



**WHOLE-BODY INDUCIBLE DISRUPTION OF DIHYDROCERAMIDE
DESATURASE: VASCULAR IMPLICATIONS**

Kiana Luu (Trevor Tippetts, Kellsey Ly, Lauren Thompson, Michele Hansen, John David Symons)

**Department of Nutrition and Integrative Physiology
Division of Endocrinology, Metabolism, and Diabetes
Molecular Medicine Program**

Type 2 diabetes mellitus (T2DM) precipitates cardiovascular complications (e.g., impaired vision, atherosclerosis, and hypertension). Each of these complications is associated with vascular dysfunction, which is a generic term to describe arteries that do not dilate or constrict appropriately. Gaining a thorough understanding of the mechanisms responsible for vascular dysfunction is requisite for the design and development of new therapeutic strategies to treat cardiovascular complications associated with T2DM.

Our laboratory has shown that when vascular accumulation of the sphingolipid ceramide is *prevented* in mice, arterial dysfunction and hypertension that otherwise develop in response to high-fat (HF) feeding does not occur. Here, we tested the hypothesis that inhibiting ceramide biosynthesis in mice wherein ceramide has already accumulated *reverses* arterial dysfunction.

Eight-week-old male mice consumed HF chow for 12 weeks. At 20 weeks of age, tamoxifen was administered (3 mg/day for 5 consecutive days via IP injection) to induce knockout (KO) of dihydroceramide desaturase (DES1), an enzyme responsible for ceramide biosynthesis. These mice were compared to a control group wherein DES1 was intact. A week after the last tamoxifen dose, mice were characterized metabolically through glucose and insulin tolerance tests. Then, the endothelial cells (ECs) from carotid arteries were obtained to determine the efficacy of knockdown, and femoral and cerebral arteries were used to assess endothelial and vascular smooth muscle function on an isobaric myograph. Non-receptor mediated vasoconstriction to potassium chloride (KCl), endothelium-dependent vasodilation to acetylcholine (ACh), endothelium-independent vasodilation to sodium nitroprusside (SNP), and intraluminal flow-mediated vasodilation (FMD) to pressure gradients from 6-30 mmHg were not different when responses were compared in cerebral and/or femoral arteries between DES1 KO mice and the control group. The results indicate that whole-body inducible KO of DES1 does not reverse vascular dysfunction that develops in mice wherein ceramide has already accumulated.