Project Title: "Establishing the impact of cellular and tissue context on malignant transformation"

Group Leader: Samra Turajlić

Research Group: Cancer Dynamics

The same genetic alteration can arise in diverse cell types across the human body, yet it drives tumorigenesis only within a permissive cellular and tissue context. Understanding the factors that drive this tissue specificity remains a fundamental question in cancer biology.

To explore this question, we focus on hereditary cancer predisposition syndromes such as *VHL* disease, where patients carry a pathogenic mutation in every cell of their body, yet tumours arise only in a remarkably restricted set of tissues, including clear cell renal cell carcinoma, hemangioblastomas, and pheochromocytoma. This stereotyped pattern of tissue specificity provides a tractable framework to understand how the same genetic alterations can lead to distinct tumorigenesis outcomes depending on the cellular and tissue context.

This PhD project will exploit hereditary cancer predisposition syndromes as a model to investigate questions including:

1. Why do the same genetic mutations cause cancer only in specific tissues?
2. What is the role of the cellular and tissue context in permitting or restricting malignant transformation?
3. Can dissecting these genotype–phenotype relationships reveal tissue-specific vulnerabilities for early interception?

One example approach is the use of patient-derived induced pluripotent stem cells (iPSCs) to generate a panel of disease-relevant tissue lineages *in vitro*. This represents a unique pre-clinical model system to study the interplay between the genetic alteration and the unique molecular, functional, and micro-environmental landscape of the permissive cellular and/or tissue contexts.

In the lab, we combine deep phenotyping of patient samples, pre-clinical modelling (patient-derived organoids, tissue fragments and iPSCs, combined with genome engineering and functional experiments), multi-omics data analysis and mathematical simulations. We welcome applicants with interests in cancer biology, tumour evolution, tumour microenvironment, and/or functional genomics. We will fit the exact project to best suit the candidate and their interest and aptitude and both wet lab and dry lab projects are feasible.

Key References

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