Fred Hutch Cancer Center

2025-2026 Research Goals

Building on lessons learned with new tools

Drs. Specht and Yeung made early observations that CAR T cells (*i.e.,* the engineered cells that are designed to attack the tumor as an immunotherapy treatment) may become “exhausted,” resulting in diminished elimination of tumors. To better understand why CAR T cells become “exhausted”, the researchers need to better understand what types of CAR T cells successfully invade the tumor and what their function is.

With continued support from the **Judith A. Lese Breast Cancer Foundation,** they have plans to investigate a new assay that will be an extension of the two assays that they recently developed (See *Research Progress Report*). This new assay aims to quantify/measure CAR T cell genetic programming transcripts inside tumor samples.

Additionally, they plan to expand their current work evaluating breast tumor spatial transcriptomics to analyze CAR T cell invasion into tumor biopsies that were collected from a different breast cancer study conducted at FHCC lead by Dr. Specht.

Genomic analysis of breast cancers help predict treatment outcomes

Drs. Specht, Yeung, and Symonds examined the whole genomes of breast cancers, focusing on patients with hormone receptor positive, human epidermal growth factor receptor 2 negative (HR+/HER-) breast cancers which are generally associated with a more favorable prognosis. While most patients with this common type of breast cancer have a very good prognosis, there are a subset who have poorer outcomes with higher risk of breast cancer recurrence and death. They hypothesized that, by looking at the whole genomes of these cancers before treatment, there may be some features to help cancer doctors differentiate among those tumors with excellent or poor outcomes.

They examined the whole genome of many different (HR+/HER-) breast cancers, which are represented in the circus plots below (**Figure 1**). The breast cancer on the left shows a stable genome with few mutations. In contrast, the breast cancer on the right shows a significantly abnormal genome with lots of chromosomal rearrangements and many alterations to the DNA sequence. Significant genomic alterations like these are associated with more aggressive tumors and potentially poorer response to therapy and worse long-term survival.

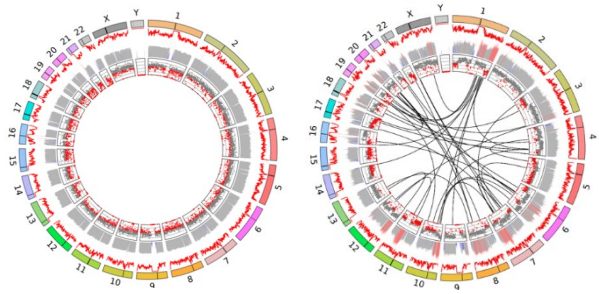


Figure 1. Two HR+/HER- breast cancer genomes represented as circus plots with the chromosomes numbered along the outer, color-coded ring.
Left: This cancer does not have significant genome rearrangements (no.interconnecting.lines.in.the.center) and only has minor changes in its DNA sequence (small.flecks.of.red–blue.in.the.grey.center.ring).
Right: This cancer has many genomic rearrangements (middle.lines) and significant changes in the DNA sequence (red.and.blue.sections.in.the.otherwise.grey.ring).

Spatial transcriptomics: A new tool to study breast cancer

Spatial transcriptomics have opened a vast new world in biomedical research. This technique can visualize up to 477 RNA markers and 54 protein markers in each cell of a microscope slide (of a tumor biopsy, for example).

In this study, the researchers performed spatial transcriptomics on breast cancer tissue, visualizing 377 different RNA markers and painting a complex (literal) picture of the genetic programming in each cell (**Figure 2**). The data is then interpreted by an AI algorithm which categorizes each cell into different types and color coded (left panel). A close-up section (shown in right panel) shows cells overlaid by small color dots (the different RNA markers).

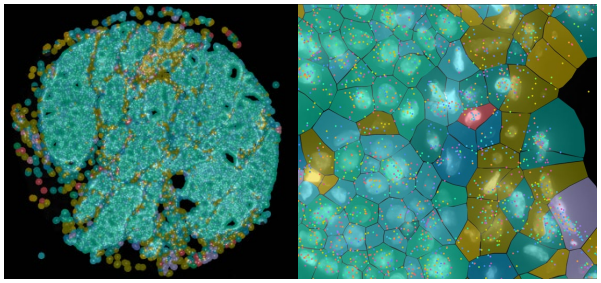


Figure 2. Breast cancer tissue under a microscope which has been categorized and color-coded by cell types, as determined by spatial transcriptomics. Each cell's nucleus is visible underneath in white.

Developing new assays understand immunotherapy side effects

As more cancer patients receive immunotherapy treatments (such as CAR-T and TCR-Ts), we observed a small fraction of patients that experience skin or gut inflammation. To understand why patients are getting these symptoms and to examine how the therapy may or may not be contributing to these bad side effects, we developed two assays using archived patient tissue samples. While the first assay (left) can be done quickly with no specialized equipment, the second assay (right) uses quantitative fluorescence and antibodies to detect the immunotherapy cells and signals. These assays **(Figure 3)** measure WPRE (a signal for the CAR-T or TCR-T cell) combined with CD3 (signal for a T cell), allowing us to find where these genetically-modified therapeutic T cells are and if they are coming into contact with cancer cells or if they are instilling unintended side effects.

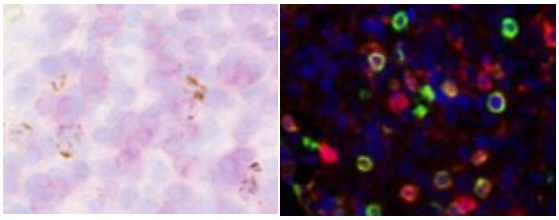
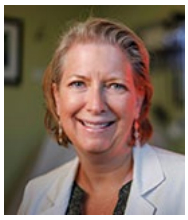


Figure 3. Assay 1 (left) shows CD3 T cells in pink, and the WPRE in brown showing CAR-T/TCR-T. Assay 2 (right) visualizes cell nuclei (blue), CD3 T cells (red), CAR-T/TCR-T (green), and where these cells interact together (slightly yellow).

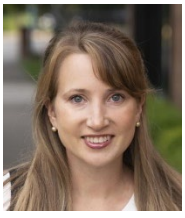
Taken together, the generous funding from the Lese Foundation continues to aid in developing techniques to understand how breast cancer evades therapy and more importantly, offers critical strategies to foster improvements in our therapeutic approaches to improve outcomes for patients with breast cancer.

Meet the Researchers



Jennifer Specht, MD, is a board-certified medical oncologist who specializes in all stages of breast cancer with expertise in triple-negative breast cancer. At Fred Hutch, she leads the Phase 1 Breast Cancer Program. Her research interests include breast cancer genetics, immunotherapy, and molecular imaging to better understand breast cancer biology. She holds the Jill D. Bennett Endowed Professorship in Breast Cancer at UW Medicine.

Cecilia Yeung, MD, is a clinical pathologist, professor, and medical director of Clinical Testing Labs at Fred Hutch and an associate professor in the Department of Laboratory Medicine and Pathology at UW Medicine. Her expertise in molecular pathology has led to novel molecular diagnostic platforms that improve the speed, accuracy and cost of diagnostic tools.



Lynn Symonds, MD, is a medical oncologist who sees patients at the Breast Health Clinic at Fred Hutch and an assistant professor in the Division of Hematology and Oncology at UW Medicine. During her fellowship, she conducted research at Fred Hutch under the advisement of metastatic breast cancer researcher, Dr. Cyrus Ghajar.