



Seeds4Hope

A program of the Windsor Essex County Cancer Centre Foundation



2009 SEEDS4HOPE GRANT RECIPIENT

Dr. Lisa Porter

“Role of Stress Factor Signaling in Breast Cancer Initiation and Progression”

SUMMARY OF RESEARCH PROJECT

Breast cancer remains the most prevalent cancer among women, currently 1 in 9 Canadian women are diagnosed with breast cancer at some point in their life. A great deal of progress has been made with regard to diagnosis, prognosis and treatment, however there is still a significant cohort of women who present initially with very aggressive, non-responsive forms of breast cancer, as well as those who relapse following treatment. It is because of this that breast cancer remains the second leading killers from cancer among women. There is a great deal of evidence accumulating that stress and other behavioural factors may affect cancer progression and patient survival, yet the underlying mechanisms for this association are poorly understood. Cortisol is the primary stress hormone in the body and abnormal levels have been linked to earlier mortality and cancer progression in breast cancer models. Cortisol is essential in the body to properly regulate metabolism and immune responses; therefore, direct inhibition of cortisol as a therapeutic strategy will be laden with side-effects, as is the case with many current treatments. The overall goal of this research project is to determine the molecular mechanism mediating cortisol effects on breast cell growth, to determine which of these effects are also implicated in human breast cancer and to begin to determine the effectiveness of these mechanisms for novel anti-cancer drug development.

To achieve this we are utilizing a variety of computer-based as well as molecular biology techniques to identify genes that are implicated in stress effects on breast cells as well as in human breast tumorigenesis. We will further test these genes in cell and animal models to determine their potential as novel targets for drug design in the treatment of breast cancer. This work holds tremendous promise for the development of therapeutics that would aid in the successful treatment and long-term remission of patients with the most aggressive forms of breast cancer.

HOW THIS RESEARCH HELPS ADVANCE QUALITY CANCER CARE IN OUR COMMUNITY

This project holds tremendous promise for the development of novel therapeutic strategies which may improve the treatment and/or the detection of advanced forms of breast cancer. Such advancement would have a tremendous impact on survival rates; thereby having high priority for advancing cancer care both locally, regionally and beyond. In addition, future direction of this work will promote collaborative research with the Windsor Regional Cancer Centre. Strengthening University-Hospital ties in the Windsor community is very important; not only for training, recruitment and retention of the medical expertise but also for attracting future funds necessary to expand the innovative technologies ongoing in the Windsor area, technologies essential to keep Windsor cancer care at the forefront in this country.



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PROGRESS REPORT

Breast cancer remains the most prevalent cancer among women, currently 1 in 9 Canadian women are diagnosed with breast cancer at some point in their life. A great deal of progress has been made with regard to diagnosis, prognosis and treatment however there is still a significant cohort of women who present initially with very aggressive, non-responsive forms of breast cancer, as well as those who relapse following treatment. It is because of this that breast cancer remains the second leading killer from cancer among women.

Evidence suggests that stress may affect cancer progression and patient survival, yet the underlying mechanisms for this association are poorly understood. Cortisol is the primary stress hormone in the body and abnormal levels have been linked to earlier mortality and cancer progression in breast cancer models. Through funding from the Seeds4Hope program, our research group has determined that cortisol, and a synthetic derivative of cortisol frequently used to treat nausea in breast cancer patients, increase the growth of some forms of breast cancer cells. They also enhance the ability of these cells to move to other regions in the body and they prevent chemotherapy drugs from successfully killing cancer cells. To determine how stress alters the growth properties of breast cells we have conducted an initial genome-wide analysis of the response of one breast cancer cell type. We are using a variety of computer-based as well as molecular biology techniques to identify specific “genes” that are regulating these effects.

Breast cancer is a stressful event; both physiologically and psychologically, it is not possible to prevent this natural response from occurring, but it is possible to prevent these effects from helping breast cancer progress and escape treatment. This work is revealing how these processes contribute to aggressive forms of breast cancer and patient relapse, as well as aiding in the discovery of potential drug targets to improve how we treat breast cancer.

“The Seeds4Hope program truly demonstrates the passion of the Windsor community to support the expansion of medical research and training right here in Windsor. In addition to enabling this new and exciting program in my lab - these funds have trained a talented graduate student and bridged new fruitful collaborations.”

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FINAL REPORT

There is significant evidence to support that stress and depression affect cancer progression and patient survival. The glucocorticoid cortisol is an effective and reliable indicator of chronic stress and/or depression levels and synthetic analogs of this compound are in fact given to breast cancer patients to combat nausea. It is absolutely essential for research to determine whether these compounds have an adverse affect on breast cancer cell growth characteristics. The overall goal of our research proposal was to address exactly this.

During this work we treated a wide variety of breast cancer cells with varying concentrations of cortisol and its clinically used analogue, Dexamethasone. We tested the response of the breast cancer cells against that of normal breast cells. Three important sets of results have emerged from this work:

- 1) short term, high levels of the stress hormone cortisol has the potential to increase the proliferative and metastatic properties of breast cancer cells; supporting a potential role for stress in the initiation and progression of breast cancer.
- 2) Long-term exposure to stress creates a new environment for the cells that mimics a state of chronic inflammation. This may prevent the body from responding properly to protective effects and may leave the body susceptible to changes associated with cancer progression.
- 3) Our results strongly support that the synthetic analogue Dexamethasone, prevents breast cancer cells from undergoing cell death when exposed to chemotherapeutic drugs. While this work needs to be confirmed using mouse models and human clinical trials, our data absolutely suggests that this commonly used antiemetic drug interferes with the effectiveness of the chemotherapy drugs; potentially having adverse effects on the promotion of breast cancer.

Hence, in conclusion this work supports that stress levels can contribute toward breast cancer progression and aggressiveness and negatively impacts patient response to therapy. Our work suggests that this is, at least in part, due to an alteration in the balancing of how breast cells respond to inflammatory signals. Importantly, our data supports the need to test the effects of Dexamethasone on patient response to chemotherapy in a clinical trial. This work could have a profound impact on the protocol for treating breast cancer patients and ultimately on patient survival rates.