

Blocking triple negative breast cancer

Basic science studies of environmental chemical carcinogenesis led **Dr David Sherr** to discover a non-toxic means of inhibiting the development and spread of the most aggressive type of breast cancers



As an introduction, what inspired you to bring this research to fruition?

It's hard to ignore statistics like 'fewer than 10 per cent of breast cancers can be attributed to gene inheritance; the rest are 'spontaneous''. Also hard to ignore is the fact that the US Environmental Protection Agency has registered over 80,000 chemicals in common use. Only about 1,500 have been evaluated for carcinogenicity. That leaves a lot of potential carcinogens (and their combinations) in the air we breathe, the food we eat and the water we drink. Finally, one only has to look around to get a sense of the high frequency of breast cancer. It is hard to miss.

Your previous research centred on allergies; what led you to focus your attention on breast cancer?

That's the beauty of basic science. You never know where it will take you.

Most of my career has been spent investigating how the immune system develops and functions. These studies led me

to the idea that we could use environmental pollutants, which were known to suppress the immune system, as probes for dissecting how immune cells work. That led me to the aryl hydrocarbon receptor (AhR), which is the target of many of these chemicals and the mediator of their deleterious effects.

I looked around to see what kinds of cells express AhR at the highest levels. That led me to breast cancers in which AhR expression can be 50 times higher than in normal cells. It turns out that the cancers 'want' that much AhR to do damaging things, like metastasise. This led to our attempts to develop AhR inhibitors as cancer therapeutics. So, this scientific journey began with very basic science in what would seem an unrelated field, and ended up with the development of potential breast cancer therapeutics. I feel that my faith in the power of basic science has been validated.

To what extent are environmental chemicals associated with increased breast cancer risk?

Probably to a large extent. While people were sceptical at the beginning, there are now many studies that clearly link environmental chemicals to breast cancer incidence: like polycyclic aromatic hydrocarbons (PAHs), produced by anything that burns; polychlorinated biphenyls (PCBs), produced through some industrial processes; dioxins, which survive in the environment for decades; and a whole series of solvents found in places from machine shops to beauty parlours. Perhaps more impressive are studies with 'xenoestrogens', chemicals that mimic oestrogen, which are clearly linked to breast cancer. It is striking to note how many environmental chemicals act like oestrogens by stimulating the oestrogen receptor. Unfortunately, the oestrogen receptor, like AhR, is very promiscuous and, after all, there are more than 80,000 manmade chemicals out there.

Can you explain the significance of AhR in relation to metastasis?

Expression of AhR continues to increase as cancers become more and more aggressive. To any biologist, that's a clue that AhR is doing something beneficial for the cancer, but clearly not for the patient. We have found that AhR acts as if it were seeing some kind of stimulator (which environmental pollutants apparently resemble) at the point where breast cancers become invasive and metastatic.

What has been your most interesting discovery to date?

The mining of existing databases to (correctly) predict a role for AhR in cancer progression was a bit mind-blowing. Even five years ago, that kind of study would have taken four to five years. Using computer algorithms, it took about 20 minutes.

Could you tell us a little about your collaboration with Hercules Pharmaceuticals on the development of a novel drug to inhibit metastasis?

The consequence of hyperactive AhR is the expression of genes that drive cancer invasion and metastasis. In essence, the cell forgets who it is and where it is supposed to live. Consequently, it migrates to and settles in other critical organs like the brain, liver or bone. Because these cells grow so fast and don't die very easily, they cause catastrophic damage.

The drugs that have been licensed to Hercules Pharmaceuticals appear to block hyperactive AhR and to inhibit metastasis. They also block the effects of environmental AhR stimulators. What is truly exciting about these drugs is that, unlike most cancer therapeutics, they are not poisons and therefore, we do not expect chemotherapy-like, debilitating side-effects.

Getting breast cancer **under control**

Informative studies at the **Boston University School of Public Health** have revealed a new mode of development and progression of breast cancer; an environmental chemical receptor that generates an aberrant signalling cascade in forms of cancer that are notoriously resistant to current therapies

TRIPLE NEGATIVE BREAST cancer is the term given to those breast cancers where the cells have been shown to test negative for the usual culprits that feed cancer growth: hormone epidermal growth factor receptor 2, and the hormone receptors for progesterone and oestrogen. It is therefore unresponsive to conventional endocrine-based therapies with drugs like tamoxifen and herceptin; it is also highly aggressive and difficult to treat. Forms of triple negative breast cancer account for 10-20 per cent of all breast cancer cases and predominantly strike younger women, those of African, Ashkenazi or Hispanic origin, or those with the BRCA1 gene mutation – genetic

inheritance being a predisposing factor. Surgery, radiation and chemotherapy are the only treatment options, but recurrence and metastasis are very likely: the prognosis for patients is therefore extremely poor. Most die within a decade of diagnosis.

ENVIRONMENTAL EFFECTS

There is still some debate about whether the environment plays a role in the development of cancers, although it is clear that exposure to some chemicals, such as hydrocarbons and polychlorinated biphenyls (PCBs), significantly

increases the risk of contracting cancer. Furthermore, it is incontestable that there are many manmade atmospheric and environmental pollutants that have deleterious effects on human health, and that some are in fact carcinogens. Dr David Sherr, Professor of Environmental Health at the Boston University School of Public Health and also Professor of Pathology and Laboratory Medicine at the Boston University School of Medicine, is convinced that the development of triple negative breast cancer can be at least exacerbated by the body's responses to some of the many thousands of manmade chemical compounds in the environment, and may eventually be found to be prompted by exposure to them. "I have two primary goals that bridge environmental science and cancer biology: to understand how environmental chemicals influence breast cancer progression and to exploit what we've learned from environmental chemicals to develop novel breast cancer therapeutics," he outlines.

Sherr has established that in breast cancer a cellular receptor that is activated by exposure to common hydrocarbons and dioxins becomes hyperactive; it continually signals the cells as if they were under threat from environmental carcinogens – even where they are absent – and this promotes the migration of the cancer cells to other parts of the body, with disastrous consequences.

TOWARDS SAFE BREAST CANCER THERAPY

In investigating the immunosuppressive mechanisms of environmental pollutants, Sherr found that levels of the aryl hydrocarbon receptor (AhR), a protein that plays an important role in immunity and controls cellular responses to environmental pollutants, are elevated at the onset and during metastasis of breast cancer. He therefore set out to investigate what would happen if levels of AhR were reduced.

Using advanced computational methods involving shape- and electrostatics-based algorithms, medicinal chemistry and genomics techniques, Sherr was able to predict what kinds of chemicals might bind to AhR, and then design and create stable, potent molecules with high AhR binding affinities that would selectively target AhR and inhibit AhR activity. Through *in vitro* assays of tumour cells and high throughput screening, he and his colleagues then monitored the changes in the cells as they occurred, after application of the molecules. They subsequently tested the approach with mice in which luciferase-tagged human mammary tumour cells had been injected, and found that it was validated: "If you block AhR using molecular tricks or using AhR inhibitor

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drugs, breast cancer cells become less invasive," Sherr asserts. "This is no small observation, since it is cancer metastases that kill."

A POWERFUL PARTNERSHIP

In partnership with the Dutch company Hercules Pharmaceuticals, Sherr's team is now refining their small molecules to make them sufficiently potent for use on humans, initially to target triple negative and inflammatory breast cancers, in which particularly high levels of AhR are expressed. So far, in tests with mice, these drugs appear to block the ability of breast cancer cells to travel through the blood stream and establish residence in distant organs; further, they appear effective for treating these cancers at any stage. A major benefit is that the drugs are non-toxic and so do not have the serious unwanted side-effects of radiation and chemotherapy: "Our philosophy is that we have enough poisons. It's now time to treat cancer with more humane drugs," Sherr reflects. "Together with our partners at Hercules Pharmaceuticals, we now see these molecules as drugs with enormous potential as breast cancer therapeutics."

WIDER APPLICATIONS OF AHR TARGETING

The way in which AhR is 'turned on' in breast cancers probably also happens in other cancers, Sherr believes. Using his advanced computational methods, he has found indications that AhR therapy may reduce bone, brain and prostate cancers and also malignant melanoma. At the very least, he hopes that drugs that impede the deleterious actions of AhR will enable people with cancer to live more normal lives, and no longer die from the disease. He also feels that there are potentially other diseases in which targeting the AhR would prove to be a valid strategy.

Sherr attributes the success of his research to long-term interdisciplinary collaborations between his laboratory in the Boston University School of Public Health, that of Dr Gail Sonenshein, a co-director of the Breast Cancer Program at Tufts University, and that of David Seldin, Chief of the Section of Hematology and Oncology at the Boston Medical Center: "Without the teamwork and camaraderie between our groups, the science would never have progressed to its current advanced stage," he muses.

FISCAL CHALLENGES

For Sherr, the major challenge for his work is not the science, but finding ways of funding it. In the current economic climate, federal and other funding is scarce. He is grateful for the financial support his work has received: from the Superfund Research Programme of the National Institute of Environmental Health Sciences, which is dedicated to addressing the effects of hazardous waste on human and environmental health; from private foundations such as the Art BeCAUSE Breast Cancer Foundation, a group dedicated to preventing and identifying the environmental causes of breast cancer; and from his partners in the private sector. Without such support, he feels that there would have been little opportunity to carry out the studies that are now necessary to verify and translate his approach into clinical practice and to build on the argument that prevention, in the form of minimising production of environmental carcinogens, is the most effective public health approach to cancer.

Looking ahead, Sherr and his collaborators will be presenting some results from their work at a meeting sponsored by the Superfund Research Programme in Baton Rouge on 15-17 October 2013, and at the annual meeting of the Society of Toxicology in Phoenix on 24-27 March 2014.

INTELLIGENCE

RESEARCH TRAINING IN IMMUNOLOGY

OBJECTIVES

The Sherr lab has two primary goals that bridge environmental science and cancer biology:

- To understand how environmental chemicals influence breast cancer progression
- To exploit knowledge gleaned from understanding environmental chemical behaviour to develop novel breast cancer therapeutics and bolster the argument for prevention through minimising chemical exposures

KEY COLLABORATORS

The Sherr Lab, Boston University School of Public Health

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FUNDING

National Institutes of Health – National Institute of Environmental Health Sciences (NIEHS) • Art BeCAUSE Breast Cancer Foundation

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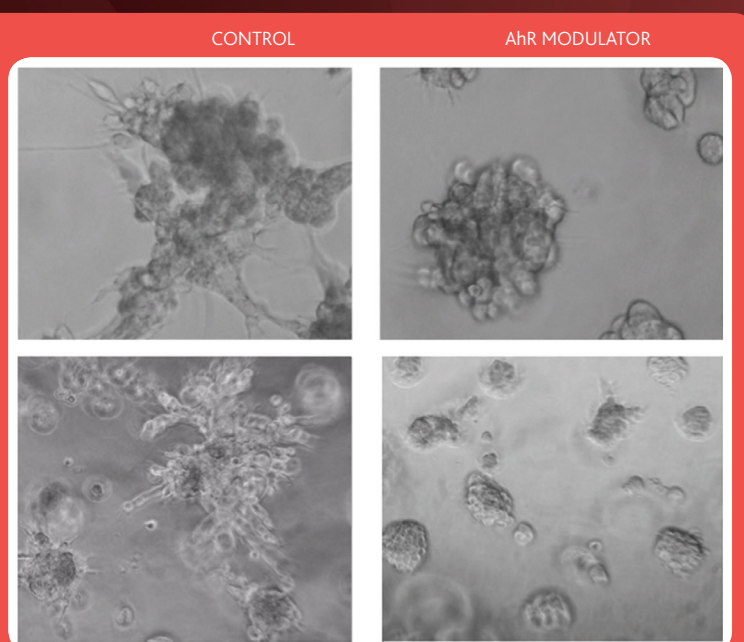
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DR DAVID SHERR received his BA, summa cum laude, with a major in Biology from Brandeis University in 1973, and his PhD in Microbiology and Immunology from Cornell University in 1978. His postdoctoral research on development of the immune system was conducted at Harvard Medical School under the leadership of Martin Dorf, PhD, and Baruj Benacerraf, MD, Nobel Laureate. He now serves as the Director of the Immunology Training Program at the Boston University School of Medicine and the Deputy Director of the Boston University Superfund Research Program. He has published over 100 peer-reviewed manuscripts.



THESE DATA SHOW THAT THE AHR DRIVES HUMAN BREAST CANCER CELL INVASION IN VITRO