



# C<sup>17</sup> Research Network

Annual Report  
2008 - 2009

April 1—March 31

*Canadian Centres Battling Cancer and Blood Disorders in Children*



## *Message from the Chair*

*From the beginning of modern chemotherapy treatment for childhood cancer, some 60 years ago, pioneers in the field recognized that there were too many different kinds of cancer, and too few patients at even the largest centre, to be able to carry out effective research alone.*

*This led to the development of the incredible collaborative networks in North America within which we work today on behalf of children with cancer. In Canada, the C<sup>17</sup> organization recognized the opportunities for progress by developing a strong collaboration between the 17 academic childhood cancer centres in Canada.*

*The success of these collaborative ventures is demonstrated by the fact that currently 82% of all children with cancer in Canada can now be expected to be cured. This success is promising, but not sufficient for children newly diagnosed with childhood cancer, for whom a successful treatment is not available for almost 1 in 5. We also continue to have an obligation to childhood cancer patients who, now cured, face too many short and long term risks and side effects.*

*I am proud of our progress in the C<sup>17</sup> Research Network, and this Annual Report demonstrates the incredible array of research we have underway in Canada in children with cancer and serious blood disorders. From the collection of biological samples from patients with rare diseases, trials of better therapy, studies of the quality of life in survivors with neurocognitive disorders, children of immigrant families, to those at the end of life, the need and strength of working together is evident.*

*Multi-centre national studies are the major endeavors. They take time, effort and funding. We are very proud to now be supporting, in part or in full, fifteen projects across Canada. I am excited as the first of these start to conclude and become ready to release results, some of which are in this report. With our early successes, we are attracting more funding support, and so we see only an upward trend for the future. Future annual reports will include ongoing results and advances, as well as, descriptions of newly funded projects.*

*Paul Grundy  
Chair, C<sup>17</sup> Research Network*

# Research Grant Competitions

Twice a year, the C<sup>17</sup> Research Network holds a two stage, peer-reviewed grant competition, funding research into cancer, serious hematological childhood diseases and bone marrow transplantation, including:

- all phases of clinical trials
- disease and population-based registries
- biological sample banks
- quality of life
- health outcomes and psychosocial research
- basic and translational research, and
- hematopoietic stem cell transplantation research

The C<sup>17</sup> Research Network is currently entering Round 10 of Letter of Intent/Grant competition in May 2009. Letters of Intent are accepted November 1st and May 1st of each year and full Grant Proposals are submitted on the same dates following acceptance of the LOI. The competitions have provided funding as follows:

	<b>Distributed / Committed Funds</b>	
	<b>Year 1</b>	<b>Year 2</b>
Round 1	\$58,500.00	\$41,500.00
Round 2	\$25,000.00	\$25,000.00
Round 3	\$54,900.00	\$59,900.00
Round 4	\$99,872.00	\$87,843.00
Round 5	\$150,205.00	\$124,932.00
Round 6	\$67,068.00	\$66,523.25
Round 7	\$117,850.00	\$114,080.00
Sandra Sharpe	\$59,484.00	N/A
Round 8	\$128,202.76	\$103,156.24
<b>Total</b>	<b>\$761,081.76</b>	<b>\$622,934.49</b>

With the partnerships of several foundations, the C<sup>17</sup> Research Network has now partially funded, completely funded or committed to fund 15 research projects for a total of \$1,384,016.25 in grant funds. These foundations include:

- Childhood Cancer Foundation—Candlelighters Canada (CCFC)
- Coast to Coast Against Cancer Foundation (CTCACF)
- Kids with Cancer Society (Edmonton) (KWCS)
- Sandra Sharpe Rhabdomyosarcoma Fund (SSRF) in partnership with CCFC
- Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)
- Optimist International

***Defining the Clinical Phenotype of Inherited Marrow Failure Syndromes and the Risk Factors for Severe Hematological Complications and Cancer by the Canadian Inherited Marrow Failure Registry (CIMFR).***

**Dr. Yigal Dror, Hospital for Sick Children**

**Round 1 (April 2005) - \$41,500 per year for 2 years  
Supported with CCFC funding**

Inherited marrow failure syndromes (IMFSs) are a collection of conditions whereby individuals are unable to make enough blood cells. Some of the recognized IMFSs include: Fanconi Anemia, Diamond-Blackfan anemia, dyskeratosis congenita, and Kostmann syndrome. Individuals with IMFSs are invited to participate in the Canadian Inherited Marrow Failure Registry, which was established in 2001 by Dr. Dror. The aim of the study is to better define the clinical characteristics of IMFSs and the risk factors for complications by investigating clinical, laboratory and genetic factors. This information will enhance a clinician's ability to diagnosis, provide a basis for the creation of a screening/monitoring program for hematological complications and identify indications for early intervention. It will also help researchers understand why a portion of patients with IMFSs develop severe complications, while others may stay stable for many years or for life .

**Progress:**

To date 235 patients with these rare conditions have been enrolled on the study. On average, four follow-ups have been conducted per patient since enrollment. Several projects have resulted from analysis of this registry:

1. The researchers have identified that 24% of IMFSs (39 of the 162 patients) are unclassifiable (UC-IMFSs), i.e. the exact category of the IMFS cannot be determined. These individuals can have either new syndromes or atypical presentations of known syndromes. Conventional staged genetic testing is becoming increasingly challenging for the management of patients with atypical IMFSs because the number of IMFS-related genes identified is increasing annually. Thus, the researchers have proposed diagnostic guidelines in approaching these UC-IMFS patients. The relative prevalence, characteristics, diagnostic and therapeutic challenges are summarized in the journal, *Pediatrics* by Dr. Julian Teo, a post-doctoral fellow. See reference below.

2. Shwachman-Diamond syndrome (SDS) is a multi-system IMFS associated with bone marrow and pancreatic dysfunction, and a risk of MDS/leukemia. The researchers have compared 31 cases to patients with four IMFSs in the CIMFR, including: (1) Diamond Blackfan anemia (2) Fanconi anemia, (3) Kostmann neutropenia, and (4) Dyskeratosis congenita. SDS is found to be one of the most prevalent IMFSs. Similar to the other IMFSs, identification of some late onset clinical manifestations have facilitated a clinical diagnosis. In challenging cases, mutation analysis of SDS genes can help establish the diagnosis. For instance, three of the present study's patients were confidently diagnosed only after completing SDS mutation analysis. Results of this project have been summarized by Ms. Saman Hashmi, a medical student. See reference below.

3. This registry continues to spark new research projects and to encourage the involvement of young investigators.

- Samples from the Biobank are used by Dr. Chet Taylor and Ms. Michelle Ray, PhD candidate, to study the role of FLVCR1 in the pathogenesis of the erythropoietic failure in RPS19 negative and RPS19 positive cells from patients with Diamond Blackfan anemia.
- Clinical characteristics of and risk factors for malignant myeloid transformation into Myelodysplastic Syndromes and Acute Myeloid Leukemia in patients with IMFSs are being studied by Dr. Segbefia, a post doctoral fellow
- A comprehensive genetic analysis of IMFSs are being studied by Ms. Elena Tsangaris, an undergraduate student.

**Publications and Presentations:**

Teo JT, Klaassen R, Fernandez CV, Yanofsky R, Wu J, Champagne J, Silva M, Lipton JH, Brossard J, Samson Y, Abish S, Steele M, Ali K, Dower N, Athale U, Jardine L, Hand JP, Tsangaris E, Odame I, Beyene J, Dror Y. Clinical and genetic analysis of unclassifiable inherited bone marrow failure syndromes. *Pediatrics*. 2008 Jul;122(1):e139-48.

Hashmi S, Klaassen R, Fernandez CV, Yanofsky R, Wu J, Champagne J, Odame I, Silva M, Lipton JH, Ali K, Brossard J, Samson Y, Abish S, Athale U, Dower N, Jardine L, Hand JP, Steele M, Beyene J, Dror Y. Shwachman-Diamond syndrome among the inherited marrow failure syndromes. A report from the Canadian Inherited Marrow Failure Registry (CIMFR). *American Society of Pediatric Hematology/Oncology*. May 14-17th, 2007. (Poster presentation)

***Prospective Cohort Study of Genetic Variation and Risk of Infection in Canadian Children with Acute Myeloid Leukemia.***

**Dr. Lillian Sung, Hospital for Sick Children**

**Round 1 (April 2005) - \$17,000 for 1 year  
Supported with CCFC funding**

In patients with acute myeloid leukemia (AML), approximately 7-10% of children will experience a life-threatening infection. There is a lot of variability in the rate and outcome of infection, even among children receiving identical chemotherapy. Thus, Dr. Sung is looking at variations in specific genes involved in immunity that could contribute to the rate and outcome of infections in children. From this information, they hope to be able to predict and perform targeted therapy on children with the highest risk.

**Progress:**

The study involves recruiting patients and a retrospective chart review. The study is in the third year of patient recruitment from 17 centres (15 Canadian and 2 American sites). As of October, 2008, 113 of the target 300 participants have been enrolled. In the retrospective chart review of 313 individuals with AML, 10.9% of the deaths list an infection as the primary cause of death. Now with sufficient amounts of DNA from all of the participants, the researchers can begin the proposed candidate gene studies. The research team has obtained additional funding through a 3 year operating grant in 2005 from NCIC, and has successfully renewed this operating grant for 4 years beginning in July 2008. NCIC funding should ensure the successful completion of the study. The project has yet to accumulate enough data for publication of results, though publications are anticipated in the next one or two years.

***The Effect of Maintaining a Higher Hemoglobin Level on Neutropenia Duration After Bone Marrow Transplantation in Children: A Pan-Canadian Multi-centre Randomized Controlled Clinical Trial.***

**Dr. Michel Duval, Hôpital Sainte-Justine**

**Round 2 (December 2005) - \$25,000 for 2 years  
Supported with CCFC funding**

Bone marrow transplantation can involve radiation/chemotherapy treatment (myeloblastic regimen) which can cause serious neutropenia (a low number of a type of white blood cells called neutrophil granulocytes or neutrophils that serve as the primary defense against infections). Prolonged neutropenia is found to result in a 2 to 5 fold increased risk of death after hematopoietic stem cell transplantation, and is associated with a higher risk of bacterial and fungal infections, and an increase in transplant-related mortality. Earlier studies suggest that maintaining a high hemoglobin level after bone marrow suppression can accelerate the production of granulocytes. Thus Dr. Duval proposes to determine in a randomized trial whether a higher hemoglobin level after bone marrow transplantation in children will accelerate neutrophil recovery.

**Progress:**

The study has encountered significant challenges in identifying an organization who can assist with study coordination and data management. After several unsuccessful explorations with various study operation centres, the study will now be coordinated through a clinical trial structure which manages multicentre transfusion pediatric clinical trials across Canada. The researchers have also received funding from Fonds de la Recherche en Santé du Québec (FRSQ).

The delays have highlighted the challenges in initiating pediatric multicentre clinical trials in Canada. These difficulties have forced several people to think about the problem and create solutions that will be helpful to other researchers in the future.

## **Genotype-Specific Approaches to Therapy in Children with Cancer (GATC Cancer)**

Dr. Rod Rassekh, BC Children's Hospital

Round 3 (June 2006) - \$54,900 year 1 & \$59,900 year 2  
Supported with CCFC funding

Adverse drug reactions (ADRs) are a major cause of childhood morbidity and mortality. In children, cancer drug-related ADRs are especially severe and debilitating and account for 22% of all pediatric oncology patient hospital admissions. The treatment of childhood cancer is difficult and requires using medications which have the potential of causing significant harm to the patient. Currently, there is no method of predicting who will have an ADR. With the introduction of new technologies and the Human Genome Project, it has now become possible to potentially identify those patients at risk of an ADR by looking at common variations at specific gene sites. This project will identify patients who have had an ADR, and look at any genetic variability (called single nucleotide polymorphisms, or SNPs) between ADR and non-ADR patients. Potential SNPs that confer a risk of an ADR to a particular medication will be identified, with the goal of using this method as a routine tool for clinicians to safely select medications and doses for individual patients. The two ADRs of highest priority will be anthracycline-associated cardiotoxicity and Cisplatin-associated hearing impairment.

*Adverse Drug Reactions (ADRs) are a major cause of childhood morbidity*

### **Progress:**

The study is open at 10 centers across Canada and has demonstrated high accrual and promising early results. The study has identified several genes of interest, including some key transporters of anthracyclines out of cardiac myocytes. The results are approaching statistical significance and further accrual may yield significant results.

Preliminary results indicate that genes that are associated with hearing loss with Cisplatin have been identified and final results will be ready for publication within the year. The odds ratios associated with the SNPs that were found are high (odds ratios approaching 30, meaning that the odds that a child will have hearing loss with Cisplatin are many times higher if a child has certain SNPs). The genes involved with these SNPs are also biologically plausible as they are involved in free radical metabolism and Cisplatin transporters. The cooperation of the C<sup>17</sup> centers has promoted the study's success. In fact, the Cisplatin and anthracycline results have enabled the researchers to secure an additional 5 years of funding for the project from Genome Canada and further work in pediatric oncology. Moreover, this project has allowed pediatric oncologists from other sites to suggest other adverse drug events that they wish to target and future proposals are being generated at other centres. It is possible that the Canadian pediatric oncology centres, through the C<sup>17</sup> Research Network, will take the world lead in the pharmacogenetics of adverse drug events in pediatric oncology.

### **Publications:**

Ross CJ, Carleton B, Warn DG, Stenton SG, Rassekh, SR, Hayden MR. Genotypic approaches to therapy in children: a national active surveillance network (GATC) to study the pharmacogenomics of severe adverse drug reactions in children. *Ann NY Acad Sci.* 2007 Sep;1110:177-92.



### ***Neuro-imaging of White Matter and Neuro-cognitive Outcome Following Cranial Radiation for Pediatric Brain Tumours.***

**Dr. Donald Mabbott, Hospital for Sick Children**

**Round 4 (January 2007) - \$47,500 for 2 years  
Supported with KWCS and CCFC funding**

With recent advances in medical treatment, many children diagnosed with brain tumours are now cured. Unfortunately, those who are treated with radiation to the brain can experience brain injury, learning problems, and experience difficulties obtaining employment as adults. The researchers hope to reduce the negative impact of radiation on children treated for brain tumours and improve their quality of life. To understand the relationship between the brain injury caused by radiation and its effect on thinking skills, they will obtain MRI pictures of the white matter in the brain as well as tests of thinking ability, including attention, speed of thinking and intelligence. The white matter is the insulation around nerve fibres that help regulate neural messages that underlie thinking. The relationship between the MRI pictures and thinking skills will be compared between healthy children and children with brain tumours. Findings from this study will help identify children at risk for difficulties, in order to develop rehabilitation programs to help children learn after they have been treated with radiation, identify medical treatment to avoid injury while maintaining efficacy, and create information to weigh new medical techniques for protecting or re-growing white matter.

#### **Progress:**

The study has been open for recruitment at The Hospital for Sick Children since fall 2007 with 20 participants – 11 brain tumour patients and 9 controls. Ethics approval is pending at Alberta Children's Hospital, British Columbia Children's Hospital, and Children's Hospital of Eastern Ontario. Sites are also undergoing additional study preparations such as standardization of the MRI protocol, development of quality control procedures, and site visits for study co-ordination and behavioral testing. It is anticipated that active recruitment at all of the remaining sites will commence shortly.

### ***Immigrant Families' Experiences of Care for their Child with Cancer.***

**Dr. Anne Klassen, McMaster University**

**Round 4 (January 2007) - \$52,372 year 1 & \$40,343 year 2  
Supported with CCFC funding**

In looking at the factors that may explain why some caregivers of children with cancer cope well with the stresses of childhood cancer and others do not, the researchers identified a gap in the research literature: the concerns and experiences of immigrant parents of children with cancer have never been addressed. The caregiving experience is based on research derived from non-immigrant caregivers that may not hold true for immigrant parents and thus the delivery of health care services may not be appropriate. Immigrants comprise a large and dynamic segment of Canada's population. Through interviewing immigrant families from Chinese and South Asian cultures in their native language, the researchers want to explore their experiences and the implications of these experiences for services, programs, and policy.

#### **Progress:**

Ethical approval for this study has been obtained from the following C<sup>17</sup> centres: McMaster Children's Hospital; The Hospital for Sick Children; BC Children's Hospital; Children's Hospital of Eastern Ontario; Stollery Children's Hospital and Alberta Children's Hospital. Ethics approval at McGill University Health Centre is pending. Eighteen of the projected 30 Asian families recruited have been interviewed representing diverse language groups — Mandarin, Cantonese, Punjabi, English, Hindi, and Urdu. An additional eighteen families await interviews at the other sites. The researchers are in the process of translating, transcribing and interpreting these interviews. Preliminary findings suggest five major overarching thematic areas: care delivery, immigrant related issues, impact on family, support and coping, and lessons learned.

#### **Presentation:**

Gulati S, Shaw N, Sung L, Dix D, Strohn S, Banerjee A, Watt L, Klassen AF. Immigrant Families' Experiences of Caring for their Child with Cancer: Preliminary Findings. Poster presented at POGO. November, 2008.

## **Evaluation of Biomarkers in Relation to Recurrence Rate in Childhood Ependymoma.**

**Dr. Juliette Hukin, BC Children's Hospital**

**Round 5 (June 2007) - \$60,000 for 2 years  
Supported with KWCS and CCFC funding**

Ependymomas are rare tumours that begin in the ependyma, the cells that line the passageways in the brain where the specialized fluid which protects the brain and spinal cord is made and stored. Ependymomas represent 10% of childhood brain tumours, of which 30% occur in children under three years of age; approximately 35 new cases are diagnosed each year in Canada. Childhood ependymomas have very high morbidity and mortality rates, and there are currently no effective tools for assessing risk or prognosis. In this study, the researchers will develop an unique

*The clinical data and TMA bank will become a valuable resource for future studies that address mechanisms, therapies and outcomes of childhood ependymoma.*

resource for this rare and serious tumour by developing a Canadian clinical database and tissue microarray (TMA) bank. The clinical data and TMA bank will become a valuable resource for future studies that address mechanisms, therapies and outcomes of childhood ependymoma. Data from this study will help researchers better understand the biology of ependymoma, the basis for a new risk stratification system for childhood ependymoma, and the building blocks for future Canadian biological and clinical trials on ependymomas. They anticipate this will lead to the development of guidelines for therapy for this childhood cancer. They will also

examine the ependymoma samples for activation of potential candidate proteins, EGFR/Her-2/Her-4/Akt/YB-1 pathway, and relate the expression profile to clinical risk factors and outcome(s).

### **Progress:**

Twelve pediatric oncology centres across Canada are participating in this study. BC Children's Hospital has initiated recruitment of participants and the other eleven centres are at various stages of approval including: Alberta Children's Hospital, Stollery Children's Hospital, IWK Health Centre, The Hospital for Sick Children, Children's Hospital of Western Ontario, McMaster University Health Sciences Center, Children's Hospital of Eastern Ontario, Montreal Children's Hospital, Centre Hospitalier Universitaire de Québec, and Manitoba CancerCare Centre.

At British Columbia Children's Hospital (BCCH) all children admitted with a diagnosis of ependymoma before 18 years of age were screened. Seventy-eight eligible ependymoma patients were identified, 49 of whom had ependymoma specimens available. Comprehensive chart reviews were conducted for all 78 eligible patients and Clinical Data Forms and Clinical Data Follow-up Forms were completed. The clinical data was subsequently compiled onto a main database. The 49 specimen blocks were reviewed and scored by two neuropathologists and the TMA slides were designed. The TMA pilot staining was performed for EGFR, HER-2 and YBI. The pathological and immunostain data were linked to the clinical data and compiled onto the main database. Analyses are pending.

### **Presentations:**

Ailon T, Hukin J, Yip S, Yamashita T, Sargent M, Singhal A, Fryer C, Henderson G, Goddard K. Late recurrences of childhood ependymoma. *CNJS* 2008 May;35(2):S87.

Ailon T, Singhal A, Michael S, Yamashita T, Fryer C, Goddard K, Hukin J. Concordance between radiological and surgical impression of extent of resection and point of attachment for posterior fossa ependymoma in children. *CNJS* 2008 May;35(2):S33.

Hukin J, Yamashita T, Yip S, Ailon T, Sargent M, Singhal A, Henderson G, Maguire J, Hawkins C, Dunn SE. Epidermal pathway growth factors in pediatric ependymoma. *CNJS* 2008 May;35(2):S19.

Singhal A, Hukin J, Ailon T. Pediatric posterior fossa ependymoma: is near total resection as effective as total resection? *CNJS* 2008 May;35(2):S86.



***The Role of Intrathecal Methotrexate, Triple Intrathecal Therapy, and High Dose Intravenous Methotrexate in Predicting Neurocognitive Outcome in Survivors of Childhood Leukemia.***

**Drs. A. Downie, S. Guger, I. Montour-Proulx  
CHWO, Hospital for Sick Children and CHEO**

**Round 5 (June 2007) - \$60,000 year 1 & \$51,740 year 2  
Supported with CCFC funding**

In the treatment of leukemia, research has demonstrated that chemotherapy drugs must be administered into the fluid that surrounds the brain. One of the most important advances in therapy for Acute Lymphoblastic Leukemia (ALL) was the introduction of protective central nervous system (CNS)-directed therapy. A number of studies have suggested that this form of treatment may affect a child's development and ability to learn. It is unknown how different drugs and the ways that they are given influence a child's skill. This study proposes to examine the effects of different drugs administered into the fluid that surrounds the brain, alone or in combination, or in combination with drugs administered intravenously, on thinking skills, memory, attention, problem solving, and academic achievement among survivors of childhood cancer. The first objective of this study focuses on examining the long-term effects of CNS protective agents—specifically intravenous methotrexate (IV MTX), intrathecal methotrexate (IT MTX) given directly into the spinal fluid, methotrexate given in combination with cytosine arabinoside and hydrocortisone (Triple intrathecal therapy—TIT), on neurocognitive outcome. The second objective is whether leucovorin, used to minimize the effects of methotrexate, moderates the neurocognitive effects of chemotherapy agents delivered as CNS protectants. And the third objective is to determine whether the effects of agents used in CNS protective therapy vary as a function of time from the end of treatment and the age at which the child was diagnosed.

*With recent advances in treatment at least 70% of children diagnosed with standard risk ALL will survive 5 years beyond the end of treatment, in contrast to 35 years ago when this condition was fatal.*

**Progress:**

Three centres have been approved to conduct the study (Children's Hospital of Eastern Ontario, London Health Sciences Centre, Alberta Children's Hospital) and three additional centres are pending approval (The Hospital for Sick Children, BC Children's Hospital and Stollery Children's Hospital). A Road map outlining the study, process for patient identification, testing, and transfer of information and information sheet on the study for the families were created and shared with the participating institutions. All of the testing material has been purchased and the researchers are in the process of communicating with all of the centres regarding further study details.

***Quality of Life (QOL) by Randomization Arm in a Trial of Stem Cell Transplantation versus Chemotherapy for High Risk Relapsed Wilms Tumour.***

**Dr. Conrad Fernandez, IWK Children's Hospital**

**Round 5 (June 2007) - \$30, 205 year 1 & \$13,192 year 2  
Supported with CCFC funding**

The most common type of kidney cancer in children is called Wilms Tumour. Despite advances in treatment some children still relapse. It is not known whether intensive chemotherapy or bone marrow transplant is the best treatment for high-risk relapse. This study will be done in parallel with a Children's Oncology Group Study which will compare these two treatments. The researchers plan to measure quality of life at four time points during treatment and follow-up of participants on the Children's Oncology Group study. If the treatments are the same in terms of cure, finding out if one treatment is better in terms of quality of life and finding out what aspects of quality of life are most affected by the treatment can help health care providers work to reduce side effects.

**Progress:**

IWK will match the funding for this study. This study has been deferred due to delays in initiating the parallel Children's Oncology Group Study.

### ***Osteonecrosis in Children with Acute Lymphoblastic Leukemia.***

**Dr. Jacqueline Halton, CHEO**

**Round 6 (January 2008) - \$67,068 year 1 & \$66,523.25 year 2  
Supported with KWCS & CCFC funding**

Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer with current treatment survival rates approaching 80%. Improved outcomes show an increased number of survivors at risk for long-term treatment related side effects including osteonecrosis (ON). ON (bone death) is caused by blood supply loss to the bone causing pain and poor quality of life. The hips, shoulders, knees and ankles may be affected. Pain is the most common symptom. Pain can progress in severity, requiring surgical decompression or replacement of the affected joint(s). Long term effects including arthritis and progressive joint difficulties may not be known for decades post treatment. MRI is a sensitive imaging tool that can detect ON in children even at ON's earliest stages. This study will use MRI imaging to determine risk factors for developing ON, which will provide the basis for future intervention and prevention guidelines, including the possible advantages of earlier detection.

The present study will evaluate (a) the pattern and severity of ON among children receiving treatment for leukemia, (b) the potential for spontaneous recovery from bone mass decrements/vertebral compression in this setting, and (c) the relative contribution of the various risk factors for ON among these children. This study will be conducted as a parallel study to an established national research program funded by CIHR known as STOPP (Steroid-induced Osteoporosis in the Pediatric Population). The STOPP study initiated in January, 2005 and is scheduled to finish in December, 2010.

**Progress:**

This study is in the early stages of development.

### ***Relationship of Prothrombotic Markers to Thrombosis in Survivors of Childhood Cancer.***

**Ms. Lesley Mitchell, University of Alberta**

**Round 7 (June 2008) - \$60,000 for 2 years  
Supported with CCFC funding**

Thrombosis (blood clotting) is a serious secondary complication in children surviving cancer. The exact number of children with cancer suffering from thrombosis is unknown, but estimates range from as little as 0.64% to as high as 73%. The variance in prevalence is related to the variety of ways research data were collected, how the clots were diagnosed and the types of cancer. The seriousness of thrombosis is further highlighted by the fact that cur-

*...not all children with cancer have thrombosis, determining those at increased risk will help tailor treatment to only children who are at increased risk.*

rent best practices are under debate as there is no consensus on how to best treat survivors suffering from this complication. Treatment for thrombosis is difficult, involving anticoagulants (blood thinners) that expose children to greater risk of bleeding. As not all children with cancer have thrombosis, determining those at increased risk will help tailor treatment only to children who are at increased risk. The primary objective of this study is to determine the relationship of prothrombotic markers (factors that stimulate blood clotting) to the risk of symptomatic thrombotic events in a large number of Canadian survivors of childhood cancer. A secondary objective is to determine other risk factors for thrombosis amongst

these survivors. The results from this study will be used to decide whether screening for prothrombotic markers is useful for the management of thrombosis and which populations to target in future prevention studies.

**Progress:**

This study is in the early stages of development. Agreements are being signed with the sites.

### ***The Estrogen Receptor Pathway as a Therapeutic Target in Rhabdomyosarcoma.***

Dr. David Malkin, The Hospital for Sick Children

Round 7 (January 2008) - \$59,484 for 1 year  
Supported with SSRF funding

Rhabdomyosarcoma (RMS) is the most common soft tissue childhood cancer that, in advanced stages, has no more than a 50% chance of survival. In previous laboratory studies, Dr. Malkin and his research team have shown that the female sex hormone estrogen can cause RMS cells to grow more rapidly. They have also shown that treatment of RMS cells with Tamoxifen (an antiestrogen used in breast cancer therapy) in a petri dish will cause the cells to stop growing and die. This means that RMS cells have estrogen receptors that can be blocked by the tamoxifen. The present study will determine whether the presence of estrogen receptors predicts outcomes in children with RMS. The study will also determine the biochemical mechanism by which tamoxifen kills RMS cells and whether tamoxifen (with or without other chemotherapy drugs) can kill RMS cells in a mouse model of RMS. These findings will provide a foundation for developing clinical trials (studies with humans) that use tamoxifen as a novel treatment for RMS.

#### **Progress:**

This study is in the early stages of development. A graduate student is focusing on the biochemical mechanism of the action of Tamoxifen on rhabdomyosarcoma cells, and examining estrogen receptor expression in a larger group of RMS tissues that have been collected. In the next year, they will start coordinating efforts with researchers in San Antonio, TX on mouse models. Early results of this study will be presented in early Spring.

### ***ADP Signaling Defect as a Potential Cause for Aplastic Anemia.***

Dr. Evan Shereck, BC Children's Hospital

Round 7 (June 2008) - \$57,850 year 1 & \$54,080 year 2  
Supported with AAMAC & CCFC funding

Aplastic anemia is primarily an autoimmune disease that causes bone marrow failure and is associated with significant morbidity and mortality. Children living with aplastic anemia do not produce enough blood cells and consequently suffer from severe infections, lack of energy, and bleeding. An estimated 15 Canadian children are newly diagnosed with this rare disease each year. Dr. Shereck and her team of researchers have observed that some children with aplastic anemia also have platelets that fail to clot or "clump" properly. It is believed that this clumping deficiency represents an inherited predisposition that makes a child's immune system more likely to cause aplastic anemia. To investigate whether platelet clumping defects and immune problems that might cause aplastic anemia are associated, Dr. Shereck wants to determine the incidence of clumping occurring in children living with the disease and whether there are differences in the children's immune systems. This study has the potential to improve clinical understanding of aplastic anemia, yielding better treatment options for this life threatening disease and identifying children who are at higher risk for developing this disease.

*Children living with aplastic anemia do not produce enough blood cells and consequently suffer from severe infections, lack of energy, and bleeding.*

#### **Progress:**

This study is in the early stages of development.

### ***Development of the P-SCS: The Pediatric Supportive Care Scale.***

**Dr. Shayna Zelcer, London Health Sciences Centre    Round 8 (January 2009) - \$58,779 year 1 & \$54,594 year 2  
Funded with CCFC, CTCACF & Optimist International funding**

Despite many advances in the ability to cure childhood cancer, many children continue to die as a result of the disease. There is little information about how clinicians can improve the quality of life (QOL) of these children at the end stage of their illness. Interviews with families indicate that current measures of QOL used with children with cancer do not adequately capture important end of life concerns. Zelcer's study aims to create a new measure of the QOL when curative therapy is no longer a goal. The Pediatric Supportive Care Scale (P-SCS) will offer valuable insight for clinicians working with children in the palliative care setting, addressing issues such as: physical comfort, psychological well-being, social interactions, spirituality and hope, and quality of care. The P-SCS will be used in future studies with children with incurable cancer.

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#### **Progress:**

This study is in the early stages of development.

### ***Thalamic Brain Tumours in Canada in the MRI Era.***

**Dr. Paul Steinbok, BC Children's Hospital    Round 8 (January 2009) - \$69,423 year 1 & \$48,562 year 2  
Funded with CCFC & CTCACF funding**

The purpose of this study is to collect necessary information about the outcomes of children with thalamic brain tumours diagnosed and treated at the twelve pediatric neurosurgical centres across Canada over the last 20 years. This tumour is too rare to adequately study at any one centre. Through chart review and tumour specimens, researchers will evaluate the clinical presentation, tumour location within the thalamus, computer tomography (CT), magnetic resonance imaging (MRI) characteristics, pattern of tumour extension and effect treatment on patient outcome. The researchers hope to gather information that will help to better understand thalamic tumours to improve patient and physician education and knowledge, including potential barriers to successful treatment. The objective of this study is to increase the current knowledge of thalamic tumours that will subsequently guide medical and surgical therapies to improve outcomes. In the second part of the study, the researchers aim at performing genetic analysis of the thalamic tumour samples obtained to study the molecular-genetic changes underlying the development of these tumours.

#### **Progress:**

This study is in the early stages of development.