Seeds4Hope

A program of the Windsor Essex County Cancer Centre Foundation

2012 Seeds4Hope Grant Recipient

Dr. Lisa Porter

"Role of the Novel Cell Cycle Regulator Spy1 in Self Renewal of Hematopoietic Stem Cells; Implications in Human Myeloma"

SUMMARY OF RESEARCH PROJECT

Multiple myeloma is a cancer of the blood cells that are responsible for producing antibodies, called plasma cells. Myeloma represents 1% of all cancers, and up to 4 people per 100,000 are diagnosed with the disease yearly. With conventional treatment, median survival is 3–4 years; this can now be extended to 5–7 years or longer with advanced treatments. Despite these significant advances, we know that patients with myeloma often succumb to their disease because they become resistant to chemotherapy. It is of high priority to find new approaches to prevent or treat this inevitable relapse.

One promising approach is to target a family of proteins known as the Cyclin Dependent Kinases (Cdks). These proteins drive proliferation of relapsed myeloma cells, and laboratory studies suggest that targeting select members of this family may re-sensitize resistant myeloma to treatment. An initial clinical trial demonstrated that ~44% of patients with resistant myeloma may benefit from this approach. These are encouraging results that could be significantly optimized from what we learn in this study. Using cells derived from relapsed myeloma patients, we will determine which of the Cdk family members are essential to target. We will further determine whether existing drugs are sufficient to block the action of these specific Cdks in myeloma. This work will provide essential information for evaluating the results that come from ongoing clinical trials in this field. Importantly, these studies will potentially improve the available therapies for myeloma toward the goal of making this a curable disease.

HOW THIS RESEARCH HELPS ADVANCE QUALITY CANCER CARE IN OUR COMMUNITY

Of the approximately 2,300 people in Canada diagnosed with multiple myeloma annually, ~40% will not live longer than 5 years. This study aims to improve the therapy available for multiple myeloma patients; it will lay the necessary groundwork for our future research that would dramatically prolong lives both regionally and beyond. This preliminary work is important for the Windsor/Essex community in that it will begin collaboration between local researchers and clinicians with a focus on myeloma. This will ensure that local patients will have access to clinical trials that open in this exciting area and will benefit from future infrastructure funds that this may attract.

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PROGRESS REPORT - YEAR ONE

Although advances have been made in the treatment of multiple myeloma, the majority of patients still succumb to drug-resistant relapse. One promising new approach for treatment of this disease has been through the use of drugs that inhibit a family of proteins (CDKs) that are responsible for driving the proliferation of relapsed myeloma cells. In the clinic, use of these drugs has been initially quite successful; however, not all patients are responsive. Our goal is to improve the use of this treatment by investing which CDKs are essential to target, and if other cell cycle proteins are involved in resistance to these drugs. To date, we have obtained a panel of human multiple myeloma cell lines, representing different subclasses of the disease, and begun to characterize the levels of different CDK proteins as well as other important cell cycle proteins. We have discovered that a particular cell cycle protein, Spy1, that is capable of activating some CDKs, is differentially expressed in the myeloma cell lines. Importantly, our data shows that expression of this protein correlates with response to drug treatment. We have optimized the manipulation of cell cycle proteins in the panel of cell lines and have begun to determine which proteins are the most critical for successful treatment with CDK inhibitors.

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PROGRESS REPORT - YEAR TWO

Blood cancers are the most common malignancy to affect youth and young adults in our country. Despite tremendous advances in this field, patients with different types of blood cancer often succumb to their disease due to drug resistant relapse. One such blood cancer is multiple myeloma (MM). This is the second most common hematopoietic cancer with approximately 2,300 Canadians being diagnosed annually. It is a malignancy of antibody-secreting B-cells, called plasma cells, which accumulate in the bone marrow. One promising new therapy for drug resistance in MM is using drugs called Cdk-inhibitors, however results in the clinic have been variable. Our lab has discovered a protein called Spy1 that binds to Cdks to activate them. We hypothesized that when this protein is present Cdk-inhibitor drugs are much less effective, and may decrease response of patients with MM to Cdk-inhibitor therapy. In this study we first determined that the Spy1 protein was at very high levels in patients with myeloma. We then used three patient-derived cell lines and demonstrated that the levels of this protein correlate with response to Cdk-inhibitor drugs. This is very promising as it supports that developing drugs against this mechanism may sensitize resistant MM patients to therapy. To determine the mechanism by which the protein Spy1 may be propogating blood cancers to grow and divide we further studied how this protein was involved in the process of maturing blood cells. There is significant data to support that a population of very immature blood cells are driving relapse in many blood cancers. Taking bone marrow stem cells from mice we show that as these cells mature levels of the protein Spy1 decrease. We then used a cell line from a patient with promyelocytic leukemia, one form of blood cancer that has been cured in many cases if these immature cells can be coaxed to mature. We demonstrated that levels of this protein correlate with resistance to mature. We hypothesize that reducing the levels of this protein will be a very valuable way of targeting resistant populations of blood cancer cells in subsets of leukemia and MM.