



The Ewings Cancer Foundation of Canada (ECFC) was inspired by a young teen named Reid who lost his battle with Ewing sarcoma. ECFC is committed to funding medical research to find new and better treatments and ultimately, the cure for Ewing sarcoma.

For more information go to www.ewingscancer.ca or email ECFC at contact@ewingscancer.ca.

Sarcomas are cancers of soft tissue or bone predominantly affecting children, adolescents and young adults. The two primary types of bone sarcomas are osteosarcoma and Ewing family tumours (EFTs). Once the primary EFT tumour has spread to other organs, patient outcomes are dismal despite aggressive chemotherapy, surgery and radiation. The presence of metastatic disease is the single most powerful predictor of patient outcomes.



Dr. Jason Berman

What biological differences underlie the ability of these more aggressive Ewing sarcoma cells to successfully metastasize?



Dr. Poul Sorensen

Dr. Jason Berman (IWK Health Centre, Halifax) and Dr. Poul Sorensen's (BC Cancer Agency Research Centre) research addresses this question, with the goal of identifying differences that can be the focus of future drug development. Their research into Ewing sarcoma focuses on the Y-box protein 1 (YB1), which has been implicated in metastasis in other tumour types.

YB1 is one of thousands of human transcription factors (see side bar). One common defect in cancer is the dysregulation of a specific transcription factor, due to either incorrect levels (either too much or none at all) or mutation (changing the function). In some cases, alteration of a single transcription factor is sufficient to initiate a chain reaction resulting in malignant transformation into cancer.

Summary of Research Findings

To determine if YB1 increases metastatic potential, Drs. Berman and Sorensen compared Ewing sarcoma cells that contain YB1 protein to those engineered to have no YB1 protein (YB1 knock-down cells). They found that YB1 promoted cell metastasis and invasion, as well as cell proliferation (an indication of tumour growth). These data support the idea that YB1 is a pro-metastatic protein in Ewing sarcoma; it helps cancer to metastasize.

Solid tumours, such as Ewing sarcoma, grow as a 3-dimensional mass that is influenced by blood vessels, the immune system, hormones, surrounding tissues, oxygen levels, nutrient levels, and the matrix that holds the tumour together. Therefore, in order to more closely replicate a tumour environment, promising research results are often confirmed in a living organism. One method for studying tumour cells is to inject a small number of cells into a defined location in a small animal. The cells will then form a tumour mass that not only grows, but also undergoes angiogenesis and metastasis.

Background Biology

Metastasis refers to the process of tumour cells leaving the primary tumour site and relocating (migrating) to a secondary site. The spread of cancer cells is not a result of drifting, but is an active process that requires invasion, migration and angiogenesis. Also, this process is not random; specific tumour types have preferred tissues and organs to which they metastasize. For example, Ewing sarcoma cells metastasize most frequently to other bones, as well as bone marrow and lung. Metastasis is a defining characteristic of aggressive cancer cells; metastatic disease accounts for 90% of all cancer deaths.

Invasion is a key component of the metastatic process and refers to the ability of tumour cells to deliberately move through the walls of blood and lymph vessels, permitting travel throughout the body. Invasion is required both to enter the blood/lymph system at the primary tumour site, as well to leave the blood/lymphatic vessel at secondary sites.

Angiogenesis refers to the process by which newly established tumours attract blood vessels—vessels branch, growing towards and attaching to the tumour. Once attached to a blood vessel, the new tumour is able to tap into the patient's metabolic system and sustain the uncontrolled growth that is a hallmark of cancer.

Transcription factors. Each of the body's cells contains the genetic information (DNA) required to make and control any cell within the body. Transcription factors function like a symphony conductor, controlling how and when genetic information is used.

C¹⁷ strives to improve health outcomes and quality of life for children and adolescents in Canada with cancer and blood disorders, and to eliminate disparities in care and outcomes wherever they occur.

Ewing Sarcoma Research Project Update—May 2014

The first test organism used was a zebrafish pioneered by Dr. Berman, in collaboration with Dr. Graham Dellaire from Dalhousie University. Zebrafish are useful for research for many reasons. For example, the control of cell growth in zebrafish parallels that of human cells, and because zebrafish are transparent, changes inside the live fish can be easily monitored. In Drs. Berman and Sorensen's research, fluorescently labeled Ewing sarcoma cells were injected into the yolk sac of zebrafish embryos and the movement of the cells recorded and measured. Using this system it was shown that Ewing sarcoma cells expressing YB1 migrated out of the yolk sac and down the tail of the fish, whereas the YB1 knock-down cells remained in the yolk sac.

These findings were then confirmed and extended in mice. Mice are remarkably similar to humans at the genetic level and pre-clinical research in mice is a key step in moving exciting research discoveries from the laboratory into clinical trials in humans. Mice with Ewing sarcoma cells injected into the kidney lining demonstrated metastasis to the lungs, whereas the YB1 knock-down cells did not metastasize. Moreover, the kidney tumour mass formed by YB1 knock-down cells showed reduced growth of blood vessels and reduced tumour growth.

Drs. Sorensen and Berman also discovered that YB1 controls the levels of a protein called HIF-1 α . HIF-1 α has been shown to influence a wide range of cell functions that sustain tumour growth, including invasion and angiogenesis. Cells engineered to have reduced HIF-1 α levels demonstrated reduced cell migration and invasion, suggesting that YB1 promotes metastasis in Ewing sarcoma, at least in part, by controlling the HIF-1 α protein.

Future Research Directions

Experiments are ongoing to understand the roles of YB1 in blood vessel development and angiogenesis. Drs. Berman and Sorensen will extend their research to other tumour types to determine if the role of YB1 in metastasis is generalizable, or specific to Ewing sarcoma.

Other researchers have found that a protein called focal adhesion kinase (FAK) can control the activity of YB1, and there are established connections between FAK and both metastasis and angiogenesis. In collaboration with Drs. Brian Crompton and Kimberly Stegmaier from the Dana-Farber Cancer Institute (Boston), Drs. Berman and Sorensen will explore the impact of a novel FAK inhibitor on the metastasis of Ewing sarcoma using the research models described above.

Publication and Dissemination

This research has been published at seven international conferences, as well as at the Canadian Student Health Research Forum, and has been submitted for publication in a high profile journal.

About the Researchers

Dr. Jason N. Berman, MD, FRCPC, FAAP is Clinician Scientist in Pediatric Oncology at the IWK Health Centre in Halifax Nova Scotia and the Cancer Care Nova Scotia Peggy Davison Clinician Scientist. The Berman laboratory recently became the Atlantic node for the Centre for Drug Research and Development (CDRD) based in Vancouver, which will greatly enhance their drug discovery capacity.

Dr. Poul Sorensen, MD, PhD, FRCPC is a board certified pathologist specializing in the molecular pathology of pediatric cancers. He is the Johal Chair in Childhood Cancer Research at the University of British Columbia and a Senior Scientist at the BC Cancer Agency Research Centre. Dr. Sorensen is the Chair of the Translational Research Committee of the Children's Oncology Group.

This research was funded through a partnership between ECFC and C¹⁷ Council. Funds have been raised to start a second research project in July 2014. Current grants under review are innovative scientific approaches trying to understand the genetic basis of Ewing tumors, to identify new drugs to treat metastatic Ewing tumours.

With your support, this partnership will continue to promote innovative discovery and clinical research in Canada, with a goal of improving outcomes for patients with Ewing tumours.

For information on how to donate electronically or mail, please visit www.ewingscancer.ca/donate.



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