CIHR IRSC

The Late Effects of Childhood Cancer Treatments Initiative

Supported by the Institute of Cancer Research (ICR) of the Canadian Institutes of Health Research (CIHR) in partnership with:
C17 Council
Canadian Cancer Society (CCS)
Cancer Research Society (CRS)
Garron Family Cancer Centre at the Hospital for Sick Children
Ontario Institute for Cancer Research (OICR)
Pediatric Oncology Group of Ontario (POGO)

Background – The Health Issue

According to *Canadian Cancer Statistics 2011*, 6,550 children between the ages of 0-19 were diagnosed with cancer between 2003 and 2007.[1] Outcomes have improved dramatically in recent years such that 82% of these children now survive their disease. It is estimated that more than 30,000 Canadians are now survivors of childhood cancer. However, a large percentage of pediatric cancer survivors develop multiple, serious, and sometimes fatal late effects as a result of their cancer treatments. This impacts on the quality of life of both the patient and their family, and is a significant burden for the health care system.

The long-term adverse effects are diverse and include damage to the central nervous system, the senses and major organs such as the heart, kidneys and lungs. The risk of developing second cancers is also elevated in childhood cancer survivors. It is estimated that more than 60% of survivors suffer from at least one chronic condition and almost 30% have severe or life-threatening conditions. Unfortunately, the incidence and severity of these chronic conditions appears to increase over time.[2,3]

Frequently, the late onset effects experienced by childhood and adolescent cancer survivors are diagnosed and treated by physicians working in the adult domain, often with no prior

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knowledge of the cancer treatments these patients received sometimes decades earlier. To improve long-term clinical outcomes, a dialogue is needed between pediatric oncologists and clinicians in other disciplines, such as cardiology, neurology, endocrinology and oncology (for second cancers), who are responsible for treating young adults, or adults, experiencing late effects. Collaborations between the adult and pediatric medical communities are essential for advancing the field and for changing treatments in order to prevent or mitigate subsequent late effects.

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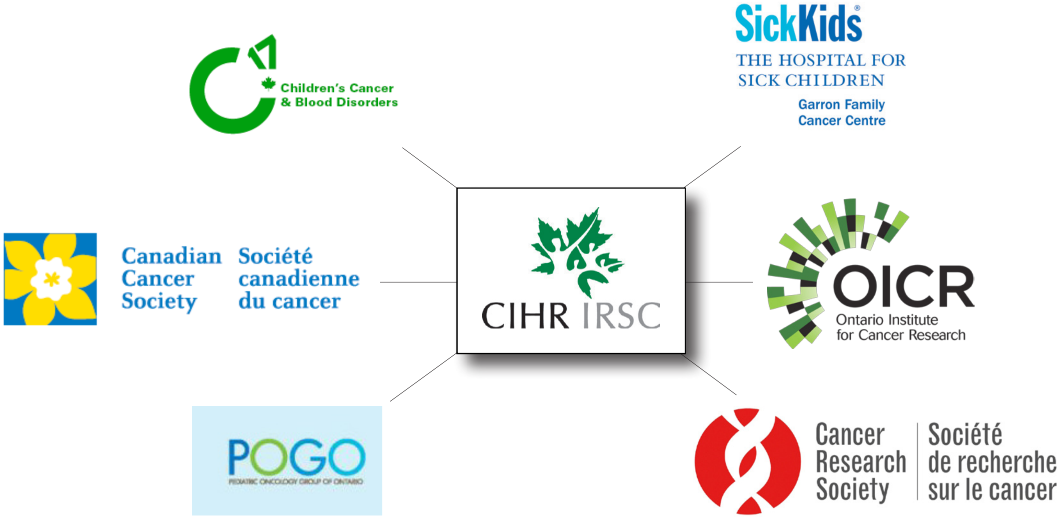
Significant work in recent years has identified mutations and/or genetic polymorphisms, facilitating the ability to predict which patients are at highest risk of developing drug toxicities – both in the short-term (e.g. hearing loss), and the long-term (e.g. cardiomyopathy). By themselves, these studies show great promise in terms of patient stratification and the development of individual cancer treatment protocols based on risk. However, it is critical to translate such discoveries into clinically relevant interventions. The Late Effects of Childhood Cancer Treatments Initiative was launched as part of the CIHR Roadmap Signature Initiative on Personalized Medicine. The initiative will promote the creation of multidisciplinary teams composed of biomedical researchers, from a variety of disciplines (e.g. biology, biochemistry, genetics, epidemiology) working alongside researchers and/or clinicians from multiple medical disciplines (e.g. cardiology, neurology, endocrinology, oncology).

This Initiative will build on the recent $2.8 million investment by Genome Canada, CIHR, CIHR-ICR, Genome BC, Genome Quebec and the C17 Council to support the Canadian Pediatric Cancer Genome Consortium, which is also a component of the CIHR Roadmap Signature Initiative on Personalized Medicine. This consortium is applying next-generation sequencing technologies to assess the impact of gene variants/mutations on tumour formation and progression and to identify molecular events and biological pathways amenable to therapeutic targeting and directed therapies. It is anticipated that there will be several opportunities for linkages between the Consortium and the four teams funded under The Late Effects of Childhood Cancer Treatments Initiative.

A Collaborative Effort

Through the combined efforts of CIHR-ICR and partners, four teams will be funded for a total investment of $12 million over five years.



Funded Teams

Nominated principal investigator	Co-PIs	Title of project	Funding over 5 years
 **Shinya Ito** Hospital for Sick Children Toronto	Sharon Guger Johann H. Hitzler Deborah L. O'Connor Russell J. Schachar Brenda Spiegler Rosanna Weksberg	Neurocognitive-Phenome, Genome, Epigenome and Nutriome in Childhood Leukemia Survivors: N-PhenoGENICS	$1.9 million

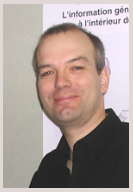
Dr. Ito's team will study how childhood leukemia treatment affects brain function, particularly attention deficit disorder, which can remain for a long time and have an impact on children's academic performance and social activity. The team will study the factors that make some children more susceptible to this effect and explore mitigation strategies. Recent reports suggest that mutation of a gene involved in metabolism of the vitamin folate, is responsible.[4] This study aims to discover if not only this gene but also other related genes are associated with this damage. If the responsible genes are found, the team will explore a strategy to avoid this side effect.

Nominated principal investigator	Co-PIs	Title of project	Funding over 5 years
 **Paul Nathan** Hospital for Sick Children Toronto	Paul Kantor Peter Liu Luc Mertens Seema Mital	Novel approaches to the prediction, diagnosis and treatment of cardiac late effects of childhood cancer	$2.8 million

Dr. Nathan's team will study cardiotoxicity and evaluate the importance of genetic differences between individuals in determining who is at greatest risk of developing heart disease as a result of exposure to chemotherapeutic agents. The team brings together several integrated research cores to test new imaging and biomarker methods with the ultimate aim of earlier detection of heart disease before clinical symptoms develop or it becomes apparent on standard imaging tests. Vulnerable children can then be targeted, by modifying their cancer therapy, or by introducing medications that protect the heart from chemotherapy damage.

Nominated principal investigator		Co-PIs	Title of project	Funding over 5 years
	**Kirk Schultz** BC Children's Hospital Vancouver	Sylvain Baruchel Geoff Cuvellier Mary L. McBride Lesley G. Mitchell Shahrad G. Rassekh Ross T. Tsuyuki Michele Zappitelli	Applying Biomarkers to Long-term Effects in Child and Adolescent Cancer Treatment (ABLE Team)	$4.3 million

Dr. Schultz's team will assess biomarkers to identify children at risk of adverse effects of their successful cancer treatments, and to predict the course of development of their long-term complications. Identifying these high-risk children will lead to preemptive and timely therapies to minimize or eliminate these effects. Studies will focus on biomarkers associated with hearing loss, kidney failure, blood clotting problems, and a specific form of tissue rejection called chronic graft-versus host disease after hematopoietic transplantation used to treat cancer. The studies include 8 pediatric centers across Canada.

Nominated principal investigator		Co-PIs	Title of project	Funding over 5 years
	**Daniel Sinnett** Ste. Justine University Health Center Montreal	Nathalie B. Alos Gregor U. Andelfinger Maja Krajinovic Caroline Laverdière Emile Levy Philippe Robaey	Genomic determinants of common long-term treatment effects in childhood acute lymphoblastic leukemia survivors	$3.0 million

Dr. Sinnett's team will focus on acute lymphoblastic leukemia (ALL), the most frequent cancer in children. Roughly 80% of cases can be cured with current treatment protocols. More than two-thirds of the survivors experience chronic or late-occurring health problems, often not clinically apparent until decades after treatment. The team will study ways to prevent or mitigate treatment related toxicities in a subset of the most common late-occurring adverse effects observed in childhood ALL survivors, including neurocognitive effects, metabolic syndrome, cardiotoxicity and bone morbidity.

References

[1] www.cancer.ca/Canada-wide/About%20cancer/Cancer%20statistics.aspx?sc_lang=en

[2] *Journal of Clinical Oncology* (review series) 27, 14 (May 10, 2009).

[3] Oeffinger, K.C. et al. "Chronic health conditions in adult survivors of childhood cancer," *The New England Journal of Medicine* 355, 15 (2006): 1572-1582.

[4] Kamdar, K.Y. et al. "Folate pathway polymorphisms predict deficits in attention and processing speed after childhood leukemia therapy," *Pediatric Blood & Cancer* 57, 3 (Sept. 2011): 454-460.

Funding Partners

Canadian Institutes of Health Research (CIHR) *The Canadian Institutes of Health Research (CIHR) is the Government of Canada's health research investment agency. CIHR's mission is to create new scientific knowledge and to enable its translation into improved health, more effective health services and products, and a strengthened Canadian health care system. Composed of 13 Institutes, CIHR provides leadership and support to more than 14,100 health researchers and trainees across Canada. The mandate of the CIHR Institute of Cancer Research is to support research that reduces the burden of cancer on individuals and families through prevention strategies, screening, diagnosis, effective treatments, psychosocial support systems, and palliation.*

Canadian Cancer Society (CCS) *is a national community-based organization of volunteers whose mission is the eradication of cancer and the enhancement of the quality of life of people living with cancer. In 2010-11, the Society funded $48.9 million in leading-edge research across the country. When you want to know more about cancer, visit our website at www.cancer.ca or call our toll-free, bilingual Cancer Information Service at 1-888-939-3333.*

Cancer Research Society (CRS) *Founded in 1945, the Cancer Research Society (CRS) is a national not-for-profit organization whose sole mission is to fund cancer research exclusively and to offer seed money to the most promising original ideas, projects and researchers across Canada. From 1990 to 2010, it has awarded more than $100 million in research funding to some 1000 cancer research projects across the country, including more than $45 million since 2005. For more information, visit www.CancerResearchSociety.ca.*

C17 Council *is a network that links all the pediatric oncology, hematology and bone marrow transplant programs across Canada dedicated to improving the outcomes for children with cancer and serious blood disorders. It is a non-profit organization supported by several large funders, including Coast to Coast Against Cancer Foundation and Childhood Cancer Canada Foundation. C17 supports national initiatives in research, grant competitions, clinical trial regulatory affairs, education and clinical guidelines development.*

Garron Family Cancer Centre (GFCC) *is a centre of excellence at The Hospital for Sick Children whose mission is to facilitate and catalyze innovation in multidisciplinary research, clinical care and education, leading to the discovery and translation of new knowledge which will transform clinical practice and improve clinical outcomes and quality of life for children and their families affected by cancer.*

Ontario Institute for Cancer Research (OICR) *is an independent not-for-profit corporation launched by the Government of Ontario in 2005 that is dedicated to the prevention, early detection, diagnosis and treatment of cancer. OICR and its research partners support more than 1,400 investigators, clinician scientists, research staff and trainees located at its Toronto headquarters and in research institutes and academia across Ontario.*

Pediatric Oncology Group of Ontario (POGO) *is a collaboration of all childhood cancer specialty programs in Ontario. POGO was founded in 1983 and serves as the official source of information and advice to Ontario's Ministry of Health and Long-Term Care on childhood cancer care and control. Through health care innovation, survivor care, financial assistance for families, population data, policy development, research and education, POGO has created a highly integrated and seamless system of pediatric cancer care – enabling the right care, at the right time, in the right place. The resulting system supports children and families throughout the spectrum of illness, recovery and survivorship. The enduring collaboration has created methods for standardized, comprehensive, quality population data, generated a broad range of service innovations, and nurtured a rapidly growing childhood cancer research program.*

CIHR Institute of Cancer Research
McGill University
3655 Promenade Sir-William-Osler, Room 701
Montreal QC H3G 1Y6
www.cihr-irsc.gc.ca

For further information, contact:
Dr. Judith Bray, Assistant Director
Institute of Cancer Research
Phone: 613-954-7223
Email: judith.bray@cihr-irsc.gc.ca