FIND THE CAUSE
Breast Cancer Foundation

Research. Education. Prevention.

Scientific Progress Report

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General considerations of progress in 2019: **Primary prevention, secondary prevention, and the immune system.** With emerging technologies, the Find the Cause Breast Cancer Foundation Consortium has been able to advance studies into a new area of breast cancer prevention that falls under the category of secondary prevention (see Figure). As opposed to primary cancer prevention, which includes identification and elimination of carcinogenic environmental chemicals, secondary prevention is the science of identifying people who have been exposed to environmental chemicals and who show molecular signs that predict development of cancer well before the cancer itself forms. Accurately predicting who may be at high risk for developing cancer may enable us to intervene and prevent cancers from occurring. Consortium work, particularly that conducted in Dr. Sherr's laboratory and with Dr. Monti's help, is now migrating to studies on how malignant cells suppress the immune system, the one biological system flexible and adaptable enough to kill rapidly changing cancer cells. The expectation is that these studies will lead to approaches to reverse the effects of environmental chemicals on both the cells that have become cancerous and on the immune system.

[1]Primary Prevention [2]Secondary Prevention [3]Immunity, [4]Basic Biology

Primary prevention: Identify what environmental chemicals are carcinogens and eliminate them**; Secondary prevention:** Identify who has been exposed, predict impending cancers, intervene**; Immunity:** Reverse immunosuppression that prevents elimination of developing cancers**; Basic biology:** Understand how cancers happen and extrapolate how environmental chemicals contribute.

Monti Lab. In efforts to advance primary cancer prevention approaches, Dr. Monti's laboratory has applied an emerging technology (Sparse Full Length DNA sequencing) to determine which of the 20,000 human genes are activated by environmental chemicals and doing so at a price that makes technologies

for screening thousands of chemicals more practical and less dependent on outside suppliers of robotic platforms (1). In collaboration with Dr. Sherr's laboratory, Dr. Monti's laboratory published an important manuscript in a journal published by the National Institute of Environmental Health Sciences, the highest ranking journal dedicated to environmental causes of cancer and other diseases (2). The data in the article demonstrated a technology through which hundreds of chemicals can be screened for their potential to induce cancer. The work involved computational analysis of literally millions of bits of data generated with a robotic version of a laboratory technician. Comparison of the results with those produced over decades with approximately 150 known carcinogens indicated that Dr. Monti's new approach correctly predicted carcinogens with about an 85% accuracy. As opposed to the standard assay for carcinogenicity, which costs about $2,000,000 per chemical tested and takes two years, this new technology costs about $15 per chemical and takes only a couple of weeks. Associated with the work and the project, the Monti team developed an on-line database portal and search tool (https://carcinogenome.org/) with which environmental scientists can query all of the data generated in the study and analyze the data for hints of carcinogenicity in their respective systems. As of August, 2019, this manuscript had been downloaded 3,085 times, referenced in 62 papers, reached the top 14% of publications in similar area of expertise (environmental carcinogens) and the top 3% of all publications of similar age, been picked up by 7 news outlets, and tweeted by users in the US, Canada, France, UK, Germany, Australia, Brunei, and Sri Lanka.

Furthermore, expanding on the types of computational analyses used in this new platform, Dr. Monti has been able to assist Dr. Sherr's work in identifying genetic changes that appear to occur prior to overt cancer formation and in determining how emerging cancer cells suppress the immune system (see below).

Leveraging the data generated in these studies, Dr. Monti was able to secure $123,750 in funding from the Superfund Research Program within the National Institute of Environmental Health Sciences (NIESH) to generate a similar database for chemical toxicity in addition to carcinogenicity. Drs. Monti and Sherr have submitted a grant application to the Department of Defense to evaluate the carcinogenicity of environmental chemicals to which military personnel are routinely exposed. The context of these studies is the environmental causes of brain cancer.

Sherr Lab. Towards the end of 2018, Dr. Sherr's team, including a Ph.D. student (Supraja Narasimhan) supported by a Find the Cause Seed the Scientist grant, published a manuscript in an international journal that demonstrated how a class of common environmental pollutants induces cancer and drives cancer progression to a lethal form (3). In early 2019 the Sherr lab published an article demonstrating, for the first time, that the most aggressive form of breast cancer, i.e., "inflammatory breast cancer", is driven by a receptor that recognizes a variety of environmental chemicals (4). The paper, published with collaborators from Cairo, Egypt, where these types of cancers are much more common, showed how environmental chemicals may contribute to a highly aggressive cancer for which the average survival period is about 2 years. Using information generated in these two studies, Dr. Sherr's laboratory, in collaboration with colleagues at Harvard Medical School and Brigham and Women's hospital, published a manuscript in an extremely high profile journal, *Nature Neuroscience*, demonstrating that, in addition to driving cancer formation and aggression, environmental chemicals, through their cellular receptor, suppress the immune system responsible for killing cancers (5). This study extends previous Find the Cause-supported studies in breast and oral cancers to demonstrate that environmental chemicals have similar effects in brain cancers. Indeed, the laboratory has now begun to investigate the dual role of

environmental chemicals in driving cancer aggression and suppressing the immune system to lung cancers. A common element in these studies appears to be environmental chemical suppression of the immune system. Although not yet published, the lab has shown that they can identify early molecular markers of environmental chemical exposure that may be used to predict who will get cancer (secondary prevention) enabling intervention before cancers form.

The work described above, particularly the studies that evaluated how environmental chemicals suppress cancer immunity, led to acquisition, in 2019, of $776,000 in support through two NIH grants and one from the Johnson and Johnson Foundation. One of the two NIH grants will continue through 2020 (~$225,000/year) and the other NIH grant will continue through 2024 (~$190,000/year). A renewal for the Johnson and Johnson grant will be submitted in December of 2019.

Sonenshein Lab. Dr. Sonenshein' s laboratory has begun to develop cutting-edge technologies to detect the presence of cancer using a blood sample. Although currently directed towards early detection of breast cancer, Dr. Sonenshein believes that the technology might be used to determine who has been exposed to environmental chemicals and the likelihood that they will develop cancer (secondary prevention). She will be working with Dr. Sherr to test this theory using a mouse model of environmental chemical-induced cancer that Dr. Sherr's laboratory has adopted. Dr. Sonenshein's laboratory has been awarded $165,000 from the Ellison Foundation to evaluate a potential intervention in people predicted to develop cancer or showing early signs of cancer.

Kuperwasser Lab. In 2019, Dr. Kuperwasser's lab published three manuscripts that address the root causes of breast cancer (6-8). Specifically, the data demonstrate the role of specific genes in blocking the inhibitors of cancer (referred to as "tumor suppressors"). Dr. Kuperwasser had previously demonstrated deletion of one of them, called "Slug", rendered mice nearly completely resistant to breast cancer formation. One of the manuscripts (8) was an invited review in a high profile publication (*Cell Stem Cell)* cancer-causing genes and their role in generating cancer "stem cells" and cancer stem cell resistance to therapy.

Publications cited above:

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2. Li, A., X. Lu, T. Natoli, J. Bittker, N. S. Sipes, A. Subramanian, S. Auerbach, D. H. Sherr, and S. Monti. 2019. The Carcinogenome Project: In Vitro Gene Expression Profiling of Chemical Perturbations to Predict Long-Term Carcinogenicity. *Environ Health Perspect* 127: 47002.
3. Narasimhan, S., E. Stanford Zulick, O. Novikov, A. J. Parks, J. J. Schlezinger, Z. Wang, F. Laroche, H. Feng, F. Mulas, S. Monti, and D. H. Sherr. 2018. Towards Resolving the Pro- and Anti-Tumor Effects of the Aryl Hydrocarbon Receptor. *Int J Mol Sci* 19.
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5. Takenaka, M. C., G. Gabriely, V. Rothhammer, I. D. Mascanfroni, C. C. Chao, K. Alves de Lima, J. E. Kenison, E. C. Tjon, T. Vandeventer, S. Rothweiler, S. Ghannam, L. Healy, D. H. Sherr, A. Pratt,

J. Antel, D. A. Reardon, S. C. Robson, G. Getz, H. L. Weiner, and F. J. Quintana. 2019. Control of tumor associated macrophages by the tumor microenvironment in glioblastoma. *Nature Neuroscience*.

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7. Gross, K. M., W. Zhou, J. L. Breindel, J. Ouyang, D. X. Jin, E. S. Sokol, P. B. Gupta, K. Huber, L. Zou, and C. Kuperwasser. 2019. Loss of Slug Compromises DNA Damage Repair and Accelerates Stem Cell Aging in Mammary Epithelium. *Cell Rep* 28: 394-407 e396.
8. Gupta, P. B., I. Pastushenko, A. Skibinski, C. Blanpain, and C. Kuperwasser. 2019. Phenotypic Plasticity: Driver of Cancer Initiation, Progression, and Therapy Resistance. *Cell Stem Cell* 24: 65-78.

Seminars/Lectures (August 2018-August 2019)

Project Leader	Title, Status, or Seminar Series	Location
D. Sherr	The AHR as a driver of cancer and cancer immunity (immunosuppression)	University of Paris, Descartes, Paris, FR
D. Sherr	**Keynote address**: The role of the aryl hydrocarbon receptor in cancer immuno-metabolism.	World Pharma Week, Small Molecules for Immuno-oncology, Boston, MA
D. Sherr	**Grand Rounds:** The Aryl Hydrocarbon Receptor: A Cancer Instigator and Immune Checkpoint Regulator	Dartmouth Hitchcock Medical Center
D. Sherr	The Cancer Interception Program, Boston, MA.	The Boston University Cancer Center Annual Symposium
D. Sherr	Intercepting the AHR in oral cancer	Dana-Farber Cancer Institute
D. Sherr	Plenary lecture: The AHR: A Major Player in Cancer Aggression and Immune Checkpoint Regulation	Dioxin 2019 Conference, Kyoto, Japan
D. Sherr	The AHR as a Novel Immune Checkpoint Regulator Influenced by Environmental AHR Ligands	Evans Research Foundation Area of Research Concentration
D. Sherr	**Plenary Lecture:** The AHR as a Driver of Cancer and Immunosuppression	American Association of Immunologists, San Diego
D. Sherr	Breast Cancer: A Panel on Causes and Prevention Possibilities	Boston University
C. Kuperwasser	UPENN Distinguished Lecture Series	U. Penn

C. Kuperwasser	Big Data in Environmental Science.	Boston University
C. Kuperwasser	Invited Speaker	NET Research Foundation, Boston
C. Kuperwasser	**Keynote Speaker**	Dana-Farber/Harvard Cancer Center Breast and Gynecologic
S. Monti	New Technologies and Their Impact on Environmental Health	Boston University; Environmental Health Seminar Series
S. Monti	**Keynote speaker**	BD2K-LINCS Data Science Symposium (DSS), Cincinnati, OH
S. Monti	Invited Speaker	3rd Annual Next Generation Sequencing Congress. Boston, MA, USA.
S. Monti	**Session Chair**	3rd Annual Next Generation Sequencing Congress. Boston,
S. Monti	Integrative Cancer Multi-Omics to advance prevention and therapy.	Novartis Institutes for BioMedical Research (NIBR), Cambridge, MA.
S. Monti	Big Data in Environmental Science	2018 Northeast Superfund Research Program Meeting, Woods Hole, MA.
S. Monti	Breast Cancer: A Panel on Causes and Prevention Possibilities	Boston University
S. Monti	Life Science Seminar Series,	ShanghaiTech University, Shanghai, China.