

## **Progress Report**

The Role of an Environmental Chemical Receptor, the Aryl Hydrocarbon Receptor,  
in Breast Cancer Cell Survival

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The age-adjusted incidence of breast cancer in the U.S. increased ~1% per year between 1940 and 1990 such that breast cancer is now the leading cause of cancer death among U.S. women aged 20 to 59. A substantial and growing body of evidence indicates that exposure to certain environmental chemicals contributes to the development of breast cancer. For several years our laboratory has focused on the role of common air pollutants and food contaminants in the development and progression of breast cancer. We have shown that hydrocarbons, commonly found in ambient air as a consequence of the burning of fossil fuels or any other carbon source, preferentially induce breast cancers in laboratory animals. The ability of these environmental hydrocarbons to turn normal breast cells into tumors is dependent on a specific receptor within breast cells which recognizes and binds a variety of ubiquitous environmental hydrocarbons (i.e., the aryl hydrocarbon receptor). Once bound by environmental pollutants, this hydrocarbon receptor delivers signals to the cells which, we hypothesize, increase cell growth, increase cell survival, and drive progression of relatively treatable breast tumors into lethal metastatic breast cancers. The work supported by Art beCAUSE is designed to test this hypothesis.

Considerable progress has been made:

1) We have shown that, once environmental hydrocarbons activate the hydrocarbon receptor in human breast cells, the hydrocarbon receptor signals the cell to produce more of a highly specialized enzyme which is capable of converting environmental chemicals into carcinogenic products. These products mutate breast cell DNA and thereby contribute to the formation and progression of human breast cancers. These results suggest a molecular mechanism through which the environmental hydrocarbons can influence breast cell function. The data from this work are being incorporated into a manuscript to be submitted for publication. The support of Art beCAUSE will be acknowledged in this manuscript.

2) We now have demonstrated in several human breast tumor cell lines that repression of the hydrocarbon receptor through molecular engineering suppresses the responsiveness of the cells to environmental pollutants and reduces the tendency of these tumor cells to grow, survive, and invade a simulated breast tissue environment (Figure 1). These results suggest that rapid growth and tissue invasion of advanced environmental chemical-induced breast cancers may be reversible by inhibition of the hydrocarbon receptor. The data from this work are being incorporated into a second manuscript to be submitted for publication. The support of Art beCAUSE will be acknowledged in this manuscript.

3) We and others have shown that activity of the hydrocarbon receptor is naturally inhibited by a “repressor” protein produced by normal breast cells. We now have demonstrated that the activity of this hydrocarbon receptor repressor protein is compromised in human breast cancer cell lines resulting in unbridled hydrocarbon receptor activity which leads to increased tumor cell growth, survival, and metastasis. The data from this work are being incorporated into a third manuscript to be submitted for publication. The support of Art beCAUSE will be acknowledged in this manuscript.

With on-going support from Art beCause, we will continue to investigate the mechanisms through which environmental chemicals aberrantly regulate gene activity in human breast cancer and we will attempt to identify non-toxic, natural inhibitors of the hydrocarbon receptor (e.g. flavonoids) to

be used as preventatives to block the effects of environmental carcinogens or as therapeutics to inhibit the activity of the receptor in advanced mammary tumors.

**Figure 1: Inhibition of the Hydrocarbon Receptor (AhR)  
Suppresses Human Mammary Tumor Cell Growth and Invasion**

An aggressive human breast cancer cell line (BP-1) was generated by culturing human mammary epithelial cells with a common environmental carcinogen and hydrocarbon receptor activator, benzo[a]pyrene. These tumor cells grow rapidly in a simulated breast environment (Matrigel) and form branched colonies characteristic of aggressive metastatic tumors (left panels). In contrast, colonies of cells in which the hydrocarbon receptor has been inhibited by molecular techniques (transfection of a specific hydrocarbon receptor repressor) grow poorly with a rounded shape characteristic of non-invasive tumors (right panels).

