An exploration of the links between mitochondrial function and splicing regulation

Supervisory team:
Main supervisor: Prof Lorna Harries (University of Exeter)
Second supervisor: Prof Mark Lindsay (University of Bath)
Dr Nicola Jeffery (University of Exeter)

Host institution: University of Exeter (Streatham)

Project description:
Alternative splicing (the ability of cells to make multiple types of RNA messages from a single gene) and problems with the function of mitochondria are both frequently found in connection with important human diseases, but the links between them are not clear. It may be that disruption of mitochondrial function causes disruption of patterns of alternative splicing, the converse may be true, or a combination of both. There is not much known about the links between the two processes, but a better understanding of how one impacts the other may lead to new treatments for disease. In this project the student will unravel the basis of this association by looking to see whether changes in patterns of alternative splicing are produced in specifically in response to low doses of chemicals which damage mitochondria. Changes to how splicing is regulated arising from this treatment and the precise effects of this on the portfolio of RNA messages made by the cell will then be determined by measuring the entire RNA output from the cell, followed by mathematical means of turning those data from a list of interesting genes to a network, which will identify which are the important genes causing changes in function. Secondly, the student will look to see if disrupting patterns of normal alternative splicing results in mitochondrial damage. We will target the agents that bring about splicing regulation and then look to see if there are changes in how well the mitochondria process glucose to make ATP, or whether there are changes to their morphology or their viability. Finally, genes at the interface of mitochondrial function and alternative splicing identified through our mathematical analysis will be manipulated in vitro to determine whether it is possible to guard the cells against mitochondrial damage by manipulating splicing patterns, or to safeguard the splicing patterns of the cell by attenuating mitochondrial function.