Unravelling the cellular mechanisms that provide specificity for insecticidal toxins against invertebrates and some cancer cells

Supervisory team:
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Project description:

Toxin_10 and aerolysin beta pore-forming toxins are reported to work exclusively on specific insects, and as such are important tools in the development of new non-chemical natural biopesticides for improved agricultural and environmental outcomes. The Toxin_10 family BinA/BinB toxin is the best-characterised family member with known structures solved and an identified receptor. However, very little is known about the cellular mechanisms by which the Bin and aerolysin toxins mediate cell death in insects. While the Bin toxin kills cells from its natural target insect, expression of the receptor in a canine kidney cell line produces initial symptoms of intoxication (vesicle formation and endolysosomal vacuolisation) without resulting in cell death. Other cell factors are, therefore, involved and our unpublished results indicate a role for glycolipids (Bin toxin) and cholesterol (aerolysin) in toxin binding, and phosphoinositol and calcium signalling in vacuolisation. Of further interest is that whilst healthy mammalian cells do not succumb to these toxins, cancer cells that have altered glycolipids are susceptible, providing further evidence for this mechanism in insects and a potential novel tool for cancer biology in future. Ultimately, the aims of this project are to improve our understanding of the molecular mechanisms of these toxins allowing us to delay/overcome environmentally friendly pesticide resistance, adapt their target range and develop new biochemical lipid binding research tools that have a wider relevance (e.g. cancer imaging or targeting). This multi-disciplinary project will determine the exact cellular mechanisms by which the insecticidal toxins mediate cell death in vitro (insect cell lines) and in situ (insects) alongside the use of mammalian cells and expression systems to identify key mechanisms in the absence of cell death. These assays will be joined by analysis of target lipid binding and 3D protein modelling of toxin-lipid interaction. The student will gain experience in cutting edge fluorescence and super-resolution confocal imaging, lightsheet microscopy, lipid biochemistry, intracellular signalling, endocytosis and organelle biogenesis, protein expression and mutation and crystallisation trials alongside protein molecular modelling/docking studies. Applicants for this PhD would benefit from having a degree in a biological subject.