SRP Diabetes Postdoctoral Fellowship Program 2025

Project Title: Dietary Nitrate to Prevent Cardiovascular Disease in Diabetes

Background: Dietary improvement is a crucial non-pharmacological strategy for patients with metabolic syndrome and diabetes. This and other lifestyle changes reduce chronic oxidative stress and increase nitric oxide (NO) bioavailability. Our research focuses on inorganic nitrate, found in high levels in green leafy vegetables and beetroot, which converts to bioactive NO in vivo. Studies show that nitrate positively affects cardiovascular function, reducing blood pressure, improving vascular function, and enhancing exercise parameters like mitochondrial efficiency and oxygen utilization. Most recently, we have found that nitrate can combine with dietary non-heme iron to form another bioactive nitrogen oxide termed di-nitrosyl iron complex (DNIC). We hypothesize that dietary inorganic nitrate combined with non-heme iron will provide cardiovascular and metabolic protection for patients with type 2 diabetes (T2D), who are at high risk for cardiovascular disease (CVD). This project involves basic research studies on how DNICs are formed in rodents and humans as well as a smal clinical trial to study the combined effects of dietary nitrate and non-heme iron on cardiovascular and metabolic health in T2D patients.

Objectives: We will study basic mechanisms for DNIC generation from nitrate and non-heme iron, and its signaling in cells, animals and humans. In animal models of metabolic syndrome, we study the antidiabetic and cardioprotective effects of dietary nitrate and iron alone, and their combined effect. Moreover, we are planning for a smal clinical trial to explore the effects of dietary nitrate and non-heme iron on metabolic and cardiovascular function in hypertensive T2D patients.

Work Plan and Methodology:
In cell and animal work we study in detail how DNICs are endogenously formed. In particular, we will explore if the gut microbiome can catalyze the formation of DNICs form nitrate and iron, and if such DNICs are absorbed intact to affect various physiological parameters in health and disease. The clinical trial involves T2D patients with hypertension. After a two-week medication washout, patients are randomized to four weeks of nitrate+iron or placebo treatment. The co-primary endpoints are: (1) the change in 24-hour blood pressure before and after the intervention, and (2) glucose tolerance.

Relevance of Project for Diabetes: Cardiovascular disease is the leading cause of death in over 50% of diabetes patients. This project explores a novel prevention strategy based on cardiovascular and metabolic benefits of a bioactive nitrogen oxide (DNIC) generated from dietary nitrate and non-heme iron. Major dietary sources of nitrate and non-heme iron are green leafy vegetables, beetroot, spinach, nuts and seeds; dietary constituents generally associated with protection against diabetes and cardiovascular disease.

References:

1. Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403.
2. Lundberg JO, Weitzberg E. Nitric oxide signaling in health and disease. Cell. 2022;185:2853-2878.
3. Lundberg JO, et al. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov. 2008;7:156-167.

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