A Novel Small Molecule Oral Therapeutic to Prevent and Reverse Skeletal Muscle Atrophy in Aging Adults

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
1R43AG084460-01A1	1R43AR082751-01A1	WILEY, ANDREA LEAHOther PIs	RIDGELINE THERAPEUTICS, LLC

Description

Abstract Text

Limited muscle use is widespread in older adults (e.g., post-injury immobilization, bed rest) and typically leads to disuse-induced muscular atrophy defined by substantial loss of muscle mass, strength, and function [1- 3]. The overall health and functional independence of aging adults can rapidly and progressively deteriorate as muscle disuse causes atrophy and promotes a vicious cycle of further muscle disuse and subsequent exacerbated atrophy. Standard-of-care treatments to counter skeletal muscle atrophy include physical therapy and exercise [4], but these approaches have limited success in elderly populations [5]. Although pharmaceutical interventions to treat muscle loss are in development, many have unfavorable side effects. The only approved intervention in the United States is for subtypes of atrophy related to HIV/AIDS and cachexia [6]. Thus, there is a critical need for novel treatments that prevent and reverse disuse-induced muscular atrophy in aging adults. Ridgeline Therapeutics is developing transformative small-molecule oral drugs to accelerate skeletal muscle regeneration and repair in aging adults. Ridgeline's clinical candidate RT-002 is completing preclinical studies, with first-in-human Phase 1 clinical trials scheduled for Q4'23. RT-002's mechanism-of-action is to inhibit nicotinamide N-methyltransferase (NNMT), an enzyme critical for maintaining cellular energy metabolism and homeostasis [7]. Inhibition of NNMT activates quiescent, dysfunctional muscle stem cells, promoting enhanced muscle fiber growth and improved muscle mass and strength in aged mice [8]. This SBIR Phase 1 project will extend these findings and test the hypothesis that RT-002 can prevent disuse-induced muscle atrophy and promote faster recovery following muscle disuse. Aim 1 will determine if RT-002 treatment can mitigate the loss of muscle mass and strength that occurs during muscle disuse. Aim 2 will determine if RT-002 treatment can improve the rate of recovery from cast immobilization-induced muscle atrophy, as measured by muscle mass, strength, and function gained over a 21-day limb remobilization (i.e., post-uncasting) period compared to the baseline measures taken on the first day of limb uncasting. The efficacy studies proposed herein will utilize a translationally-relevant unilateral hindlimb casting model of muscle atrophy in rats [9]. Casting immobilizes the hindlimb, prevents localized muscle use, and results in significant atrophy, evidenced in aged rats by substantial muscle loss and severe deficits in hindlimb muscle strength that last for several days even after cast removal [10, 11]. Furthermore, hindlimb casting is a widely- accepted model for disuse-induced muscular atrophy with translational relevance to human muscle atrophy pathologies [9, 12]. Preclinical validation of RT-002's efficacy using this model will lay the foundation to rapidly advance its development into the clinic as a novel drug to accelerate recovery of muscle function following disuse in aging adults.

Public Health Relevance Statement

PROJECT NARRATIVE This project will establish the efficacy of an oral therapeutic with a novel mechanism of action to both prevent and reverse disuse atrophy-mediated loss of muscle function

and mass. Completion of this work will support the expansion of Ridgeline Therapeutics' clinical pipeline.

Project Terms

Acceleration | Adult | Aging | Animal Model | Animals | Area | Arthralgia | Atrophic | Bed rest | Body Weight | Cachexia | Clinic | Clinical | Deterioration | Development | Disuse Atrophy | Dose | Dual-Energy X-Ray Absorptiometry | Elderly | Energy Metabolism | Enzymes | Event | Excision | Exercise | FBXO32 gene | FRAP1 gene | Failure | Female | Femur | Flexor | Foundations | Gait speed | Gastrocnemius Muscle | Gene Expression | Growth | HIV/AIDS | Health | Hindlimb | Hindlimb Suspension | Homeostasis | Human | Hypertrophy | Immobilization | ervention | Limb structure | Lipids | Measures | Mediating

Read More

Details

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Department Type
Unavailable

Organization Type
Domestic For-Profits

State Code
TX

Congressional District
07

Other Information

Opportunity Number
PA-22-176

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

Fiscal Year
2023

Award Notice Date
23-August-2023

Administering Institutes or Centers
National Institute on Aging

CFDA Code
866

DUNS Number
078394570

UEI
KM9RHDLMHTI

Project Start Date
01-September-2023

Project End Date
31-August-2024

Budget Start Date
01-September-2023

Budget End Date
31-August-2024

Project Funding Information for 2023

Total Funding

Direct Costs

Indirect Costs

$322,432	$226,394	$74,944

Year	Funding IC		FY Total Cost
2023	National Institute on Aging	$322,432	

Sub Projects

No Sub Projects information available for 1R43AG084460-01A1

Publications

› Disclaimer

No Publications available for 1R43AG084460-01A1

Patents

No Patents information available for 1R43AG084460-01A1

Outcomes

The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

No Outcomes available for 1R43AG084460-01A1

Clinical Studies

No Clinical Studies information available for 1R43AG084460-01A1

News and More

Related News Releases

No news release information available for 1R43AG084460-01A1

History

No Historical information available for 1R43AG084460-01A1

Similar Projects

No Similar Projects information available for 1R43AG084460-01A1