

# Overcoming Gene Therapy Development Barriers for Ultra-Rare Diseases

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Dr. Grishchuk leads a lab working on therapy development for rare pediatric neurologic diseases. Her work focuses on the neurobiology of the lysosomal storage disorder mucopolysaccharidosis type VI (MLIV) and related conditions. Current efforts are focused on developing a gene therapy for MLIV as well as understanding the applicability to the broader family of lysosomal diseases.

Current advances in drug development and personalized medicine bring new hopes of creating curative therapies for patients with rare diseases and high unmet needs. Of the roughly 7,000 rare diseases, approximately 80% are caused by a single gene defect, making them ideal candidates for gene therapy development, however, less than 5% currently have a treatment. The challenges of ultra-rare disease gene therapy development include high upfront expenses of vector manufacturing and safety/toxicology studies, often incomplete natural history data, poorly established genotype/phenotype correlation, and a limited number of patients available for clinical studies. To overcome these limitations, innovative approaches are needed to allow development of gene therapy for small patient populations.

The laboratory at the MGH Center for Genomic Medicine and Department of Neurology is focused on the understanding of two cellular processes, autophagy and lysosomal function, in the context of brain health and disease, and on using this knowledge to develop new therapies. More specifically, the laboratory is developing AAV-based therapies for two ultra-rare neurologic pediatric diseases, an autophagy disease Beta-propeller protein-associated neurodegeneration (BPAN), and mucopolysaccharidosis IV (MLIV), a lysosomal storage disease. Both have very high unmet medical need.

For MLIV, the laboratory has generated robust proof-of-concept data showing efficacy of AAV9-mediated gene replacement therapy approach to reverse neurological decline and extend survival in the MLIV animal model. Working closely with the MLIV patient advocacy group, the Mucopolysaccharidosis IV Foundation, and the MLIV clinical team at MGH, translational efforts are underway to advance this program to the clinic. Using insights from this work, the laboratory is exploring whether the MLIV gene therapy vector can be efficacious in other ultra-rare indications and lysosomal diseases. This "pathway engagement" gene therapy approach offers the potential to reduce drug development expenditures for individual gene therapies, increasing the commercial attractiveness of targeting ultra-rare diseases.