Dose-ranging safety and efficacy studies to advance novel mechanism-of-action drug candidates to reverse age-related muscle degeneration

Project Number
1R41AG061989-01

Contact PI/Project Leader
WATOWICH, STANLEY

Awardee Organization
RIDGELINE THERAPEUTICS, LLC

Description

Abstract Text

In the US, the number of individuals aged 65 and older will increase by 30% over the next decade. Concurrently, Medicare costs are expected to double to treat chronic diseases that will plague this increasing number of older adults. One of the most wide-spread chronic diseases that affects older adults is sarcopenia, which is observed in 30% of adults over 60 years of age and 50% of adults over 80 years of age[1,2]. This disease is characterized by progressive age-associated skeletal muscle atrophy; the degenerative loss of muscle mass and tissue quality cause significant reductions in muscle strength, function, and regenerative capacity of the tissue, greatly deteriorating overall health and quality of life. Moreover, sarcopenia is a core component of the debilitating frailty syndrome, which severely impacts an individual's independence and longevity. Current recommendations to prevent and treat sarcopenia include resistance exercise and protein- rich diets. While these recommendations appear logical, there is no substantial evidence to suggest these treatments consistently increase muscle mass and improve physical function and performance in aged individuals[3,4]. Given the current scope and projected impact of sarcopenia, there is a clear unmet need for effective therapies to slow and reverse sarcopenia to support healthier lives for older Americans. The objective of this Phase I project is to demonstrate proof-of-principal and safety for novel mechanism- of-action therapeutic candidates using translationally-relevant muscle growth/function models in aged animals and appropriate in vivo safety models, respectively. Ridgeline Therepeutics is developing first-in-class oral drugs that selectively target and inhibit nicotinamide N-methyltransferase (NNMT), an enzyme upregulated in aged skeletal muscle and newly discovered to regulate cellular metabolic pathways, particualrly NAD+ biosynthesis that is highly compromised in aged muscle. The lead series of small molecule NNMT inhibitors have excellent physicochemical properties (i.e., highly soluble, stable, permeable) and good oral bioavailability, with no early signs of toxicity. Preliminary results using our candidate lead NNMT inhibitor in an aged-mouse model for muscle regeneration and functional improvement[2] revealed significantly improved muscle mitochondrial oxidative capacity, enhanced muscle fiber growth, and increased muscle stem cell proliferation/activity. These promising results suggest that our lead series has the potential to improve defects in aged muscle pathophysiology and reverse sarcopenia. To further derisk our lead candidates as potential therapeutics to greatly improve muscle growth, mass, and function in aged individuals, this Phase 1 project will complete (1) dose-ranging efficacy studies in aged animals to demonstrate proof-of-principal for our drug candidates to improve muscle growth and function, and (2) in vivo long-term safety/toxicity studies. Preclinical GLP-safety, formulation development, and IND-enabling studies for FDA submission will follow this Phase I project.

Public Health Relevance Statement

PROJECT NARRATIVE This project will complete critical dose-ranging studies to significantly derisk our novel small molecule therapeutic leads that selectively target nicotinamide N-methyltransferases to increase muscle growth and function in aged animals.

NIH Spending Category

Aging | Sarcopenia | Stem Cell Research | Stem Cell Research - Nonembryonic - Non-Human

Project Terms

Acute | Address | Adult | Adverse effects | Adverse event | Affect | Age | Age-Years | American | Anabolism | Animal Model | Animals | Biological Availability | Biopsy | Cardiac | Cellular Metabolic Process | Chemistry | Chronic Disease | Comorbidity | Contracts | Defect | Development | Diagnostic | Diet | Disease | Dose | Drug Kinetics | Drug Targeting | Drug effect disorder | Elderly | Enzymes | Epigenetic Process | Equilibrium | Family | Formulation | Functional disorder | Funding | Growth | Health | Health Personnel | Human | In Vitro | Individual | Injury | Lead | Liver | Longevity | ...erated Dose | Medicare | Metabolic | Metabolic Pathway | Modeling

Read More

Details

No information available for 1R41AG061989-01

Project Funding Information for 2018

Total Funding	Direct Costs	Indirect Costs
$357,630	**$286,300**	**$48,000**

Year	Funding IC		FY Total Cos
2018	National Institute on Aging	$357,630	