Combination therapy to Enhance Antisense Mediated Exon Skipping for Duchenne Muscular Dystrophy

Grant Award Details

Combination therapy to Enhance Antisense Mediated Exon Skipping for Duchenne Muscular Dystrophy

Grant Type: Early Translational from Disease Team Conversion

Grant Number: TRX-05426

Project Objective: The goal of this project is to establish the feasibility of using orally administered dantrolene to "dose save" and/or enhance the efficacy of exon skipping oligonucleotides in DMD model (mdx) mice. The project includes dose ranging studies and in vitro proof-of-concept in reprogrammed DMD patient-derived myotube cultures.

Investigator:

Name:	Stanley Nelson
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Muscular Dystrophy, Pediatrics, Skeletal/Smooth Muscle disorders

Human Stem Cell Use: Adult Stem Cell

Award Value: $1,823,545

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	Combination therapy to Enhance Antisense Mediated Exon Skipping for Duchenne Muscular Dystrophy
Public Abstract:	Duchenne muscular dystrophy (DMD) affects 1 in every 3,500 boys worldwide. DMD is caused by mutations in the gene encoding dystrophin, a protein key to muscle health. DMD patients are typically weaker than normal by age 3, and with progressive muscle weakness most loose the ability to walk by age 11. DMD progresses to complete paralysis, respiratory insufficiency heart failure, and death, usually before the age of 25. No therapies exist that address the primary defect or dramatically alter the debilitating disease. Exon-skipping is an emerging therapy in which anti-sense oligonucleotide (AO) guided-RNA splicing rescues expression of a partially functional dystrophin; but it is unclear if efficacy will be optimal for clinical gain. We identified a combination therapy that improves the efficacy of exon-skipping in mouse muscle and human DMD patient-stem-cell-derived muscle cells. The DMD mouse model will be used to establish dosing and efficacy. To determine if combination therapy promotes exon skipping in human DMD patient cells with different DMD mutations, DMD patient derived stem cells converted into muscle-like cells in culture and screened for efficacy of combination drug relative to AO alone. The proposed research program will complete studies to identify a single drug/AO combination as a developmental candidate anticipated to treat up to 13% of DMD patients; although the strategy is likely generalizable to enable treatment of 70% of DMD patients.
Statement of Benefit to California:	Duchenne muscular dystrophy (DMD) is a fatal genetic disorder, caused by a defect in the gene that produces dystrophin, a protein critical for normal skeletal muscle function. DMD affects more than 1,000 boys in California. Muscle weakness first appears in boys in the hips and legs and progressively extends to every muscle in the body such that most affected individuals require a wheelchair by age 11, have trouble feeding themselves by their late teens and ultimately loose most muscle function. Patients usually die by age 25 from respiratory or cardiac insufficiency. In addition to the human suffering, DMD places a large economic burden on patients, their families and society. Patients require intensive medical care because they cannot perform the simplest activities of daily living. Eventually, each individual requires ventilation and 24/7 care. The proposed combination therapy is predicted to cause skeletal muscle cells to skip DMD exon 51 and express a partially functional dystrophin protein, lessening the severity of DMD. A therapy that effectively slows or reverses disease will allow patients to lead longer, more productive lives and reduce costly supportive services—progress that will benefit patients, their families and society. Our proposal stands to specifically benefit Californians in another way: Because the University of California owns the intellectual property to the combined therapy, our success could ultimately lead to revenue for a state institution.