Report to the Catherine Peachey Fund

October 2021

INDIANA UNIVERSITY
MELVIN AND BREN SIMON
COMPREHENSIVE CANCER CENTER

SCHOOL OF MEDICINE
VERA BRADLEY FOUNDATION CENTER
FOR BREAST CANCER RESEARCH

Catherine Peachey Fund Normal Breast Taxonomy Project

Established in 2018, Additional Support in 2019

The gift to initiate the Catherine Peachey Fund Normal Breast Taxonomy Project made history for the Catherine Peachey Fund and Heroes Foundation, and now the work it funds is proving to be historic for the Vera Bradley Foundation Center for Breast Cancer Research at the IU Melvin and Bran Simon Comprehensive Cancer Center.

Dr. Nakshatri used sophisticated single-cell sequencing technology to compare normal and cancerous breast cells to determine the exact cells where cancer originates. The normal cells were contributions from tissue donors to the Susan G. Komen Tissue Bank, and the samples had to be processed within minutes after biopsy. It is the very samples that Connie, Stephanie and other Peachey Fund supporters were able to see Dr. Nakshatri hurriedly carrying from the KTB collection event to his lab that made this work possible.

Ultimately, Dr. Nakshatri, Dr. Storniolo and Dr. Yunlong Liu identified 23 cell types in the normal breast and pinpointed four that give rise to most breast cancers. This finding upended previous assumptions about the origins of breast cancer. The Peachey gift kicked off the project, and the researchers went on to receive $865,000 for this effort from the Chan-Zuckerberg Initiative. The work is now a part of the Human Cell Atlas, a global reference map of all cell types in the human body. Now that these originator cells have been identified, prevention research can focus on disrupting disease development with the potential of developing targeted, non-invasive strategies. His group has now extended these studies to breast tissues of BRCA1 and BRCA2 mutation carriers and find unique differences compared to breast tissues from healthy donors. These findings may help in better understanding breast cancer susceptibility in these mutation carriers.

Dr. Nakshatri received his first funding from the Catherine Peachey Fund. That initial trust launched an impressive career, with many publications made possible through partnership with the Peachey Fund. The first publication listed below is a true milestone in his career. The work is groundbreaking and has allowed prevention research to zero in on only four cell types that give rise to breast cancer. There is no question this new discovery would not have happened without the unique team that is the Catherine Peachey Fund, IU researchers and the Komen Tissue Bank.

Papers and articles featuring the work of the taxonomy project:

A single-cell atlas of the healthy breast tissues reveals clinically relevant clusters of breast epithelial cells

Behind the Scenes of the Human Breast Cell Atlas Project

How Three Scientists Are Working to Make Genetics Research More Diverse

Application of Emerging Proteomics Technologies to Breast Cancer

Supported in 2020

Report from Investigator:

Amber Mosley, PhD
Associate Professor of Biochemistry & Molecular Biology
Indiana University School of Medicine

Since our last update we have been able to acquire the mass spectrometry data and analyze it for ½ of the proposed samples that we had. Unfortunately, the budget was not sufficient to cover the costs of all the samples so we prioritized the ones that we thought would be the most informative. My research group has developed a new version of our computational biology tool – Inflect – which has statistical tests better incorporated into its workflow. Using this approach we have found that low dose treatment (0.1uM) of triple-negative breast cancer cells with the bioactivatable compound IB-DNQ leads to changes in the thermal stability of a number of cell cycle kinase related factors. This is a very interesting result which we hope to follow up with analysis of the 0.4uM IB-DNQ treated cells that we reserved from our initial cell growths. We hope to use internal funds from the Mosley lab to complete this part of the project. If the 0.1uM findings are correct, we would expect to see an increased change that perhaps encompasses more of the signaling cascade with the higher concentration IB-DNQ treatment. The combination treatment with 0.1uM IB-DNA and Rucaparib (a PARP inhibitor) also resulting in some unique insights with the largest alteration seen that histone H2AX phosphorylation – a mark of DNA damage in the genome – leads to destabilization of the H2AX protein. Although H2AX phosphorylation is a frequently used marker of DNA damage, to our knowledge this finding would be the first to show that the phosphorylation is destabilizing to the histone protein. This finding makes sense in light of the fact that histone proteins bundle up and protect DNA, shielding it from other proteins. However, in the case of DNA damage, the histones would need to be removed from the DNA to facilitate DNA repair. If H2AX phosphorylation destabilizes the protein, it would in essence "relax" it at the molecular level which could facilitate it's removal from the DNA to allow for DNA repair to occur. It is an intriguing model! The data on the 0.4uM IB-DNQ treatment will also be very informative to compare to the combination treatment data to identify similarities and differences. I have presented this data in part or in its entirety to the TMM (tumor microenvironment and metastasis) group, the pancreatic cancer working group, and the Department of Medical and Molecular Genetics in the last few months. These data, along with others from the laboratory, clearly show the utility of thermal proteome profiling in uncovering unique mechanisms in diverse cell systems including triple-negative breast cancer cells. We are very grateful to the Catherine Peachey Fund for their support of this work. Each time I have presented this work, I highlight that it was supported by the Peachey Fund on the slide with the data as well as at the end of the presentation.

Identifying the Motivations of Minority Women to Donate Healthy Breast Tissue

Supported in 2020

Report from Investigator:
Katherine E. Ridley-Merriweather, MA

The project is moving forward nicely. I needed to have dedicated assistance on this project, so it is worked on only in the summers, when I participate in an internship program sponsored by the IU School of Medicine. Two phases of the three-phase data collection are complete. In the summer of 2020 we interviewed 20 Black women who had already donated breast tissue, and in the summer of 2021 we interviewed 20 Asian donors. The resulting data is rich and helpful! I have attached here a poster that my intern, Cynthia, presented at the intern final symposium. Next summer I and the newest intern will recruit and individually interview a group of Latinas. The beauty and benefit of conducting this research in this manner is that I have been able to mentor and guide young medical students and work to instill a knowledge and love of research in them.

Link to Grounded Theory Phase 2 presentation

Link to Grounded Theory Phase 2 poster

The grounded theory work is conducted with women who have already donated, to better understand their motivations for doing so. Communication messaging is created during this kind of work.

The current project [2021 proposal] involves women who are unfamiliar with the KTB, to better understand what they might want or need to hear to create or increase an intention to donate. This purpose of this project is to test the messaging created from previous, formative research.

Increasing the Tumor Penetration of Cancer Drugs to Improve the Treatment of Metastatic Tumors

Supported in 2021

The researcher who planned to lead this project has moved to another institution. Dr. Miller and Dr. Nakshatri will soon make a recommendation for how best to move forward. We are thankful to have a partner like Peachey to work so closely with us on making IU breast cancer research possible, and we are committed to ensuring these funds are invested in breast cancer research in the current fiscal year.

Komen Tissue Bank Intern Program

Continued support in 2020 and 2021

Report from the KTB on the Most Recent Intern Support:

Gabriela Zamarripa was our Fall 2020-Spring 2021 intern through the Life Health Science Internship program. She worked 5-8 hours a week, 100% remotely. Some of her projects included Tyrer Cuzick calculations, working on a part of the mammogram project, by reviewing mammograms for any personal health information, and participating with a focus group that interviewed Black women with little to no knowledge of the KTB.

You can check out Gabby's e-portfolio she created about her internship at this link. It includes the summary she wrote of her internship and a slide she created about the KTB.

Megan Wurth has been an intern with us since Spring of 2020. Once of her large projects for 2021 is digitizing the consent and questionnaire donor paperwork so that it can be accessed electronically. She also reviews mammograms remotely and is the point person for social media posting across the different platforms.

Kamryn Benscoter continues to head up our Mammogram Project and has been responsible for the requesting and uploading of mammogram images. She has also been able to use the PowerShare, which allows us to access images through the cloud, eliminating the need for office and hospitals to mail CD's.

Audrey Chesney took over for Gabriela and calculated Tyrer Cuzick scores. She was in the office for much of her summer with us and was able to assist in lab projects such as pulling DNA for the NCI GWAS project and assisting our biospecimen manager with pulling and organizing samples. She was also in charge of updating the status of the samples, depending on certain factors like gene mutations and donors that developed breast cancer after their donation. You can read more about Aubrey's experience with the KTB in this piece she wrote about her internship: A Summer at the Susan G. Komen Tissue Bank with Audrey Chesney.

Catherine Peachey Breast Cancer Prevention Program Fund Updates

The endowed Catherine Peachey Breast Cancer Prevention Program Fund provides income dedicated each year to breast cancer prevention research. This fund is an important tool our researchers use to advance efforts and plan for the future of breast cancer prevention research.

Report from Investigators on Projects Supported in 2020:

Anna Maria Storniolo, MD
Andrew and Peggy Thomson Professor of Hematology/Onco logy
Indiana University School of Medicine

Natascia Marino, PhD
Assistant Research Professor
Indiana University School of Medicine

Epigenetic Changes Among High-Risk Women

To identify molecular differences linked with breast cancer risk, we analyzed cancer-free breast tissue cores donated by 146 healthy women (median age: 39 years) including 112 Caucasian, 24 African American and 10 Asian subjects. Out of 146 participants, 117 were pre- and 29 postmenopausal women. Tyrer-Cuzick model was employed to estimate the lifetime risk of developing BC and allocated the subjects to either high- (score≥20%, N=68) or average-risk group (score<20%, N=78).

The support from the Catherine Peachey Prevention Program Fund helped us to perform the methylome analysis with the goal of identifying alterations in regulatory regions leading to breast cancer susceptibility. We observed DNA methylation changes in high-risk breasts, consisting mostly of hypermethylation (98.8%) in the intronic regions (88%). Hypermethylation in specific gene promoters is linked to carcinogenesis as it may shut down the expression of tumor suppressor genes leading to dysregulation of cell growth, cancer initiation and progression.

We identified a 4-10% overlap between methylome aberrations in high-risk breasts and previously reported cancer-related signatures, suggesting that cancer–related epigenetic marks are newly acquired during cancer initiation rather than being imprinted into the genome.

Moreover, although the expression DNA methylation modifiers such as DNMTs remain unaffected, we detected the upregulation in high-risk breasts of other molecules modifying the DNA, suggesting that other genetic and epigenetic mechanisms rather than DNA methylation may drive the transcriptomic aberrations in high-risk breasts.

In summary, this is the first study defining the molecular features of the true normal breast and revealing transcriptomic and epigenetic aberrations linked with breast cancer risk.

The finding from this study generated two manuscripts, one of which is under consideration in Clinical Epigenetics journal and the other soon to be submitted to Biomarker Research journal
Can bacteria influence breast cancer progression and metastasis patterns?

The main goal of this study is to determine the bacterial composition of the normal breast and correlate it with risk factors for breast cancer. Moreover, we also aim to track the changes in bacteria population during breast cancer progress by analyzing the microbiome of breast cancer tissues, normal breast adjacent to tumors, and breast cancer metastases.

This funding bridged a gap left by a different project funding source and allowed for the analysis of an additional 50 normal breast tissues donated by African American women. This will allow us to ook at any difference in the bacterial composition of the breast in relation with racial background.

Microscope Upgrade

The Peachey endowment income allowed for the purchase of an important software update package for a microscope in the Komen Tissue Bank lab that was originally brought to the tissue bank with philanthropic funds in 2015.