



Taking on the Challenges of Gene Therapy

Gene therapy has been a vital part of strides in neuromuscular disorders, but why is it so promising and what does its future hold? We talked with Katherine Mathews, MD, professor and vice chair of clinical research in the department of pediatrics at the University of Iowa, to learn more about how this therapy is offering change and hope.

The promise of gene therapy

“Many neuromuscular diseases are recessive genetic disorders with mutations causing loss of function,” Dr. Mathews says. “So, delivering a functioning version of a gene that’s not working is a logical approach to treatment.”

The neuromuscular disease community has seen first-hand the promise gene therapy offers through the spinal muscular atrophy (SMA) gene replacement therapy, Zolgensma.

“For presymptomatic infants with SMA, we have seen a dramatic change in clinical course; from a disease often resulting in neonatal death or need for long-term ventilation to children who survive and gain motor function,” she says. “Promising preclinical research together with

the increasing clinical experience with gene replacement in SMA and other diseases results in optimism about the potential for gene replacement therapy in multiple neuromuscular diseases.”

Dr. Mathews noted the extensive research leading up to the current hope about gene replacement therapies. Basic science researchers spent decades developing, testing, and optimizing vectors prior to human trials. Deep understanding of the pathophysiology and natural history of diseases to be treated are also important to successful gene replacement.

Understanding the challenges

While Zolgensma is mostly a success story, there are barriers to developing other gene therapies. One is understanding which cells must get the gene replacement to have a therapeutic benefit and how to target all the affected cells.

Dr. Mathews also is concerned about gene dosage modulation. “Too much of a protein can make you sick, and not enough of a protein can also make you sick,” she says. “With gene replacement therapy right now, the delivered gene is ‘turned on,’ and it stays on; we don’t have a way to modulate the amount of protein expressed from the delivered gene.”

The method of delivering gene therapy is another challenge. The current vectors for in vivo gene transfer are adeno-associated viruses (AAV). “These viruses cannot replicate like viruses that cause infections, but they have emerging side effects, including liver toxicity and activation of an immune response,” she says. “Viral-mediated gene therapy still poses significant risks and is irreversible.”

Some people are not candidates for gene therapy because they have preexisting antibodies against the viral vector.

“Additionally, the current vectors have limited cargo space and large genes do not fit into a single vector,” Dr. Mathews says.

The work continues

Vectors and delivery systems are continuing to be improved, but there is still work to be done.

“There are strides to be made in modulating transgene expression, understanding immune responses and side effects following gene transfer, as well as understanding patient- or disease-specific factors that make some individuals susceptible to severe adverse events,” Dr. Mathews says. “Overall, when it comes to gene therapy, there is reason for optimism, but also caution.”