Title of Project	Structural Basis for the CENP-V Mediated Maintenance of Centromere Structure
Cell Mechanism Supervisor Name	Bill Earnshaw
Quantitative Supervisor Name	JP Arulanandam

Summary of project

Chromosome condensation and correct centromere structure are key features essential for error-free chromosome segregation. Several essential mitotic regulators, including the Chromosomal Passenger Complex (CPC) and hSgo1, concentrate at the primary constriction site on the chromosomes to exert their function. CENP-V is a novel centromere-associated protein originally identified in a proteomic screen carried out in the Earnshaw lab. Structural bioinformatics analysis suggested that CENP-V is a putative formaldehyde-detoxifying enzyme. Formaldehyde is a potentially harmful byproduct of histone demethylation reactions. Depletion of CENP-V resulted in abnormal expansion of the primary constriction of the mitotic chromosome and mislocalization of CPC and hSgo1 leading to defective chromosome alignment, segregation and cytokinesis followed by cell death. To understand the molecular mechanism by which CENP-V exerts its function, this interdisciplinary PhD project will combine biochemical, structural, biophysical and cell biological approaches to address the following specific questions:

1. What is the three-dimensional structure of CENP-V and is CENP-V an active enzyme?
2. Which proteins do CENP-V interact with and how do these intermolecular interactions help CENP-V maintain chromosome condensation of the primary constriction on mitotic chromosomes?

High resolution structure analysis (using X-ray crystallography) and *in vitro* biochemical analysis will be used to characterise the enzyme activity of CENP-V. Mass spectrometry will be used to identify novel interactors of CENP-V and promising candidate interactions will be characterised using biochemical and structural approaches. To obtain mechanistic insights, structure-guided mutants will be tested in cell-based assays to evaluate the roles of the enzymatic activity and intermolecular interactions.