Roundtable Session 1 – Table 5 - Analytical/Biophysical Methods for Good Developability of Molecule(s) Selection

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Abstract:

Large-molecule antibody biologics play an increasingly important role for the development of new drugs across multiple therapy areas. The term 'developability' encompasses the feasibility of molecules to successfully progress from discovery to development via evaluation of their physicochemical properties. These properties include the tendency for self-interaction and aggregation, thermal stability, colloidal stability, and optimization of their properties through sequence engineering. Selection of the best antibody molecule based on biological function, efficacy, safety, and developability allows for a streamlined and successful CMC phase.

Discussion Questions:

1.**Why do you study biologics drug?**

- Moderator starts with overview of Discovery/Early development workflow. Leads to discussion on HTP screen of protein molecules, including biophysics tools such as HIC, CIC and DSF in high throughput methods.
- Regarding HIC analysis, in addition to traditional chromatography method, if any alternative method can be applied. To develop *in silico* prediction models, using published data from literature for machine learning is one way, but limited by the data size.
- A proposed integrated framework for *in silico* assessment of antibody developability was discussed and mainly focus on the hydrophobicity and viscosity properties.
- In early discovery stage, lack of sufficient protein amounts for various biophysics analysis is a common concern for developability assessment.
- One topic was brought up that even though some very good biophysics/developability molecules may not exhibit good translational medicine results, i.e. good animal efficacy did not translate to the efficacy in human. How can we overcome this issue?

2. **How will applying new analytical biophysical tools further biologics drug design?**
   - How to assess immunogenicity? Current prediction software, e.g. EpiVax, does not work well. One suggestion proposed that PBMC assays to assess immunogenicity.
   - ADC molecules: Hydrophobicity is an issue for antibody ADC molecules. How to cope with the hydrophobicity? pI values of the molecules and formulation screen may contribute to their developability.
   - Discussion on the timeline of the drug development from the hit generation to first in human may take longer than 2 years. How to shorten the timeline? Toxicity studies take time.
   - Parallel approaches for discovery, development and manufacturing may shorten the drug development timeline. But need to put all the resources together for one drug development.
   - Viscosity of antibody molecules: It has been reported that λ light chains exhibit more negative charges than κ light chains do. This may explain that antibodies with λ light chains show more hydrophobic. Regarding viscosity of IgG1 vs IgG4 molecules, it seems CH3 domain of IgG1 exhibits more positive charges, and CH3 domain of IgG4 exhibits more negative charges.

3.**What are the best practices for biological properties evaluation?**
   - Optimization of stability and binding affinity are the normal practices for developing biological therapeutics.
   - Considering competitive landscape and selecting the specific binding epitope group are the ways to differentiate the drug products.
   - Biosimilar therapeutics discussion: FDA expects Pharma to provide extensive analytical data for comprehensive similarities together with full clinical trials.
   - How to predict protein stability or viscosity in high concentration condition (150-200 mg/mL) using the low concentration proteins was discussed. Different tools, such as kD, B_{22} measurements or using SAXS analysis were brought up for discussion without conclusion. AC-SINS may be applied for cross-interaction of non-specific interaction evaluation, but lack of consistency and difficult to validate the results.
   - Biomolecular Interaction Technologies Center (BITC) was mentioned in the discussion for biologics properties evaluation.
   - Automation for developability analysis of Biological molecules was discussed on the efficiency, throughput increase and the data analysis.
   - Finally, how to design the clinical trials and using the right models matter.