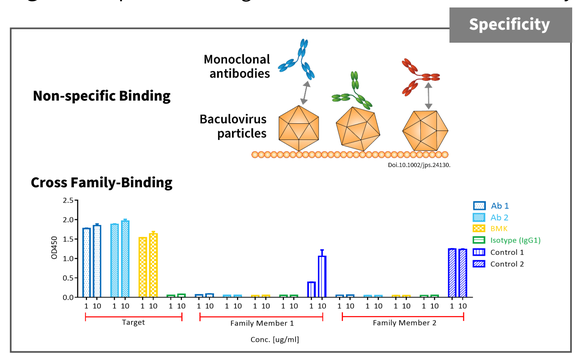



**Fig 9.** Non-specific binding could be measured in different ways.



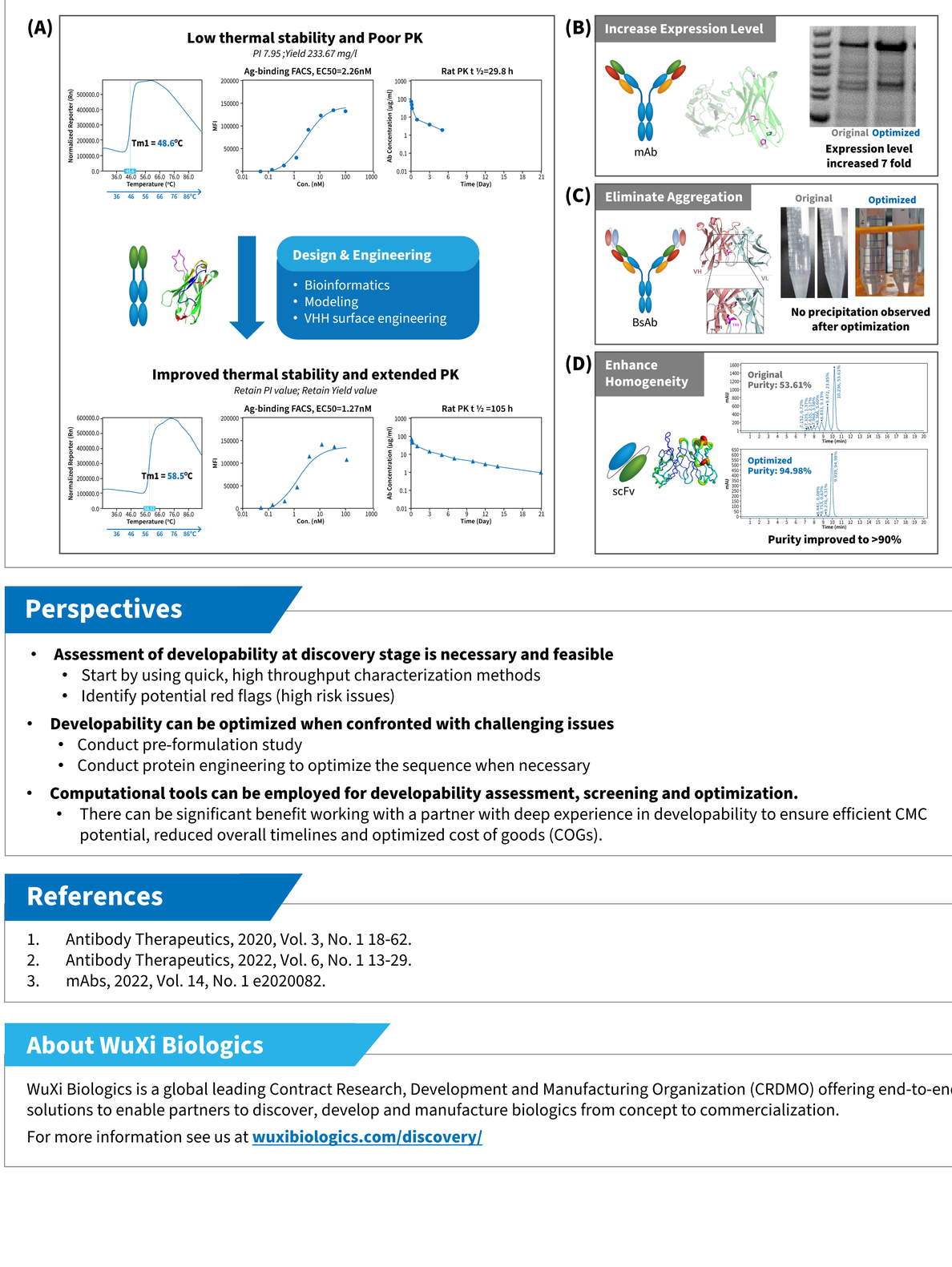

## Computational Tools for Developability Assessment & Optimization

**Fig 10.** Biopharmaceutical informatics tools for computational developability assessment of antibody therapeutics.

| General Developability | Solubility | PTM | Aggregation | Molecular Docking | Antibody Modelling | Immunogenicity |
|---|---|---|---|---|---|---|
| • Therapeutic Antibody Profiler<br>• Developability Index<br>• NaturalAntibody<br>• AbMapper<br>• Abpred<br>• QikProp<br>• abYsis | • CamSol<br>• Protein-Sol<br>• SODA<br>• SOLpro<br>• SOLart<br>• PROSO II | • MusiteDeep<br>• Mupro<br>• FindMod<br>• SIDEpro<br>• SCWRL4.0<br>• PEARS | • GAP<br>• SAP<br>• Solubis<br>• AggScore<br>• AGGRESCAN 3D<br>• PASTA 2.0<br>• TANGO | • DockThor<br>• SwissDock<br>• HADDOCK<br>• GOLD<br>• RosettaDock<br>• FTDock 2.0<br>• AbAdapt | • abYmod<br>• ABodyBuilder<br>• Repertoire Builder<br>• MODELLER<br>• RosettaAntbody<br>• PIGS<br>• MOE<br>• LYRA | • NetMHCIIpan<br>• DiscoTope<br>• TOPKAT<br>• ElliPro<br>• MetalDrug<br>• SVMTriP<br>• MHCEpitopeEnergy<br>• … |

## Case Studies of Developability Optimization

**Fig 11.** Developability could be improved by protein engineering. (A). Combining bioinformatics and modeling analysis, amino acids on VHH surface were mutated to improve thermal stability and PK, retaining antigen-binding. The developability of different molecular modalities including mAb (B), BsAb (C) and scFv (D) were improved through protein design and engineering.




## Perspectives

- **Assessment of developability at discovery stage is necessary and feasible**
  - Start by using quick, high throughput characterization methods
  - Identify potential red flags (high risk issues)
- **Developability can be optimized when confronted with challenging issues**
  - Conduct pre-formulation study
  - Conduct protein engineering to optimize the sequence when necessary
- **Computational tools can be employed for developability assessment, screening and optimization.**
  - There can be significant benefit working with a partner with deep experience in developability to ensure efficient CMC potential, reduced overall timelines and optimized cost of goods (COGs).

## References

1. Antibody Therapeutics, 2020, Vol. 3, No. 1 18-62.
2. Antibody Therapeutics, 2022, Vol. 6, No. 1 13-29.
3. mAbs, 2022, Vol. 14, No. 1 e2020082.

## About WuXi Biologics

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