The laboratory examines signalling pathways in relation to cardiac disease, especially atrial dilatation and atrial fibrillation.

Research Brief
Starting with diseased human atrial tissues, we have identified an early mediator of pathological cardiac hypertrophy as a minor variant of an enzyme, phospholipase C (PLCβ1b). Such signalling is specific to cardiomyocytes and represents a possible therapeutic target. We next identified the protein responsible for its cardiac-activity (Shank3) a protein that localises PLCβ1b so as to facilitate pathological responses. We have developed specific inhibitors of the Shank3/PLCβ1b interaction and are currently underway with studies to test efficacy in vivo. Subsequently, we identified Homer1c, also associated with Shank3, as possibly responsible for calcium changes that initiate downstream pathological growth signalling. Other studies investigate the importance of the generally observed heightened IP3-receptor expression in heart failure. We study miRNA changes in valvular heart disease patients.

Methodologies
- Generation of adenoviruses and AAV, transfection of hearts and cardiomyocytes
- Generation of cardiac-targeted conditional transgenic mice
- Studies on cardiac function in genetically modified mice
- qRT-PCR, westerns, immunoprecipitation, yeast-2-hybrid, co-IP
- Anion exchange HPLC

Selected Publications
- Filtz TM, Grubb DR, McLeod-Dryden T J, Luo J, Woodcock EA. Gq-initiated cardiomyocyte hypertrophy is mediated by phospholipase cbeta1b. Faseb J. 2009;23:3564-3570
- Grubb DR, Vasilevski O, Huynh H, Woodcock EA. The extreme c-terminal region of phospholipase cbeta1 determines subcellular localization and function; the "b" splice variant mediates alpha1-adrenergic receptor responses in cardiomyocytes. Faseb J. 2008;22:2768-2774
Early Hypertrophic Signalling in Cardiomyocytes

Diagram showing how PLCβ1b, Shank3 and Homer1c work together to influence cardiac growth signalling.

miR-490-30 is Expressed in Myocytes & is Regulated by Atrial Dilatation

A miR-490-3p, not previously identified in heart, is expressed only in myocytes (non-myocytes shown in yellow). B Expression is highly negatively correlated with LA volume in human valvular heart disease.

Effectiveness of the Mini-gene Inhibitor in Reducing Hypertrophy in Cardiomyocytes

The mini-gene was designed to inhibit the binding of PLCβ1b to shank3. This reduces enzyme activity as shown in the left panel and reduces hypertrophy (right panel). The a mini is a control mini-gene, b mini is the active construct.