Preclinical Development of a Novel Therapeutic to Rejuvenate Aging Muscle Stem Cells and Enhance Muscle Strength and Function Post Hip Fracture

Project Number	Contact PI/Project Leader	Awardee Organization
1U44AG074107-01	NEELAKANTAN, HARSHINI	RIDGELINE THERAPEUTICS, LLC

Description

Abstract Text

Muscle-aging is defined by progressive declines in mass and strength that poses a high risk for falls, fatal injury, and trauma-related fractures among older Americans (age 60+). Each year, >30% of older adults suffer a fall, resulting in ~2.8 million traumatic fractures that significantly reduce mobility, independence, overall health, and quality of life for the elderly. Among fall-related injuries, hip fractures are the most prevalent and serious; the 300,000 elderly Americans hospitalized each year with hip fracture repairs face long-term post-surgery rehabilitation with a low probability of returning to independent living and a 1-year mortality rate that staggers around 10-30%. Dampened muscle strength predisposes to and predicts poor recovery among the elderly following hip fracture. Standard-of-care including resistance exercise and protein-rich diets only marginally improve muscle strength and functional outcomes post hip fracture. Attempts to improve muscle strength in elderly individuals using pharmacotherapies have not succeeded to date. To address this challenge, Ridgeline Therapeutics has developed first-in-class small molecule nicotinamide N-methyltransferase inhibitors (NNMTis) that reactivate aged muscle stem cells (muSCs). As skeletal muscle and muSCs age, they increasingly express NNMT that interferes with NAD biosynthesis and the downstream events that control muSC regenerative function and cellular energy metabolism. Thus, NNMT is a vital contributing factor to aging muSC dysfunction and associated declines in muscle strength. Since muSCs are fundamental to regeneration and repair, rejuvenation of aged muSCs (including using NNMTi) has proven useful to boost muscle regenerative capacity and improve muscle strength and function in aged mice. Ridgeline's therapeutic development efforts have swiftly progressed from discovery, to lead optimization, mechanistic and preclinical proof-of-concept validations in clinically relevant aged muscle injury models. Treatment of aged, injured mice with the lead NNMTi RT-001 showed 2-fold increase in muSC activity and myofiber fusion index, 35-80% increase in muscle growth, and 70% increase in muscle strength. Robust efficacy and early safety index demonstration for RT-001 have de-risked and positioned it for late-stage preclinical and IND-enabling studies. Ridgeline is advancing RT-001 as a safe and effective small molecule therapeutic for clinical use in improving muscle strength and function among older adults following hip fracture surgical repairs. The objectives of this project directly aligns with this goal and focuses on completing necessary in vivo PK/PD studies to optimize oral dosing regimens, scale up synthesis of a 2 kilogram batch of RT-001, and non-GLP and GLP toxicity studies; accessory metabolism and clinically relevant biomarker assessments will be completed to complement and support IND filing and first-in-human clinical trials.

Public Health Relevance Statement

The novel mechanism-of-action small molecule therapeutic developed by Ridgeline effectively rejuvenates aged skeletal muscle satellite cells and stimulates recovery following muscle injury. This project will complete critical preclinical PK/PD and dosing regimen validations, non-GLP in vitro metabolism and in vivo safety toxicity studies, and scale-up manufacturing of drug substance to support the completion of necessary GLP-regulated nonclinical toxicity studies; clinically relevant biomarkers to identify at-risk elderly patients will be validated. Successful completion of this proj

will enable approval of our investigational new drug for clinical trials to promote muscle strength and function following hip fracture injury in the elderly.

NIH Spending Category

Aging | Physical Injury - Accidents and Adverse Effects | Physical Rehabilitation | Regenerative Medicine | Rehabilitation | Sarcopenia | Stem Cell Research | Stem Cell Research - Nonembryonic - Human

Project Terms

Address | Adult | Age | Aging | American | Anabolism | Antibodies | Biological Markers | Canis familiaris | Chemicals | Chronic | Clinical | Clinical Trials | Complement | Data | Diet | Dose | Drug Kinetics | Drug Transport | Elderly | Energy Metabolism | Epigenetic Process | Event | Face | Fatal injury | Fracture | Fracture Healing | Functional disorder | GDF8 gene | Goals | Growth | Health | Health Care Costs | Hepatocyte | Hip Fractures | Hip region structure | Human | Impairment | Independent Living | Individual | Injury | Investigational Drugs | Kilogram | Lead | Length of Stay

Read More

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Department Type
Unavailable

Organization Type
Domestic For-Profits

State Code
TX

Congressional District
07

Other Information

FOA
RFA-AG-21-026

Study Section
Special Emphasis Panel[ZAG1 ZIJ-1 (M1)]

Administering Institutes or Centers
NATIONAL INSTITUTE ON AGING

CFDA Code
866

DUNS Number

UEI
KM9RHDLMHTI

Project Start Date
30-September-2021

Project End Date
31-August-2024

Budget Start Date
30-September-

	078394570		**2021**
Award Notice Date		Budget End Date	**31-August-2022**
Fiscal Year **2021**	**20-September-2021**		