Peer Reviewed Medical

Preclinical Advancement of Novel Mechanism-of-Action Therapeutics to Combat Type 2 Diabetes in US Veterans

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Dr. Harshini Neelakantan (*Photo Provided*)

Type 2 diabetes (T2D) is a chronic condition that affects the body's ability to produce and use insulin, a hormone that regulates the amount of glucose in the bloodstream. Excess glucose, also called blood sugar, can damage the body's circulatory, nervous, and immune systems. T2D disproportionately affects Veterans. The U.S. Department of Veterans Affairs estimates that nearly a quarter of the Veterans enrolled in the Veterans Health Administration have diabetes.

Obesity is a known high-risk factor for developing T2D. Over 44% of Veterans who served in Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn are obese and at risk for T2D; this obesity rate is significantly higher than the obesity rate observed in similarly aged American civilians (Wischik et al, 2019). Unfortunately,

traditional weight-loss interventions like diet and exercise rarely achieve effective long-term management of obesity and T2D. The Peer Reviewed Medical Research Program (PRMRP) has addressed Metabolic Disease or Diabetes as Topic Areas since fiscal year 2014 (FY14).

With funding from an FY14 Discovery Award to the University of Texas Medical Branch at Galveston, Drs. Stanley Watowich and Harshini Neelakantan investigated an alternative approach to reducing excess body mass by identifying and successfully testing a series of first-in-class drugs that increase the energy expenditure within white adipose tissue, commonly known as body fat. These drugs decrease the activity of an enzyme called nicotinamide *N*-methyltransferase (NNMT), which is a key regulator of metabolism within white adipose tissue. The most promising of these drugs, an NNMT inhibitor derived from quinoline called RLT-72848, was shown to reduce body weight by more than 10% and shrink abdominal fat by over 30% in mice. The research team led by Dr. Watowich subsequently licensed RLT-72848 to Ridgeline Therapeutics and filed a patent for the new chemical entities and use of these candidate therapeutics to treat metabolic and related chronic diseases.

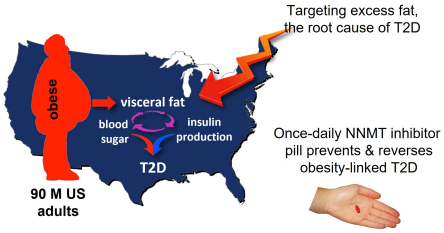

Figure 1: NNMT inhibitors target excess fat to reduce obesity and prevent or reverse obesity-induced type 2 diabetes (T2D). (*Figure Provided*)

An FY18 Expansion Award to Ridgeline Therapeutics supported additional drug development research for RLT-72848. The researchers partnered with Contract Research Organizations to complete the rigorous preclinical safety and manufacturing studies required by the U.S. Food and Drug Administration (FDA) to advance the drug RLT-72848 into human clinical studies. The research team developed drug production, quality, and control methods and completed safety/toxicity assessments per FDA regulations, alongside comprehensive studies to understand drug metabolism and tissue distribution in numerous animal models. Upon successful completion of these studies, the research team led by Drs. Neelakantan and Watowich completed a series of toxicology and safety studies of RLT-72848 under FDA-regulated laboratory conditions to qualify for an Investigational New Drug designation that will allow this drug to be tested in clinical trials.

If the upcoming clinical trials prove successful, NNMT-inhibiting drugs offer a promising new approach to effectively manage body weight and reduce obesity-related diseases such as T2D among Veterans, active-duty Service Members, and the general public.

Reference:

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Links:

Public and Technical Abstracts: Discovery of Novel N-Nicotinamide Methyltransferase Inhibitors to Combat Obesity-Linked Osteoarthritis and Metabolic Disease Among Veterans and Beneficiaries (https://cdmrp.health.mil/search.aspx?LOG_NO=PR141776)

Public and Technical Abstracts: Preclinical Advancement of Novel Mechanism-of-Action Therapeutics to Combat Type 2 Diabetes in US Veterans (https://cdmrp.health.mil/search.aspx?LOG_NO=PR180216)

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