Preclinical studies to validate the efficacy of novel mechanism-of-action small molecule inhibitors to treat Duchenne muscular dystrophy

Project Number	Contact PI/Project Leader	Awardee Organization
1R41AR076871-01	NEELAKANTAN, HARSHINI	RIDGELINE THERAPEUTICS, LLC

Description

Abstract Text

Progressive muscle weakness and degeneration is a hallmark of Duchenne muscular dystrophy (DMD). In DMD patients, the lack of dystrophin reduces muscle fiber structural integrity, making muscles vulnerable to persistent injury and damage. Repairing these damaged muscles requires the continual activation of muscle stem cells (muSC), which leads to muSC dysfunction and senescence, and ultimately the muscle degeneration and weakness phenotype observed in DMD patients. Unfortunately, existing FDA approved drugs (eteplirsen, deflazacort) do not sufficiently improve muscle regeneration, and appear to provide only marginal improve- ments in muscle function and quality of life for DMD patients. Ridgeline Therapeutics has developed novel oral- ly-bioavailable small molecule NNMT (nicotinamide N-methyltransferase) inhibitors (e.g., RTL-72484) that reactivate dysfunctional and senescent muSC. While initially developed as a therapeutic to reverse age-related muscle degeneration, recent in vivo studies suggest the NNMT inhibitor RTL-72484 could improve muscle re- generation and function in DMD patients. This project will expand on our preliminary research and complete proof-of-concept studies to rigorously test the efficacy of RTL-72484 two complementary DMD mouse models. Overexpression of NNMT interferes with the NAD salvage pathway, muSC regenerative function, and cellu- lar metabolism (including mitochondrial bioenergetics). Skeletal muscles of DMD patients have greatly in- creased expression of NNMT, suggesting NNMT could be a vital contributing factor to muSC dysfunction and metabolic dysregulation observed in DMD patients. As a potential DMD treatment, RLT-72484 functions by se- lectively inhibiting NNMT, resulting in increased muSC activity, enhanced mitochondrial function, and ultimately improved muscle strength and function. These unique mechanisms-of-action makes RLT-72484 (and other NNMT inhibitors in our pipeline) distinct from the few DMD therapeutics that are FDA-approved or in early- stage clinical trials. This Phase I STTR project will build upon our encouraging in vivo DMD efficacy studies and test the effectiveness of RLT-72484 in more advanced and translationally-relevant murine models of DMD. The following two Aims will be completed to assess the potential of RLT-72484 to serve as an oral DMD drug. Aim 1 will complete an oral chow-admixed pharmacokinetic (PK) study to assess plasma profiles of RLT- 72484 and compare to systemic exposures observed via oral gavage administration of the drug. This PK study will validate the optimal drug delivery route for longitudinal efficacy studies in DMD mice. Aim 2 will complete in vivo dose-ranging efficacy studies using B10/mdx and D2/mdx mice models of DMD, evaluating muSC activity, mitochondrial function, diaphragm contractile function, and fibrosis ex-vivo, and in vivo functional endpoints (e.g., muscle strength, endurance, and grip strength). Following successful demonstration of the therapeutic effects of RTL-72484 in animal models, Ridgeline will rapidly advance RTL-72484 to clinical trials as a potential DMD treatment, since RLT-72484 is in GMP scale-up and GLP safety studies for a separate clinical indication.

Public Health Relevance Statement

PROJECT NARRATIVE This project will complete critical dose-ranging in vivo proof-of-concept efficacy studies using translationally-relevant mouse models to significantly derisk our novel small molecule therapeutic lead that selectively targets nicotinamide N-methyltransferases to effectively

regenerate muscle, improve muscle mitochondrial function, and enhance muscle strength and function in Duchene muscular dystrophy.

NIH Spending Category

Biotechnology | Duchenne/ Becker Muscular Dystrophy | Muscular Dystrophy | Orphan Drug | Pediatric | Rare Diseases | Stem Cell Research | Stem Cell Research - Nonembryonic - Non-Human

Project Terms

Address | Adolescent and Young Adult | Affect | Animal Model | Anti-inflammatory | Area Under Curve | Bioavailable | Biochemical | Bioenergetics | Caenorhabditis elegans | Cessation of life | Child | Clinical | Clinical Pathology | Clinical Trials | Deterioration | Disease Progression | Dose | Drug Delivery Systems | Drug Exposure | Drug Kinetics | Duchenne muscular dystrophy | Dystrophin | Effectiveness | Enzymes | FDA approved | Fibrosis | Functional disorder | Funding | Generations | Genes | Genetic | Glucocorticoids | Growth | Hand Strength | Human | In Vitro

Read More

Details

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Department Type
Unavailable

Organization Type
Domestic For-Profits

State Code
TX

Congressional District
07

Other Information

FOA
PA-18-575

Study Section
Special Emphasis Panel[ZRG1 MOSS-D (10)]

Administering Institutes or Centers
NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

CFDA Code
846

Project Start Date
16-September-2019

Project End Date
31-August-2022

Budget Start Date
16-September-

	Award Notice Date	DUNS Number	UEI		
Fiscal Year				Budget End Date	
2019	**16-September-2019**	**078394570**	**KM9RHDLMHTI**	**31-August-2022**	**2019**

Project Funding Information for 2019

Total Funding	Direct Costs	Indirect Costs
$252,131	**$202,753**	**$32,884**

Year	Funding IC	
2019	National Institute of Arthritits and Musculoskeletal and Skin Diseases	$252,131

NIH Categorical Spending

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Funding IC	FY Total Cost by
NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES	$252,131