Dose-ranging safety and efficacy studies to advance novel mechanism-of-action small molecule leads to treat obesity-linked type 2 diabetes

Project Number
1R41DK119052-01

Contact PI/Project Leader
WATOWICH, STANLEY

Awardee Organization
RIDGELINE THERAPEUTICS, LLC

Description

Abstract Text

ABSTRACT A staggering 38% of US adults are obese. Since obesity greatly dysregulates glucose homeostasis, almost all obese individuals suffer from Type 2 diabetes (T2D) or prediabetes. These diseases, and accompanying comorbid chronic health complications, are largely responsible for burgeoning US healthcare costs. Unfortunately, life-style modification programs, typically the first-line treatment for obesity-linked T2D, rarely produce sustained weight loss that is necessary to alter T2D and prediabetes severity and progression. Thus, anti-diabetic drugs (e.g., insulin, metformin) are required to lower plasma glucose levels in obese diabetic patients. These drugs do not target the root cause of glucose dysregulation in obese individuals, but largely modulate downstream glucose production and/or excretion mechanisms to symptomatically lower blood glucose levels. It is, therefore, not surprising that current anti-diabetic drugs require lifelong administration, produce numerous chronic use adverse effects, have high non-adherence rates, and do not generate long-term cost savings. Given the high prevalence of obesity-linked T2D and inadequate treatment options, there is a critical need for new drugs that sustainably reduce T2D and prediabetes in obese Americans. To address this challenge, Ridgeline Therepeutics is developing novel oral drugs that reduce excess body fat to restore glucose homeostasis in obese diabetic patients. Our small molecule drugs selectively target nicotinamide N-methyltransferase (NNMT), an adipocyte-centric enzyme newly discovered to regulate white adipose tissue (WAT) metabolism and mediate obesity-linked insulin resistance. These new therapeutics are expected to improve the underlying WAT-linked dysfunctional metabolic state of obese diabetic patients, leading to sustained and persistant reductions in body weight and excess WAT, until circulating glucose levels are normalized. When tested in the translationally-relevant mouse model of diet-induced obesity (DIO), our lead candidate significantly reduced whole body weight, produced drastic shrinkage of WAT mass and adipocyte size, and returned blood cholesterol to levels observed in normal weight individuals. Importantly, food intake was not altered with compound treatment, suggesting no impact on appetite suppression. Moreover, preliminary pharmacokinetic, safety, and functional studies have shown that our leads are stable, safe, highly oral bioavailable, and efficacious. These results suggest our technology has enormous potential as a new treatment for obesity-linked T2D/prediabetes. To further derisk our technology, we will complete dose-ranging oral-delivery studies to characterize the safety and efficacy of our drug lead. Project aims include (1) in vitro ADME-Tox profiling, (2) rigorous long-term safety studies, and (3) comprehensive efficacy studies to demonstrate significantly improved T2D biomarkers in treated animals. Our accomplished scientific team will complete these aims and guide our technology- derisking program. Preclinical development and IND-enabling studies will follow this STTR Phase I project.

Public Health Relevance Statement

PROJECT NARRATIVE This project will complete critical dose-ranging studies to significantly derisk our novel small molecule anti-diabetes therapeutic leads that selectively target nicotinamide N-methyltransferase and increase the metabolism of white adipose tissue (i.e., belly fat).

NIH Spending Category

Diabetes Nutrition Obesity Patient Safety Prevention

Project Terms

Accounting Acute Address Adipocytes Adipose tissue Adolescent Adopted Adult Adverse effects Affect American Animals Antidiabetic Drugs Bioavailable Biological Markers Blood Blood Glucose Body Weight Body Weight decreased Body fat Body mass index Cardiac Chemicals Chemistry Cholesterol Chronic Clinical Comorbidity Complex Cost Savings Desire for food Diabetes Mellitus Diet Disease Disease Management Disease Progression Dose Drug Kinetics Drug effect disorder Eating Electrolytes Enzymes Excretory function

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Details

No information available for 1R41DK119052-01

Project Funding Information for 2018

Total Funding	Direct Costs	Indirect Costs
$299,972	**$237,468**	**$42,880**

Year	Funding IC	
2018	National Institute of Diabetes and Digestive and Kidney Diseases	$299,972