ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by: ICR

Project details

Project title:	Uncovering mutational processes associated to immune surveillance during breast cancer development and therapeutic interventions

Supervisory team

Primary Supervisor:	Dr. Luis Zapata Ortiz
Associate Supervisor(s):	Dr Beatriz Monterde
Secondary Supervisor:	Prof. Chris Lord

Divisional affiliation

Primary Division:	Molecular Pathology - CEC
Primary Team:	Evolutionary Immunogenomics
Site:	Sutton

Project background

Breast cancer remains a leading cause of cancer-related deaths in women globally, influenced by both genetic and environmental factors. While molecular classifications like luminal A/B, HER2-positive, or triple-negative guide clinical decisions, they often overlook the crucial role of the immune system in cancer development and progression.

Immunoediting, a process that selects for cells with low immunogenicity, is vital in controlling malignant growth. Recent research by Zapata et al. has shown that immunoediting leads to tumor cells with fewer neoantigens or enhanced immune evasion capabilities. They introduced a metric based on mutations within the immunopeptidome to quantify immune selection across tumors, demonstrating that strong immunoediting is associated with high CD8-T cell infiltration and depletion of antigens.

Genetic predisposition, particularly BRCA mutations, significantly increases breast cancer risk. However, the interplay between these genetic factors and the immune system in healthy and premalignant tissues remains poorly understood. This project aims to bridge this knowledge gap by studying immune cell populations and their spatial distribution in healthy breast tissues, including those from individuals with BRCA mutations.

Furthermore, treatment strategies like PARP inhibitors have shown promise in BRCA-mutated breast cancers. However, patients often acquire resistance through additional somatic mutations generated during treatment. However, the treatment impact on mutational signatures and subsequent immune responses is not fully elucidated. Understanding how these treatments influence the tumor immune microenvironment could provide insights into treatment efficacy and potential combination therapies.

By integrating analyses of healthy tissues, premalignant lesions, and treated tumors, this project seeks to unravel the complex dynamics of immune-mediated cancer control. This comprehensive approach aims to enhance our understanding of breast cancer evolution, the role of immunoediting in both cancer prevention and treatment response, and potentially pave the way for improved therapeutic strategies.

Project aims

- To characterize immune cell populations and their spatial distribution within healthy and premalignant breast tissues, with a focus on BRCA mutation carriers.
- To determine how genetic predisposition, particularly BRCA mutations, shapes the immune landscape of premalignant tissues.
- To investigate the impact of PARP inhibitor treatment on mutational signatures and subsequent immune responses in breast cancer.

Research proposal

This research proposal aims to unravel the complex interplay between genetic predisposition, immune response, and treatment effects in breast cancer development and progression. By integrating analyses of healthy tissues, premalignant lesions, and treated tumors, we seek to gain a comprehensive understanding of immune-mediated cancer control and its implications for therapy.

1. Characterizing Immune Cell Populations in Healthy and Premalignant Breast Tissues

To investigate immune selection and the nature of immune cells within breast tissues, we will utilize a unique cohort from the Breast Cancer Now Biobank repository. This cohort comprises 57 non-cancerous resected breast tissue sections, including 20 cosmetic reductions (without genetic predisposition), 17 prophylactic/contralateral mastectomies (indicating hereditary predisposition), and 20 tumor-adjacent normal tissues. This diverse set provides an exceptional opportunity to explore mammary cell-environment interactions in healthy and premalignant tissues with and without predisposition to malignancy.

Methodology: a) Laser microdissection will be used to retrieve mammary cell DNA/RNA from tissue slides for Bulk Whole Exome Sequencing (WES) and RNA-seq. b) Advanced computational methods will be employed to unravel breast-specific somatic variations, decipher tumor purity, and subclonal structures. c) SOPRANO, an in-house method, will aid in ascertaining immune-mediated negative selection and identifying diverse immune evasion mechanisms. d) Single-cell RNA sequencing (scRNA-seq) will be performed to reveal distinct immune signatures, particularly focusing on differences between BRCA mutant and BRCA wild-type samples. e) Spatial transcriptomics (Visium-HD) will be used to determine the spatial distribution and interactions of clonal populations of healthy and immune cells. f) Immunofluorescence and multiplex immunofluorescence (mIF) will be employed to detect a range of lymphocytes and evaluate the expression of immune modulatory receptors. g) Single-cell TCR sequencing will augment our analysis, shedding light on the T-cell repertoire.

This multi-faceted approach will provide a comprehensive view of the immune landscape in healthy and premalignant breast tissues, with a particular focus on how BRCA mutations influence this landscape.

2. Investigating the Impact of PARP Inhibitor Treatment on Mutational Signatures and Immune Response

PARP inhibitors have shown significant promise in treating BRCA-mutated breast cancers. However, patients acquire resistance through additional mutations that restore BRCA function making cells insensitive to the treatment. Whether these mutations were pre-existing or where acquired de novo remains to be determined. For this, we will explore the impact of treatment on mutational signatures and subsequent immune responses.

Methodology: a) Analyze genomic and transcriptomic data from breast cancer patients treated with PARP inhibitors, focusing on pre- and post-treatment samples. b) Employ advanced computational methods to identify treatment-

induced mutational signatures. c) Investigate how these mutational signatures correlate with changes in neoantigen load and immune cell infiltration. d) Analyze the expression of immune-related genes and pathways in response to PARP inhibitor treatment. e) Utilize single-cell RNA sequencing to characterize changes in immune cell populations and states following treatment. f) Develop and apply computational models to predict immunogenicity of treatment-induced mutations.

This analysis will provide insights into how PARP inhibitor treatment shapes the tumor immune microenvironment, potentially revealing mechanisms of treatment response and resistance.

3. Identifying Genetic Programs Associated with Immune Evasion

Tumors refine their genetic blueprint to evade immune defenses. By studying these genetic adaptations, we aim to uncover both common and suppressed genetic programs that assist tumors in skirting the immune system.

Methodology: a) Utilize datasets from Genomics England (GEL) and TCGA to search for genetic patterns suggestive of immune evasion. b) Identify recurrent genetic tactics and track suppressed sequences due to immune pressure. c) Reconstruct the genetic timeline to determine whether evasion mechanisms are inherent or develop over time. d) Analyze if therapeutic interventions inadvertently bolster the tumor's evasion capabilities by comparing pre- and post-treatment genetic profiles. e) Use the immune dN/dS metric to discern if the tumor's evolution was influenced by the immune system.

Expected Outcomes:

1. A comprehensive atlas of immune cell populations and their spatial distribution in healthy and premalignant breast tissues, with a focus on BRCA mutation carriers.
2. Insights into how BRCA mutations shape the immune landscape of premalignant tissues, potentially revealing early events in cancer development.
3. A detailed understanding of how PARP inhibitor treatment influences mutational signatures and immune responses in breast cancer.

Literature references

[1] Zapata, L., Caravagna, G., Williams, M. J., et al. (2023). Immune selection determines tumor antigenicity and influences response to checkpoint inhibitors. Nature Genetics.
[2] Lips, E. H., Kumar, T., Megalios, A., et al. (2022). Genomic analysis defines clonal relationships of ductal carcinoma in situ and recurrent invasive breast cancer. Nature Genetics, 54, 850–860.
[3] Priestley, P., Baber, J., Lolkema, M. P., et al. (2019). Pan-cancer whole-genome analyses of metastatic solid tumours. Nature, 575, 210–216.
[4] Dunn, G. P., Bruce, A. T., Ikeda, H., Old, L. J. & Schreiber, R. D. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. Nature Immunology, 3, 991–998.
[5] Lhuillier, C., Rudqvist, N. P., Elemento, O., Formenti, S. C. & Demaria, S. (2019). Radiation therapy and anti-tumor immunity: Exposing immunogenic mutations to the immune system. Genome Medicine, 11, 1–10.

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:	Bsc. Biology, Bsc. Computational Engineering, Bsc. Mathematics, Bsc. Physics, Bsc. Biotechnology, Bsc. Bioinformatics

Intended learning outcomes:	• Comprehensive understanding of cancer immunology, with a focus on immunoediting and its role in breast cancer development and progression. • Proficiency in advanced genomic and transcriptomic analysis techniques, including whole exome sequencing, RNA-seq, and single-cell RNA sequencing. • Expertise in spatial transcriptomics and multiplexed imaging techniques for analyzing the tumor microenvironment. • Advanced computational skills for integrating and analyzing multi-omics data, including the development of novel algorithms for quantifying immune selection. • In-depth knowledge of breast cancer biology, including the impact of genetic predisposition (e.g., BRCA mutations) on cancer development and treatment response. • Understanding of how cancer treatments, particularly PARP inhibitors, influence mutational signatures and immune responses. • Ability to design and execute complex, multidisciplinary research projects, integrating wet lab experiments with computational analyses.

Advertising details

Project suitable for a student with a background in:	☒ Biological Sciences ☒ Physics or Engineering ☐ Chemistry ☒ Maths, Statistics or Epidemiology ☒ Computer Science