FIND THE CAUSE
Breast Cancer Foundation

Scientific Progress Report

December 2017

Thanks to our researchers and to YOU, Find the Cause Breast Cancer Foundation now sees tangible strides being made toward a world where we are protected from getting cancer from existing carcinogenic chemicals while, at the same time, they are eliminated from our environment and not replaced.

Learn more: www.FindTheCauseBCF.org

The dawn of a new era ... *Real Prevention*

Drugs and the immune system:
Cancer vaccines have been a long sought-after goal for cancer prevention. Our consortium believes that the drugs currently being researched that inhibit the effects of environmental carcinogens may also boost cancer-specific immune responses to fight cancers. The drugs that Dr. David Sherr's laboratory (Boston University School of Public Health) have developed and the mechanisms that Dr. Charlotte Kuperwasser's laboratory (Tufts School of Medicine) have been researching are designed to enhance the immune system. Any enhancement of the immune system can contribute to cancer prevention. That would be all cancers. This approach, if successful, will truly be a game changer.

Drugs for high risk populations:
Dr. Sherr's lab is developing drugs that could block the effects of many environmental chemicals and might be used for people who are at high risk of getting breast cancer. For example, people with high occupational exposures to carcinogens (e.g., Armed Forces personnel) and particularly susceptible populations (e.g., children).

Drugs for preventing cancer recurrence:
As an offshoot of the consortium's environmental chemical studies, Dr. Sherr and Dr. Gail Sonenshein's (Tufts School of Medicine) labs are developing drugs that could be used to prevent cancer recurrence in people that have been treated with standard chemotherapies and/or radiation therapy. This is particularly true since it is cancer stem cells that survive the initial treatment. It is those cancer stem cells that these drugs target.

The dawn of a new era ... *Truly Eliminating Environmental Toxins*

Identifying toxic chemicals in our environment:
Dr. Stefano Monti's (Boston University School of Public Health) high-throughput computational biology predictive model can quickly identify which chemicals are likely to be carcinogens. With this information, we could be able to eliminate these chemicals from our environment AND prevent them from being replaced by new chemicals that may be just as carcinogenic.

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September 2016 - August 2017

All four laboratories in the "Investing in Prevention" Consortium have made significant progress over the past year. As you read the exciting updates below, know that this kind of progress could not happen without your continued support of Find The Cause. We stand strong in our mission to prevent breast cancer and create a safer world for future generates!

www.FindTheCauseBFC.org

At Boston University School of Public Health

Dr. Sherr's

lab has advanced the plausibility argument by demonstrating that common environmental chemicals accelerate conversion of relatively benign breast and oral cancer cells to highly aggressive, metastatic cancers through mechanisms that do not involve genetic mutations. As a spinoff, the Sherr lab demonstrated that a novel new drug is capable of blocking the effects of environmental chemicals and of reversing the aggression of tumors even after the environmental chemical exposure has ceased. This drug appears to have efficacy in triple negative breast cancer, oral cancer, melanoma, and brain cancer. Indeed, the most recent studies suggest that this drug works both by blocking signaling of the aryl hydrocarbon receptor (AHR), a cellular receptor that recognizes environmental chemicals and drives cancer cell metastasis, and by blocking the AHR in cells that suppress the immune system. Hence, the drug blocks AHR-driven cancer metastasis and enhances the immune response to the cancer. Interestingly, in a collaboration with a neurobiologist at Boston University, Dr. Sherr's laboratory demonstrated that the same signaling pathway may be responsible for environmental chemical induced ALS (amyotrophic lateral sclerosis). This work was published in 3 manuscripts during 2017. Dr. Sherr will be presenting some of his work on cancer at the National Cancer Institute later in August, at the University of Memphis in November, and at an international (AHR) cancer conference in Paris early in 2018.

Dr. Monti's

computational biology laboratory has beta tested a robotic platform to rapidly predict what new chemicals may be carcinogenic. Using human breast cells his team was able to accurately predict 3 out of 4 carcinogens. Projections indicate that another round of approximately 100 known chemicals will raise the accuracy of prediction well over 80%. More chemicals = more accuracy. Amy Li, the Find The Cause Seed-The-Scientist awardee from 2016, is working in Dr. Monti's laboratory and has generated a web portal through which other scientists can access and mine the literally million bits of information collected in the robotic platform for hints of cancer-causing signaling pathways. This work has been presented at 2 NIH-sponsored conferences and a manuscript describing the work is being prepared. The portal can be accessed at *https://carcinogenome.org*

At Tufts University School of Medicine

Dr. Sonenshein's

lab has made significant progress in mapping the downstream molecular effects of environmental chemicals. Specifically, she has demonstrated that a cascade of events is triggered by changes in cells resulting from environmental insults. Surprisingly, the most profound outcome observed was an increase in a molecule, "Adam 8", which enables cancer cells to migrate through the body. Proof of principle was demonstrated by the nearly complete inhibition of breast cancer migration with antibodies, generated by Dr. Sonenshein's laboratory, that bind to Adam 8 on the surface of breast cancer cells.

Dr. Kupperwasser's

laboratory, has also made progress in demonstrating that environmental chemicals, many of them the same as those implicated in Dr. Sherr's work, bias development of normal breast cells to the types of cells that mature into the most aggressive form of breast cancer. Furthermore, her laboratory now has evidence that other types of environmental chemicals, known generally as endocrine disruptors, generate the same adverse outcome, i.e., skewing of the normal cell development pathway towards cells capable of becoming aggressive cancers.

Scientific Progress Report

September 2015 - August 2016

What follows is a summary of the *"Investing In Prevention"* Lab Consortium's recent progress report to the Find The Cause Breast Cancer Foundation, the complete copy of which can be found on the Foundation's website, **www.FindTheCauseBFC.org**

In the world of medical research, results are measured in "baby steps." One of the Consortium's primary goals is to expand public awareness of cancer-causing chemicals through published manuscripts in high profile scientific journals and through presentations to international scientific associations, government agencies and funding organizations.

Since the Consortium was organized in mid-2014, these baby steps have been accomplished as follows:

1. 19 full-length, peer reviewed manuscripts directly related to our funding have been published by our scientists specifically acknowledging the support of Find The Cause.
2. 16 Abstracts, acknowledging Find The Cause, were presented at national and international conferences.
3. 13 by-invitation lectures, seminars, and presentations were delivered, all acknowledging Find The Cause, with two more scheduled this Fall.

To view a complete list of our scientist's research papers visit *http://findthecausebcf.org/scientist-published-papers/*

Because of these steps, the Consortium scientists are more convinced than ever that breast cancer prevention is a realistic goal. Using multiple human and animal models the Consortium has advanced their understanding of the molecular mechanisms behind breast cancer and the means through which environmental agents contribute to both the incidence and severity of human breast cancer. As you recall, each scientist and lab has a specific focus that compliments the work of the other consortium members. The following is a summary of progress made in each lab.

At Boston University School of Public Health

Dr. Sherr's

lab has demonstrated how the AhR (an environmental chemical receptor in the breast cell) induces the development of cancer stem cells in both breast and oral cancers, which invade tissues and migrate to the brain. They have also discovered that the AhR can be activated, causing cancer, by our own body's bacteria (our "microbiome") which has been altered by exposure to environmental chemicals.

Dr. Monti's

computational biology lab has added several hundred suspected carcinogens to its high-throughput, genomic cancer-causing chemical predictive model. Since it's initial development two years ago, this model has a predictability success rate approaching 85%. Dr. Monti is presenting his work to the National Institutes of Health in Bethesda in September.

At Tufts University School of Medicine

Dr. Sonenshein's

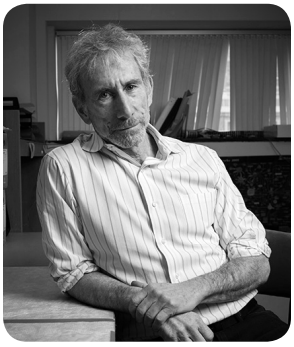
lab has identified a unique signaling pathway that promotes the migration and metastasis of breast cancer. Further, they have developed a technology that detects residual breast cancer cells circulating in human blood and tells scientists what chemicals the human was exposed to.

Dr. Kupperwasser's

lab has generated preliminary data which indicates that estrogen-mimicking chemicals dramatically alter the normal development path of human breast cells. This finding suggests that early exposure to these chemicals may cause healthy cells to transform into full blown malignancies.

Meet Our Scientists

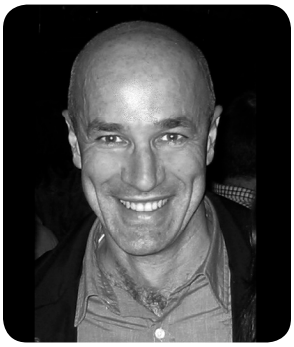
At Boston University School of Public Health



David H. Sherr, PhD, Consortium Director

Professor of Environmental Health, Professor of Pathology and Laboratory Medicine,
Boston University School of Public Health, School of Medicine
Director, Boston University Immunology Training Program
Director, Boston University Superfund Research Program

Dr. Sherr is a molecular biologist and toxicologist who studies cellular receptors that recognize a wide variety of environmental pollutants that signal cells to both grow and metastasize. He is an internationally recognized expert on the aryl hydrocarbon receptor (AhR), a protein that binds to environmental carcinogens and begins the aberrant signaling that results in a full-blown cancer cell.



Stefano Monti, PhD

Associate Professor of Medicine
Adjunct Professor, Bioinformatics Program
Boston University School of Medicine
Affiliate Member, Broad Institute of MIT & Harvard

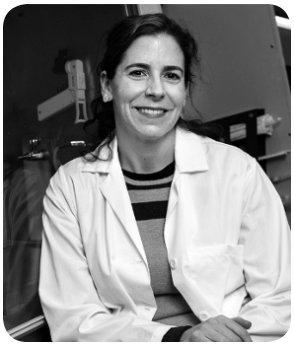
Dr. Monti has developed a cutting-edge technology for rapidly and economically screening thousands of chemicals for their ability to influence expression of virtually all cancer-related signaling pathways within human cells, including but not limited to the AhR, the Wnt, and the NF-κB pathways. The National Institutes of Health (NIH) has acknowledged that this type of high-throughput screening assay may be the only practical way to determine how we are affected by mixtures of environmental pollutants.

At Tufts University School of Medicine

Gail E. Sonenshein, PhD

Professor of Biochemistry
Tufts University School of Medicine

Dr. Sonenshein's laboratory was the first to demonstrate inappropriate activation of NF-κB by environmental carcinogens and their role in promoting cancer growth and survival. While at Boston University, she established and directed the Women's Health Interdisciplinary Research Center, a center dedicated to determining the underlying causes of several diseases in women including breast cancer. She is now working at Tufts and committed to further investigating the links between breast cancer and the environment.



Charlotte Kuperwasser, PhD

Associate Professor of Anatomy and Cellular Biology
Tufts University School of Medicine

Dr. Kuperwasser is an internationally recognized researcher with expertise in the biology of cancer stem cells, the cell subset likely responsible for cancer relapses and ultimately death, and in the role of the tumor microenvironment in malignant cell growth. She pioneered the development of a unique and enormously powerful mouse model in which discarded normal human breast cells are transplanted into the mammary glands of mice to study how these normal cells influence outgrowth of cancerous cells.