Breast Cancer Research Foundation to Fund Seven Cancer Consortium Researchers

BCRF awards $2.6M in grants to Fred Hutch/University of Washington/Seattle Children's Cancer Consortium researchers. Here's what they're investigating.

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Seven scientists with the Fred Hutch Cancer Center/University of Washington/Seattle Children's Cancer Consortium received another year of funding from the Breast Cancer Research Foundation, or BCRF, to pursue research into new therapies, new biomarkers and new vaccines meant to improve outcomes in this deadly disease.

Fred Hutch physician-scientists funded for another year include Executive Vice President and Chief Academic Officer Nancy E. Davidson, MD, holder of the Raisbeck Endowed Chair for Collaborative Research; epidemiologist and Vice President of Faculty Development Christopher "Chris" Li, MD, PhD; epidemiologist and internist Anne McTiernan, MD, PhD; and principal staff scientist Catherine Duggan of Fred Hutch's Public Health Sciences Division.

Fred Hutch breast cancer oncologist and clinical researcher Hannah Linden, MD, who holds the Athena Distinguished Professorship of Breast Cancer Research at UW Medicine, also received funding, as did University of Washington School of Medicine physician-researcher Nora Disis, MD, and American Cancer Society professor of Medicine and Genome Sciences at UW Mary-Claire King, PhD.

Disis, King and Linden are all faculty members in Fred Hutch's Clinical Research Division. All are part of the Cancer Consortium's Breast and Ovary Cancer Research Program, long supported by BCRF. Read on for details of their research projects.

Using multi-omic data to predict metastatic recurrence

Fred Hutch's Li received $225,000 to continue his work in developing specific predictors of breast cancer recurrence.

"More than 90% of breast cancer deaths are due to metastatic recurrence, but our ability to

predict which patients will and will not develop a recurrence and respond well to current therapies remains limited," he said.

The holder of the Helen G. Edson Endowed Chair for Breast Cancer Research, Li is developing molecular subtype-specific predictors that are clinically meaningful, that is, will result in biomarker tests that enable clinicians to determine if a treatment is working for their patients or not.

Li and his team are using spatial transcriptomic analyses for the project, which enables deep characterization of the tumor microenvironment and immune response; both have been shown to have potential translational relevance.

This year, the team will continue to perform deep immune cellular profiling — at single cell resolution — of three molecular subtypes of breast tumor tissue, using biospecimens from more than 200 breast cancer patients recruited through the Fred Hutch BRAVO study (Breast Cancer Risk Factors And Various Outcomes). The BRAVO cohort contains 1,216 luminal A, 607 luminal B, 487 HER2-overexpressing and 1,267 triple-negative breast cancer patients.

Basal-like breast cancer is a subset of triple negative, meaning it lacks common molecular targets like ER, PR and HER2; Luminal A is a slower-growing ER+, HER2- subtype and Luminal B is a more aggressive type of ER+, HER2- disease. By interrogating these tissues, Li and his team aim to develop novel spatial predictors of recurrence that can guide clinical decision-making.

"We hypothesize that there will be important topographical differences in immune and cancer cells that will have clinical utility with respect to predicting risk of recurrence for each of the three breast cancer subtypes studied," he said.

Next steps for the study will be to develop and validate multi-omic predictors of cancer recurrence for the three subtypes using machine learning, then leveraging the multi-omic data generated through this project.

Investigating NRF2 and its impact on tumor microenvironment

Fred Hutch clinical researcher and breast oncologist Davidson received $225,000 to continue collaborating with Fred Hutch translational researcher James Alvarez, PhD, on an investigation of the NRF2 pathway and how it shapes the breast tumor microenvironment, with an eye toward exploiting it to overcome immune checkpoint inhibitor resistance.

NRF2 is associated with tumor recurrence, metastasis and poor prognosis in patients with NRF2-high cancers, which can include colorectal, esophageal, lung, ovarian, breast and other cancers. Preliminary research on NRF2 shows it may also have another role: regulating the tumor immune microenvironment.

"We have developed a panel of preclinical breast cancer models in which NRF2 can be degraded using the dTAG system [a tool for studying protein function]," she said. "These models provide a

powerful system to dissect the temporal effects of NRF2 inhibition on tumor growth and immune regulation in vivo [in living organisms]."

Previous research by Alvarez showed NRF2 knockdown led to slower tumor growth, decreased tumor-infiltrating neutrophils and increased $CD4^+$ (or helper) T cells, "suggesting a specific role for $CD4^+$ T cells in the antitumor response elicited by NRF2 inhibition."

Through pilot studies, they have also confirmed NRF2-high breast cancer tumors do not respond well to single-agent therapy or combined therapy using checkpoint inhibition.

In the coming year, the team will continue to explore the role of the NRF2 pathway in mediating the response and resistance of breast cancers to immune checkpoint inhibitors.

"Building on our current work, we will extend our studies to address how NRF2 functions in distinct immune cell subtypes, and how these functions impact immune checkpoint inhibitor, or ICI, response," Alvarez said. "We will generate mice with NRF2 deleted or activated in specific immune cell types known to be important for ICI response, including CD8 T cells, CD4 T cells and dendritic cells."

These mice will then be used as hosts for studies using breast tumor cell lines known to respond well to checkpoint inhibitors. By comparing ICI response between wild-type, or "control" mice, and mice with immune cell-specific NRF2 knockout/activation, Davidson said they should be able to decipher how the NRF2 pathway functions in immune cells to regulate the anti-tumor immune response.

"NRF2 inhibitors are in clinical development now," she said. "So this work will set the stage for testing NRF2 inhibition as a clinical approach in NRF2-high breast cancers."

Exercise and breast cancer risk

An epidemiologist and internist, Fred Hutch's McTiernan will continue researching the association between physical activity and the reduction of breast cancer risk, working with systems biologist Taran Gujral, PhD, and Public Health Sciences staff scientist Catherine Duggan.

The principal investigator of Fred Hutch's ACE1 and ACE2 study, McTiernan and her team recently published results of their study looking at various biomarkers of women after either exercise, or rest. The ACute Effects of Exercise in Women (ACE), funded by BCRF, examined changes in biomarkers related to inflammation and blood vessel growth in blood and muscle tissue of 102 women without breast cancer. Samples were taken both before and after 45 minutes of acute exercise (riding a stationary bike) or 45 minutes of rest (sitting down).

Their analysis showing that "acute exercise has specific effects on circulating metabolic and inflammatory biomarkers implicated in breast cancer etiology, which differ from weight-loss-induced changes."

While obesity-related chronic inflammation induces insulin resistance, angiogenesis (that is, the formation of new blood vessels) and other changes to the microenvironment that increase the likelihood of a cancer developing, the researchers found exercise-induced skeletal muscle damage triggers a beneficial type of inflammatory response, one that plays a crucial role in muscle regeneration.

In the coming year, McTiernan and collaborators will use the $225,000 in funding to continue to analyze the biological samples from the ACE trials as well as another randomized controlled trial, completed in 2012, that looked at Nutrition and Exercise in Women (NEW), to see whether a change in dietary and exercise patterns resulted in a change in biomarkers of breast cancer risk.

Recent BCRF grantees also included (left to right) ACS professor of Medicine and Genome Sciences at the University of Washington Dr. Mary-Claire King, Fred Hutch staff scientist Dr. Catherine Duggan and Dr. Nora Disis, director of the UW's Cancer Vaccine Institute.

Overcoming 'metabolic obesity' – and cancer – with a vaccine

Is it possible to turn around the damage obesity does to your body's metabolism? Disis, director of the UW's Cancer Vaccine Institute, is working to find out.

In the "metabolically obese," dysfunctional fat or adipose tissue releases pro-inflammatory proteins known as adipokines. This results in metabolic dysfunction in both the adipose tissue and the immune system's T cells, which in turn can lead to impaired immune function and surveillance. Impaired immune function can sometimes result in a malignant transformation, that is, the cells will begin to acquire genetic mutations that lead to uncontrolled growth which can then lead to cancer.

"Importantly, weight loss does not resolve the problem," said Disis, who will be continuing her research on a vaccine to circumvent this process. "Immunologic memory sustains inflammation even after normalization of body weight."

Previously, Disis and her team identified six proteins upregulated in obese adipose tissue, that they then used to create a vaccine capable of restoring metabolic function in immune cells. With last year's BCRF funding, they created and tested the optimal formulation for their adipocyte-directed vaccine, or ADVac, confirming that that the ADVac-specific T cells can traffic to adipose tissue in vaccinated mice.

"Genetic analyses revealed increased expression of four pathways associated with immune response and three pathways associated with cellular metabolism, providing evidence that ADVac may help restore a normal metabolic phenotype," Disis said.

This year's award of $225,000 will go towards determining the optimal doses for the single-antigen vaccines and combining multiple antigens into a single DNA construct for improved immune response.

“The construct that elicits the highest levels of antigen-specific IL-10, a key immunosuppressant, across multiple antigens will be selected as the clinical candidate,” Disis said.

Disis and team will also further investigate vaccine-induced changes to the metabolic function of fat tissue and immune cells and test the safety of the vaccine.

More funding for imaging and genetic studies

Linden, a Fred Hutch breast oncologist and clinical researcher, is lead investigator of a $1.5 million BCRF award to the UW through the Translational Breast Cancer Research Consortium to investigate whether a PET/CT progesterone tracer known as FFNP can better predict response to endocrine therapy coupled with the CDK4/6 inhibitor abemaciclib (Verzenio).

The collaborative clinical trial is being run in conjunction with Washington University in St. Louis, Missouri, and the University of North Carolina, with support from Lilly.

“We’re hoping that the use of FFNP as an imaging agent will provide more precise information about the endocrine activity of metastatic cancer than an FDG-PET scan alone can provide,” said Linden, who previously investigated an estrogen tracer for ER+ breast cancer patients known as FES-PET, approved by the U.S. Food & Drug Administration in 2020.

Linden said due to manufacturing limitations, the FFNP tracer trial is only available at three sites. She also noted it might be of interest to patients with a particular subtype known for its imaging issues.

“The trial is open and accruing well at Fred Hutch and it just opened at UNC,” she said. “The study is for all ER+ metastatic breast cancer patients and is a good study for patients with lobular.”

The first person to determine breast cancer could be inherited, geneticist Mary-Claire King, PhD, whose research was dramatized in the film Decoding Annie Parker, will continue to focus on undiscovered mutations for inherited breast cancer.

King’s $225,000 in BCRF funding will go towards further development of a new technology platform that enables researchers to sequence large swaths of DNA in single very long strands, rather than thousands of short bits. King is also exploring dysregulation of gene expression as a basis for inherited breast cancer.

“For many families severely affected with breast cancer, no inherited causal allele has been detected in any tumor suppressor gene,” she wrote in a recent paper in the Proceedings of National Academy of Science. “The goal of this project was to test whether for some of these ‘unsolved families,’ inherited cancer predisposition could be due to genes with functions other than DNA repair.”

King and her team did whole genome sequencing on affected members of 136 families affected by

breast and/or ovarian cancer but without any common gene mutations found in these diseases, locating 79 SNPs (single nucleotide polymorphisms) of interest. Of those 79 variants, they found one that showed up more often in the affected families.

“Many families who are severely affected with breast cancer have no severely damaging mutation detected by current genomic technology in any of these genes,” she wrote in the paper’s discussion section. “These results demonstrate coinheritance with breast cancer of rare alleles that increase activity of ESR1 promoters and suggest that rare ESR1 regulatory alleles may contribute to inherited predisposition to breast cancer.”

Founded in 1993 by Evelyn H. Lauder, the Breast Cancer Research Foundation is the largest private funder of breast cancer research in the world. By investing in the best minds in science to examine every aspect of the disease from prevention to metastasis — and fostering cross-disciplinary collaboration — BCRF is accelerating the entire field and moving us closer to the answers we urgently need to end breast cancer. Learn more and get involved at BCRF.org.

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