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

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
3U44AG074107-02S1	5U44AG074107-02	NEELAKANTAN, HARSHINI	RIDGELINE THERAPEUTICS, LLC

Description

Abstract Text

ABSTRACT Ridgeline's U44 direct to Phase 2 cooperative agreement award (U44AG074107) from the National Institute on Aging has enabled rapid therapeutic development studies of RT-002, a novel oral therapeutic to promote full functional recovery and enhance the quality-of-life in elderly adults following traumatic hip fracture. Several critical studies were completed in Year 1 of the award which successfully earned the Year 2 funding for Ridgeline. Particularly, the project completed in vitro cross-species (mouse, rat, dog, mini-pig, monkey, human) metabolite identification for RT-002 using cultured hepatocytes, in vitro translational valdiations in aged human muscle- derived progenitor cells, in vivo PK/PD studies in aged mice and rats, process optimization and scale up synthesis of ~4 kilogram GMP-like batch of RT-002, non-GLP and GLP toxicity and safety pharmacology studies in rats, in vivo oral dosing tolerability and toxicokinetic assessments for RT-002 in male and female dogs, and preliminary in vivo PK/oral bioavailability and dose escalation tolerability study in male and female mini-pigs. This supplemental project will aid in the completion of the FDA-mandated safety/toxicity studies in the chosen mini-pig nonrodent species. Our pivotal cross-species metabolism studies showed that our clinical candidate NNMT inhibitor drug RT-002 was metabolized similarly in rat, mini-pig, and human hepatocytes, with comparable biotransformation rates and identical metabolites. In contrast, the turnover rates for RT-002 in mouse and monkey hepatocytes were found to be remarkably rapid but negligable in dog hepatocytes. Importantly, the primary metabolites identified for RT- 002 in human, rat, and mini-pig hepatocytes were nearly absent in dog hepatocytes due to the absence of the major RT-002 metabolizing enzymes, aldehyde oxidase (AO) and N-acetyltransferase (NAT) in dog liver. Taken together it was concluded that dogs are not the appropriate nonrodent species to characterize safety and toxicological effects of RT-002, which was further substantiated by the poor tolerability observed in dogs following RT-002 oral dosing. Given these result, mini-pigs are chosen as the non-rodent species for the necessary RT- 002 safety/toxicology studies as proposed in this award. This supplemental project will complete the necessary RT-002 safety/toxicology studies in male and female mini-pigs to establish the maximum tolerated dose of RT- 002 and evaluate safety and toxicity following repeated oral dosing of the drug. Outcomes from this de-risking study will further validate mini-pigs as an ideal choice of nonrodent species for continued regulated GLP toxicology studies and enable Ridgeline to continue developing the novel NNMT inhibitor clinical candidate RT- 002 to reach the IND-filing milestone by the end of this project period.

Public Health Relevance Statement

PROJECT NARRATIVE 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 supplemental study will complete critical preclinical non-GLP safety/toxicity studies in mini-pigs to support the GLP-regulated nonclinical toxicity studies and

enable clinical trials of the investigational new drug to promote full functional recovery of elderly patients following hip fracture.

Project Terms

Acetyltransferase | Administrative Supplement | Adult | Adverse effects | Aldehyde oxidase | Animals | Award | Biological Availability | Blood | Body Weight | Canis familiaris | Cardiovascular system | Chemicals | Clinical | Clinical Pathology | Clinical Trials | Complement | Data | Dose | Elderly | Elements | Enzymes | Female | Funding | Funding Mechanisms | Grant | Half-Life | Hepatocyte | Hip Fractures | Histology | Human | In Vitro | Injury | Investigational Drugs | Kilogram | Liver | Maximum Tolerated Dose | Metabolic Biotransformation | Miniature Swine | Monkeys | Mus | Muscle | ion | Muscle satellite cell | National Institute on Aging | Oral

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-20-272

Study Section

Fiscal Year
2023

Award Notice Date
26-May-2023

Administering Institutes or Centers
National Institute on Aging

CFDA Code
866

DUNS Number
078394570

UEI
KM9RHDLMHTI

Project Start Date
30-September-2021

Project End Date
31-August-2024

Budget Start Date
01-June-2023

Budget End Date
31-August-2023

Project Funding Information for 2023

Total Funding
$247,436

Direct Costs
$247,436

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2023	National Institute on Aging	$247,436

Sub Projects

No Sub Projects information available for 3U44AG074107-02S1

Publications

Disclaimer

No Publications available for 3U44AG074107-02S1

Patents

No Patents information available for 3U44AG074107-02S1

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 3U44AG074107-02S1

Clinical Studies

No Clinical Studies information available for 3U44AG074107-02S1

News and More

Related News Releases

No news release information available for 3U44AG074107-02S1

History

No Historical information available for 3U44AG074107-02S1

Similar Projects

No Similar Projects information available for 3U44AG074107-02S1