



## WHY A REVOLUTION?

### *Cancer genome's ability to vigorously evolve often leads to metastasis*

Cancer is the number one killer of Americans, and the World Health Organization indicates that cancer cases are expected to surge 57 percent worldwide over the next 20 years. A major reason for this continued mortality is the ability of the cancer genome to undergo dynamic evolution and adapt to otherwise non-permissive environments. Metastatic breast cancer is a striking example of such an evolving disease. Despite significant progress in the treatment of primary breast cancer, metastatic breast cancer remains lethal and responsible for more than 40,000 deaths per year in the United States.

To meet this challenge, we have taken full advantage of the extraordinary resources and expertise in the Pittsburgh region to build a highly-integrated team from the University of Pittsburgh Drug Discovery Institute (UPDDI), the University of Pittsburgh Cancer Institute (UPCI), the Institute for Precision Medicine (IPM), and the Women's Cancer Research Center (WCRC), as well as multiple departments at the University of Pittsburgh and Carnegie Mellon University. Adrian Lee, PhD, is the director of the IPM and the WCRC and is an international leader in breast cancer research. Our metastatic breast cancer program spans the fields of clinical and translational medicine, cancer biology, drug development, computational and systems biology, and engineering. Additionally, this team includes members from the GE Global Research Center to assist in the implementation of a recently developed hyperplexing technology, MultiOmyx (MxIF), an important computational pathology platform.

Breast cancers recur late, often more than five years after initial treatment, allowing a long period for evolution and clonal selection of the cancer cells. Recent advances have highlighted the complexity of intratumor heterogeneity (ITH) that comprises a multitude of tumor clones associated with host stromal and immune cells. Amid this complexity, temporal and spatial patterns of clonal diversification within primary breast tumors have been identified that are beginning to provide important clues regarding the order, rate, and mechanisms involved in the dissemination and continual evolution of the particular clones that lead to advanced metastatic disease. Spatial ITH, resulting from the reciprocal coevolution of tumor clones and their specific microenvironments (i.e., stromal and immune cells, and associated extracellular matrices), is a prominent feature of breast cancer that correlates with clinical outcomes.

Our focus is to understand the mechanistic relationship between spatial ITH evolution and disease progression with the goal of translating this knowledge into improved prognostic indicators and therapeutic strategies for individual breast cancer patients. We plan to do this by harnessing the new field of quantitative systems pharmacology (QSP), which is defined as determining the mechanisms of disease progression and drug reactions through iterative and integrated experimental and computational methods to optimize the development of diagnostic and therapeutic strategies.

Our team makes full use of a patient-focused, comprehensive, unbiased QSP strategy to do the following:

- Implement MxIF to quantify and understand spatial ITH in breast cancers
- Integrate this hyperplexed image data with genomics including commercial gene tests, transcriptomics, epigenomics, and clinical data to model the molecular evolution of spatial ITH and its relationship to disease progression

- Test, refine, and validate these models through iterative, multiscale experimental and computational analysis that includes the development of human “organ-on-chip” models that emulate critical aspects of metastatic disease

Our work will be transformative to fundamental cancer biology and translational research. It enables the determination of spatial ITH evolution and signaling interactions with the tumor microenvironment (TME), thereby identifying the following:

- Prospective tumor sub-clones that could give rise to metastasis
- Potential clinical benefits of treating sub-clonal actionable mutations
- Novel therapeutic strategies involving targetable heterotypic interactions with host cells in the TME
- Ways to predict and strategies to address the mechanisms of therapeutic resistance

Translational efforts are underway with the filing of patents on an organ-on-a-chip technology used to build in vitro metastatic niches that are patient-specific. Furthermore, we have a patent application for quantifying spatial heterogeneity in tissues. These technologies will allow us to investigate the dynamics of metastases and individual drug testing.

Our short-term goal is to understand spatial relationships that are systematically linked to disease progression, both in patient samples and experimental models. Longer-term goals include the development of optimal diagnostics, therapeutic strategies, and drug discovery projects for genetically-related groups of breast cancer patients.

## Questions?

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