Plenary Session 4 – Potency Assays for Gene Edited Products
Andrew Byrnes, FDA CBER – "Potency Assurance for Cellular and Gene Therapy Products"
Debaditya Bhattacharya, ElevateBio – "Potency Development for an in Vivo AAV Gene Editing Therapy"
Kristy Wood, Intellia Therapeutics – "Approaches to Potency Assays for CRISPR Genome Editing Therapeutics"

Summary by Alkeiver Cannon, PhD

The CASSS Cell and Gene Therapy Products (CGTP) 2024 Symposium is an annual event where pertinent challenges and updates relevant to the cell and gene therapy field are discussed by industry, regulatory, and academic professionals. A variety of plenary sessions and roundtables were hosted to encourage discussions of topics ranging from comparability and manufacturing to genomic editing technologies and ICH guidelines. One popular plenary session was about Potency Assays for Gene Edited Products. This session contained 3 presentations followed by a panel discussion featuring audience questions.

The first presenter was Andrew Byrnes, PhD of the FDA's Center for Biologics Evaluation and Research (CBER). His presentation featured information regarding the new draft guidance document on Potency Assurance for Cellular and Gene Therapy Products. He emphasized that a potency assurance strategy (PAS) isn't just about potency assays and how a successful strategy should cover all aspects of potency. Because a PAS is "a comprehensive approach to help ensure that every lot of a product will have the potency necessary to achieve the intended therapeutic effect,"[1] Dr. Byrnes details that a PAS entails a sponsor understanding and conducting a risk assessment for potency-related characteristics specific to their product, mitigating risks to potency-related critical quality attributes, and reassessing and refining the PAS as more understanding of the product and manufacturing process is obtained. This draft guidance includes recommendations and general advice regarding all aspects related to the PAS, including potency assays, specifically regarding their use, development, and acceptance criteria.

Following Dr. Byrnes, Debaditya Bhattacharya, PhD from ElevateBio presented on the development of a potency assay for an in Vivo AAV gene editing therapy for Huntington's Disease (HD). As the Vice President of Analytical Development at ElevateBio, he is responsible for the CMC analytical development, strategy, and testing operations for a variety of different modalities. Considering the intended activity of an investigational HD therapy, Dr. Bhattacharya discussed the developmental strategy for a potency assay and how attributes, such as determination of a suitable cell line, were decided. The major attributes considered in this case were 1) whether it contained the target SNP for RNP target engagement, 2) its AAV transduction efficiency, and 3) how "easy" growth and maintenance are in culture. These were addressed by performing Sanger sequencing to screen for the SNP, flow cytometry to access transduction, and

[1] "*Potency Assurance for Cellular and Gene Therapy Products: Draft Guidance for Industry*." U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. 2023. Web. Accessed 30 June 2024.

cell viability and population doubling to determine ease of growth. Once the cell line was selected, clonal purity was confirmed and an INDEL detection potency assay by ddPCR was developed for the therapy.

The final presentation was given by Kristy Wood, PhD of Intellia Therapeutics where she oversees process and analytical development and internal manufacturing for their gRNA, mRNA, LNP, AAV, cell therapy, and small molecule platforms. Dr. Wood begins by explaining the difference between In Vivo and Ex Vivo CRISPR therapies. In Vivo CRISPR therapies exist when CRISPR itself is the therapy. It is used to fix the target gene and is a common approach in genetic diseases. CRISPR creates the therapy in Ex Vivo CRISPR therapies. The technology is used to rewire and redirect cells and is frequently used in the immune-oncology and autoimmune realms. Dr. Wood further discusses how Intellia uses platform manufacturing and how these complex manufacturing processes require numerous equally complex methods to define and characterize the product. The advantages of relative potency assays, where a shift in a response between a sample and a known reference are observed, were explained as well as challenges and solutions. She discusses a cell-based assay for protein reduction, emphasizing how each step should be optimized to ensure assay performance. In addition to potency assurance at the drug product level, Dr. Wood discusses how potency assurance can be supported at the drug substance level. Together, she highlights how Intellia's approach enables a faster path to the clinic.

The presentations were followed by a Q&A session where the presenters were joined by Keith Wonnacott, PhD who is the Vice President of Regulatory Affairs at LEXEO Therapeutics. Questions were aimed at better understanding the FDA's draft guideline as well as considerations for potency assays for both ex and in Vivo genome-edited products. Overall, this session sparked pertinent conversations regarding the draft guidelines and how sponsors should approach potency moving forward, especially in the context of gene edited products.