Mechanistic integration of replication origin control and chromatin remodelling at centromeres: implications for chromosomal instability in colorectal cancer

Supervisory Team: Professor Christian Speck, Institute of Clinical Sciences (Imperial) and Professor Jessica Downs, Division of Cell and Molecular Biology (ICR)

Project Summary: Chromosomal instability (CIN) is a key driver of cancer evolution, fuelling tumour heterogeneity and resistance to therapy. A major source of CIN arises when DNA replication and chromatin organisation are mis-coordinated at centromeres - the chromosomal regions that ensure accurate segregation during cell division. How replication origins are regulated within centromeric chromatin, and how this process fails in cancer, remains a fundamental unanswered question.
This interdisciplinary PhD project will explore how the Origin Recognition Complex (ORC) and SWI/SNF chromatin remodelling complexes interact to control replication timing and centromere integrity, and how their disruption contributes to CIN in colorectal cancer (CRC). The student will investigate how these pathways coordinate CENP-A, the histone variant that defines centromere identity, using state-of-the-art molecular, computational, and imaging approaches.

Working jointly between Imperial College London (Prof. Christian Speck) and the Institute of Cancer Research (Prof. Jessica Downs), the student will apply a true convergence science approach, integrating multiple disciplines:

- Quantitative proteomics (ChIP–MS) and genome-wide mapping (ChIP–EXO, OK-seq) to define replication and chromatin interactions.
- Computational structural biology using AlphaFold2-Multimer, SPOC, and SpatialPPI to predict and validate protein interaction networks.
- CRISPR genome editing and super-resolution microscopy (STED and lattice-SIM) to visualise centromere dynamics in living cancer cells.

Through this work, the student will uncover the molecular links between replication origin control, chromatin remodelling, and genome instability, generating insights relevant to cancer initiation and therapeutic vulnerability.

The project provides outstanding training across molecular biology, biochemistry, bioinformatics, and cancer cell biology, within the collaborative environment of the CRUK Convergence Science Centre. The student will spend time in both partner laboratories (approximately 55% Imperial, 45% ICR), gaining access to world-class facilities, structured cross-disciplinary training, and professional development through the Convergence Training Programme.

This PhD offers a unique opportunity to join a vibrant, collaborative research community and contribute to understanding how genome maintenance mechanisms fail in cancer-knowledge that could inform new strategies to predict and overcome therapeutic resistance.

Literature references

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Key words:
1. Cancer Biology
2. AlphaFold
3. DNA replication
4. Mass-spectrometry
5. Centromere

Project suitable for a student with a background in: Life Sciences