Multi-criteria decision-making tools to select optimal therapeutic proteins for successful development and manufacturing

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Pharma & Biotech

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ABSTRACT

The ability to assess the developability of therapeutic candidates as early as possible in the selection and development stages can be a very powerful tool to enhance chances of success and minimise risk of failure during manufacturing and clinical trials. The concept of developability involves an assessment of therapeutic candidates across multiple properties, addressing aspects of manufacturability, safety, pharmacology and mode of action. Efficient and objective selection of optimal candidates requires the implementation of decision-making tools that would enable ranking or scoring of molecules according to multiple criteria. Here we demonstrate a multi-criteria decision-making tool to perform ranking of biological molecules and to guide selection of optimal candidates with improved manufacturability and safety profiles. The ranking tool is applied to a diverse set of 227 antibodies, utilising *in silico* predicted properties (potential sites of post-translational and chemical modifications, immunogenicity risk) and experimentally measured data on expression and aggregation.

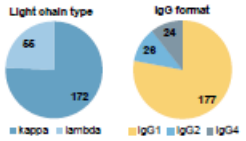
DEVELOPABILITY ASSESSMENT

- A successful biological drug needs to fulfil multiple criteria. It needs to show adequate biological activity and potency, but it also has to have good developability properties, such as suitability to be manufactured at acceptable yields and costs, stability during storage and safety for patients.
- *In silico* and *in vitro* methodologies can be employed to perform a developability assessment to highlight potential risks of failure, *e.g.* aggregation, low productivity, lack of chemical stability and immunogenicity. Decision-making tools enabling ranking of candidates across multiple criteria can aid selection of optimal leads with improved overall profiles.
- The BioStreamline project was designed to develop new approaches for the more efficient development and manufacture of next generation biologics.
- One of the objectives of the project was to develop a multi-criteria decision making tool, able to guide the selection of optimal biopharmaceutical candidates during preclinical development.

BIOSTREAMLINE ANTIBODY SET

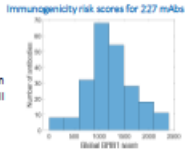
A set of 227 antibodies was compiled with the aim to create a library of diverse molecules representative of current therapeutics on the market and having different biophysical properties and liabilities.

- The selection was driven by sequence diversity aiming to represent common germline families and a variety of heavy/light chains pairings
- Mostly human and humanised mAbs
- Selected from internal projects and public databases
- 35 marketed mAbs are included



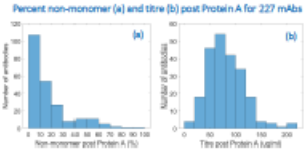
In silico assessment

- The antibodies were predicted to have a wide range of potential sequence liabilities and post-translational modifications (PTMs), including
  - N-glycosylation sites
  - Deamidation and isomerisation sites in CDRs
  - Free-Cysteine Thiol groups
  - Exposed Methionine oxidation sites
- The antibodies were profiled using Lonza's platform Epibase® *In Silico*, a tool for identification of potential T cell epitopes and immunogenicity risk screening
  - DRB1 scores reflect potential immunogenicity risk



Expression and experimental characterisation

- The antibodies were expressed transiently in 10ml in CHOK1SV GS-KO™ cells in triplicate
- Protein concentration and aggregation were measured using the Octet system and Lonza's Oligomer Detection Assay (ODA) in supernatant samples, and post Protein A purification by A280 and size-exclusion chromatography
- 52 antibodies were selected for expression in stable pools in 10L bioreactors and further detailed characterisation
- 52 antibodies had various levels of titre and aggregation



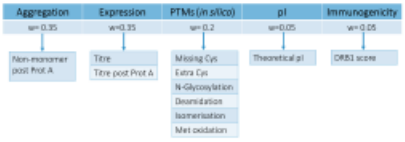
MULTI-CRITERIA RANKING OF ANTIBODIES

Analytical Hierarchy Process (AHP)

Antibodies are ranked using AHP method, a multi-attribute decision making algorithm utilising pairwise comparisons to assign criteria weights and applicable to decision problems with a hierarchical structure.

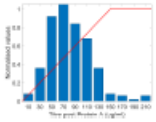
- Multiple criteria / properties are arranged in a hierarchy
- Importance weights are assigned to criteria via pairwise comparisons matrices
- The method ensures objective weights assignment and enables stakeholders consensus

Hierarchy of ranking criteria/properties for BioStreamline 227 antibodies



- Property values are normalised to [0,1] scale to be able to compare and combine data of different formats
- Normalisation is performed with a help of property profiles
- The overall score is calculated as a weighted sum of normalised property values for each molecule

Property profile for Titre post Protein A



Overall developability scores

- The overall score reflects the antibody success against multiple developability properties
- The ranking can guide lead selection; the antibodies with optimal profiles will have high scores
- The individual antibody view allows assessment of how an antibody scores against each property and identify developability risks

mAb	Overall score
AMS-001	0.757
AMS-002	0.346
AMS-003	0.555
AMS-018	0.263
AMS-083	0.751
AMS-111	0.910
AMS-122	0.861

Individual antibody view for three mAbs. Examples of high, low and average scoring antibodies

CONCLUSIONS

- The molecule ranking tool enables assessment of molecules across multiple properties and can guide selection of optimal candidates with improved manufacturability and safety properties.
- The decision making framework is applicable to any biological molecule and can include different sources of data, *in silico* or experimentally obtained.
- The ranking results for the 52 antibodies progressed for in-depth characterisation will be compared to manufacturing and safety profiles of the antibodies to determine if the ranking tool based on 'early' developability properties can help to identify problematic candidates.

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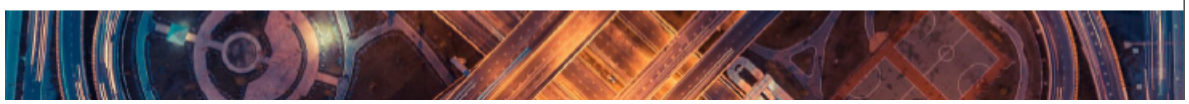
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