

Keynote Speaker: Becky Schweighardt, PhD CSO and COO, *Grace Science, LLC*  
“Gene Therapy Drug Development for Ultra Rare Disease: Challenges and Opportunities”  
CASSS CGTP 2023: Manufacturing, Quality, and Regulatory Considerations

Summary by Simran Kaur

The CASSS Cell and Gene Therapy Products 2023 Symposium kicked off with a welcome introduction from Svetlana Bergelson of Biogen and Rob McCombie of CARGO Therapeutics, initiating discussions to take place regarding regulatory, manufacturing, and quality challenges emerging in the cell and gene therapy landscape. The first presentation to follow the symposium introduction was by keynote speaker Dr. Becky Schweighardt, CSO and COO at Grace Science, LLC.

Dr. Schweighardt is “an innovative drug developer with broad development experience across multiple global drug approvals in rare disease[...]a trained immunologist and virologist who specializes in disease pathology”<sup>1</sup> with 20+years of experience. At Grace Science, she is developing a therapy to treat NGLY1 deficiency, a rare autosomal; recessive disease that devastates the central nervous system. At the keynote presentation, Dr. Schweighardt discussed the challenges she encountered in development of a GS-100, an AAV9 single-stranded viral vector gene therapy.

Dr. Schweighardt began by explaining NGLY1 deficiency and its impact on patients. A patient with NGLY1 deficiency gets diagnosed at the average of 6.5 years old, and has a life expectancy of 15 years old. There are currently 100 known patients worldwide. NGLY1 is an essential enzyme involved in cutting out sugar chains from misfolded glycoproteins, and its absence disrupts proteasome function. She discussed the diagnosis methods, such as whole exome sequencing (WES), whole genome sequencing (WGS), and GNA biomarker analysis. The disease is characterized by higher levels of GNA biomarkers in cerebrospinal fluid (CSF) and plasma. Dr. Schweighardt describes their study using an AAV9 vector, to deliver a codon-optimized version of HNGLY1 gene. Intracerebroventricular (ICV) delivery was chosen, and the treatment showed dose-dependent reduction of GNA biomarkers and improvement in motor function in their animal model (~30-40%). Dose-dependent neuronal cell loss was detected, which Dr. Schweighardt mentioned was at the injection site and could be attributed to the smaller animal size. Dr. Schweighardt addressed the concerns from the FDA about the animal deaths that resulted from this upon IND submission, and the FDA had requested a larger animal study.

Challenges in cell and gene therapy were identified in this conversation, including patient recruitment and diagnosis, trial design, statistical analysis, regulatory approval, reimbursement, and manufacturing complexities. Dr. Schweighardt emphasized that limited patient availability, disease heterogeneity, and lack of standardized testing approaches pose obstacles in clinical trials. AAV manufacturing for ultra-rare diseases faces high costs and limited commercial opportunities due to small patient population. Process development and manufacturing optimization are complicated due to complex and non-standardized processes, expensive studies, and limited batches for critical process parameter determination. Analytical development, characterization, and validation timelines are limiting, in addition to the lack of standardization in approach. Dr. Schweighardt addressed the tendency to stay with a suboptimal status quo, since innovation comes with risk and cost.

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<sup>1</sup> "Meet Our Leadership." Grace Science, n.d. Web. Accessed 3 July 2023.

Opportunities in cell and gene therapy arise from rapid innovation, specialized regulatory pathways, funding programs, and collaboration. Dr. Schweighardt discussed the Orphan Drug Act of 1983, and how it financially incentivizes rare disease drug development. Specialized regulatory pathways were mentioned, including fast track designations, priority review, and accelerated approvals. Dr. Schweighardt offered a call to action to normalize open collaboration and information sharing between CDMOs, sponsors, and regulatory agencies, to help define quality attributes, testing approaches, standard ranges, stability standards, and to avoid unnecessary non-clinical studies.

The presentation was followed by a Q&A session. When asked why AAV9 was selected and whether it's therapeutic impact was limited to one symptom, Dr. Schweighardt explained the choice by its proven therapeutic applications in cerebrospinal fluid (CSF) and that the studies actually showed expression in different areas. A member asked Dr. Schweighardt to list the top hinderances of development. Hindrances in the development process included the cost of non-human primate (NHP) studies, lack of information sharing and models, and the need for regulatory guidance and expedited pathways.

A few more questions were asked and answered, all along the lines of what has been already investigated and regulatory interactions, further emphasizing the importance of having these discussions. The conversations following Dr. Schweighardt's presentation initiated a dialogue that resulted in the information sharing that this community of scientists, innovators, and industry professionals can grow the industry with, which carried on throughout the rest of the CASSS Cell and Gene Therapy 2023 Symposium. Dr. Schweighardt's call to action of collaboration, information sharing, and regulatory support are crucial for addressing the aforementioned challenges and accelerating the development and approval of therapies for rare diseases like NGLY1 deficiency, and evolve the industry as we create more cures.