The cardiac dyad signalling proteome and its modulation during cardiac protection

Supervisory team:
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Collaborators: Prof Xander Wehrens (Baylor College of Medicine, TX, US), Dr Vijay Rajagopal (University of Melbourne, AUS)

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Project description:
Increasing evidence demonstrates that perturbation of a process in heart muscle called excitation-contraction coupling leads to cardiac dysfunction. Excitation-contraction coupling is the name given to the process of molecular events that translates the electrical signal, ‘the heartbeat’, that arrives on the cell membrane in the form of the action potential, into the release of intracellularly stored calcium into the cytoplasm of the heart cell. This process is vital because calcium activates contraction of heart cells to expel blood from the chambers of the heart and pump it through the circulation. Critical to excitation-contraction coupling are cardiac dyads, membrane microdomains at contact sites between the cell membrane and the sarcoplasmic reticulum (a specialisation of the endoplasmic reticulum) membrane.

Recently, a molecular study has identified proteins that interact at the dyad and form the “dyad proteome”. Based on this finding we will investigate the dyad proteome in health and protection from disease arising from overexpression of a key dyad protein. We will test the hypothesis that maintaining integrity of protein complexes in the dyad proteome is the basis of protection. In this project a number of new molecular tools as well as novel insights into protein-protein interactions (PPI) in heart cells are coming together to create qualitatively new understanding. In addition to Ca2+-signalling, components of the dyad proteome are involved in controlling membrane curvature, protein phosphorylation and lipid interactions all of which will be studied by super-resolution microscopy.

Supervisor CS laboratory has recently introduced a new super-resolution imaging method to detect and localise PPI in situ. Co-supervisor DB discovered and first described a key protein-complex in the dyad proteome, the myospryn complex. Using the combined approaches in their laboratories we will use the in-situ PPI imaging approach to quantitatively determine the changes in the dyad proteome in a mouse model of heart failure and the effect of protection with the support of international collaborator Xander Wehrens (XW). XW has used overexpression of the protein junctophilin-2 (JPH2) to protect against heart failure in a mouse model.

The new approach will map the changes in the dyad proteome for the first time and provide the first comprehensive molecular view of the role of PPIs in maintaining normal cardiac physiology.

Successful application of the multidisciplinary approaches to this important aspect of cardiovascular health has the potential to generate high impact outputs and will for a form a strong skill base for the candidate’s further career.