FIND THE CAUSE
Breast Cancer Foundation

Research. Education. Prevention.

Scientific Progress Report

June 2020

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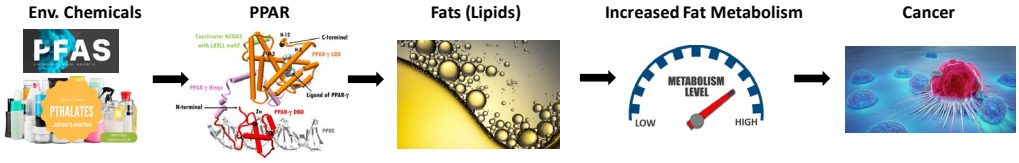
Attacking cancer on a second front. Despite shutting the laboratories down the first week in March because of the COVID-19 pandemic, the Find Cause Breast Cancer Consortium continued to make significant progress toward cancer prevention. While the Consortium continues work towards identifying environmental chemicals that induce or exacerbate breast cancer, a second front of attack has been opened in the area of cancer interception (i.e., secondary prevention). The development of increasingly sensitive molecular technologies, facilitated by state-of-the-art instrumentation purchased through Find the Cause donations, now makes it theoretically possible to identify cells that are destined to become cancers. Consequently, the consortium is beginning to define approaches that may enable it to intervene prior to overt tumor formation. This second front represents a midpoint between the identification of carcinogenic environmental chemicals (primary prevention) and cancer therapy. With an anticipated doubling of the incidence of cancer in the next 20 to 25 years, and a significant rise in the number of untested consumer chemicals entering consumer and industrial use (already at 85,000 chemicals), this approach to secondary prevention may end up being the most practical and the most actionable approach to cancer prevention.

[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.

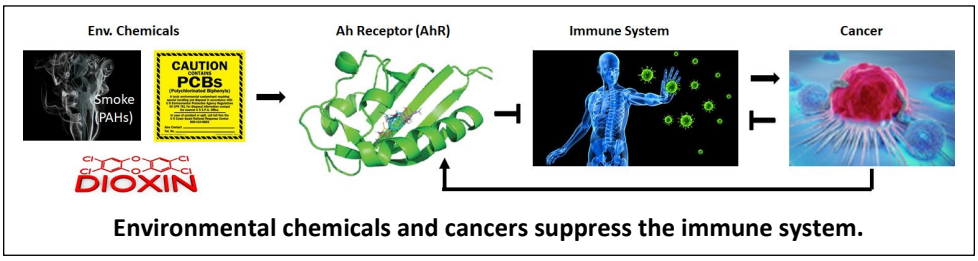
Monti Lab. In collaboration with Dr. Jennifer Schlezinger, an environmental toxicologist at Boston University, The Monti Lab has submitted a manuscript to the leading journal in the field of environmental health published by the National Institute of Environmental Health Sciences (*Environmental Health Perspectives*). The manuscript focuses on a genetic signature of chemicals that induce the formation of fat, a phenomenon known to contribute to breast cancer. In their paper entitled "*A Data-Driven Transcriptional Taxonomy of Adipogenic Chemicals to Identify White and Brite Adipogens*", the Monti Lab describes how common environmental chemicals can activate a cell receptor (PPAR) to generate a specific signature of molecular changes that cumulatively increase formation of fat. Since fat and distorted metabolic activity are linked to increased breast cancer risk, the studies suggest mechanisms through which environmental chemicals could either induce or accelerate cancers. Furthermore, definition of the specific molecular signatures associated with chemical exposure may eventually make it possible to determine what chemicals someone has been exposed to and what their increased risk of metabolic disorders or cancer may be. The manuscript has been evaluated by primary reviewers and will be resubmitted with minor changes within the month. Some of this work will be presented in a national webinar recording hosted by the National Institute of Environmental Health Sciences and archived at SRP Risk e-Learning .



Exposure to environmental chemicals induces fat development increasing cancer risk.

Leveraging data generated through the support of FTC, the Monti Lab has submitted two comprehensive grant applications to two institutes within the National Institutes of Health. Both grants scored in the top 10% of those received by the respective institutes at the fall submission deadline. The first grant application, which is currently under final review at the National Cancer Institute (NCI-the largest of the 27 NIH institutes and centers), is a computational analysis investigating breast cancer aggressiveness as it may correlate with type II diabetes and obesity. (This study reflects some of the work submitted for publication in which connections between breast cancer and aberrant metabolism are delineated). The second grant is under final review at the National Institute of Dental and Craniofacial Research (NIDCR) and focuses on the molecular changes that result in oral cancers after exposure to a chemical carcinogen.

Sherr lab. The Sherr laboratory is validating an approach to identifying cancers before they happen by looking at molecular changes that occur after exposure to environmental carcinogens and prior to cancer formation. Specifically, the lab used a common environmental carcinogen found in cigarette smoke, diesel exhaust, and ambient airborne particles (particularly in cities) to define a set of 55 genes the expression of which is altered specifically by this class of environmental carcinogen. The lab demonstrated that several of these genes are up regulated either prior to or very early on in the formation of lung cancer. If validated by independent approaches over the next couple of years, this technology may eventually be used to define environmental chemical exposures and future cancer risk. (Some of this work was presented in a recent Find The Cause Webinar). Of note is the interaction of these chemicals with a receptor, the AhR (aryl hydrocarbon receptor), which the lab is discovering plays a key role in suppressing anti-tumor responses (see below).



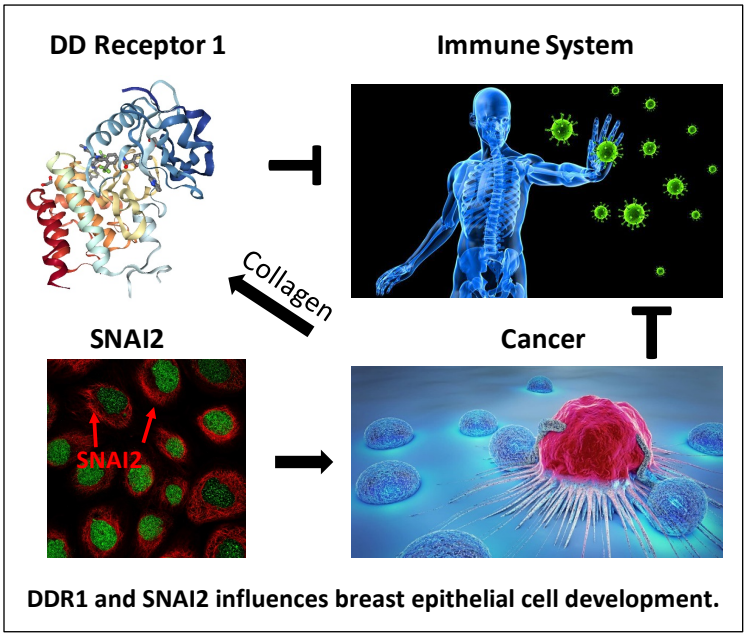
Environmental chemicals and cancers suppress the immune system.

In a related series of studies, the Sherr laboratory has determined at least some of the mechanisms through which environmental chemicals suppress the immune system and enable cancers to form. More specifically, the lab demonstrated that certain well-known checkpoints in the control of the immune system are aberrantly activated in cancer cells and by carcinogens through activation of the AhR. (Once formed, the tumors produce AhR activators that act like some environmental AhR activators). The consequence of activating the AhR and inducing these checkpoints is the well-known suppression of the immune system during cancer formation. Small molecules that inhibit the AhR (potential drugs) developed in the Sherr laboratory can block this effect and render mice completely resistant to a second bout of cancer. Therefore, it is possible that the lab could eventually be able to determine who is at high risk of developing cancer by virtue of genomic fingerprints produced after chemical exposure and prior to cancer formation and to intercept cancer formation using these types of small molecules. Of particular note, since these studies demonstrate that part of the carcinogenicity of environmental chemicals relates to their ability to suppress the immune system, the results can be applied to many different kinds of cancers, all of which induce immune suppression. Therefore, these results are likely to apply at least to breast, oral, brain, and lung cancers. A manuscript on this work, entitled "*The aryl hydrocarbon receptor suppresses immunity to oral squamous cell carcinoma through immune checkpoint regulation"*, has been submitted for publication.

As often occurs in biological research, these results have implications far beyond the cancer context. Having noted how cancers suppress the immune system, Dr. Francisco Quintana's laboratory at Brigham and Womens' Hospital, in collaboration with the Sherr laboratory, evaluated a potential overlap between immunosuppression induced by cancers and immunosuppression induced by viruses. In a paper recently published in an extremely influential journal, *Nature Genetics*, they demonstrated a similar type of immunosuppression mediated by activation of the environmental chemical receptor, AhR, in Zika virus disease and, importantly, the ability of AhR inhibitors designed in the Sherr laboratory to nearly completely block the pathologic effects of his Zika virus including Zika-induced microcephaly (abnormal brain development) (1). The Quintana and Sherr laboratories are now collaborating with scientists in Brazil to determine if the small molecules generated in the Sherr lab are similarly effective against SARS-COV2 (COVID-19).

In the last two months, the Sherr laboratory has leveraged the data produced with the support of Find The Cause Breast Cancer Foundation to generate a second year of funding from the Johnson & Johnson company, Lung Cancer Initiative. The continuation grant, worth $412,000 ($250,000 direct funding to the Sherr laboratory; $162,500 to Boston University), will be used for studies on the molecular signatures that define exposure to environmental chemicals and impending cancer formation.

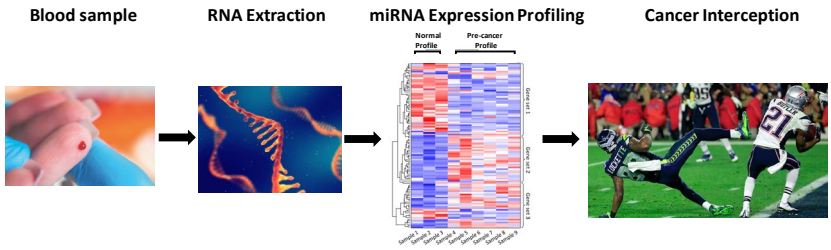
Kuperwasser lab. The Kuperwasser laboratory has been collaborating with the Sherr laboratory to determine which components of the immune system are most important in killing nascent cancers and which are most commonly suppressed by emerging malignant cells. Over 100 slides of tissue from tumor-bearing mice have been prepared and await re-opening of the laboratories for analysis of infiltration of immune cell types into the tumor microenvironment. In the meanwhile, Dr. Kuperwasser has authored a review manuscript that summarizes the state of understanding of a unique molecule, called "Slug" (or "*Snai2*"), that her lab has shown plays a critical role in breast cancer metastasis, survival, DNA (dys)repair and generation of a web of blood vessels that support the rapid metabolism of aggressive cancers. Indeed, the complete deletion of this molecule through molecular editing renders mice nearly completely resistant to cancer. The manuscript, entitled "*Molecular regulation of Snai2 in development and disease*" was published in the Journal of Cell Science (2).



DDR1 and SNAI2 influences breast epithelial cell development.

Other studies supported by FTC in the Kuperwasser lab involve a cellular receptor called DDR1 that, when activated by proteins from the tumor microenvironment (collagen), signals breast stem cells to develop into several other breast cell types. Notably, DDR1 has been associated with suppression of tumor immunity, a theme common to the work of the Sherr laboratory. A manuscript entitled "*Breast tissue regeneration is driven by cell-matrix interactions that coordinate multi-lineage differentiation through DDR1*" has passed the initial review phase in a top-ranked journal, *Nature Communications*, and is soon to be resubmitted for publication.

Sonenshein laboratory. During the COVID shut down, Dr. Sonenshein has worked with Drs. Monti and Sherr to design a new approach to screening patients for molecular signatures of pre-cancer. This work is related to that being done by the Monti and Sherr laboratories in that the goal is to be able to determine if a precancerous, genomic profile can be identified in susceptible tissues of mice exposed to environmental carcinogens. Specifically, FTC Consortium scientists are designing a protocol for ultimately sampling blood (i.e., a "liquid biopsy") for the genetic signs of impending cancers. The approach to be taken will involve a technology called "NanoString" through which one can sample the expression of over 500 "micro" RNAs in precancerous tissue within two days for about one dollar per gene per sample. Using an animal model of environmental chemical-induced lung cancer, they have already obtained blood and lung samples and await the re-opening of labs to test the hypothesis that this carcinogen leaves a "genetic fingerprint" in lung tissue before cancers form.



Using blood (micro)RNA profiling to determine a pre-cancer state.

1. Giovannoni, F., I. Bosch, C. Manganeli Polonio, M. Torti, M. Wheeler, Z. Li, L. Romorini, S. Rodriguez, V. Rothhammer, A. Barroso, E. C. Tjon, L. Sanmarco, M. C. Takenaka, S. Modaresi, C. Gutiérrez-Vázquez, N. G. Zanluqui, N. Barreto dos Santos, C. D. Munhoz, Z. Wang, E. B. Damonte, D. H. Sherr, L. Gehrke, J. P. Schatzmann Peron, C. C. Garcia, and F. J. Quintana. 2020. AHR is a Zika virus host factor and a target for antiviral therapy. *Nature Neuroscience* In Press.
2. Zhou, W., K. M. Gross, and C. Kuperwasser. 2019. Molecular regulation of Snai2 in development and disease. *J Cell Sci* 132.