Characterising and targeting sub-clonal diversity for improved patient stratification in therapy resistant (metastatic) lobular breast cancer

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Invasive lobular breast carcinomas (ILC) is the most frequent special histological subtype of BC characterised by the loss of the cell adhesion glycoprotein E-cadherin, and accounts for 10-15% of all breast cancers (BC). Overall ILC’s show distinct clinical responses to standard of care compared to invasive ductal carcinomas showing poorer 10-year survival rates (1,2) and low Oncotype DX recurrence scores suggesting a lack of benefit from adjuvant chemotherapy but a better outcome to adjuvant endocrine therapy with aromatase inhibitors (3). In addition, the differential response to CDK4/6 inhibitors in the metastatic setting is unknown (4).

Recent evidence suggests that ILC are unique at the molecular level and differ in their repertoire of driver genes and also their micro-environmental composition (5), highlighting an aggressive subgroup of ILCs that are characterised by an enrichment of immune infiltrate (6). This suggests a subgroup of ILC’s may benefit from immunotherapy. However, the prognostic role and characterisation of immune subpopulations in ILC remains unclear.

Although the majority of ILC relapse after 5 years there are a subgroup of women with ILC who relapse within 5 years and it is not clear whether this subgroup would benefit more from chemotherapy, CDK4/6 inhibitors or immunotherapy. The molecular basis of therapy resistance in ILC remains poorly understood in part due to the lack of methodologies and models to address the sub-clonal and spatial diversity. This in turn limits the ability to investigate rare subpopulations most likely associated with therapy response. We hypothesise that both the genomic and immune microenvironment influence prognosis in ILC and response to therapy and that a combination of these could be useful for patient stratification and for future therapies.

This project will focus on investigating and modelling sub-clonal heterogeneity in therapy resistant forms of lobular breast cancer as a means to identify novel biomarkers and potentially targetable vulnerabilities. In particular we aim to:

1) Determine which tumour subclones within an individual patient are responsible for relapse
2) Test the functional relevance of these subclonal alterations in mediating therapy resistance (and relapse)
3) Ascertain whether the sub-clones responsible for relapse are spatially separated and influenced by the stromal landscape and test whether these correlate with outcome in independent cohorts of ILC.

We will use a combination of molecular barcoding in patient derived and in vivo models to understand the sub-clonal evolution of resistance to endocrine and CDK4/6i. Subclonal alterations that are enriched in therapy resistant samples will be functionally tested as potential targetable vulnerabilities in cell models. Using prospectively collected longitudinal patient samples, we will define the subclonal evolution of ILC using state of the art single cell sequencing approaches and integrate this with our models. Candidate alterations will be assessed as potential prognostic biomarkers in large clinical cohorts of ILC.

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By combining state of the art molecular profiling technologies, integrated genomics analysis and functional interrogation, this project will provide new insights into ILC therapy treatment resistance and derive predictive biomarkers and new therapeutic targets.

This project would be suitable for a pathologist, or clinical or molecular oncologist.

The Functional Genomics team at the ICR focuses on understanding the molecular basis of progression and evolution of therapy resistant forms of breast cancer to identify novel drivers and therapeutic targets of the disease.

Professor Elinor Sawyer’s team at KCL focus on invasive lobular breast cancer genetics and predisposition.

References: