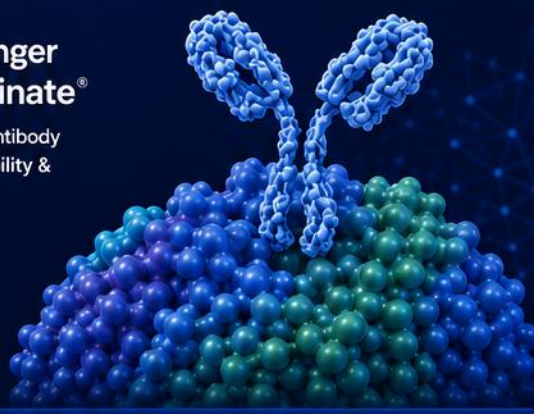
PrecisionBio
Accelerating Antibody Discovery

Schrödinger BioLuminate®
Integrated suite for antibody modeling, developability & risk assessment

CASE STUDY

From Aggregation Hotspot Prediction to Risk Mitigation: Improving MEDI-1912 Developability

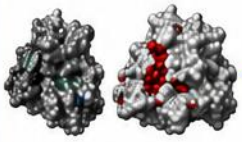
Using Schrödinger's BioLuminate to identify aggregation hotspots, engineer low-risk mutants, and improve developability.



COMPUTATIONAL PLATFORM

END-TO-END AGGREGATION RISK MITIGATION WORKFLOW WITH SCHRÖDINGER'S BIOLUMINATE

1 Identify Aggregation Hotspots (AggScore)



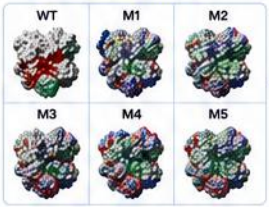
Surface analysis in BioLuminate identifies hydrophobic, surface-exposed residues driving self-association.

2 Per-Residue AggScore (Heavy Chain)

Residue	AggScore	Contribution (Kcal/mol)
TRP30 (H)	21.32	84.28
PHE31 (H)	21.36	56.42
LEU56 (H)	9.65	44.56

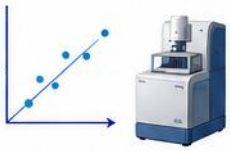
Trp30 and Phe31 contribute most to aggregation risk. Leu56 shows moderate contribution.

3 Design & Evaluate Mutants (Single, Double & Triple)



Panels of mutants were designed to reduce surface hydrophobicity and lower aggregation propensity.

4 Predict vs. Experiment (HP-SEC)



Predicted patch Sum AggScore correlates with experimental HP-SEC retention time, enabling reliable ranking of variants.

5 Select Low-Risk Candidates

Top-performing variants selected for improved developability and continued development.

THE CHALLENGE

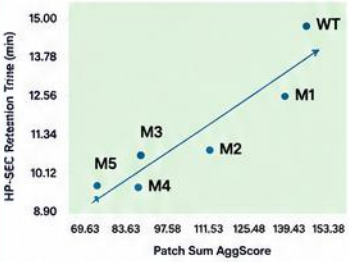
MEDI-1912 is a human monoclonal antibody (mAb) targeting nerve growth factor (NGF). Despite excellent NGF affinity, it shows a tendency for self-association and abnormal SEC behavior due to hydrophobic, surface-exposed residues in its heavy chain.

Self-association & aggregation | Abnormal SEC retention | Poor solubility & stability | High developability risk

Addressing aggregation hotspots is essential to improve yield, reliability, safety and clinical suitability.

RESULTS: PREDICTION CORRELATES WITH EXPERIMENT

Patch Sum AggScore vs. HP-SEC Retention Time



Wildtype & Mutant Antibody	HP-SEC Retention Time (min)
MEDI-1912 (WT)	15.0
Mutant 1 (M1)	12.23
Mutant 2 (M2)	111.39
Mutant 3 (M3)	86.55
Mutant 4 (M4)	71.99
Mutant 5 (M5)	9.0

Strong correlation: Lower patch Sum AggScore associates with lower HP-SEC retention time and reduced aggregation.

KEY OUTCOMES

Reduced Aggregation Risk
Mutant 5 (M5) shows ~40% reduction in retention time vs WT.

Improved Developability
Lower aggregation propensity translates to better manufacturability, stability and PK profile.

Data-Driven Decisions
Computational insights guide which mutations to prioritize before entering the lab.

Accelerated Development
Faster, more predictive workflow reduces experimental cycles and timelines.

Therapeutic Advantage
Enables a safer, more robust antibody therapeutic with higher clinical potential.

OUR APPROACH WITH BIOLUMINATE

1. **Surface Analysis & AggScore**
   - Used BioLuminate Protein Surface Analysis and per-residue AggScore to identify aggregation hotspots.
2. **Mutant Design**
   - Designed single, double and triple mutants at key hotspot positions (Trp30, Phe31, Leu56).
3. **Patch Sum AggScore Calculation**
   - Computed patch Sum AggScore for each variant to quantify overall aggregation risk.
4. **Experimental Validation**
   - Compared predicted scores with HP-SEC retention time to assess real-world impact.
5. **Rank & Prioritize**
   - Ranked variants to identify best-balance designs for developability improvement.

BioLuminate®

KEY INSIGHTS

Hydrophobic hotspots drive aggregation
Trp30 and Phe31 are dominant contributors to self-association.

Computational prediction is reliable
Patch Sum AggScore strongly correlates with HP-SEC retention time, enabling accurate risk ranking.

Multi-site engineering is most effective
Combinations of mutations reduce aggregation risk more than single-site changes.

Structure-guided design reduces risk
BioLuminate enables rational optimization while preserving structural integrity and affinity.

Better developability, lower risk
Engineered mutants show improved stability and reduced aggregation propensity.

IMPACT

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CONCLUSION

Using Schrödinger's BioLuminate, we established an integrated, structure-based workflow that accurately identifies aggregation hotspots, guides rational engineering, and delivers variants with significantly improved developability—transforming MEDI-1912 into a more robust therapeutic candidate.

In Silico Insight → Engineered Antibody → Safe & Effective Therapeutic

PrecisionBio
Accelerating Antibody Discovery

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