Researchers Awarded $175K Grant from Parent Project Muscular Dystrophy to Optimize CRISPR/Cas9 for DMD Gene Therapy

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Researchers at the University of California in Los Angeles (UCLA) have been awarded a $175,000 grant from Parent Project Muscular Dystrophy (PPMD) to make CRISPR/Cas9 as safe and effective as possible as a gene therapy tool to treat Duchenne muscular dystrophy (DMD).

According to the researchers, their planned CRISPR/Cas9 gene editing platform could be applicable to almost half of the people living with DMD because it deletes exons 45 to 55 of the dystrophin-producing (*DMD*) gene, where many of the mutations that cause the disease are found.

The grant was awarded to Melissa Spencer, PhD, from the David Geffen School of Medicine, and April Pyle, PhD, from the Center for Duchenne Muscular Dystrophy at UCLA. Funding comes from the nonprofit, family organizations Hope for Gus and PPMD, the latter as part of its ongoing Gene Therapy Initiative.

"We are thrilled to be a part of this important research grant with PPMD," Tonya Dreher, founder of Hope for Gus said in a press release. "We firmly believe in finding opportunities for collaboration in order to continue exploring the potential of gene editing."

Spencer and her team at UCLA have been working on ways to improve the effectiveness and safety of CRISPR/Cas9, a powerful technology for editing genes.

Prior research led by Courtney Young, PhD, Spencer's student, resulted in the design of a CRISPR/Cas9 platform capable of deleting human *DMD* exons 45-55, which generates a shortened, but functional form of dystrophin, similar to exon skipping or micro-dystrophin gene therapy. Importantly, this platform proved successful to restore dystrophin function when applied directly in DMD mice.

A similar type of genetic deletion is found in patients with milder Becker muscular dystrophy patients, a less severe form of MD that results from lower amounts or abnormal forms of dystrophin.

Due to the region being targeted, this CRISPR/Cas9 platform "would be applicable for mutations observed in almost half the Duchenne population and will help improve future CRISPR/Cas9 design, " Spencer said.

Abby Bronson, senior vice president for research strategy at PPMD, explained how CRISPR/Cas9 works: "There are two main components to CRISPR. One is Cas9, a protein that acts as the molecular scissors to cut DNA. Second is RNA, which acts as a guide that specifies where Cas9 should cut DNA in the cell."

"Using CRISPR, gene editing has the potential to permanently exon skip or correct small mutations in a gene. At its current stage in development, CRISPR requires further optimization and safety profiling and we remain positive about its potential. PPMD is proud to support UCLA's ongoing exploration of this technology under the direction of Drs. Spencer and Pyle, " Bronson said.

Researchers are working on several points in order to improve CRISPR/Cas9 for DMD: Designing guide RNAs that may be more efficient; testing strategies to improve Cas9 stability in order to reduce off-target cuts in DNA, and; test a more accurate type of Cas9 protein.

Grateful for this recognition and hoping that her team's research could confirm the potential of CRISPR/Cas9 as a therapy, Spencer said: "The biggest hurdle any potential therapeutic technology faces is in showing a level of safety and efficacy that warrants translation to human trials. Therefore optimizing these gene editing platforms is a foundational step to ensure they are safe for treating those with Duchenne. We appreciate PPMD's support of this study and look forward to further optimizing and testing the CRISPR/Cas9 platform in Duchenne."

Since its launch in 2017, PPMD's Gene Therapy Initiative has funded more than $3 million in research for gene therapy and related approaches, including micro-dystrophin gene transfer, CRISPR/Cas9, Dup2, and GALGT2.