The goal of our laboratory is to develop better treatment strategies for patients with heart failure and atrial fibrillation by studying molecular mechanisms in genetic mouse models and cell culture.

Research Brief
Our research is focused on identifying genes/proteins that mimic the protective effects of exercise. Growth of the heart (also termed cardiac hypertrophy) can be induced by physiological stimuli (e.g. chronic exercise training) or pathological stimuli (e.g. high blood pressure). Physiological hypertrophy (“good” heart growth) is characterised by normal or enhanced heart function; whereas pathological hypertrophy (“bad” heart growth) is associated with cardiac dysfunction, and increased morbidity and mortality. Our laboratory are examining the possibility of activating “good” genes and signalling pathways that may normally be activated during the induction of physiological hypertrophy e.g. in the “athlete’s heart”. We previously reported that the insulin-like growth factor 1 (IGF-1)-phosphoinositide 3-kinase (PI3K) pathway plays a critical role for the induction of exercise induced heart growth. Thus, activation of PI3K, or targeting novel regulators of this pathway (e.g. genes, proteins and microRNAs), represents a new strategy to treat heart failure.

Methodologies
- Cardiac function studies (echocardiography, electrocardiography) in genetically modified mouse models
- In vivo delivery of AAV
- In vivo delivery of agents that inhibit microRNA
- qRT-PCR, Northerns, Westerns, immunoprecipitation, kinase assays, cell culture

Selected Publications
Identifying new therapies based on differences in physiological & pathological heart growth

Exercise is an intervention that can improve heart function

Genes that mediate the protective properties of exercise

Heart Growth

Chronic exercise training (Athlete’s heart) - Increase in heart size - Normal or enhanced function

Disease (high blood pressure, heart attack, genetics) - Increase in heart size - Depressed cardiac function - Complications including heart failure & atrial fibrillation

Drug targets - Delays heart failure progression

PI3K gene therapy improves function of the failing heart

Single administration of adeno-associated viral vector (rAAV6) containing PI3K improves heart function (fractional inhibition of PI3K-regulated microRNAs can improve heart function)

Inhibition of PI3K-regulated microRNAs can improve heart function

AntimiR was delivered to mice with pre-existing cardiac dysfunction due to pressure overload (TAC). Heart function (fractional shortening) improved in antimiR treated mice but not control. Heart size and atrial size were lower in antimiR-treated mice.