Marking the way to healthier outcomes

Professor Daniel Sinnett is leading a major multidisciplinary study into the long-term adverse effects of childhood leukaemia treatment. Here, he discusses his pioneering work.

Can you discuss your background and explain how your research focus on genomics and cancer, specifically deciphering the determinants of childhood leukaemia, developed?

I developed a passionate interest in molecular genetics during my PhD studies at the University of Montreal. I was able to pursue this interest in my postdoctoral work at the Children’s Hospital Boston and Harvard University Medical School, where I developed expertise in mapping loci for genetic syndromes.

I established the molecular oncogenetics laboratory in the Division of Hemato-Oncology at the Sainte-Justine University Hospital Centre on my return to Montreal in 1994, and collaborated on studies of colon and breast cancer before deciding to focus on childhood leukaemia – specifically, the use of genomics to decipher its underlying mechanisms. Our group was one of the first to perform genetic epidemiology studies to assess the role of genetic determinants in susceptibility to childhood acute lymphoblastic leukaemia (ALL).

What does your role as a principal investigator within the Late Effects of Childhood Cancer Treatments Initiative entail?

As team leader, I’m responsible for managing and coordinating the overall research programme, including the follow-up of all subprojects, as well as the dissemination of results though my collaborations with international networks such as the Childhood Leukemia International Consortium. My most important role is to create a synergistic and productive environment for our diverse multidisciplinary team.

I am Director of the Quebec childhood ALL (QcALL) biobank, which is an important platform for this project; my research team oversees the genomics aspects of the study, such as whole exome sequencing and bioinformatics, the integrative analysis of the data, and the design and maintenance of the database itself.

Could you outline the key objectives of the initiative?

Although childhood cancer outcomes have improved dramatically over the past decade, more than two-thirds of paediatric cancer survivors develop multiple, serious and sometimes fatal late effects as a result of their cancer treatments. Occasionally occurring more than 20 years after treatment, such long-term effects are diagnosed and treated by physicians working in the adult domain, often with no prior knowledge of the cancer treatments available or their potential for causing problems later in life. The Late Effects of Childhood Cancer Treatments Initiative promotes the creation of multidisciplinary teams to identify diagnostic biomarkers that could predict the adverse long-term effects in different tissues, including the heart and cardiovascular system, central nervous system, endocrine tissues and musculoskeletal system, as well as secondary tumours; these will ultimately translate into routine clinical biomarkers for the early detection of such effects.

Another important goal is to bridge the gap between paediatric oncologists and clinicians in other disciplines, such as cardiology, neurology, endocrinology and oncology, who are responsible for treating the young adults, or adults who experience late effects. We aim to establish a network through which the health of these children can be followed to catch long-term effects early or prevent them altogether, thus improving their quality of life and reducing the burden on the healthcare system.

How do you expect the findings – of both your own team and the Initiative as a whole – to lead to the development of new strategies and clinical tools with a view to improving the detection, diagnosis and treatment of childhood leukaemia?

A better understanding of the mechanisms associated with therapy-related long-term effects in childhood ALL survivors, the identification of new targets for diagnosis, preventive intervention and treatment, and the prospect of clinical trials within eight to 10 years using validated biomarkers are the key deliverables of this project; by studying the genomic determinants that underlie neurocognitive, metabolic, cardiac and bone problems in adult survivors, the project will contribute towards a healthy future for children with leukaemia.

The results of this study could provide new guidelines for drug dose adjustment, changes in treatment modalities, and enhanced intervention and prevention strategies based on the identified markers. Finally, the distinct layers of information that will be generated and integrated using our cohort will provide one of the best characterised childhood ALL survivor cohorts; a unique Canadian resource which could be used by the scientific community to address questions beyond the issues raised in this initiative.
Taking the initiative

Researchers at the Sainte-Justine University Hospital Centre in Montreal, Canada, are conducting a study that aims to mitigate the damaging late effects of childhood cancer treatment, improving outcomes for survivors.

ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) is the most common form of childhood cancer. Characterised by continuous overproduction of white blood cells in the bone marrow and presenting most commonly in children aged between two and five years, ALL is a rapidly progressing blood cancer that, if left untreated, can cause death in a matter of weeks. Only four decades ago the prognosis was poor for those diagnosed, with little chance of lasting remission. However, thanks largely to advances in the optimisation of chemotherapy and radiotherapy regimes in recent years, survival rates have soared to over 80 per cent.

While this statistic represents tremendous progress, the increase in patient longevity has brought a corresponding rise in the number of childhood leukaemia survivors experiencing adverse treatment-related effects later in life. Around two-thirds of the total number of patients treated as children with multi-agent regimes will experience at least one of a range of effects before they reach the age of 40. This seems to stem from patients’ exposure to chemotherapeutic agents, often along with high doses of radiation, during a sensitive and vulnerable stage of their development.

The underlying mechanisms behind this causal link are not well understood. In recent years it has become apparent that genetic factors play a significant role in determining a patient’s risk of developing long-term health complications, but the precise mechanisms have yet to be unravelled.

A NEW INITIATIVE

The Late Effects of Childhood Cancer Treatments Initiative is a major strategic research enterprise funded by the Canadian Institutes of Health Research (CIHR), which aims at improving long-term clinical outcomes for childhood cancer survivors by addressing the need for more effective collaboration between paediatric oncologists and other health professionals.

The Initiative has secured funding for four separate multidisciplinary teams with expertise in different childhood cancer types and addressing a variety of long-term treatment effects. One of them, a mix of paediatric oncologists, biomedical researchers and clinical scientists based at the Sainte-Justine University Hospital Center (SJUHC), Montreal, Canada, is focusing exclusively on ALL patients in a research programme called ‘Genomic determinants of common long-term treatment effects in childhood ALL survivors’.

Postulating that the genetic makeup of a patient modifies the risk of developing treatment-related complications, the programme’s main objective is to identify and validate the genetic variants influencing the most common adverse effects, utilising next-generation sequencing to resequence the exomes of a discovery cohort of 350 ALL survivors. Following the identification of clinically-relevant biomarkers, the predictive impact of genetic markers can be assessed by validating them in larger cohorts, with the final stage of the study involving the verification of its findings through prospective and intervention trials.

To deal with the broad scope of this study, the makeup of the SJUHC team necessarily reflects the Initiative’s guiding philosophy, which holds that only a multidisciplinary collaborative approach will be adequate to meet such complex scientific challenges. Researchers with specific areas of expertise are heading up the various research teams, which collectively fall under the management of team leader Professor Daniel Sinnett. As a member of several national and international consortia and large research initiatives, Sinnett brings extensive experience of managing large interdisciplinary teams to the table, and considers the multidisciplinarity of the programme as a key component of success: “The synergy generated by unifying these disciplines under one flag gives us insight into different modes of intervention and prevention. Importantly, it gives rise to multiple cross-discipline collaborations, and offshoot projects for which additional grant applications are currently being discussed. The active involvement of first level users with the healthcare professionals and clinicians on our team yields stimulating interactions and prompts further questions,” he explains.

Sinnett’s research team is also responsible for research data management, meaning that as
INTELLIGENCE

GENOMIC DETERMINANTS OF COMMON LONG-TERM TREATMENT EFFECTS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA SURVIVORS

OBJECTIVE

To identify (using next-generation sequencing) and validate genetic variants influencing treatment-related long-term effects in childhood acute lymphoblastic leukaemia (ALL), and identify associated biological/biochemical markers involved in the most common long-term clinical outcomes.

KEY COLLABORATORS

Dr Maja Krajnovic; Dr Caroline Laverdière; Dr Nathalie B Alos; Dr Gregor U Andelfinger; Dr Emile Levy; Dr Philippe Robaey; Dr Chantal Séguin; Dr Valérie Marci; Dr Sarah Lippé; Dr Serge Sultan; Dr Chantal Séguin; Dr Valérie Marci; Dr Sarah Lippé; Dr Serge Sultan; Sainte-Justine University Health Center (SJUHC)

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well as maintaining the collective database for all studies in the programme, the researchers oversee the crucial next-generation sequencing and integrative analysis tasks. Sinnett has been able to report brisk progress, with Phase I (exome sequencing for 300 participants) complete, and Phase II well under way – collection of all clinical follow up data for the first 100 participants had been performed without a hitch; an impressive feat in itself, involving the collaboration and coordination of more than 15 individuals over the course of a single day for each participant.

CRUCIAL CLINIC

An invaluable asset to the study is of course the SJUHC itself, being one of the largest childhood cancer clinics in Canada and readily equipped with Long Term Follow Up Units (LTFU), established in 2005 by the medical director of the LTFU programme for childhood cancer survivors, Dr Caroline Laverdière. For the ‘Genomic determinants of common long-term treatment effects in childhood ALL survivors’ project, Laverdière is involved with coordinating patient care and responsible for the collection and management of clinical data, while Dr Maja Krajnovic, a renowned scientist in childhood cancer pharmacogenetics, supervises the analysis of the large dataset.

It is now recommended that all paediatric cancer survivors obtain a systematic plan for periodic screening, surveillance and prevention. As studies like this one add to our understanding of the mechanisms through which genetic variations contribute to long-term effects, the advances in personalised care necessary to boost the quality of life of all childhood cancer survivors may not be far behind.

Complex task, complex team

The project is focusing on long-term effects which fall into four main categories, each representing a separate area of study within the programme:

Bone morbidity

Musculoskeletal problems such as osteonecrosis (ON) and osteoporosis are common for ALL patients in remission; asymptomatic ON may affect as many as 40 per cent of patients, with terrible quality-of-life implications. The research team of Drs Alos, Rauch and Séguin is exploring the relationship between bone density and musculoskeletal complications, by assessing the impact of clinical profile and genetic variants on susceptibility to bone morbidities.

Cardiac toxicity

Paediatric cancer survivors suffer high rates of long-term anthracycline cardiotoxicity (ACT) associated with the cumulative doses of anthracycline antibiotics used in chemotherapy. The research team headed by Drs Andelfinger and Friendrich is working on the precise characterisation of the genetic determinants of ACT outcomes, to test the hypothesis that genetic variants in the coding sequence of cardiovascular genes either protect or predispose the cardiovascular system to ACT, irrespective of other risk factors.

Symptoms of obesity, hypertension, insulin resistance and dyslipidemia are indications of a metabolic syndrome phenotype, accounting for high rates of cardiovascular disease and Type 2 diabetes in ALL survivors. This programme, represented by the team of Drs Levy and Marci, will test the hypothesis that the predictive factors for therapy-related MetS development can be determined by identifying the genetic, biochemical and clinical markers associated with the oxidative stress that is central to MetS pathogenesis.

Metabolic syndrome (MetS)

The harmful effects of cranial radiation therapy and chemotherapy on visual-spatial and fine motor functioning, concentration and nonverbal memory on some young patients are attested to by comprehensive tests of neurocognitive function. Early identification of individual risk differences via physiological and genetic markers could enable the development of targeted rehabilitation strategies for the most vulnerable children, avoiding the risk of lowering the intensity of treatment unnecessarily for those with greater resilience. Neuropsychological assessment, data collection and analysis will be carried out by Drs Robaey and Lippé, with expert magnetic resonance imaging and electroencephalogram brain imaging modelling performed by Dr Evans.