**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Epigenetics of early human development: From molecular mechanisms to regenerative medicine |
| **Project Summary**  |
| **Ever wondered how nature maintains balance of gene expression between sex chromosomes?** Well, the 46th chromosome of XX females, the second X, has to be switched off. That way females equalize gene dosage of X-linked genes with XY males. The process of X-inactivation is an incredible event of whole chromosome silencing which occurs during embryonic development. Without this act of self-silencing of the X, female embryos won't survive, while X-inactivation can influence human health, from genetic diseases to cancer.  **But how does this "switch off" button work? And what happens if it malfunctions?** If you've got a passion for understanding the foundations of life, developing strategies for regenerative medicine and you're in for a multidisciplinary research journey, join our mission to unravel the secrets of X-inactivation! **What You'll Explore:** * **XIST-SMACs**: We've recently discovered these tiny molecular machines, which are key players in the silencing of the X chromosome (Markaki et al., 2021). We now want to investigate how XIST-SMACs form and control X-inactivation during human embryonic development when the process is established.
* **Frontline Tech:** Dive deep into human development using human pluripotent stem cells and super-resolution microscopy to observe changes on the inactivating X chromosome.
* **Cold Revelations:** Harness the power of cryo-electron microscopy to get up close and personal with XIST-SMACs, RNA-protein supercomplexes that regulate X-inactivation.
* **Chemical Resets:** Experiment with cutting-edge chemical tools to reset X-inactivation, paving the way for improved cell therapies.

**Why This Matters:** Many pregnancies terminate during the mysterious time of X-inactivation while human pluripotent stem cells exhibit defects in the maintenance of the silenced X when being cultured and are thus inappropriate for regenerative medicine applications. With your help, we can unravel why this happens and develop new therapeutic strategies for X-linked diseases. **Where You'll Thrive:** You'll be part of the Department of Cell and Molecular Biology and become a proud member of the Leicester Institute of Structural and Chemical Biology (LISCB), a research institute of excellence offering access to world class facilities. Through the guidance of our expert team in developmental epigenetics, imaging, structural and chemical biology you'll embark on a holistic learning journey, mastering stem cells, genome editing, super-resolution microscopy, and more! **Ready to make a mark in science? Embark on a PhD journey that takes you to the very heart of life's mysteries.** **Techniques that will be undertaken during the project*** Pluripotent stem cell culturing methods
* Cloning and other molecular biology methods
* Gene editing and bioengineering techniques using CRISPR/Cas9
* RNA/DNA Fluorescence In Situ Hybridization (FISH), immunofluorescence
* Super-Resolution and Confocal Laser Scanning Microscopy
* Biochemical protein-RNA/protein-protein interaction assays and affinity purification
* High-resolution structural studies: small angle X-ray scattering, cryo-electron microscopy and other structural biology methods
* Data analysis and visualization in Fiji, R and Python
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| **References** |
| 1. **Markaki Y\***, Chong JG, Wang Y, Jacobson EC, Luong C, Tan SYX, Jachowicz JW, Strehle M, Maestrini D, Dror I, Mistry BA, Schöneberg J, Banerjee A, Guttman M, Chou T**\***, Plath K**\***. *Xist nucleates local protein gradients to propagate silencing across the X chromosome*. Cell. 2021. 2. Bailey LT, Northall SJ, **Schalch T.** *Breakers and amplifiers in chromatin circuitry: acetylation and ubiquitination control the heterochromatin machinery*. Curr Opin Struct Biol. 2021; 71:156-163. 3. Kraus F, Miron E, Demmerle J, Chitiashvili T, Budco A, Alle Q, Matsuda A, Leonhardt H, Schermelleh L, **Markaki Y.** *Quantitative 3D structured illumination microscopy of nuclear structures.* Nat Protoc. 2017;12(5):1011-28. |

**To apply please refer to**

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