Blueprints of disease: precision platforms for modelling breast cancer

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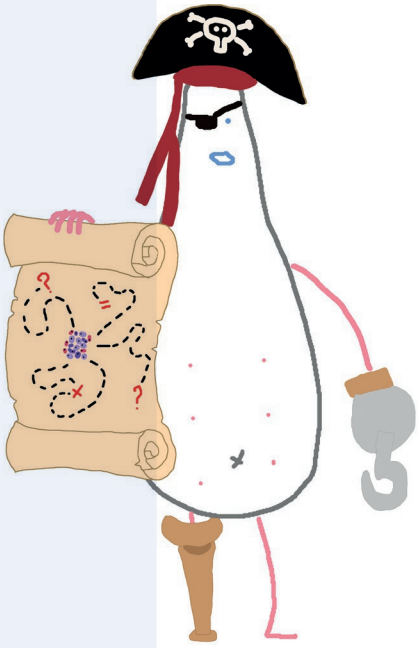

CHAPTER 1

Outline of this thesis

Breast cancer (BC) is a clinically and biologically heterogeneous disease. Luminal BC, the most prevalent subtype, is characterised by its dependence on hormones and presents ongoing challenges for treatment stratification and mechanistic understanding, in large part due to the lack of clinically relevant models. The overarching aim of this thesis is to develop, refine, and apply diverse preclinical modelling platforms to interrogate the drivers of luminal BC progression, heterogeneity, and therapeutic response. By combining *in vivo* modelling, genomic engineering, and large-scale phenotypic profiling, this work provides novel tools and insights into the functional biology of luminal BC. The thesis is structured around multiple platform modelling strategies, each applying new and refined techniques to address complementary aspects of (luminal) BC modelling and tumour biology.

Chapter 2 provides a comprehensive overview of luminal BC, discussing its clinical, molecular, and evolutionary complexity. It reviews the current understanding of hormone receptor-positive (HR+) disease, therapeutic challenges such as endocrine therapy (ET) resistance, and the limitations of existing preclinical models. This chapter establishes the conceptual framework and clinical relevance that underpin the experimental work presented in the following chapters.

Focussed on preclinical luminal BC modelling, **chapter 3** presents the development and characterisation of HR+ BC models, employing rats, an underutilised species with several biological advantages for luminal tumour modelling. The study highlights the anatomical and hormonal fidelity of the rat mammary gland, demonstrating its suitability for modelling oestrogen receptor-positive (ER+) disease and laying the foundation for the somatic modelling strategies that follow.

Building on the expertise of over 100 years of rat modelling described in the previous chapter, **chapter 4** introduces the SMART (somatically modified autochthonous rat tumour) platform, an *in vivo* modelling system enabling the induction of specific oncogenic drivers via intraductal lentiviral delivery. Through systematic genetic perturbation, these models reveal genotype-phenotype relationships in luminal BC and uncover how distinct combinations of driver mutations influence tumour morphology, ER expression, and immune contexture. These models also reveal PPARG as a novel driver of ET resistance.

Chapter 5 focuses on refining modelling techniques by applying CRISPR-Cas9 base editing in the mammary epithelium of mice, establishing a novel method for introducing clinically relevant point mutations with high precision. This work demonstrates the feasibility of single-nucleotide resolution editing *in situ*, providing a powerful tool for dissecting the functional consequences of patient-observed mutations within a somatic modelling framework.

Cell line-derived xenograft (CDX) models are widely used in preclinical research due to their ease of establishment and the formation of relatively homogeneous lesions. **Chapter 6** presents a large-scale phenotypic and transcriptomic characterisation of orthotopic CDX models, generated from a diverse panel of BC cell lines. By evaluating these models *in vivo*, the study identifies conserved transcriptional programmes that drive tumour morphology and aggressiveness beyond traditional subtype classifications, highlighting a central role for TGF-β signalling. This work illustrates how scale and model diversity can reveal insights not apparent in individual systems.

Chapter 7 synthesises the findings across all studies, discussing their broader implications for luminal BC modelling and translational research. It reflects on the value of platform-based modelling strategies, considers current limitations and future directions, and outlines how these approaches may inform the development of more predictive, patient-relevant cancer models.

Together, these chapters form an integrated body of work aimed at bridging the gap between preclinical models and the clinical realities of luminal BC.