PhD opportunity September 2019.

Fully funded PhD opportunity from the MRC, in conjunction with Imperial College and AstraZeneca.

"Understanding the role of cohesin and the impact of structural variation on gene expression regulation in the 3D genome"

Professor Nigel Gooderham, Imperial College, London.
Dr Rhiannon David, AstraZeneca, Cambridge.

The genome has a three-dimensional (3D) configuration and is interconnected with nuclear architecture, both of which are critical for gene regulation and cell functionality in normal physiology and disease. An important yet unexplored area of research is how gene expression is regulated in the 3D genome. Structural variation (SV) can disrupt the 3D architecture resulting in dysregulated gene expression, which importantly can affect genes distant from the SV. If these genes are tumour promoters or suppressors this could lead to cancer.

In the 3D genome, DNA is organised into clusters of loops called Topologically Associated Domains (TADs) and cohesin is essential for TADs and chromatin loops at sites of DNA replication or repair. CTCF is a protein that binds to a highly conserved DNA motif to regulate TADs and chromatin loops, and mutations have been reported in CTCF/cohesin binding sites (CSBs); these sites are frequently mutated in cancer. The causes and consequences of these mutations are not fully understood but may lead to aberrant gene expression and epigenetic changes, as well as genetic instability.

Micronuclei (MN) form from damaged DNA; however, the sequence context of these MN is not known. If the consensus sequence associated with CTCF binding domains is present in MN, it would help determine the importance of the CTCF sequence as a site for mutation. Moreover, linking this to aberrant gene expression and potentially associating this with different compound classes may provide a 'mutation signature', the power of which is being realised for cancer diagnosis and treatment, and could provide a more predictive measure of genotoxicity.

This PhD will combine the use of cutting-edge techniques such as next generation sequencing (NGS; e.g. single cell, low error-rate) and associated bioinformatics, MER-FISH, and high content robotic imaging with the development of novel assays to identify mutation signatures and investigate the functional consequences of these.

Applicants should have a Master's degree in a biological sciences discipline. Experience of cell culture techniques, NGS, and/or bioinformatics is desirable. The student will be expected to spend a significant portion of the project at AstraZeneca in Cambridge. This is

an excellent opportunity to gain industrial research experience whilst maintaining academic links.

Informal enquiries to Professor Nigel Gooderham (n.gooderham@imperial.ac.uk) or Dr Rhiannon David (rhiannon.david@astrazeneca.com).

Stipend: Current MRC rates plus an Imperial College/AstraZeneca supplement (4 years). Tuition fees paid. Start date Sept 2019.

Please send applications, including a CV and personal statement to:
n.gooderham@imperial.ac.uk or rhiannon.david@astrazeneca.com

Deadline for applications 31st July 2019.
Interviews to be held during August 2019 at AstraZeneca, Cambridge