INVESTING IN PREVENTION

A Research Project to Find the
Environmental Causes of Breast Cancer

Can $5 million invested in targeted research lead to preventing breast cancer?

The Art beCAUSE Breast Cancer Foundation

plans to raise $5 million to fund

a multi-year research project

undertaken by a consortium of scientists

to identify the environmental causes of breast cancer

and the methods of preventing the disease.

Research Rationale

Breast cancer is the second leading cause of cancer-related deaths for women in the U.S. More than 40,000 women are expected to die in 2014 (1, 2). It is also the second-most common cancer diagnosed in women with more than 250,000 new cases predicted this year (3, 4).

Statistics from epidemiological studies, lab-based research studies and national breast cancer organizations support the conclusion that chemicals in the environment play a significant, if not dominant, role in the incidence of human cancer (5, 6).

Some of these key statistics are:

- ✔ Today, the lifetime risk for an American woman to develop breast cancer is 1 in 8. Forty years ago it was 1 in 20.
- ✔ Less than 10% of all human breast cancers are attributable to known, inherited cancer-related genes. The distribution of these genes in the human population has not changed significantly since the 1940s.
- ✔ With over **90%** of breast cancer cases being unrelated to family history, the increase in breast cancer incidence seen since the mid-1940s can logically be attributed, at least in part, to increased exposure to adverse environmental factors.
- ✔ Women living in Japan have a significantly lower risk of breast cancer than those living in the United States. However, when these women move to the United States, they acquire the increased breast cancer risk of women living in the U.S.
- ✔ More than 84,000 man-made chemicals are registered with the Environmental Protection Agency. Only 1,500 have been tested for potential carcinogenic characteristics. More than ten percent were found to be carcinogenic. Prior to the establishment of the EPA in 1970, there was no coordinated, targeted effort by the U.S. government to register newly created chemicals.
- ✔ The U.S. Centers for Disease Control and Prevention regularly detects, in human blood or urine, the presence of hundreds of these man-made environmental chemicals including, but not limited to heavy metals, pesticides, plasticizers, flame retardants, and hydrocarbons.

These and other statistics have led two recent government-sponsored studies to conclude that there is a significant environmental component to the risk of getting breast cancer.

In 2010, the President's Cancer Panel concluded that *"…the true burden of environmentally-induced cancers has been grossly underestimated."* The panel urged that a greater emphasis be placed on research designed to define exactly how, on the molecular level, these environmental chemicals induce cancer.

In February 2013, the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC - established by Congress in 2008) concluded that, *"Based on a review of the state-of-science, current programs, and investments by federal agencies and nongovernmental organizations, as well as relevant communications efforts and policies, the IBCERCC offers seven recommendations to highlight the urgent need for coordinated, targeted efforts to identify and mitigate the environmental causes of breast cancer."*

"Investing in Prevention," funded by the Art beCAUSE Breast Cancer Foundation, is the first targeted effort to address the issues raised by these studies by providing meaningful funding and focus on the impact of adverse environmental factors on breast cancer.

Determining scientifically how adverse environmental factors cause breast cancer is critical to motivating government officials to mandate that exposure to these chemicals must be minimized. This scientific evidence is absolutely required to counter the lack of awareness and concern about these factors causing breast cancer and other related cancers e.g., prostate, lung, colon, and ovarian cancer.

Art beCAUSE believes that identifying "cause" can lead directly to preventing most cases of breast and related cancers.

A Strategy to Prevent Breast Cancer

Proving there is a link between the environment and breast cancer has been elusive. However, progress in the biological sciences is now moving at an accelerated pace due to the development of advanced laboratory technologies. These include high-tech molecular biology tools as well as computers that can interpret complex "big data."

With this staggering array of technologies now available, complicated biological problems, such as defining how environmental chemicals cause breast cancer, are best approached collaboratively. Forming a consortium of individual laboratories can bring unique skill sets and multiple technologies to bear on a single biological challenge.

Members of a consortium are able to leverage resources, such as high-end instrumentation, in a fashion not economically feasible for individual investigators. Furthermore, the collaborative atmosphere in a consortium maximizes the use of human knowledge and creativity, and enhances communication among scientists.

Experience shows that a team approach, especially for complex disciplines such as cancer biology, is optimally productive and synergistic. It leads to far more scientific progress than can be accomplished by even the best researchers working independently.

The principal investigators of the "Investing in Prevention" consortium have cooperated with each other over the past several years concerning the environmental causes of breast cancer and how to prevent the disease. Recent findings from their research have made formalizing their complementary efforts logical and timely. They will be able to more quickly and efficiently attack breast cancer and achieve the "Consortium Deliverables" outlined on Page 4.

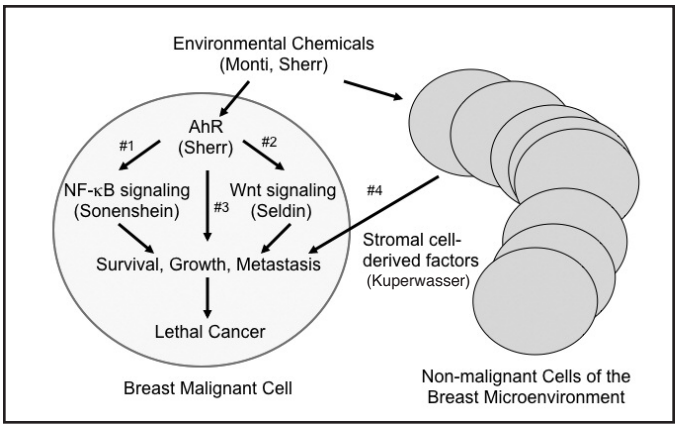
The Consortium Approach

The work of the consortium will be organized around the single issue of how, from a molecular viewpoint, man-made chemicals induce and drive the progression of breast cancer. Once cause is determined, routes to prevention will be identified including measures to decrease exposure to cancer-causing chemicals as well as potential therapeutics.

Cancer is caused by the confluence of several events within a malignant cell and the surrounding tissue in which this malignant cell grows. Within this microenvironment, the malignant cells and the non-malignant cells are collectively referred to as a tumor. Several interacting signaling pathways within the tumor become hyperactive, and force malignant cells to:

- increase their growth rates,
- survive for long periods of time, and
- migrate (metastasize) to distant organs.

To understand how man-made chemicals induce cancer, one must identify exactly how the chemicals alter each of the individual signaling pathways within a malignant cell. Then, one must define the signals being communicated between the malignant cell and the surrounding microenvironment.



Breast Cancer Tumor

The consortium's working model of chemical-induced breast cancer is summarized in the accompanying *Breast Cancer Tumor* chart. Each principal investigator's name is noted in parentheses on the chart indicating their area of expertise.

Many classes of environmental chemicals, including those already implicated in causing human breast cancer (e.g., dioxins, polychlorinated biphenyls/PCBs, and hydrocarbons), bind to a protein receptor called the "aryl hydrocarbon receptor" (AhR), within human breast cells. Once bound by an environmental chemical, this receptor triggers changes within normal breast cells that directly result in increased cell growth and the tendency to invade distant organs (metastasize), forming tumors.

Two signaling pathways within the cell partially control this progression to the lethal stage of breast cancer (pathways "#1" and "#2" in the figure). Both of these pathways have been implicated in increasing growth, survival and metastasis of the majority of human cancers. However, the exact mechanism through which the AhR may activate both pathways is unknown. Furthermore, the chemical-activated AhR appears to directly increase cancer invasion through a third pathway (pathway "#3"). Finally, it is not known how, within a tumor, the non-cancer cells surrounding the malignant cells supply the malignant cells with nutrients and growth signals (pathway "#4").

Also of significant note is the very high likelihood that man-made chemicals and these same signaling pathways contribute to prostate, lung, colon, ovarian and other cancers. The proposed research to be undertaken by the consortium has great relevance for both prevention and treatment of many human cancers.

Defining exactly how man-made chemicals induce and drive breast cancer progression to the lethal stage requires an understanding of the interaction of all the aforementioned pathways.

Consortium Deliverables

Through its collaborative efforts, the consortium expects to achieve several objectives.

These are:

- ✔ To provide compelling scientific evidence that man-made chemicals in our environment cause breast cancer, drive its progression into a lethal metastatic state, and induce cancer stem cells responsible for relapse and death.
- ✔ To further develop a high-tech, high-throughput, genomic screening platform capable of predicting the carcinogenicity of thousands of as-yet-untested chemicals.
- ✔ To produce publications in high-profile scientific journals and make presentations at significant scientific meetings so that government agencies will raise public awareness of the ubiquity of man-made chemicals and how they cause breast cancer.
- ✔ To develop evidence to jump-start grass roots arguments for breast cancer prevention through a decrease in exposure to adverse man-made chemicals.
- ✔ To potentially identify novel, non-toxic breast cancer therapeutics and preventatives and the likelihood of their preventing breast cancer.
- ✔ To generate future research grants from government sources and private donors.

There is only limited funding available for research on the prevention of breast cancer.

This game-changing, private undertaking will make a significant impact on our understanding of what causes breast cancer and how to prevent the disease and the terrible emotional and physical damage caused by it.

Principal Investigators

Each member of the consortium has been selected specifically because of their expertise and technological capabilities in one or more areas of aberrant breast cancer cell signaling, as illustrated in the chart on page 3. Each investigator's research has focused on the impact of the environment on breast cancer.

Collectively, these investigators have published more than 500 manuscripts in peer-reviewed journals including such high-profile journals as *Breast Cancer Research, Cancer Research, Cell, Journal of Experimental Medicine, Nature, Nature Cell Biology, Nature Genetics, Nature Immunology, Nature Protocols, Oncogene, Proceedings of the National Academy of Science,* and *Science*. Their detailed biographies follow.

Key members of the consortium include:

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 will serve as the Director of this consortium. His graduate work was performed at the Cornell University School of Medicine and his postdoctoral work was conducted under Nobel Laureate Baruj Benacerraf at Harvard Medical School. On the faculty at Harvard Medical School for 14 years, he was recruited to Boston University as Professor of Environmental Health. 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.

David C. Seldin, MD, PhD
Professor of Medicine and Microbiology
Chief, Hematology/Oncology Section
Boston University School of Medicine, Boston Medical Center

A physician-scientist, Dr. Seldin received both his BA from Harvard College in 1978 (Physics) and his MD and PhD degrees from the Harvard University/MIT Program in Health, Science, and Technology. He performed his internship and residency at Brigham and Women's Hospital and his postdoctoral work in Genetics at Harvard Medical School. He served on the faculty of Harvard Medical School for three years before being recruited to Boston University School of Medicine. Since coming to Boston University, Dr. Seldin has led a world-class laboratory that studies a set of breast cancer signaling molecules, collectively referred to as the "Wnt signaling pathway," known to facilitate breast cancer cell invasion. In collaboration with Drs. Sherr and Sonenshein, Dr. Seldin has shown that activation of the Wnt pathway results from exposure of human cells to environmental pollutants and is a prerequisite for aberrant cell function.

Gail E. Sonenshein, PhD
Professor of Biochemistry
Tufts University School of Medicine

Dr. Sonenshein received her BA from Brooklyn Polytechnic Institute, her PhD from MIT, and performed her postdoctoral work at Institut de Recherches Scientifiques sur le Cancer, Villejuif, France, Tufts University and MIT. She served on the faculty at Boston University for more than 30 years. 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. Dr. Sonenshein's laboratory was the first to demonstrate inappropriate activation of the NF-κB in cancers. Drs. Sonenshein, Sherr and Seldin have co-authored over 20 articles on breast cancer signaling pathways.

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 received his baccalaureate degree in computer science from the University of Udine in Italy. He received Masters degrees from the University of Houston in computer science and the University of Pittsburgh in artificial intelligence. His PhD work on artificial intelligence, as it relates to medical issues, also was performed at the University of Pittsburgh. He conducted his postdoctoral work at the Robotics Institute of Carnegie Mellon University. Prior to being appointed Senior Computational Biologist at the Broad Institute of MIT & Harvard University, he was a research scientist at the Center for Genome Research at the Whitehead Institute at MIT. 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.

Charlotte Kuperwasser, PhD
Associate Professor of Anatomy and Cellular Biology
Tufts University School of Medicine

Dr. Kuperwasser received her BA and PhD degrees from the University of Massachusetts and her postdoctoral training in breast cancer development at the Whitehead Institute at MIT in the laboratory of Dr. Robert Weinberg, a member of the U.S. National Academy of Sciences and winner of the National Medal of Science. 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.

References

1. Howlader, N., A. Noone, M. Krapcho, N. Neyman, R. Aminour, W. Waldron, S. Alterkruse, C. Kosary, J. Ruhl, Z. Tatalovich, H. Cho, A. Mariotto, M. Eisner, D. Lewis, H. Chen, E. Feuer, K. Cronin, and B. Edwards. 2011. Surveillance, Epidemiology and End Result (SEER) Program Cancer Statistics Review, 1975-2008, National Cancer Institute.Bethesda, MD.
2. Surveillance, Epidemiology and End Results (SEER) Program 2008. Cancer of the Breast Statistics.
3. Edwards, B. K., M. L. Brown, P. A. Wingo, H. L. Howe, E. Ward, L. A. Ries, D. Schrag, P. M. Jamison, A. Jemal, X. C. Wu, C. Friedman, L. Harlan, J. Warren, R. N. Anderson, and L. W. Pickle. 2005. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. *Journal of the National Cancer Institute* 97:1407-1427.
4. Wingo, P. A., T. Tong, and S. Bolden. 1995. Cancer Statistics, 1995. *CA*: *A Cancer Journal for Clinicians* 45:8-30.
5. Brody, J. G., K. B. Moysich, O. Humblet, K. R. Attfield, G. P. Beehler, and R. A. Rudel. 2007. Environmental pollutants and breast cancer: epidemiologic studies. *Cancer* 109:2667-2711
6. Rudel, R. A., J. M. Ackerman, K. R. Attfield, and J. G. Brody. 2014. New Exposure Biomarkers as Tools For Breast Cancer Epidemiology, Biomonitoring, and Prevention: A Systematic Approach Based on Animal Evidence. *Environmental Health Perspectives*. Eprint.

Investing in Prevention

A Research Project to Find the
Environmental Causes of Breast Cancer

Can $5 million invested in targeted research lead to preventing breast cancer?

We think it can!

Art beCAUSE™
Breast Cancer Foundation

Fund the Research...Find the CAUSE

Eleanor F. Anbinder, Founder/Executive Director
508-877-4543
ellie@artbecause.org
PO Box 3025, Framingham MA 01705
www.artbecause.org