MISSION
TO ADVANCE CLINICAL CARE WORLDWIDE BY CATALYZING AND LEADING RESEARCH IN MOLECULAR MEDICINE.

VISION
TO BECOME A GLOBAL LEADER IN THE APPLICATION OF MOLECULAR DISCOVERY TO CLINICAL CARE.

GOALS
CATALYZE TRANSLATIONAL RESEARCH CAPABILITIES IN TORONTO FORGE EFFECTIVE LOCAL, NATIONAL, AND INTERNATIONAL PARTNERSHIPS BUILD A SUSTAINABLE FUNDING MODEL EDUCATE CLINICIANS IN MOLECULAR MEDICINE ESTABLISH AN INTERNATIONAL BRAND AND REPUTATION FOR EXCELLENCE AND IMPACT IN TRANSLATIONAL MEDICINE.
DIRECTOR’S MESSAGE

Everything in nature goes through cycles. Some cycles are so long that their beginning or end is not yet recognized. In our man-made world, such cycling is also healthy, particularly if it is planned and balanced.

The McLaughlin Centre for Molecular Medicine (MCMM) began about 10 years ago through the efforts of a handful of our scientific leaders, who shared the simple vision of enhancing the support for outstanding science and education to better medicine. Starting small, MCMM grew to exceed its mandate, influenced science and medicine in Toronto and the world, and now cycles back to prepare for the next decade. As you will see throughout this report, MCMM’s impact has been significant. It is always surprising to see how much can be accomplished in such a short time.

In the past few years, through many partnerships, MCMM scientists have been involved in some of the biggest breakthroughs and projects in biomedical research. The advances span the fields of applied stem cell and regenerative medicine, molecular therapeutics, genomics, proteomics, and global medicine. The McLaughlin-Rotman Centre for Global Health and the McEwen-McLaughlin Stem Cell Seminar Series have gained energy and reputations of their own. The MCMM Education Program has been the Centre’s foundation for constantly renewing its idea and talent pool.

The years 2007-2009 will be remembered as the time when medicine became “personal”. The first genome sequence of an individual human was completed, ushering in an era of personalized medicine. Cancer therapies started to become more targeted through cellular profiling. Cells from patients were induced to form specified tissues for therapeutic applications. Direct-to-consumer genetic testing became hip. And when the science played out in the media and policy, our members were often the ones raising and responding to the questions. MCMM always had some presence. I only wish there were more funding for more discoveries and advances.

It has been my great pleasure to work with Dean Catharine Whiteside and Vice-Dean Peter Lewis, the Steering Committee comprising the Vice-Presidents of Research of the hospital-partner institutions, and the MCMM Board of Trustees, including University of Toronto President David Naylor. Over the past 18 months, we have planned for the next cycle of MCMM. There were many wide-ranging proposals and vigorous discussions. At one Board meeting, I recall our Chair, Christopher Wansbrough, saying of our philanthropic founder Colonel Robert Samuel McLaughlin, “His original ideas were never wrong; sometimes they were just so simple or so visionary, it took a while for history to catch up and realize he was right.”

In the next phase, MCMM will need to be leaner and more focused, as it was at the beginning. I think our founders, like Colonel Sam, had it right. Remaining steadfast in supporting outstanding science and education applied to medicine will be the foundation for our perpetual success.

STEVE SCHERER
Interim Director, MCMM
ORGANIZATIONAL STRUCTURE

OVERSIGHT COMMITTEE

PRESIDENT,
UNIVERSITY OF TORONTO

EXECUTIVE COMMITTEE

MCMM DIRECTOR

PARTNER INSTITUTIONS

ETHICS & POLICY EDUCATION

- SickKids
- University Health Network
- Mt. Sinai Hospital
- University of Toronto
- Global Health
- Computational Genomics
- Drug Discovery
- Regenerative Medicine
- Sunnybrook Health Sciences Centre
- Immunogenomics
- Computational Genomics
- Regenerative Medicine
GOVERNANCE

EXECUTIVE COMMITTEE – GOVERNING COUNCIL OF THE UNIVERSITY OF TORONTO

An Executive Committee governs the MCMM with representation from each partner institution. The University of Toronto’s delegate, Peter Lewis, Vice-Dean Research, chairs the Executive Committee. The Executive Committee reports to the President of the University of Toronto.

MICHAEL JULIUS
Vice-President, Research,
Sunnybrook Research Institute
PETER LEWIS (CHAIR)
Vice-Dean, Research, Faculty of Medicine,
University of Toronto
STEPHEN LYE
Vice-President, Research, Mount Sinai Hospital
CHRISTOPHER PAIGE
Vice-President, Research, University Health Network
JANET ROSSANT
Chief of Research, SickKids
STEPHEN SCHEERER
Interim Director, MCMM
ART SLUTSKY
Vice-President, Research, St. Michael’s Hospital
as invited observer
CATHARINE WHITESIDE
Dean, Faculty of Medicine, University of Toronto
JIM WOODGETT
Director of Research,
Samuel Lunenfeld Research Institute

BERKELEY, CA
CATHARINE VERFAILLIE
Stem Cell Biology Program, University of Minnesota,
Minneapolis, MN
HUNTINGTON WILLARD
Genome Sciences & Policy, Duke University,
Durham, NC

EXTERNAL ADVISORY BOARD – MCLAUGHLIN-ROTMAN CENTRE

As part of the Donation and Charitable Trust Agreement between MCMM, UHN and Sandra Rotman to demonstrate commitment to excellence, an Advisory Board was struck with distinguished and respected experts involved in the field of global health.

DANIEL CARUCCI
Foundation for National Institutes of Health,
Bethesda, MD
ALLAN GOTTIEB
Stikeman Elliott LLP, Toronto, ON
PHILIPPE GROS
McGill University, Montreal, PQ
ROBERT RAE
Goodmans LLP, Toronto, ON
ALLAN RONALD
St. Boniface Hospital, Winnipeg, MB
MAURICE STRONG
Tayuan Diplomatic Office, Beijing, China

OVERSIGHT COMMITTEE

At the time the MCMM grant was received, a committee was formed to ensure the purpose of the grant is pursued and that major changes to the Centre remain faithful to the purpose of the grant. Governing Council of the University of Toronto appoints members on the nomination of the President of the University of Toronto. The Committee receives the MCMM Annual Report and Reports prepared by the External Advisory Board.

GEORGE CONNELL
CHAVIVA HOSEK
ALAN HUDSON
PETER LEWIS
DAVID NAYLOR
ROBERT S. PRICHARD
STEPHEN SCHEERER
CHARLES TATOR
J. CHRISTOPHER C. WANSBROUGH (CHAIR)
CATHARINE WHITESIDE
Three projects are currently receiving investments: Structural Variation in the Human Genome, Autism Genome Project, and Genetic Networks. The MCMM funds are also significantly leveraged with investments from other agencies, including Genome Canada, the Canada Foundation for Innovation, the Canadian Institutes of Health Research (CIHR), the Wellcome Trust, and Autism Speaks.

The MCMM-Cg team also participates in projects with other MCMM program themes. Aled Edwards, for instance, is collaborating with the Global Health program to determine structures of malarial proteins. The newest MCMM-CG initiative is an Ontario Biobank Project with the Ontario Cancer Research Network and The Centre for Applied Genomics. In this term, new collaborations have also been initiated with numerous members of the MCMM Global Health and Stem Cell groups in the themes of genome annotation and chromosome stability, respectively. In the past two years, MCMM-CG discoveries have generated noteworthy attention from the scientific press and headlined news worldwide.

PROJECTS

1. STRUCTURAL VARIATION IN DISEASE.
   Membership: Stephen Scherer, Abdallah Daar, Rosanna Weksberg, Anne Bassett and clinical geneticists from Toronto.

   Early information from the Human Genome Project suggested that the DNA in the genome of any two individuals is 99.9 per cent identical with the 0.1 per cent variation arising primarily from some three million single chemical base (nucleotide) changes. In a series of papers supported by MCMM funding and published in Nature, Nature Genetics and Genome Research in the fall of 2006, far exceeding anyone’s predictions, the team found that thousands of chunks of DNA, sometimes encompassing millions of nucleotides, can vary between individuals. This points to possible new explanations for individual uniqueness, as well as how disease develops. The MCMM-sponsored “Database for Genomic Variants” (DGV) is now the standard source of information in this new field and collaboration with the Wellcome Trust Sanger Institute on the
“By knowing our genomes, we will begin to truly know ourselves.”

PROGRAM DIRECTOR
STEPHEN SCHERER, PhD
“DECIPHER” database is significantly impacting the clinical genetics and diagnostic community. The team has also embarked on individual genome-sequencing initiatives in an effort to catalogue all genetic variation in the human genome. The group participated with the J. Craig Venter Institute in generating the first complete genome sequence of an identified individual (Craig Venter). DGV now works with the European Bioinformatics Initiative (EBI) to prepare for data deposition from the 1000 Genomes Project. DGV has also hosted numerous training and outreach sessions, in particular with the Canadian and international cytogenetics community. DGV and the structural- and copy-number variation (CNV) have been featured in articles in Nature, Science, Scientific American and numerous others.


2. AUTISM GENOME PROJECT. Membership: Steve Scherer, Wendy Roberts, John Vincent, Andrew Paterson, international collaborators.

Autism is a neuropsychiatric disorder associated with lifelong disabilities that affects one in 160 newborns worldwide. Working with 137 researchers from eight other countries, the MCMM scientists analyzed DNA from 1,600 families. By combining new types of gene copy number variation analyses the team pioneered along with traditional genetic linkage studies, it revealed for the first time in studies published in Nature Genetics (2007) and the American Journal of Human Genetics (2008), the genetic architecture underlying autism susceptibility, promising better diagnostics and possibly new therapeutics. A $26.7 million second phase of the project was also launched to find all of the susceptibility genes.

Following on these discoveries, the Canadian team has published numerous papers describing discoveries of new copy number variations in autism and also more recently in schizophrenia. The team has uncovered three specific genes, which they have patented for clinical diagnostic testing. In late 2009, the group will finish its latest analysis of more than 2,000 new autism families from around the world. Once annually, the team meets with the parents and families involved in the study to share its results and plan for the future.


We know the genetic properties of living systems result from the collaborative interaction of many alternate forms of genes that occur within different individuals of a population. The challenge
now is to identify the combination of natural genetic variants that modulate the activity of specific disease-associated pathways.

Complete maps of genetic networks are being generated and both the intra- and inter-network relationship rules are being defined. This project team has developed an automatic genetic analysis system to map the entire genetic network in a yeast model system. Through databases, it is relating this network to human genetic disease. This is key for interpreting chemical-gene interactions and linking bioactive compounds to their targets. In the past year, significant scientific papers have been published in Nature, Proteomics, and other high-impact periodicals documenting scientific progress.

In the past two years, the group has performed research on several biologically important fronts, including reconstruction of yeast protein-protein interaction networks, curation and compilation of catalogues of yeast multi-protein complexes, and development of algorithm for genetic interaction data analysis. Reliable information on the physical and functional interactions between gene products is an important prerequisite for deriving meaningful system-level descriptions of cellular processes. The available information about protein interactions in the yeast S. cerevisiae has been vastly increased recently thanks to systematic mapping studies using tandem affinity purification/mass spectrometry (TAP/MS) and other high-throughput techniques. In collaboration with Jack Greenblatt’s and Andrew Emil’s groups, we have reconstructed proteome-scale protein-protein interaction networks by analyzing high-throughput TAP/MS data in S. cerevisiae, and identified protein complexes (a form of functional modules) from such networks using the Markov clustering algorithm (MCL).

Epistatic or genetic interactions, representing the effects of mutating one gene on the phenotypes caused by mutations in one or more distinct gene(s), can be helpful in uncovering functional relationships between genes. Recently, the epistatic miniarray profiles (E-MAP) method has emerged as a powerful approach for identifying such interactions systematically. For E-MAP data analysis, hierarchical clustering is used to partition genes into groups based on the similarity between their global interaction profiles. The resulting descriptions assign each gene to only one group, thereby ignoring the multifunctional roles played by most genes.

The group has developed an original local coherence detection (LCD) algorithm for identifying groups of functionally related genes from E-MAP data in a manner that allows individual genes to be assigned to more than one functional group. This enables investigation of the pleiotropic nature of gene function. The performance of the algorithm is illustrated by applying it to two E-MAP datasets and an E-MAP-like in silico dataset for the yeast S. cerevisiae. In addition to recapitulating the majority of the functional modules and many protein complexes reported previously, the algorithm uncovers many recently documented and novel multifunctional relationships between genes and gene groups. The algorithm is therefore a valuable tool for uncovering new roles for genes with annotated functions and for mapping groups of genes and proteins into pathways.


AWARDS

STEPHEN SCHERER
- 2007, GlaxoSmithKline/CIHR Endowed Chair in Human Genetics and Genomics
- 2007, First Distinguished Alumni Award, Faculty of Science, University of Waterloo
- 2008, Premier’s Summit Award for Medical Research

COMPUTATIONAL GENOMICS TEAM

Stephen Scherer – SickKids
Charlie Boone – Donnelly Centre for Cellular and Biomolecular Research
Shoshana Wodak – SickKids
Aled Edwards – UofT

“...our goal is to treat patients based on their protein profiles.”

PROGRAM DIRECTOR
MIKE MORAN, PhD
DRUG DISCOVERY

The MCMM Drug Discovery Program consists of a team of investigators whose complementary interests and expertise range from analytical and medicinal chemistry and molecular biology, to cancer treatment and drug development. The team’s five-year plan, initiated in 2005, includes a vision to improve outcomes for cancer patients through the integration and translation of biomolecular information towards (i) biomarker and innovative drug discovery and development, and (ii) biomarker-guided patient stratification and combination therapies.

In addition to the research conducted in the MCMM scientists’ laboratories, team activities also take place at two facilities funded in part by MCMM: The Sinai-McLaughlin Assay and Robotics Technologies (SMART) facility at the Samuel Lunenfeld Research Institute (SLRI), Mount Sinai Hospital; and the Clinical Proteomics Laboratory at Toronto Medical Discovery Tower, MaRS.

- The SMART facility, under Dr. Jeff Wrana’s leadership, supports several cell-based, high-throughput screening strategies aimed at leveraging MCMM strengths in stem cell and molecular oncology research.
- The Clinical Proteomics Laboratory, next to the laboratories of Drs. Moran, Raught, and Jurisica, is engaged in the generation and integration of information on proteins and Post-translational Modifications (PTMs) in model systems, and blood and epithelial cancers towards the discovery and validation of pharmacodynamic biomarkers and drug targets.

PROGRESS UPDATE

One of the team’s near-term goals was to establish collaborations among team members to initiate translational research activities. As evidenced by a growing list of publications, this objective is being met. The team’s longer-term goals remain the further development and application of small molecule drug discovery and clinical proteomics technologies to help identify novel drug targets and biomarkers and to establish an innovative drug pipeline. These activities are augmented by team efforts in medicinal and analytical chemistries and rational drug design.

Recent publications by collaborating Drug Discovery team scientists, as listed below, include the development and application of new methods to profile protein PTMs and evidence for their utility in clinical trial settings, and the discovery of new small molecules or new indications as a product of innovative high-throughput screens and new screening methods.
The Drug Discovery team is also active in new technology development. Dr. Moran established collaborations with scientists at Thermofisher that led to their donation of a high-end mass spectrometer and software to the MCMM Clinical Proteomics Laboratory. This is enabling the development of methods (known as selected reaction monitoring, or SRM) to quantify PTMs in response to drug treatments (Tong et al. submitted, St-Germain et al. submitted). Dr. Brian Raught, together with Dr. Charlie Boone (MCMM Computational Genomics Program), presented exciting results on the profiling of a newly appreciated PTM, Sumoylation (Mylvaganam et al. 2009). Dr. Wheeler developed an integrated proteome profiling method and a multiplexed screening tool, and demonstrated enzyme- and cell-based assays by digital microfluidics, and an interface between microchannels and nanoelectrospray mass spectrometry (Miller & Wheeler 2008).

Dr. Lakshmi Kotra has investigated structure-activity relationships and developed and applied rational drug design methods to target a variety of nucleotide-binding drug targets, some in collaboration with Dr. Kevin Kain (MCMM Global Health Program) (e.g. Bello et al. 2007; 2008).

A major success criterion for the program continues to be the demonstration of clinical impact stemming from its activities. Recent examples include:

- Drs. David Kaplan and Jeff Wrana used high-throughput screens of 5,000 compounds to identify drugs that were cytotoxic for primary human neuroblastoma cancer stem cells, but not normal pediatric stem cells. Drug hits included anti-malarials, anti-microbials and neuroactive drugs (Smith et al. submitted). Several were active in the picomolar range, and greatly decreased cancer stem cell self-renewal in culture and in xenograft models. One of the drugs, rapamycin, has been administered to neuroblastoma patients on a compassionate basis with three positive responses.
- Dr. Schimmer led a project that identified a new molecule with promising pre-clinical activity in certain blood cancers (Mao et al. 2008).
- Drs. Trudel and Moran demonstrated the utility of mass spectrometry-based proteomics profiling to investigate drug mechanisms and targets as a part of a Phase 2 study of lenalidomide in leukemia (Chen et al. 2007).
- Similar studies are underway with Drs. Tsao and Hedley to investigate the pharmacodynamics of protein kinase-directed drugs in lung, colorectal, and pancreatic cancers.

AWARDS

- Kristen Smith in the Kaplan lab’s MCMM high-throughput screening project at the AACR-NCI-EORTC International Conference on “Molecular Targets and Cancer Therapeutics,” October 2007, was chosen for a press release and featured on the AACR website.
- David Kaplan was awarded the Prize for “Best Paper” at the Advances in Neuroblastoma Research 2008 meeting in Japan for the MCMM high-throughput screening project.
- Aaron Wheeler was awarded both the Canadian Society for Chemistry Fred Beamish Award for Innovation in Analytical Chemistry, and the Eli Lilly and Company ACACC Young Investigator Award in Analytical Chemistry.
- Lakshmi Kotra won the Ontario Research Commercialization program (ORCP) Innovation Award for advancing research into the commercialization of novel antimalarial compounds, BioDiscovery Toronto, Toronto, Canada.

HIGHEST IMPACT PAPERS FROM MRC PROGRAM, PUBLISHED FROM 2007 TO PRESENT


EDUCATION

During 2007-2009, the MCMM Education portfolio supported (i) training salary stipends awarded to MD-PhD students and postgraduate trainees in the Clinician Investigator Program at the University of Toronto, and (ii) seminars related to molecular medicine directed primarily at clinician research trainees. Publications arising from salary support awards as of the date of this report are listed.

**SALARY SUPPORT AWARDS**

McLaughlin MD-PhD Studentships: Highly meritorious MD-PhD students at the University of Toronto receive awards aimed at supporting their training. Below, students supported by the MCMM are listed.

**BENJAMIN STEINBERG** (supervisor Sergio Grinstein) “A biophysical characterization of the phagosome.” Ben, a fifth year MD-PhD student, successfully defended his PhD in December 2008 and has now returned to complete medical school.


**GRAEME SCHWINDT** (supervisor Sandra Black) “Functional and structural brain imaging in Alzheimer’s Disease: Towards a biomarker of treatment response and decline.” A third year MD-PhD student, Graeme is currently undertaking PhD studies.

**BRIAN BALLIOS** (supervisors Derek van der Kooy/ Molly Shoichet) “Novel Stem Cell Delivery Systems to Treat Retinal Degenerative Diseases.” As a second year MD-PhD student, Brian moved into the graduate phase in January 2009.

**MIKE BOHDANOWICZ** (supervisor Sergio Grinstein) “Recruitment and regulation of Rab5 during phagocytosis.” Mike is also a second year MD-PhD student who began graduate work in January this year.

**JANINE HUTSON** (supervisor Gideon Koren) “Mechanisms of drug transport across the human placenta and its role in drug safety during pregnancy.” A second year MD-PhD student, Janine has returned to the lab where she previously undertook a Masters degree to continue a PhD program.

**MARKO SKRTIC** (supervisor Aaron Schimmer) “Drug Development – Novel therapies for Acute Myeloid Leukemia.” In the second year of the MD-PhD program, Marko also began graduate work in January 2009.

**DAVID TSUI** (supervisor Freda Miller) “Fate specification of cortical precursors.” David is also a second year MD-PhD student who recently left his MD class to begin full-time graduate studies.
"Educating the next generation of researchers towards excellence and innovation is fundamental to our future success."

EDUCATION PROGRAM DIRECTOR
NORMAN ROSENBLUM, MD
The following students in the first year of the MD-PhD Program are supported by the MCMM. They are currently in the process of identifying a research program for the PhD phase of their program. So, no supervisor is named.

SUSAN ARMSTRONG, WARREN BERGER, GREG COSTAIN, PATRICK MCVEIGH, JARED WILCOX

Fellowship in Translational Research: Several years ago, MCMC initiated a program to support postgraduate scientist trainees engaged in translational research. One such award was supported during this reporting period:

JOSEPH ANTONY (supervisor Freda Miller) “Microglia are an essential component of the cortical stem cell niche in embryonic brain.”

Fellowships for Clinician Investigator Program trainees: The MCMC has supported clinicians engaged in training within the University of Toronto Clinician Investigator Program. The following trainees received awards in 2007-2008:

MARIO MASSELLIS (supervisor S. Black) “Corticobasal Syndrome: heterogeneity across clinical, neuroimaging, genetic and pathological features” (July 2006 to June 2008)


GREG HAWRYLUK (supervisor MG. Fehlings) “Transplantation of neural stem cells & tissue engineering to repair spinal cord injury” (July 2006 to June 2008)


• Hawryluk GW, Fehlings MG. The center of the spinal cord may be central to its repair. Cell Stem Cell 2008 Sep 11;3(3):230-2

MICHAEL TSEN (supervisor T. Young) “BDNF-TRPC3 Coupled Signal Transduction in the Pathophysiology of Bipolar Disorder and Mood Stabilizer Action” (July 2007 to June 2009)


MCMM LECTURE SERIES FOR CLINICIAN SCIENTIST TRAINEES

The following educational seminars were supported during this reporting period:

• Bioinformatics Workshop – April 30-May 1, 2007

• Dr. Richard Smith, Former Editor, BMJ: “Can you trust medical journals? Workshop on Publication Ethics” – November 22, 2007

• Dr. David Urbach: “An introduction to health services research” – February 14, 2008

• Women as Clinician Scientists: An interactive discussion panel – February 26, 2008

• Bioinformatics Workshop: Exploiting public resources for clinical research” – March 18 and 19, 2008

• Dr. Thomas Waddell: “Bone marrow derived pulmonary epithelial progenitor cells: Progress towards cell therapy of the lung” – April 7, 2008

SCIENTIFIC SEMINARS

The McEwen Centre for Regenerative Medicine, together with the McLaughlin Centre for Molecular Medicine, host a seminar series to profile exciting new research in stem cell biology and regenerative medicine. Leading scientists from around the world are invited to present their research to the Toronto scientific community.
PAST SEMINARS

JULY 20, 2009 – DR. MICHAEL RUDNICKI, OTTAWA HEALTH RESEARCH INSTITUTE
Dr. Rudnicki is a Senior Scientist and Director of the Regenerative Medicine Program and the Sprott Centre for Stem Cell Research, Ottawa Hospital Research Institute. He is also Scientific Director of the Stem Cell Network and holds a Canada Research Chair in Molecular Genetics. “Molecular Regulation of Muscle Stem Cell Function”

JUNE 3, 2009 – DR. TSVEE LAPIDOT, WEIZMANN INSTITUTE
Dr. Lapidot is a Professor of Immunology and the Edith Aronoff Stein Professorial Chair in Stem Cell Research at the Weizmann Institute, Israel. “Dynamic interactions between the nervous and immune systems with the microenvironment regulate hematopoietic stem cells”

MAY 21, 2009 – DR. FIONA DOETSCH, COLUMBIA UNIVERSITY
Dr. Doetsch is an Assistant Professor of Pathology at the Columbia University Medical Center, New York. “Stem cells and their niche in the adult mammalian brain”

MAY 8, 2009 – DR. AUSTIN SMITH, UNIVERSITY OF CAMBRIDGE
Dr. Smith is Director of the Wellcome Trust Centre for Stem Cell Research at the University of Cambridge, UK. “Capturing pluripotency”

MARCH 26, 2009 – DR. AMY WAGERS, HARVARD MEDICAL SCHOOL
Dr. Wagers is a faculty member in the Section on Developmental and Stem Cell Biology at Joslin Diabetes Center and Assistant Professor of Pathology at Harvard Medical School. “Stem cell maintenance and function in aged and regenerating tissues”

FEBRUARY 20, 2009 – DR. SHIN-ICHI NISHIKAWA, RIKEN CENTER FOR DEVELOPMENTAL BIOLOGY
Dr. Nishikawa is Director of the Lab for Stem Cell Biology at the RIKEN Center for Developmental Biology in Japan. “Purification of hematopoietic stem cells without negative selection markers”

OCTOBER 16, 2008 – DR. TIMM SCHROEDER, GERMAN RESEARCH CENTRE FOR ENVIRONMENTAL HEALTH
Dr. Schroeder is Deputy Director of the Helmholtz Zentrum München – German Research Center for Environmental Health, Institute of Stem Cell Research. “Tracking of stem cell behavior at the single cell level: New tools for old questions”

SEPTEMBER 8, 2008 – DR. TONY GREEN, UNIVERSITY OF CAMBRIDGE
Dr. Green is University Chair in the Department of Haematology at the University of Cambridge, UK. “From the birth of a HSC enhancer to death in the myeloproliferative malignancies”

AUGUST 13, 2008 – DR. LEIF CARLSSON, UMEÅ UNIVERSITY, SWEDEN
Dr. Carlsson is a Professor at the Umeå Center for Molecular Medicine at Umeå University in Sweden. “The role of the LIM-homeobox gene Lhx2 in stem cell function, organ development and disease”

JUNE 26, 2008 – DR. JOSEPH WU, STANFORD UNIVERSITY
Dr. Wu is an Assistant Professor in Cardiovascular Medicine in the Department of Medicine at Stanford University. “Molecular imaging of adult and embryonic stem cell fate”

MAY 15, 2008 – DR. CARLA BENDER KIM, CHILDREN’S HOSPITAL, HARVARD UNIVERSITY
Dr. Kim is a member of the Department of Genetics and the Children’s Hospital Stem Cell Program at Harvard University. “Examining stem cells in normal lung and lung cancer”

APRIL 24, 2008 – DR. CHARLES MURRY, UNIVERSITY OF WASHINGTON
Dr. Murry is Co-Director of the Institute for Stem Cell and Regenerative Medicine at the University of Washington. “Embryonic Stem Cells: Differentiation Pathways and Cardiac Repair Applications”

APRIL 3, 2008 – DR. KONRAD HOCHEDLINGER, HARVARD MEDICAL SCHOOL AND HARVARD STEM CELL INSTITUTE
Dr. Hochedlinger is an Assistant Professor in the Department of Medicine at the Cancer Center and the Center for Regenerative Medicine at Harvard University. “Reprogramming of adult cells into pluripotent cells”

NOVEMBER 13, 2007 – DR. AUSTIN SMITH, UNIVERSITY OF CAMBRIDGE
Dr. Smith, Director of the Wellcome Trust Centre for Stem Cell Research at the University of Cambridge, presented his work in “Capturing Pluripotency.”

NOVEMBER 1, 2007 – VISITING SPEAKER DR. ANAND ASTHAGIRI, CALTECH
Dr. Asthagiri, from the California Institute of Technology (“Caltech”), presented his work to a Toronto audience in a presentation entitled “Quantitative variations in molecular networks and the emergence of multicellular phenotypic diversity.”
The McLaughlin-Rotman Centre for Global Health (MRC)’s mission is to conduct translational research in global health and help researchers and companies get their life sciences technologies to those who need them in the developing world. Our vision is to illuminate the path towards a world where everyone benefits from new diagnostics, vaccines, drugs, and other life science solutions. This research-based academic centre at the University Health Network and University of Toronto is located in the MaRS Discovery District.

We have created a unique approach to address the lab-to-developing world problem via two programs:

• the Sandra A. Rotman Laboratories, led by Dr. Kevin Kain, Director of the MCMM Global Health program, strive to solve clinically relevant and priority problems in global health with the modern tools of molecular discovery and an emphasis on translational research.

• the Program on Ethics and Commercialization focuses on developing new models and approaches to commercialization by linking science and business, and involving the domestic private sector in the developing world. We use scholarly research to help move health technologies for researchers and companies from “lab to village” through the convergence of science and business. The program comprises the following four themes, each one focusing on a set of related issues:

1. The Commercialization in Emerging Economies theme identifies solutions to the commercialization barriers of health biotechnology products in emerging economies. Its aim is to understand how companies in emerging economies meet local and global health needs. It also examines and facilitates partnership opportunities between industrialized companies and their counterparts in emerging economies.

UPDATE

MRC’s Commercialization in Emerging Economies (CEE) program has led to both global health and economic impacts by fostering new economic opportunities for emerging economies and facili-
“We will not have enduring peace without addressing global health inequities.”

ABDALLAH DAAR, D. PHIL (OXON), FRCP, FRCS, FRCSC
tating access to new markets for international biotechnology firms. For example, treatments for diseases such as leprosy, tuberculosis, cholera, yellow fever and other infections that have a significant impact on the health of poorer populations are, in general, not pursued by biotech firms in more developed parts of the world because of their perceived limited profitability. However, biotech firms in emerging economies not only have the potential to develop effective treatments for these diseases, but their products also can be more affordable and more easily accessible. MRC's CEE program has conducted in-depth studies on the capabilities of emerging economies to develop novel health products for local needs.

**IMPACT**
This work has expanded the awareness of the international community regarding how emerging economies can be better engaged as participants in ongoing global health initiatives. MRC's CEE program has also helped to facilitate linkages and partnerships between innovative firms in emerging economies with the global health community and other international partners. This work has helped increase biotechnology commercialization for emerging economy firms and has led to improved access to global markets.

2. The Life Science Innovation Centres in sub-Saharan Africa theme brings together diverse stakeholders, such as policy-makers, research institutions, capital providers, the private sector and donor groups, to develop and commercialize domestic life sciences research, products and services that meet local and regional health needs.

**UPDATE**
During the past year, the team has continued to work with the governments of Ghana, Rwanda and Tanzania, while expanding to Uganda at the invitation of the Hon. Vice-President of Uganda to study its health innovation system and help develop ways to commercialize it.

**GHANA**
- Supported the preparation of a business plan for the creation of a virtual innovation platform by facilitating a Ghanaian working group composed of local stakeholders.
- Developed an analysis of the Ghanaian system of innovation that will soon be published.

**RWANDA AND TANZANIA**
- Submitted business plans and operational plans to the Minister of Science and Technology to develop innovation platforms that will enable accelerated health product commercialization and improve innovation capacity locally.
- Held stakeholder consensus workshops.

**UGANDA**
- Interviewed 30 key stakeholders and liaised with local collaborators.
- Currently analyzing the data collected and will be traveling to Uganda to present the findings.
- Commenced a study of documenting stagnant health technologies in selected sub-Saharan African countries to showcase the potential of homegrown innovation.

**IMPACT**
The findings from our teams in Ghana, Rwanda and Tanzania and the resulting conceptual framework around the innovation centres were featured in two publications. The “Commercializing African Health Research: Building Life Science Convergence Platforms – Global Forum Update” paper was presented at the Global Ministerial Forum on Health Research at Bamako, Mali. The second paper, “Accelerating African Health Innovation” (Kamunyori S, Al-Bader S, Shah R, Simiyu K, Singer PA, Daar AS), was published in winter 2008 in a special issue of the Africa Journal, a quarterly publication of the Corporate Council for Africa. This non-profit membership organization is dedicated to enhancing trade and investment relations between the United States and the 53 countries of Africa. It highlights the barriers to commercialization of indigenous health products African countries face.

The Minister of Communications, Science and Technology of Tanzania, the Hon. Peter Msolla, has appointed a steering committee to help the ministry implement the development of the proposed innovation centre. The MRC is part of the Tanzanian Steering Committee’s secretariat.

The Rwandan government has also accepted the business and operational plans for the innovation centre and approved a budget line for the centre in its 2008-2009 budget.

3. The Ethical, Social, Cultural and Commercial (ESCC) theme provides original research and consultation services for the Bill and Melinda Gates Foundation’s Grand Challenges in Global Health Initiative and for the Water Efficient Maize for Africa
Project to maximize their success and increase the likelihood of appropriate adoption of science and technologies in the developing world.

a) The Grand Challenges in Global Health Initiative is modeled after the grand challenges formulated more than 100 years ago by mathematician David Hilbert. It has funded 44 projects, focusing on 14 major global health challenges, with the aim of working on solutions that will lead to breakthrough advances for those in the developing world.

**UPDATE AND IMPACT**

In the last two years, we have been involved in 29 consultations that cover a wide range of topics. For example, in 2008, significant contributions were made to the development of ethics capacity in China to address regulatory issues relating to US-Chinese research on animal models used to develop new vaccines. The team also developed and began to help implement a framework for community engagement in the context of research on genetic control of vectors. Similarly, there was development of shared principles of ethics on complementary feeding products for infants and children in the developing world. The hope was that this would inspire dialogue and cooperation among estranged stakeholders, thus helping to facilitate the vital scale-up of complementary feeding products. Finally, we looked into the ethical considerations around the exportation of tissues and databases and of stopping clinical trials early.

b) The Water Efficient Maize for Africa (WEMA) Project is a public-private partnership founded by the Bill and Melinda Gates Foundation, as well as by the Susan Thompson Buffett Foundation, and is managed by the African Agricultural Technology Foundation (AATF). Its goal is to develop drought-tolerant and royalty-free maize varieties for Africa.

**UPDATE AND IMPACT**

The team performed the first social audit of the WEMA project and consulted with 85 stakeholders in the five WEMA partner countries. They obtained multiple perspectives on the ethical, social, and cultural and commercialization issues related to the WEMA project and other agro-biotechnology initiatives in sub-Saharan Africa. Three working papers were drafted around issues encountered in the social audit. They were titled: “A Social Audit Model for Agro-biotechnology Initiatives in Developing Countries”; “Addressing Conflicts of Interest in Public Private Partnerships”; and “Gender Relevance in the Adoption of Agro-Biotechnology Initiatives in Africa.”

The Global Grand Challenges theme helps foundations and agencies to identify, prioritize and develop programs for science-based breakthrough solutions to global challenges.

**UPDATE**

As part of the Grand Challenges in Chronic Non-communicable Diseases, which were published in *Nature* (November 2007), work continued with the National Institutes for Health (US), the Oxford Health Alliance, the UK Medical Research Council, the Canadian Institutes for Health Research, as well as with other foundations and agencies to deliver an implementable platform that will address some of the recommendations discussed in the 5-10 highest impact papers published by the MRC. Our collaboration with these various foundations and agencies has helped us move forward towards the creation of a global alliance to address Chronic Non-Communicable Diseases.

In 2008, the federal government budget announced a Development Innovation Fund. Together with our SEB committee, we have been advising the Finance Department and the Department of Foreign Affairs over the past year on how to deliver this fund using the Grand Challenges in Global Health approach.

**IMPACT**

- Providing the Canadian federal government with a novel Grand Challenges approach to funding its health and related projects as part of its international aid portfolio.
- Providing leadership and working with key partners to develop an implementation mechanism to address chronic non-communicable diseases in the developing world.

**SOME HIGHEST IMPACT PAPERS FROM MRC PROGRAM, PUBLISHED FROM 2007 TO PRESENT**


**AWARDS**

**DR. ABDALLAH DAAR**

• Fellow of The Academy of Sciences for the Developing World (TWAS)
• Fellow of the Royal Society (Canada)
• Fellow, Canadian Academy of Health Sciences
• Senior Fellow, Massey College, University of Toronto
• UNESCO Avicenna Prize for Ethics in Science, UNESCO

• Anthony Miller Award for Research Excellence, University of Toronto

**DR. PETER SINGER**

• Michael Smith Prize in Health Research: Canada’s Health Researcher of the Year
• Fellow of the Royal Society (Canada)

**MEDIA, ARTICLES BY**

**DR. ABDALLAH DAAR**

• Berndtson K, **Daar AS**. Faithfully fighting malaria together. *Globe and Mail*, December 23, 2007
• Profiled in University of Toronto, Dalla Lana School of Public Health, Volume I, Issue 1, March 2009

**MEDIA, ARTICLES BY**

**DR. PETER SINGER**

• **Singer PA**. Appearance on CBC TV program about Dr. Ezzeldeen Abu al-Aish, February 28, 2009
• **Singer PA**, **Daar AS**. Gaza Heartbreak. *Sunday Star. The Toronto Star*, February 1, 2009
• **Singer PA**, **Daar AS**. The tragic test of a peace-loving man. *National Post [Full Comment]*, January 19, 2009
• **Singer PA**. Is Canada Ready for Bioterrorism? *Globe and Mail*, January 4, 2009
• **Singer PA**. Built from Scratch. *National Post*, January 29, 2008
• **Singer PA**. A New Year’s resolution: Create a living will. *National Post*, December 26, 2007
• **Singer PA**. Turning Health Workers into Torturers. *Comment*, *National Post*, December 18, 2007
• **Singer PA**. Healing the World with Canadian Know-How. *National Post*, November 21, 2007
• **Singer PA**. PM Harper’s new science and technology strategy hardly mentions China and India. *The Hill Times*, June 11, 2007
• **Singer PA**. Put science at the centre of CIDA’s agenda. *National Post*, April 26, 2007

**MCMM TRAINEES**

• Claudia Emerson, Research Associate, Commercialization in Emerging Economies
MRC STORIES OF IMPACT
MOBILIZING THE PRIVATE SECTOR FOR GLOBAL HEALTH DEVELOPMENT CONFERENCE
MRC organized a three-day conference in Toronto at the MaRS Convergence Centre from May 2 to 4, 2007, which brought together the global community to discuss and facilitate international partnerships for global health. The conference attracted over 200 experts and included plenary talks by renowned experts such as Prof. C.K. Prahalad (author of *The Fortune at the Bottom of the Pyramid*) and Dr. Carol A. Dahl (Chief of Staff, Global Health program, Bill and Melinda Gates Foundation). In addition, executives of 70 biotechnology firms from many countries, including India, China, Brazil, South Africa, Ghana, Nigeria, Canada and the United States, gave presentations and participated in partnering meetings. We are aware of at least five international partnerships that have resulted from this event. For example, FK Biotechnologia (Porto Alegre, Brazil) has finalized partnerships with two Canadian firms. In the first example, FK Biotech will complete clinical validation in Brazil of an HIV resistance diagnostic developed with proprietary technology by Spectradigital (Guelph, Ontario). This partnership has the potential to generate valuable proof-of-concept data needed by Spectradigital to attract future investment. In the second example, FK Biotech has entered into a joint venture agreement with ZBx Corporation (Toronto, Ontario) to co-develop rapid diagnostics.

THE STORY OF MISSING LINKAGES IN AFRICA AND THE ROLE OF INNOVATION CENTRES
Unfortunately, the linkages between African researchers and research institutions, and companies – even those that are domestically based – are weak.

Consider the following:
A to Z Textile Mills, a company in Arusha, Tanzania, in a joint venture with the Japanese company Sumitomo, is the largest manufacturer of long-lasting insecticide-impregnated bed nets in Africa. A to Z currently manufactures about 12 million bed nets a year, which are WHO-certified and reasonably priced. Moreover, A to Z has created more than 3,200 jobs for Tanzanians, supporting at least 20,000 people. As an example of manufacturing a science-based health product for one of Africa’s most burdensome diseases, A to Z is a huge success.

Now imagine a company like A to Z that relied not on imported technology, but on domestic African health research. Over the same time period that A to Z was manufacturing malaria bed nets, distinguished East African researchers were studying and publishing on the malaria parasite and mosquito vector. Imagine if this domestic East African research were the source of the technology for innovations in long-lasting insecticide-treated bed nets. The interesting fact is such domestic research does exist.

At the same time as A to Z textiles was starting up in the bed nets area, Prof. Wen Kilama, the Director General of Tanzania National Institute for Medical Research, was also working on the technical aspects and efficacy around insecticide-treated nets. It took 20 years for both sides to meet for the first time at a stakeholders meeting held by the MRC in collaboration with the Ministry of Science and Technology (Tanzania) in December 2007. This story is representative of the many we encountered as part of the LSIC project where there is a lack of synergy and knowledge flow among various stakeholders, resulting in the underexploited potential to commercialize local innovative “stagnant technologies”.

Our concept of Innovation Centres embodies a new approach to innovation, bringing together science, business and capital to create a dynamic environment where scientific knowledge, the demands of the marketplace and the realities of funders exist together – within an Innovation Platform. An example of a Convergence Platform is the MaRS Centre based in Toronto, Ontario. The Innovation Platform has a Physical and Virtual Component, which would facilitate the linkages, along with an associated Product Development Fund, which would award grants to support the development of the most promising pre-commercial technologies.
GLOBAL HEALTH

Global infectious disease threats – the McLaughlin-Rotman Centre for Global Health’s focus – are responsible for the greatest burden of illness and death worldwide. They account for the most pronounced disparities in health between the advanced and developing countries, have traditionally been neglected by western research, and can profoundly impact both regional and global economies. The centre’s mission is to bring together new minds, novel ideas, and innovative solutions to address emerging infectious disease threats. Its focus is on translating biomedical advances all the way to field trials.

PROJECTS

1. INNATE IMMUNITY AND MALARIA. MCMM has established an exciting multidisciplinary team of Canadian and international (USA, Thailand, Kenya, Malawi and Uganda) scientists with complementary expertise for this initiative. It focuses on delineating the molecular basis for adverse outcomes in malaria and using this knowledge to create novel classes of therapeutics. These would be designed to modify deleterious innate host responses to improve outcome, drive acquired immunity, and prevent drug resistance and treatment failure. The approach has successfully employed cell and molecular biology, animal models of infection, and informative human field studies to examine both sides of the host-pathogen interface. These include identifying host and parasite determinants that regulate the onset and ultimate outcome of malaria infections. New pathways mediating pathogenesis and biomarkers for these pathways have been identified. Several synthetic inhibitors of these determinants (especially focusing on compounds already FDA-approved for other indications) have been evaluated for efficacy in animal models and are being studied in randomized human clinical trials in Thailand, Cambodia, Kenya and Uganda.

2. MALARIA-HIV CO-INFECTIONS DURING PREGNANCY. Malaria and HIV infections in pregnant women are massive public health problems. Despite this, relatively little is known about the mechanisms underlying susceptibility to and protection against pregnancy-associated malaria (PAM) and the impact of HIV co-infection on these processes. This project assembles a team of skilled scientists with complementary expertise to tackle this important global health priority. This team is investigating the mechanisms underlying pathology and protection against PAM and how they are influenced by HIV infection. Specifically, whether C5a mediates or enhances PAM-specific inflammatory and
“Many people get infections yet few develop life-threatening disease. The discovery of biomarkers that identify individuals at risk of critical illness would represent transformative advances.”

PROGRAM DIRECTOR
KEVIN KAIN, MD, FRCPC
Scientists Make Breakthroughs in Malaria Research

InTheNews.co.uk
Monday, 8 Dec 2008 00:01

A team of Canadian scientists have made a double breakthrough in malaria research. The team, from Toronto’s McLaughlin-Rotman Centre for Global Health (MRC), have discovered biomarkers that could help identify crippling, often fatal forms of malaria.

1. Purification of hundreds of malaria-related proteins has been very successful with the expression and purification of hundreds of malaria-related proteins and has fostered new research partnerships based on malaria structural biology and drug design/medicinal chemistry.

2. New drug and vaccine targets. This collaboration has received more than $14 million in funding from the private sector.


The lack of accurate and rapid diagnosis of infectious disease is a major barrier to improving global health. The goal of this initiative is to develop the next generation of diagnostic devices capable of simultaneously detecting multiple infectious pathogens at point-of-care. This unique biomedical research program brings together exciting advances in nanomaterials and expertise in biomedical engineering, nanotechnology, genomics, proteomics, microfabrication, imaging, bio-informatics, and commercialization. Collaborative field trials are designed with Mahidol University, Thailand; CDC, Atlanta; and Harvard University. A start-up biotech company has been created to commercialize the diagnostic device; it has received more than $14 million in funding from the private sector.

4. Structural Proteomics of Malaria – A Collaborative Genomics Consortium (SGC) Collaboration. New effective therapies for drug-resistant malaria are urgently needed. This initiative exploits high-throughput genomics and proteomics strategies to clone, express, purify and crystallize malaria proteins to identify new drug and vaccine targets. This collaboration has been very successful with the expression and purification of hundreds of malaria-related proteins and has fostered new research partnerships based on malaria structural biology and drug design/medicinal chemistry.

Highest Impact Papers from MRC Program, Published from 2007 to Present

- Lovegrove FE, Gharib SA, Patel S, Hawkes C, Liles WC, Kain KC. Genome-wide expression microarray analysis implicates important roles in apoptosis and interferon-responsive transcripts in resistance and susceptibility to experimental cerebral malaria. American Journal of Pathology 2007;171(6):1894-1903. (This article was the lead article and accompanied by a laudatory editorial).
- Mei SH, McCarter SD, Deng Y, Parker CH, Liles...

AWARDS
SERGIO GRINSTEIN
• International Scholar of the Howard Hughes Medical Institute
• Recipient of the CIHR Distinguished Scientist Award
• Michael Smith Award
• Fellow of the Royal Society of Canada

KEVIN KAIN
• CIHR Tier I Canada Research Chair (renewed 2009)
• Honorary Fellow of the Royal Society of Physicians and Surgeons of Glasgow, University of Glasgow (2008)
• The Fred Barrett Lectureship in Medicine Visiting Professor: Kevin Kain; Host University: University of Tennessee (2008)
• Distinguished Service Award for Sustained Leadership in Global Health; Global Health Education Consortium (2007) Presented by Dr. A. Velji, Co-founder GHEC; Chief, Infectious Disease, University of California School of Medicine

RUPERT KAUL
• CIHR Tier II Canada Research Chair (renewed)

CONRAD LILES
• CIHR Tier I Canada Research Chair

MEDIA ARTICLES (SELECTED):
1. Pyruvate kinase deficiency and resistance to malaria. The Kain lab made an intriguing discovery that the 2nd commonest red cell disorder, pyruvate kinase deficiency (PKD), protects against human malaria. This was done using PK-deficient patients recruited to the Hospital for Sick Children and the Toronto General Hospital. This work demonstrated that homozygosity and heterozygosity for PK-deficient alleles have a protective effect against malaria in humans (Ayi K, Min-Oo G, Serghides L, Crockett M, Kirby-Allen M, Quirt I, Gros P, Kain KC. Pyruvate kinase deficiency and malaria. N. Engl. J. Med. 358:1805-1810, 2008). This paper was accompanied by an editorial in the NEJM (A footprint in the human genome. Daily J et al. New Eng J Med 2008;358:1855) and generated considerable media attention.

2. Kain lab identified novel biomarkers and new potential therapeutic targets for cerebral malaria and pregnancy-associated malaria, which collectively represent leading causes of infant and childhood mortality worldwide. Findings from these studies were covered by 14 news agencies. These findings have been patented and have received considerable interest in licensing from Biotech.

3. Kain lab identified novel interaction between HIV and malaria in pregnancy. This provided new insights into the deleterious interaction between these global health priorities. This study generated press releases and was covered by several news agencies.

MCMM TRAINEES
• Fiona Lovegrove MD, PhD Program
• Laura Erdman MD, PhD Program

“Working with Kevin Kain at the MCMM has provided amazing opportunities for collaboration with outstanding scientists – both peers and mentors. Among the goals of the MCMM global health group is to research and apply innovative biomedical solutions to global infectious disease priorities such as malaria. One of the most rewarding projects I contributed to while in Kevin’s lab was identifying and verifying biomarkers of cerebral malaria (CM), one of the most severe malarial complications. We examined these markers in the serum of both Thai adults and Ugandan children and showed that it distinguishes beautifully between patients with cerebral and mild disease and predicts clinical outcome in CM. Despite the fact that millions of people are affected by CM every year around the globe, there is no good way to predict which malaria patients will progress to or die from CM. Identifying people who are at risk of a poor outcome at an early stage in disease will facilitate timely intervention or reallocation of limited health resources in developing countries. It’s a wonderful feeling to have worked on a project that will likely impact malaria diagnosis and treatment going forward.” – Mark Ungrin, Post-Doctoral Fellow

THE CENTRE HAS INITIATED A NUMBER OF INNOVATIVE PROJECTS THAT ARE CONVERGENT AND LIKELY TO HAVE GLOBAL IMPACT, INCLUDING:
• the study of innate immunity and infectious diseases.
• the development of collaborative overseas research sites and partners to validate new diagnostics, theranostics and interventions.
• nanotech multiplex diagnostics – simultaneous genomic and proteomic profiling – detection and characterization of multiple pathogens at point-of-care.
• collaboration with the Structural Genomics Consortium using genomics and proteomics to identify new drug and vaccine targets for malaria.
ImmunoGenomics

Inflammatory autoimmune diseases, exemplified by rheumatoid arthritis, inflammatory bowel disease and Type 1 diabetes, are associated with high morbidity and a very significant medical and socioeconomic burden. The molecular therapeutics program aims to identify and develop molecular markers for diagnosis and risk and outcome prediction for these chronic conditions.

Led by five core investigators, Laurent Briollais, Dan Drucker, Andrew Emili, Kathy Siminovitch and Boris Steipe, the program has focused on two projects: Inflammatory autoimmune disease-biomarker discovery and design of genomic/proteomic biomarker discovery tools.

These projects bring together national and multinational research consortia, such as the Canada-wide Michael J. Howorth Inflammatory Bowel Disease Genetic, Environmental, and Microbial (GEM) Project; the juvenile inflammatory arthritis REACH consortium; the North America rheumatoid arthritis consortium (NARAC); and a broad network of international collaborators, and have attracted numerous leveraged government and private sector investments. Capitalizing on its partnership with the Analytical Genetics Technology Centre (AGTC), MCMM Molecular Therapeutics’ (MT) team continues to collaborate with other MCMM programs, providing, for example, technology support for a Global Health program on determinants of malaria outcome, and to build new collaborative relationships with the Ontario Institute for Cancer Research and Centre for Research in Neurodegenerative Disease.

Projects

1. Inflammatory Autoimmune Disease Biomarker Discovery. Membership: Laurent Briollais, Vivian Bykerk, Dan Drucker, Jenny Heathcote, Ed Keystone, Kathy Siminovitch, international collaborators.

Rheumatoid arthritis (RA) and primary biliary cirrhosis (PBC) are exemplars of inflammatory autoimmune diseases – a class of chronic human disease with multifactorial, but poorly understood etiologies. Resolution of the genetic causes of such diseases has only recently been made possible...
"The new understanding of disease etiology now emerging from genomics research has created an unprecedented opportunity for more effective, personalized healthcare delivery."

PROGRAM DIRECTOR
KATHERINE SIMINOVITCH, MD, FRCPC
with the emergence of dense single nucleotide polymorphism (SNP) genotyping platforms. These enable genome-wide association surveys for discovery of disease risk alleles. Our team has recently performed such surveys on large cohorts of Canadian patients with RA and PBC and controls, identifying genetic variants contributing to risk for each of these diseases. Our team has also identified new risk variants for inflammatory bowel disease and is currently conducting a genome-wide survey to identify risk variants for a severe, often lethal form of vasculitis.

By combining our extensive clinical data with genetic data, we are also screening for gene variants that influence disease course and outcome for this class of diseases. To that end, our team has established a pilot translational genomic medicine program that enables collection of biologic materials from every patient with RA allowed at the Mount Sinai Hospital Arthritis Centre. In this way, correlates between newly emergent genetic, proteomics and other biomarkers and clinical course, drug responsiveness and disease outcome can be identified and used to inform clinical treatment decisions.

This project has also developed and studied new mouse models of disease to characterize molecular pathways of possible relevance to treatment of inflammatory autoimmune disease. Capitalizing on such models, the Drucker lab has, for example, further explored the role of glucagon-like peptide as a possible therapy for inflammatory bowel disease. Focusing on the role of this gut peptide in intestinal mucosal function and growth, the group has identified a critical role for GLP-2 receptor signaling in control of nutrient absorption and epithelial permeability, played key roles in Phase 3 clinical trials testing GLP-2 therapeutic potential in treating short bowel syndrome, and shown that altered GLP-2 function does not influence gut cell neoplastic transformation. This knowledge is critical to the potential use of GLP-2 in treating inflammatory bowel disease. This work led to Dr. Drucker receiving the 2008 Prix Galien Canada Research Award for outstanding biopharmaceutical research.

2. DESIGN OF GENOMIC/PROTEOMIC BIOMARKER DISCOVERY TOOLS.
Membership: Laurent Briollais, Andrew Emili, Helene Massam, Kathy Siminovitch, Boris Steipe and international collaborators.

Applying new genetics and proteomics technologies to molecular dissection of disease continues to depend largely on concomitant advances in biometric and computational biology, advances our team is enabling by creating tools and methods that allow genome/proteome-scale datasets to be visualized, annotated and analyzed. Led by Drs. Laurent Briollais and Boris Steipe, the MCM-MMT project team has successfully developed novel statistical methods and data mining algorithms that support disease gene discovery and its clinical application.

Output from this work includes, for example, development of a Bayesian graphical modeling approach enabling modeling/prediction of SNP combinations that best predict disease and/or clinical outcome(s) of interest. This model, recently extended to include informative prior biologic knowledge, is currently being validated using rheumatoid arthritis and several other project-derived genetic datasets.

A second team-created statistical tool involves a novel, sequential design for microarray studies that reduces study costs by allowing for reduced study sample size. To enable prediction of gene mutation effects on protein structure/function, the team has also developed an annotated “dictionary” of protein structure motifs, predicted on a newly developed algorithm in which structural analyses enable unsupervised discovery of such motifs. From a database of almost 100 non-homologous protein structures containing over 120,000 residues, over 25,000 non-local motifs have been discovered using this method. Further statistical and computational modifications of the algorithm are underway to delineate statistical, sequence and semantic (i.e. biologic) significance of each motif. The data are being streamlined into a database, enabling further motif sorting and analysis of the data to gauge potential effect(s) of coding SNPs on protein structure and stability. Together, these methods provide powerful tools for coupling genetic datasets with discovery of disease-causal gene variants.

A second arm of this project, led by Dr. Andrew Emili, involves optimization of highly sensitive liquid chromatography tandem mass spectrometry (LC-MS)-based proteomic assays to enable quantification of low abundance proteins representing disease activity/outcome biomarkers. This work addresses a need for more sensitive LC-MS screening procedures capable of detecting, across multiple samples, low abundance proteins and multi-protein complexes that may be perturbed in the context of disease. To this end, our

“During my research at AGTC, I was able to learn about many of the latest genomic technologies that have allowed genetic disease research to produce such fast results.”

Dr. Erin Walker,
Post-Doctoral Fellow
team has developed a new proteomic paradigm for isolating low abundance proteins. This involves high-throughput reference peptide synthesis for assay development and the engineering of binding reagents to selectively enrich for targets of interest prior to mass spectrometry. Using these novel enrichment methods, “Multiple Reaction Monitoring” (a modified form of LC-MS), and high density synthetic peptide panels, we have created an optimized target-capture platform that boosts LC-MS sensitivity and specificity, making possible the routine monitoring of peptide levels in clinical samples from representative patient cohorts. This approach is now being applied to the team’s patient samples to search for disease “signatures” that enable, independently or in conjunction with genetic and other biomarkers data, prediction of disease risk and outcome. Together, these novel methods and tools provide an improved analytic and computational framework to identify disease biomarkers and to mine complex structured, multidimensional genomic/proteomic datasets.

**SOME HIGHEST IMPACT PAPERS FROM MRC PROGRAM, PUBLISHED FROM 2007 TO PRESENT**


**AWARDS**

- **DR. DANIEL DRUCKER:**
  - 2008 Prix Galien Canada Research Award
  - Endocrine Society 2009 Clinical Investigator Award

**MCCMM TRAINEES**

- **DR. EMILI’S LAB:**
  - Dr. Johannes Hewel (Post-Doctoral Fellow)
- **DR. STEIFE’S LAB:**
  - Philip Tong (Graduate student)
- **DR. DRUCKER’S LAB:**
  - Dr. Jackie Koehler (Post-Doctoral Fellow)
- **DR. BRIOLLAIS’ LAB:**
  - Dr. Jinnan Liu (Post-Doctoral Fellow)
  - Dr. Sohee Kang (Post-Doctoral Fellow)
- **DR. SIMINOVITCH’S LAB:**
  - Dr. Erin Walker (Post-Doctoral Fellow)
  - Dr. Gang Xie (Post-Doctoral Fellow)
“Stem cell biology provides the basis for a regenerative medicine that can replace cells lost due to disease or injury.”

PROGRAM DIRECTOR
DEREK VAN DER KOOY, PhD
REGENERATIVE MEDICINE

Stem cells are at the heart of regenerative medicine; if tissue has degenerated, these are the major substrate for missing cell regeneration. The Regenerative Medicine program seeks to stimulate translational research using innovative therapeutic strategies based on ground-breaking basic research. It seeks an international leadership role by translating basic stem cell discovery into therapy, focusing on a few carefully selected projects from one of the following areas: (i) cardiovascular, (ii) neuro-regeneration and (iii) stem cell biology. To broaden the vision and the reach of the program, it will provide support and organize meetings in Toronto. These additional activities will bring the discoveries and expertise of the basic stem cell biology researchers directly in contact with advances made and issues faced by clinician/researchers pioneering human stem cell treatments.

PROJECTS

1. ENHANCED ANGIOGENIC CELL THERAPY: ACUTE MYOCARDIAL INFARCTION (ENACT-AMI) TRIAL. Membership: Mike Kutryk, Tom Parker, Howard Leong Poi, Sandy Dick, Vlad Dzavik.

   We have been very successful at leveraging funding for this trial with a successful award from the CIHR Randomized Clinical Trial Committee for $2.7 million and another $1 million from the Canadian Stem Cell Network. We are finalizing the submission to Health Canada and research ethics and plan to initiate the trial in the fall of 2009. This is a multicentre trial involving three cities (Toronto, Ottawa and Montreal). In Toronto, the sites are Sunnybrook, St. Michael’s and UHN.

2. HUMAN EMBRYONIC STEM CELL AND XENOGRAPH FACILITIES. Membership: Peter Zandstra, John Dick, Derek van der Kooy, Norman Iscove, Janet Rossant, Andras Nagy.

   The objective of the human embryonic stem cell hESC core facility has always been to collect, characterize, bank and distribute derived, established hESCs as well as provide training in their use. To that extent the facility has established a memorandum of understanding (MOU) with WiCell to obtain hESC lines derived by that centre. This MOU covers all labs at the University of Toronto. We have obtained H1 and H9 cells and expanded and characterized them.

   The emergence of induced pluripotent stem cells (iPS) has created a new venue for the research of stem cells. The facility recognizes the impact these cells will have and is working to expand its capabilities to include iPS cells. With this in mind, the facility has undergone a slight name change from the MCMM-McEwen hESC Core Training Facility to the MCMM-McEwen Pluripotent Stem Cell Core Training Facility.

   The facility also incorporated this new technology into the expansive training seminar it put on with the Stem Cell Network in August 2008. Twelve trainees from across Canada were trained in standard hESC protocols, from maintenance and characterization to differentiation along with some basic protocols, for the derivation of iPS cells. This was the second year this facility had given this four-day training session, to positive reviews.

   The facility also incorporated this new technology into the expansive training seminar it put on with the Stem Cell Network in August 2008. Twelve trainees from across Canada were trained in standard hESC protocols, from maintenance and characterization to differentiation along with some basic protocols, for the derivation of iPS cells. This was the second year this facility had given this four-day training session, to positive reviews. The
Imagine if doctors could put a cardiac-cell “bandage” over a damaged heart, or inject a gel loaded with insulin-responsive cells into a diabetic’s bloodstream. For Peter Zandstra, professor of tissue engineering and principal investigator at University of Toronto’s Institute of Biomaterial and Biomedical Engineering, envisioning such medical advances is not so much an exercise in imagination as it is an educated speculation of things to come.

The Globe and Mail, May 6, 2008


AWARDS
DR. PETER ZANDSTRA:
• McLean Award, University of Toronto (2008)
• Canada’s Top 40 Under 40 (2008)
• Fellow of the American Institute for Medical and Biological Engineering (2007)
• Fellow of the American Association for the Advancement of Science (2007)
• John Simon Guggenheim Fellow (2007-2008)

DR. MOLLY SHOICHEt:
• Elected to the Mathematical and Physical Sciences Division of the Academy of Science of RSC (2008)
• Canada Council for the Arts Killam Research Fellowship (2008-2010)
• Fellow, Biomatertials Science and Engineering (FBSE), (2008-present)
• Fellow, American Institute for Medical and Biological Engineering (2006-present)

MEDIA ARTICLES
Our science superheroes: The XY-Men (and women) in Toronto working to save the world one medical breakthrough at a time featured in the Toronto Star on Mar 07, 2009 05:06 AM

MCMM TRAINEES
DR. ZANDSTRA’S LAB:
• Mark Ungrin, Post-Doctoral Fellow

DR. FEHLINGS’S LAB:
• James Rowland, Graduate Student
• Gregory Hawryluk, Graduate Student

“Human embryonic stem cells (hESC) provide a window into early human development, and a renewable source of cells for regenerative medicine. However, the embryoid bodies (hEB) typically employed to reveal hESC developmental potential are heterogeneous and exhibit disorganized and inefficient differentiation. We therefore developed a method to form large numbers of well-defined aggregates exhibiting multi-lineage differentiation and substantially improved self-organization from single-cell suspensions in well plates. Various other cell types including mouse ESC, fibroblasts, and cultured tumor cells have also been successfully aggregated in preliminary investigations.” – Mark Ungrin
# Financial Statements

## Statement of Operation
For the Year Ended April 30

### Sources of Funding

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<td><strong>Revenue</strong></td>
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<td>Investment income from Endowments (Note 4)</td>
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<td>Cash from Partners, Education Program</td>
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### Expenditures

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<tr>
<td>Administrative &amp; Program Directors, Salary &amp; Benefits</td>
<td>1,116,861</td>
<td>956,446</td>
<td>980,042</td>
</tr>
<tr>
<td><strong>Research</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Health</td>
<td>222,814</td>
<td>–</td>
<td>282,421</td>
</tr>
<tr>
<td>Genomics</td>
<td>315,000</td>
<td>493,145</td>
<td>416,079</td>
</tr>
<tr>
<td>Molecular Therapeutics</td>
<td>418,000</td>
<td>547,784</td>
<td>248,633</td>
</tr>
<tr>
<td>Drug Discovery</td>
<td>390,000</td>
<td>20,023</td>
<td>350,000</td>
</tr>
<tr>
<td>Regenerative Medicine</td>
<td>250,000</td>
<td>347,000</td>
<td>363,631</td>
</tr>
<tr>
<td>Start-up and other operational commitments</td>
<td>–</td>
<td>70,000</td>
<td>295,416</td>
</tr>
<tr>
<td>SHSC</td>
<td>100,000</td>
<td>100,000</td>
<td>–</td>
</tr>
<tr>
<td>SMART/hES Facility – Stem Cells</td>
<td>–</td>
<td>125,000</td>
<td>–</td>
</tr>
<tr>
<td><strong>Total Research</strong></td>
<td>1,695,814</td>
<td>1,702,952</td>
<td>1,956,180</td>
</tr>
<tr>
<td><strong>Educational Initiatives &amp; Programs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCM support to Education programs &amp; Initiatives</td>
<td>241,500</td>
<td>484,267</td>
<td>597,517</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppliers/Services/Travel/Other</td>
<td>87,157</td>
<td>69,508</td>
<td>156,112</td>
</tr>
<tr>
<td><strong>Total Administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Expenses</strong></td>
<td>3,141,332</td>
<td>3,213,172</td>
<td>3,689,850</td>
</tr>
</tbody>
</table>

### Net surplus (deficit) for the year

- 2008-09: (2,088,427)
- 2007-08: (585,128)
- 2006-07: (1,198,676)

### Cumulative Carry Forward

- 2008-09: 1,478,538
- 2007-08: 2,063,666
- 2006-07: 3,262,342

### Fund Balance, End of the Year

- 2008-09: (609,889)
- 2007-08: 1,478,538
- 2006-07: 2,063,666
### SUMMARY OF THE McLAUGHLIN ENDOWMENT
For the Year Ended April 30

<table>
<thead>
<tr>
<th></th>
<th>2008-09</th>
<th>2007-08</th>
<th>2006-07</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BOOK VALUE OF ENDOWMENT</strong> (NOTE 2):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>49,009,694</td>
<td>49,009,694</td>
<td>50,007,194</td>
</tr>
<tr>
<td>Donations (additions)</td>
<td>0</td>
<td>0</td>
<td>2,500</td>
</tr>
<tr>
<td>Transfer (out) to establish GSEF</td>
<td>0</td>
<td>0</td>
<td>(1,000,000)</td>
</tr>
<tr>
<td>GSEF-McLaughlin Fellowships (Fund 306084)</td>
<td>2,000,000</td>
<td>2,000,000</td>
<td>0</td>
</tr>
<tr>
<td>Transfer (in) from McLaughlin Endowment</td>
<td>0</td>
<td>0</td>
<td>1,000,000</td>
</tr>
<tr>
<td>GSEF Matching from Government</td>
<td>0</td>
<td>0</td>
<td>1,000,000</td>
</tr>
<tr>
<td><strong>BV OF ENDOWMENT</strong> (FUND 304107 &amp; 306084)</td>
<td>51,009,694</td>
<td>51,009,694</td>
<td>$51,009,694</td>
</tr>
</tbody>
</table>

**Annual Payout**

<table>
<thead>
<tr>
<th></th>
<th>2008-09</th>
<th>2007-08</th>
<th>2006-07</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>0</td>
<td>2,099,835</td>
<td>1,987,448</td>
</tr>
<tr>
<td>GSEF-McLaughlin Fellowships (Fund 306084)</td>
<td>0</td>
<td>70,995</td>
<td>16,566</td>
</tr>
<tr>
<td>GSEF Matching for 50% of Annual Payout</td>
<td>0</td>
<td>(6,902)</td>
<td>6,902</td>
</tr>
<tr>
<td>GSEF Matching from Government</td>
<td>0</td>
<td>2,163,928</td>
<td>2,010,915</td>
</tr>
<tr>
<td><strong>Annual Payout (% of Book Value)</strong></td>
<td>0.00%</td>
<td>4.33%</td>
<td>4.02%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2008-09</th>
<th>2007-08</th>
<th>2006-07</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>39,874,912</td>
<td>57,686,457</td>
<td>60,892,480</td>
</tr>
<tr>
<td>GSEF-McLaughlin Fellowships (Fund 306084)</td>
<td>1,348,164</td>
<td>1,950,369</td>
<td>2,058,764</td>
</tr>
<tr>
<td><strong>MV OF ENDOWMENT</strong> (FUND 304107 &amp; 306084)</td>
<td>41,223,076</td>
<td>59,636,826</td>
<td>62,951,244</td>
</tr>
</tbody>
</table>

**Annual Payout (% of Market Value)**

<table>
<thead>
<tr>
<th></th>
<th>2008-09</th>
<th>2007-08</th>
<th>2006-07</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>0.00%</td>
<td>3.63%</td>
<td>3.20%</td>
</tr>
</tbody>
</table>
BALANCE SHEET
As at April 30

<table>
<thead>
<tr>
<th>ASSETS</th>
<th>2008-09</th>
<th>2007-08</th>
<th>2006-07</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cash and cash equivalents (Note 1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>33,860</td>
<td>1,371,683</td>
<td>1,887,913</td>
</tr>
<tr>
<td>GSEF-McLaughlin Fellowships (Fund 306084)</td>
<td>87,561</td>
<td>87,561</td>
<td>23,468</td>
</tr>
<tr>
<td></td>
<td>121,421</td>
<td>1,459,243</td>
<td>1,911,381</td>
</tr>
<tr>
<td><strong>Short-term investments (Note 1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>0</td>
<td>19,296</td>
<td>152,285</td>
</tr>
<tr>
<td></td>
<td>121,421</td>
<td>1,478,539</td>
<td>2,063,666</td>
</tr>
<tr>
<td><strong>Endowments, book value (Note 2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLaughlin Endowment (Fund 304107)</td>
<td>49,009,694</td>
<td>49,009,694</td>
<td>49,009,694</td>
</tr>
<tr>
<td>GSEF-McLaughlin Fellowships (Fund 306084)</td>
<td>2,000,000</td>
<td>2,000,000</td>
<td>2,000,000</td>
</tr>
<tr>
<td></td>
<td>51,009,694</td>
<td>51,009,694</td>
<td>51,009,694</td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td>51,131,115</td>
<td>52,488,233</td>
<td>53,073,360</td>
</tr>
<tr>
<td><strong>LIABILITIES (Note 3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>731,309</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>NET ASSETS</strong></td>
<td>50,399,806</td>
<td>52,488,233</td>
<td>53,073,360</td>
</tr>
</tbody>
</table>

NOTES TO FINANCIAL STATEMENTS
NATURE OF FINANCIAL STATEMENTS
These financial reports are prepared on a cash basis. They do not provide for goods and services received but not paid for at the statement date nor do they provide for investment income earned but not received at the statement date.

1. CASH AND SHORT-TERM INVESTMENTS
Cash is held by the University of Toronto (the "University") on behalf of the Centre. Surplus cash is invested in the University's expendable funds investment pool ("EFIP") on a quarterly basis. The asset mix of this pool is disclosed in the University's audited financial statements available at www.finance.utoronto.ca/alerts/finreports.htm.

2. ENDOWMENTS, BOOK VALUE
Endowment funds are invested in the University's long-term capital appreciation pool ("LTCAP") in perpetuity for the purpose of funding specific activities of the Centre. The asset mix of this pool is disclosed in the University's audited financial statements available at www.finance.utoronto.ca/alerts/finreports.htm. The book value is the nominal amount of dollars contributed to the endowment fund recorded at the time of the contribution. The investment income generated from endowments must be used in accordance with various purposes established by donors.

3. LIABILITIES AND FINANCING
As a result of no endowment payout in April 2009, financing of $731,309 in 2008-09 was required. Financing repayment terms are to be decided.

4. INVESTMENT INCOME FROM ENDOWMENTS
The investment income from the LTCAP represents the University's payout per LTCAP unit. In 2009, as a reflection of poor investment market, no payout has been made from the endowment.

5. INVESTMENT INCOME FROM EXPENDABLE FUNDS
Investment income from expendable funds represents the return paid by the University on funds invested in EFIP. The average of return depends on the timing of investment into EFIP and liquidation from EFIP. The interest income paid in April of each year reflects the 90 day T-Bill rate for each quarter during the year.

6. ENDOWMENTS, MARKET VALUE
The market value is the number of units in the LTCAP multiplied by the market price of a unit on April 30 of each fiscal year.