Roundtable Session 2 - Table 5 – Analytical/Biophysical Methods for Good Developability of Molecule(s) Selection

Facilitator: Anne Kim, *J&J*

Scribe: Binyam Belachew, USA

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:

- Why do you study biologics drug?
- How will applying new analytical biophysical tools further biologics drug design?
- What are the best practices for biological properties evaluation?

Key Points from the Discussion:

- **Drug Candidate Selection Process:**
    - **Hit Generation:** Typically done using high-throughput screening (HTS) to test large libraries of compounds for target interaction.
    - **Hit Screening:** Functional assays to assess efficacy.
    - **Lead Optimization:** Refining hits to improve properties.
    - **Lead Selection:** Choosing the best candidates based on their overall profile.
    - **Single Candidate Selection:** Selecting the most promising lead for further development.
    - **Development Assessment:** Thorough evaluation of physicochemical properties, manufacturing, and regulatory compliance before clinical trials.
- **Focus of Discussion:** Analytical/biophysical tools for good developability of single candidate selection.

- **Impurity Monitoring:** Emphasized the need to monitor and control impurities during the development assessment stage to ensure commercial viability.
- **Development Issues:** Shared an example involving homodimer bispecifics with the same isoelectric point (pI).
- **Key Assays for Development Assessment:**
    - Hydrophobicity Assays
    - Cross Interaction Column (CIC) Assays
    - Differential Scanning Fluorimetry (DSF)
    - Fc Receptor (FcR) Binding Assays
    - Integration of machine learning and prediction models for molecule selection.
- **In Silico Predictions:** Discussed the use and potential issues of relying solely on computer-generated structures, including concerns about accuracy and errors in complex structures.
- **Validation of In Silico Predictions:** Highlighted the need for parallel experiments and the importance of experimental data.
- **Challenges with Limited Sample Size:** Discussed the challenges of working with limited sample sizes (< 1mg) in the discovery stage. In the development phase, larger sample sizes allow for methods like NMR, CD, and IR to study secondary and tertiary structures. In the discovery stage, only critically important experiments such as HIC, DSF, and mass photometry are conducted due to limited sample availability.
- **Forced Degradation Studies:** Inquired about the typical use of forced degradation studies or stress testing during development.
- **Degradation Studies:** Typically conducted after selecting 2-3 drug candidates with a 100mg yield.
- **Initial Molecule Selection:** Asked about the initial number of molecules and the typical number of drug candidates selected for development, as well as the timeline from hit generation to lead selection.
- **Molecule Selection Process:** Explained that typically about 100 molecules are expressed and purified using high-throughput automation methods, with 2-3 molecules selected for additional analysis. The timeline from hit generation to lead selection varies by company and drug type, though many projects are now being accelerated.
- **Automation and Time Efficiency:** Asked if time would be the most critical factor if all experiments during the discovery phase were automated.
- **Role of Automation:** Even with automation, scientists remain actively involved to ensure accuracy and address potential errors.

- **Importance of Efficacy:** Agreed that while time is important, the efficacy of the drug is paramount. Asked the group about the most critical analyses during the development phase.
- **Critical Analyses:** Highlighted the importance of binding assays.
- **Additional Important Assays:** Agreed on the importance of binding experiments and added that hydrophobicity, CSF, CIC, conformational and stability assays, and mass spectrometry are also crucial, especially when sample size is limited. Emphasized the need to reduce sample size for NMR to use it during the discovery phase.
- **Development Phase Issues:** Discussed issues like particle formation and susceptibility to aggregation, and inquired about techniques to address these problems.
- **Predicting Human Efficacy:** Mentioned that some drugs show good biophysical properties in vitro and efficacy in mouse models but fail in humans. Asked about prediction models to forecast human efficacy before clinical trials.
- **Outcome of Failed Drugs:** Asked about the fate of drugs that fail in clinical trials after passing the discovery and development phases.
- **Drug Fate:** Explained that the outcome depends on the specific drug.
- **Drug Repurposing:** Mentioned that some drugs can undergo repurposing or repositioning to find new therapeutic uses, including those that failed in their original clinical trials.
- **Closing Remarks:** Thanked everyone for their participation and contributions.

Summary:

This roundtable discussion focused on the challenges and best practices in drug candidate selection and developability assessment in pharmaceuticals. The discussion highlighted the limitations of sample availability in early discovery stages, emphasizing the use of methods such as DSF and mass photometry. The conversation also covered the significance of binding experiments, hydrophobicity, and cross-interaction chromatography in assessing molecule properties and potential issues in translation to human efficacy.