A/PROF ELIZABETH WOODCOCK

MOLECULAR CARDIOLOGY

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**

- Fitz TM, Grubb DR, McLeod-Dryden TJ, Luo J, Woodcock EA. Gq-initiated cardiomyocyte hypertrophy is mediated by phospholipase cbeta1b. *Faseb J.* 2009;23:3564-3570

**KEY FACTS**

- **Team:** Researchers: 4
  Technicians: 1
  PhD students: 1
  Postdoc fellows: 3

- **Translation:** Patents: 1

- **Links:** USA, multiple

- **Keywords:** Atrial fibrillation
  Signalling
  Atrial dilatation
  Inhibitory mini-gene
  Phospholipase C

- **Bio-resources:**
  Cardiomyocytes
  Transgenic mice
  Adenovirus technology
  Adeno-associated virus
  Human atrial tissue collection

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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 And 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.