Research Project

Duchenne muscular dystrophy typically result from mutations that disrupt the reading frame of the dystrophin gene (DMD) and interrupt protein translation so that no dystrophin is made. The milder Becker muscular dystrophy typically results from mutations that maintain a reading frame that allows translation of a protein containing the critical actin-binding front end and the dystroglycan-binding back end of the dystrophin protein.

Very recent research by Dr. Kevin Flanigan’s team at Nationwide Children’s Hospital, and sponsored by CureDuchenne, has identified a new highly functional isoform of dystrophin – “N-deleted” dystrophin – that is missing part of the critical actin-binding first part of the protein, yet is associated with minimal muscle symptoms. Translation of this protein results from an alternative start site found within exon 6 of the DMD gene, and patients who express it walk into their eighth decade.

Translation of this dystrophin isoform can be stimulated by skipping of exon 2, which makes a therapy directed at exon 2 skipping particularly exciting. Duplication of exon 2 is the most common duplication mutation, and in patients with this mutation, treatment could result in either skipping of one copy (resulting in a normal dystrophin protein) or skipping of both copies (resulting in the highly functional N-deleted version). Either one would be predicted to be highly beneficial to patients with exon 2 duplications. Exon 2 skipping may also activate alternate translation in patients with other mutations within the first exons of the gene. Altogether, this offers for the first time an exciting new therapeutic approach for patients with mutations within the first few exons of the DMD gene.

Current Results

• Created a new mouse model (Dup2) of Duchenne that contains a duplication of exon 2 for the direct testing of exon-skipping therapies
• Identified a new novel internal ribosome entry site that allows for production of a highly-functional N-truncated dystrophin protein
• Demonstrated significant exon 2 skipping as well as increased dystrophin production and functional rescue through virally mediated exon 2 skipping.
• Treatment leads to increased production of the truncated dystrophin protein six-month post treatment in Dup2 mouse

Donate Now

Please help fund Dr. Flanigan’s IND enabling toxicology study so the duplication 2 therapy can move into human clinical trials as soon as possible. Every dollar counts.

Timeline

• Conduct IND-enabling studies during 2017
• Allow enrollment of the first patients in the first quarter of 2018