HEART FAILURE PHARMACOLOGY

The goal of our laboratory is to develop better pharmacotherapies to prevent and treat myocardial dysfunction and heart failure.

Research Brief
Our research focuses on identifying intra-cardiac regulators of growth and function, to better prevent and treat the cardiac complications of diabetes, hypertension (high blood pressure) and myocardial infarction (heart attack). These disorders are key precursors of heart failure if not well managed. Structural changes include cardiac hypertrophy (an enlarged heart and/or cardiac muscle cells) and fibrosis (increased extracellular matrix deposition), which are known as cardiac remodelling. Impairments in cardiac function include reduced contractile (pumping) function (systolic function), and/or impaired cardiac relaxation and delayed re-filling of the heart with blood following each contraction (diastolic dysfunction, particularly in diabetes). Recent achievements include: (i) nitroxyl as innovative therapy for limiting cardiac remodelling; (ii) annexin-A1 as an endogenous regulator of ischaemia-reperfusion injury (relevant to heart attack); and (iii) novel means of suppressing oxygen free radicals for managing diabetic cardiomyopathy. These precursors of heart failure, and new means to prevent and treat them, are studied from the isolated cardiac muscle cell (cardiomyocyte), to the isolated heart and the intact heart in vivo. This approach allows us to understand, and develop new treatments for, heart failure and its causes.

Methodologies
- Cardiac function in rodents in vivo & ex vivo (echo, catheterisation)
- In vivo, ex vivo & in vitro models of cardiac hypertrophy, reperfusion injury & diabetes
- In vivo, ex vivo and in vitro drug delivery
- Isolation & culture of primary cardiomyocytes
- Real time PCR, ELISA, Westerns, histology, apoptosis, cell culture

Selected Publications
Mechanisms of protective actions of nitroxyl (HNO) & other cGMP-mediated responses for preventing pathological heart growth

Annexin-A1 improves recovery of cardiac contractile function after injury

Interruption in coronary flow (myocardial ischaemia) impairs heart function (LV developed pressure, LVDP). Treatment with annexin-A1 peptide (left) improves, whereas deficiency of endogenous annexin-A1 (right) worsens, recovery of heart function.

Suppression of oxygen radical generation improves the function and structure of the diabetic heart

Mice with pre-existing type 2 diabetic cardiomyopathy were treated daily with the antioxidant coenzyme Q10. Cardiac relaxation (diastolic function, LVEDP), cardiac fibrosis and cardiac apoptosis were all improved in treated diabetic mice.