BIENNIAL REPORT 2011-2013

THE MCLAUGHLIN CENTRE

ROBERT S. MCLAUGHLIN (1871-1972)

UNIVERSITY OF TORONTO

EXECUTIVE'S MESSAGE

DIRECTOR'S MESSAGE

The McLaughlin Centre remains steadfast in advancing genomic medicine through support of research and education. The Accelerator Grant program has funded investigators performing outstanding genomics research close to the patient. Under this definition, projects are designed to generate dynamic synergy between basic genomics research and clinical application. Genomic data that can be used both in discovery and validation experiments are translated immediately into information for clinical care. In turn, questions that arise from patient care trigger genomic research and technology, fuelling the cycle for opportunity to impact delivery of health services, which feeds back to the families. The McLaughlin Centre believes that this process, in fact, defines personalized medicine, and that this conceptual innovation will drive a new paradigm of health care for Canadian families.

As a practising scientist, and as leader of an organization dedicated to advancing biomedicine, I believe that every decision we make can and must have impact. The stories we tell in this report provide good evidence that our experimental plan is taking the right path.

Stephen Scherer PhD DSc FRSC, Director

CHAIR OF OVERSIGHT COMMITTEE'S MESSAGE

In 1951, Robert Samuel McLaughlin (1871-1972) endowed a foundation to provide assistance to medical graduates who intended to devote their lives to academic medicine. In the same year, he granted the Royal College of Physicians and Surgeons an endowment for the McLaughlin-Gallie Visiting Professorship. At the time, Dr. Gallie predicted, "in 25 years, most of the senior positions in our medical schools and hospitals across Canada will be occupied by McLaughlin Fellows." That prediction became true as 850 young physicians, including myself, were helped by the Foundation to start their careers.

Traditional clinical diagnosis and management have focused on the patient's symptoms. This is often a reactive approach, where treatment starts after the signs appear. In the new paradigm of medicine, decisions will be predictive in nature, and tailored to the individual by use of genetic information. Like McLaughlin, our Oversight and Executive Committees recognize the need to support training of the new generation of doctors in the genome sciences. Like Gallie, I can confidently predict that the Canadian medical establishment will continue to be led by McLaughlin Centre-funded trainees and investigators.

Alan Hudson MD OC, Chair Oversight Committee

Accelerator Grants for 2011. Peer-Reviewed Projects in Personalized Medicine

10 BIG STORIES

ONE Epilepsy affects 1% of the population, and juvenile myoclonic epilepsy (JME) accounts for one out of ten such diagnoses. JME runs in families and has a well-defined clinical presentation, but little is known of its underlying genetic causes. Neurologist Danielle Andrade (MD) of the Krembil Neuroscience Centre at the University Health Network has used breakthrough genome-sequencing technologies to identify mutations that cause JME in families with multiple affected individuals. Insights gained from this elucidation are now being applied in tailored treatment regimens for JME and other forms of epilepsy.

TWO Infants born with a heart defect known as Tetralogy of Fallot (TOF) are commonly known as "blue babies" and, without corrective surgery, survival rates are low. Surgical advances mean that those with a repaired TOF now survive into adulthood, and some go on to have children with the same defect, suggesting that a genetic component is involved. Psychiatrist Anne Basset (MD) of the Centre for Addiction and Mental Health and cardiologist Candice Silversides (MD) of Toronto General Hospital used high-resolution gene-chip technology to discover that the important developmental gene, PLXNA2, causes human congenital cardiac disease. This is opening new areas for diagnostics and theraupeutics.

THREE Alzheimer Disease and other dementias affect more than 30% of individuals over the age of 85. By the time symptoms are detected – relatively late in the disease – irreversible damage to the brain has already occurred, making early pre-symptomatic detection imperative for effective intervention. Human diseases are often associated with abnormalities in gene regulation due to splicing defects. Professor Benjamin Blencowe (PhD) of the Donnelly Centre in the Faculty of Medicine has applied computational approaches to identify defective gene splicing in Alzheimer Disease patients, establishing new biomarkers for early detection of this devastating disorder.

FOUR Health care professionals have long recognized variability in drug response among individuals, and this has become a principal focus of personalized medicine. The sub-discipline of personalized medicine called pharmacogenomics builds from the premise that treatment regimens can be individually tailored to fit a person's unique genetic profile. McLaughlin trailblazer Gideon Koren (MD) of the Child Health Evaluative Sciences at the Hospital for Sick Children has built a provincial pharmacogenomics program that utilizes genome-scanning technologies to inform individualized drug treatments for pediatric and adult patients.

FIVE Among congenital defects, those involving the heart are the number-one cause of infant death. More than 1% of children live with a congenital heart defect (CHD), and in most cases the cause is unknown. Cardiologist Seema Mital (MD) has established the SickKids Heart Centre Biobank, housing biological specimens and clinical data on more than 2,500 CHD patients from the province of Ontario. Examining this important clinical resource with genome-sequencing technologies has identified novel disease-causing variants in a number of families with CHD.

SIX Twenty percent of patients with type 1 diabetes develop renal disease, and while a genetic predisposition is clearly evident, finding the genes responsible has been a challenge. Using available genome-wide data, statistician Andrew Paterson (MD) of the Hospital for Sick Children developed new statistical tools to differentiate patients with genetic risk factors for renal disease from those who are protected. The identification of patients at high genetic risk is allowing physicians to closely monitor and control factors that would otherwise lead to renal failure.

SEVEN Immunoglobulin A nephropathy (IgAN) occurs when a protein that normally helps fight infection erroneously settles in the kidneys, triggering terminal renal disease. IgAN appears to be a systemic immunological disorder, and treatment options are limited. Despite its high heritability – suggesting genetic influences – the genes involved are unknown. McLaughlin clinical scientist York Pei (MD) of the University Health Network is searching for the genetic cause(s) of IgAN by applying DNA sequencing technologies. His team has identified novel genes, which now serve as targets for drug development.

EIGHT Advances in decoding genome sequences holds tremendous promise for understanding, preventing and better managing disease. Currently, however, the ability to interpret the information generated from these technologies in the context of clinical care is limited. Cheryl Shuman (MSc), director of the genetic counselling program at the Hospital for Sick Children and University of Toronto, is leading a study to examine the clinical utility of genome-based technologies in the context of adult and pediatric clinical care. In collaboration with the Toronto-based private health clinic Medcan, her team has uncovered strategies to evaluate and effectively integrate these technologies into clinical practice.

NINE Cystic fibrosis (CF) is a devastating disease caused by mutations in the CFTR gene, affecting one in 3,000 newborns. Individuals who carry identical disease mutations can present with a different course of disease severity that affects long-term outcomes. A team led by mathematician Lei Sun (PhD) of the University of Toronto Dalla Lana School of Public Health developed a statistical method to pinpoint those genes that modify the clinical severity of CF. This revealed multiple genes associated with meconium ileus, a severe intestinal obstruction present at birth in 15% of patients with CF. This general strategy is now being applied to study variability in other diseases.

TEN Medulloblastoma (MB) is the most common type of malignant childhood brain tumour, and has had no effective targeted therapy as part of standard care. Current treatment is aggressive, and can cause permanent damage to the nervous system, as well as lead to secondary cancers. Brain surgeon Michael Taylor (MD PhD) of the Arthur and Sonia Labatt Brain Tumour Research Centre at the Hospital for Sick Children aims to find new treatments that will leave the developing brain unharmed. His team recently created the Medulloblastoma Advanced Genomics International Consortium (MAGIC) to gather a biobank of over 1,200 samples. It has been sub-grouped based on genetic profiles, enabling the application of treatment regimens specific to the target population.

MCLAUGHLIN EDUCATION

EDUCATION ASSOCIATE DIRECTOR'S MESSAGE

The McLaughlin Centre supports the MD/PhD program and career development of physician scientist trainees at the University of Toronto. The Centre also sponsors the Comprehensive Research Experience for Medical Students (CREMS), allowing medical students to make a 20-month commitment to a mentored research experience within the medical school curriculum. This past year, the McLaughlin Centre supported students performing genetics research in the fields of congenital malformations, stem cells and cancer.

Two of these students are Kevin Wang of the Hospital for Sick Children and Marko Skrtic of the Ontario Cancer Institute at Princess Margaret Hospital. Kevin, who is supervised by McLaughlin investigator Dr. Michael Taylor, uses a functional genomics approach to study pediatric brain tumours. This study was recently published in the highly esteemed journal *Nature*. Marko uses genomic technologies to discover and develop novel therapeutics for the treatment of leukemia. Under the supervision of Dr. Aaron Schimmer his work was published in the prestigious journal *Cancer Cell*.

Norman Rosenblum MD, Education Associate Director

UNIVERSITY OF TORONTO MD/PHD PROGRAM

Armstrong, Susan
Ballios, Brian
Bohdanowicz, Mike
Costain, Greg
Deshwar, Ashish
Dey, Ayan
Dissanayake, Dilan
Donaldson, Laura
Elphinstone, Robyn
Erdman, Laura
Fuller, Jonathan
Hutson, Janine
Kim, Jieun
Lam, Grace
Lane, Natasha
Lin, Alvin
McSheffrey, Gord
McVeigh, Patrick
Mukovozov, Ilya
Nestor, Sean
Ng, Enoch
Perrin, Andrew
Pouget, Jennie
Rotin, Lianne
Rullo, Jacob
Schwindt, Graeme
Skrtic, Marko
So, Jonathan
Tsui, David
Vanner, Rob
Vi, Linda
Wang, Xin (Kevin)
Wilcox, Jared
Woodford, Curtis
Wu, Florence
Zaslavsky, Kirill

COMPREHENSIVE RESEARCH EXPERIENCE FOR MEDICAL STUDENTS (CREMS) SCHOLAR PROGRAM

2011

Cheung, Evelyn
Grant, Robert
Handrigan, Greg

2012

Basilious, Alfred
Mesci, Aruz
Thom, Robyn

RESEARCH HIGHLIGHTS

GRANTS FUNDED FOR 2012

Paul Arnold MD PhD, The Hospital for Sick Children, Obsessive-Compulsive Disorder

Candice Silversides MD, University Health Network, Genomics of Cardiac Malformations

Jayne Danska PhD, The Hospital for Sick Children, Diabetes

Carlo De Angelis DPharm, Sunnybrook Hospital, Pharmacogenomics

Sharon Dell MD, The Hospital for Sick Children, Primary Ciliary Dyskinesia Sequencing

Yaron Finkelstein MD, The Hospital for Sick Children, Pharmacogenomics

Christian Hendershot MD, Centre for Addiction and Mental Health, Genetics

Keith Jarvi MD, Mount Sinai Hospital, Male Infertility

Jordan Lerner-Ellis PhD, Mount Sinai Hospital, Clinical Genomics

Stephen Lye MD PhD, Mount Sinai Hospital, Preeclampsia

Berge Minassian MD, The Hospital for Sick Children, Epilepsy

Zdenka Pausova MD, The Hospital for Sick Children, Epigenetics

Brian Robinson MD, The Hospital for Sick Children, Metabolic Disorder Sequencing

Tracy Stockley PhD, The Hospital for Sick Children, Genomic Diagnostics in Pediatrics

Derek van der Kooy MD, University of Toronto, Schizophrenia

John Vincent PhD, Centre for Addiction and Mental Health, Intellectual Disability Diagnostics

MCLAUGHLIN-FUNDED PUBLICATIONS

1. Scherer SW and Dawson G. Risk factors for autism: translating genomic discoveries into diagnostics. *Human genetics.* July 2011

2. Sun L et al. Multiple apical plasma membrane constituents are associated with susceptibility to meconium ileus in individuals with cystic fibrosis. *Nature genetics.* May 2012

3. Northcott P et al. Subgroup-specific structural variation across 1,000 medulloblastoma genomes. *Nature.* August 2012

4. Silversides CK et al. Rare copy number variations in adults with tetralogy of fallot implicate novel risk gene pathways. *PLoS genetics.* August 2012

OVERSIGHT COMMITTEE

EXECUTIVE COMMITTEE

FINANCIAL HIGHLIGHTS

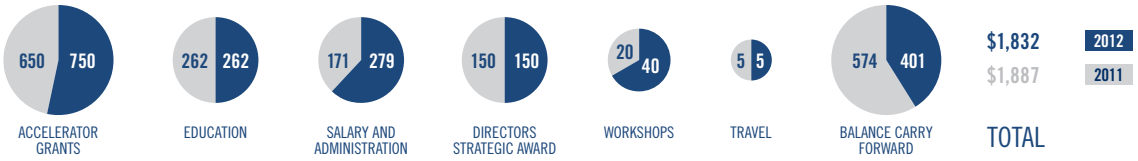
THE MCLAUGHLIN CENTRE was founded in 2001 by a $50M bequest from the R. Samuel McLaughlin Foundation. In 2006-07 $1M of the principle was matched by the Ontario Government to establish the GSEF-McLaughlin Fellowships.

SUMMARY OF THE MCLAUGHLIN ENDOWMENT (FOR THE YEAR ENDED APRIL 30 2012)

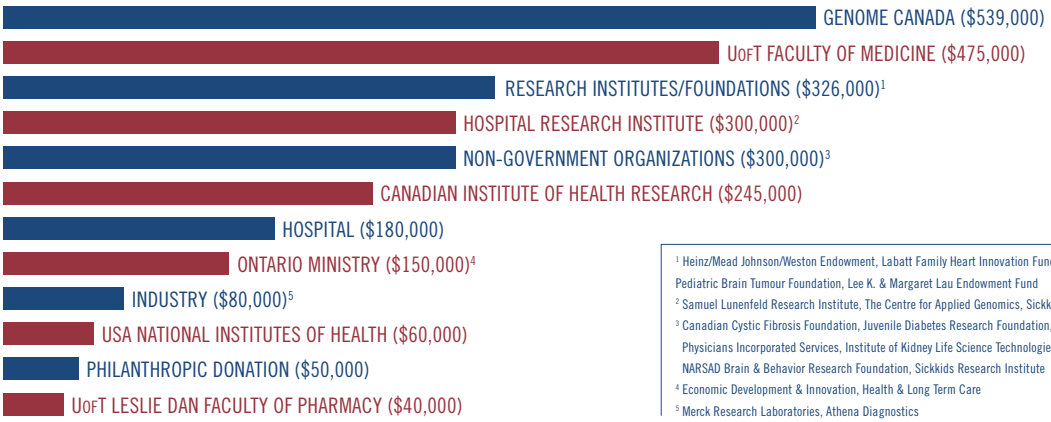
	2011-12	2010-11	2009-10
BOOK VALUE OF ENDOWMENT			
McLaughlin Endowment	49,000,694	49,000,694	49,009,694
GSEF-McLaughlin Fellowships	2,000,000	2,000,000	2,000,000
	51,009,694	**51,009,694**	**51,009,694**
MARKET VALUE OF ENDOWMENT			
McLaughlin Endowment	46,701,436	47,535,880	43,739,433
GSEF-McLaughlin Fellowships	1,578,967	1,607,180	1,478,822
	48,280,403	**49,143,060**	**45,218,255**
ANNUAL PAYOUT			
Annual Payout (% book value)	4.21%	4.12%	4.04%
McLaughlin Endowment	2,075,131	2,033,958	1,992,785
GSEF-McLaughlin Fellowships	70,160	68,768	67,376
	2,145,291	**2,102,726**	**2,060,161**
GSEF-McLaughlin Fellowships	(70,160)	(68,768)	(67,376)
Financing payback on McLaughlin Endowment (note 1)	(146,262)	(146,262)	(160,000)
ENDOWMENT PAYOUT FOR DISBURSEMENT	**1,928,869**	**1,887,696**	**1,832,785**

NOTE 1. FUNDS AVAILABLE FOR DISBURSEMENT ARE THE MCLAUGHLIN ENDOWMENT PAYOUT LESS ANNUAL REDUCTIONS TO REPAY FINANCING

MCLAUGHLIN CENTRE DISBURSEMENTS ($ THOUSANDS)



PARTNER INVESTMENTS TO MCLAUGHLIN CENTRE FUNDS (TOTAL $2,746,000)



[1] Heinz/Mead Johnson/Weston Endowment, Labatt Family Heart Innovation Fund, Pediatric Brain Tumour Foundation, Lee K. & Margaret Lau Endowment Fund
[2] Samuel Lunenfeld Research Institute, The Centre for Applied Genomics, Sickkids Research Institute
[3] Canadian Cystic Fibrosis Foundation, Juvenile Diabetes Research Foundation, Physicians Incorporated Services, Institute of Kidney Life Science Technologies, NARSAD Brain & Behavior Research Foundation, Sickkids Research Institute
[4] Economic Development & Innovation, Health & Long Term Care
[5] Merck Research Laboratories, Athena Diagnostics

Concept & Design: Fresh Art & Design Inc. Illustration: Monica Hellström