**University of Leicester**

**BBSRC MIBTP Studentship Project 2025-6 entry.**

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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.
* **Next-generation sequencing Revelations:** Harness the power of omics technologies to get up close and personal with the transcriptional output of XIST-SMACs and how they regulate genes on the inactive X.
* **Genomic Resets:** Experiment with cutting-edge genome editing 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 Molecular and Cell Biology and become a proud member of the Leicester Institute of Structural and Chemical Biology (LISCB), an institute of excellence offering access to world class facilities. You will collaborate with the University of Warwick, Cell and Developmental Biology Cluster with a team harbouring unique expertise in developmental models and omics technologies. Through the guidance of our expert teams in developmental epigenetics, imaging and transcriptomics 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* Human pluripotent stem cell culturing and differentiation 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
* Next-generation sequencing, transcriptomics
* Data analysis and visualization in Fiji, R and Python
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| **References** |
| **1.** Dror I, Chitiashvili T, Tan, SYX, Cano CT, Sahakyan A, **Markaki Y**, Chronis C, Collier  AJ, Deng W, Liang G, Sun Y, Afasizheva A, Miller J, Xiao W, Black DL, Ding F, Plath K. *XIST directly regulates X-linked and autosomal genes in naive human pluripotent cells.*[**Cell**](https://www.sciencedirect.com/science/article/pii/S0092867423013193)**.** 2024 **2. 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**](https://www.cell.com/cell/fulltext/S0092-8674%2821%2901275-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867421012757%3Fshowall%3Dtrue)**.** 2021  **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**](https://www.nature.com/articles/nprot.2017.020). 2017  |