**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | RI LISCB Fox |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Unravelling the dynamics of BAK oligomerisation in apoptotic cell death | |
| **Project Highlights:** | 1. | Utilisation of Cryo-EM to visualise the structure of BAK oligomers |
| 2. | Single molecule imaging of the dynamics of BAK oligomerisation |
| 3. | Defining a mechanism for the self-assembly of BAK into oligomers capable of rupturing the mitochondrial membrane |
| **Project Summary** | | |
| Whether a cell dies or not has profound consequences on health. If programmed cell death (apoptosis) is not correctly executed it can lead to numerous human diseases, including AIDS, degenerative diseases, autoimmune diseases and particularly cancer.  Understanding the regulation of apoptosis is essential to ensure the highly controlled process of cell death proceeds correctly and cellular homeostasis is maintained. Commitment to and regulation of apoptosis is dependent largely on protein-protein interactions and the formation of multi-protein complexes that disrupt the outer mitochondrial membrane committing the cell to apoptotic cell death.  The intrinsic or mitochondrial apoptotic pathway is triggered by stresses including oxidative stress, irradiation, DNA damage and treatment with cytotoxic drugs. Crucial in regulating the intrinsic pathway is the Bcl-2 family of proteins, which contains both pro and anti-apoptotic proteins. For apoptosis to proceed the BCL-2 effector proteins BAK and BAX must be activated. The relative abundances and interactions that occur between the anti- and pro- apoptotic BCL-2 family proteins determines whether a cell is committed to apoptotic cell death.  Effector protein BAK is an essential member of the apoptosis machinery, it is tethered to the outer mitochondrial membrane and once activated, BAK undergoes conformational changes which enables it to first form dimers, then higher order oligomers. The clustering of the dimers in the membrane results in mitochondrial outer membrane permeabilization (MOMP). MOMP allows the release of factors, such as cytochrome c, which activate the caspase cascade and commit a cell to death. Although the protein structures of the BAK monomer and dimer have been solved by crystallography, these represent snap-shots of a highly dynamic process.  This project aims to utilise different approaches to characterise the process of BAK oligomerisation. Firstly, to solve the structure of the BAK oligomer using Cryo-EM in the presence and absence of lipids. Secondly, to use single molecule microscopy to study the process of BAK dimerization and oligomerisation, both using novel synthetic supports and in the context of liposomes which mimic the lipid make up of mitochondrial membrane. | | |