UHN

THE RESEARCH HOSPITAL REPORT 2006

Inspire.
Innovate.
Impact.

University Health Network

UHN RESEARCH: SIZE AND SCOPE

Staff and Students

Senior Scientists	156
Scientists	51
Affiliate Scientists	49
CSRC/CRU Members	222
Total Researchers	**478**

Fellows	430
Graduate Students	368
Total Trainees	**798**

Technical and Support Staff	**1170**

Research Space	**637,000 sq ft**
Publications	**1284**
Total Funding	**$189,257,000**

Contents

The Research Hospital: *Inspire. Innovate. Impact.*
University Health Network Research Report 2006
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Some figures may be rounded and/or may include data not represented in institute data. Publications jointly authored by investigators at multiple UHN institutes are counted only once in UHN total.

Inspire.
Innovate.
Impact.

PHOTO: MASTERFILE ROYALTY-FREE

Inspiring questions.
Innovative solutions.
Impact on care.

These are the hallmarks of a research hospital—a unique institution combining excellence in clinical practice with innovation and discovery.

UHN is Canada's leading research hospital. Read on to find out why.

University Health Network International Research Advisory Board

UHN salutes outgoing IRAB Chair **Dr. Victor Ling (2002-2005).**

Philip Branton, Chair
Scientific Director,
Institute of Cancer Research, CIHR;
and Gilman Cheney Professor
of Biochemistry, Faculty of Medicine,
McGill University

Victor Dzau
Chancellor for Health Affairs,
Duke University;
President and CEO,
Duke University Health System;
James B. Duke Professor of Medicine and
Director of Molecular and
Genomic Vascular Biology,
Duke University

Ralph Steinman
Director,
Chris Browne
Center for Immunology and Immune Diseases;
Henry G. Kunkel Professor,
Rockefeller University;
Senior Physician,
Rockefeller University Hospital

Hans Wigzell
Professor of Microbiology
Tumor Biology Center
Karolinska Institute, Sweden

Inspire. Innovate. Impact.

University Health Network has global ***impact*** as its goal: to impact on understanding disease, to impact on patient care, and to impact on medical history.

At the basis of our drive to impact is ***innovation***: the ability to develop and use new tools to establish the basis for disease, and to translate research findings into data-driven treatment advances.

But fundamental to all of this are our patients, who ***inspire*** us: to prevent illness, to develop better treatments, and to improve their quality of life.

Our research programs are critical in this process. I invite you to read on to learn more.

Dr. Robert S. Bell
President and CEO

Advances in Research
Advances in Care

Fifteen years ago there were few successful ways to manage advanced Parkinson's disease; today there are two important surgical methods in wide use and showing great promise in reducing motor complications. Five years ago we hadn't heard of SARS; today we have a PCR-based test for it, and a potential treatment should it emerge again. Three years ago there was no treatment for advanced incurable prostate cancer; today men with this disease have novel options that can improve and extend life.

These three advances in care—and many others like them—were pioneered at UHN, where innovation and care are interrelated. Thus UHN researchers, hospital staff and patients are critical partners in our mission as a research hospital.

Another important set of partners are funding agencies and governments. There has been an extraordinary commitment on the part of federal and provincial governments which has translated into major increases in UHN annual research spending. In the last seven years our funding has increased from $77M to $189M and we have more than doubled our research space to 637,000 sq ft. UHN also values its relationships with private sector partners whose complementary skills and funding capacity help us to achieve our goals. Both groups recognize research hospitals as part of their investment in innovation and competitiveness agendas.

Philanthropy also plays a large part in putting the "research" into the research hospital. The three UHN Foundations—Princess Margaret Hospital Foundation, Toronto General & Western Hospital Foundation and the Arthritis & Autoimmunity Research Centre Foundation—help fund core research programs and provide the base upon which UHN investigators were able to raise sufficient funds to support a research team that now numbers more than 2400. This team, our scientists and clinician-scientists, our technical and support staff, and our students and fellows, are the most important contributors to UHN's drive to global impact in health care.

They, along with our colleagues at the University of Toronto and other Toronto Academic Health Science Network institutions, are co-creating the dynamic intellectual environment—the inspiration, innovation and impact—that is the defining characteristic of our research hospital.

Dr. Christopher J. Paige
Vice President, Research

2005/06 Year in

PMH Stem Cell Pioneers Recognized

(September 2005) Drs. James Till and Ernest McCulloch are honoured with the 2005 Albert Lasker Award for Basic Medical Research. Recognition continues in October, when they are awarded a Royal Society medal. Dr. McCulloch's fifty-year scientific career is celebrated in spring 2006 with a symposium featuring speakers from Stanford University, MD Anderson Cancer Centre and Dana Farber Cancer Institute.

New OCI Division Heads Named

(May 2005) In the first phase of OCI divisional re-structuring, five new divisions headed by Drs. Fei-Fei Liu, Linda Penn, Rob Rottapel, Brian Wilson and Mitsu Ikura are created. In early 2006 a new division headed by Dr. Gary Rodin is added.

Dr. Bob Bell Installed as UHN's New President & CEO

(June 2005) A clinician, researcher and administrator, Dr. Bell was formerly Chief Operating Officer, PMH, and Medical Director of the UHN Oncology Program.

First MaRS Moves

(August 2005) The first wave of UHN tenants—the UHN Research Business Development Office and UHN Global Ventures—moves into the new MaRS Centre Heritage Building.

Trainees Get CREdiT

(September 2005) UHN trainees are the focus as UHN creates its first ever Centre for Research Education and Training (CREdiT), a hub for institute-specific information about policies, lab training and funding as well as a link to the University of Toronto for trainee issues.

Research Day Marked

(October 2005) The UHN Research community gathers for UHN Research Day. Five hundred attendees enjoy poster sessions and a keynote address on regenerative medicine. Coincident with Research Day, the UHN International Research Advisory Board says farewell to outgoing Chair Dr. Victor Ling and welcomes incoming Chair Dr. Philip Branton and new members Drs. Victor Dzau and Ralph Steinman.

Review

New Corporate Tool Streamlines Information Access

(November 2005) UHN launches its new Research Intranet v 2.0, a newly revamped version developed in a collaborative project involving Research Support Services departments and the Research community.

Drug Discovery Goes International With New Collaboration

(November 2005) A new laboratory opened by UHN halfway around the world will accelerate a drug development program aimed at cancer, cardiovascular disease and other disorders. The Shanghai-Toronto Institute for Health Research is a joint initiative between UHN and two member institutes of the Chinese Academy of Sciences.

The same day, the UHN Research programs at TMDT are celebrated with a symposium attended by researchers and industry and with a keynote address by UHN President and CEO Dr. Bob Bell.

Research Tower Fills

(October 2005) A long-awaited milestone as UHN researchers reach new heights in the recently constructed laboratories of the Toronto Medical Discovery Tower (TMDT) at MaRS.

New Sponsored Award Announced

(March 2006) UHN welcomes support from Johnson & Johnson Corporate Office of Science and Technology in the form of a new Development Acceleration Award. Funded jointly with UHN Global Ventures, this award will provide up to $1M to accelerate the commercialization of discoveries in diagnostics, medical devices and new therapies by UHN researchers over three years.

$393M for Research in UHN Fundraising Campaign

(June 2006) The UHN Foundations announce the culmination of their ambitious five-year fundraising campaign. A record 71% of the $554M raised supports research programs at UHN.

Ontario Cancer Institute

Research Space	329,000 sq ft
Publications	518
Total External Funding	$83,385,000

Staff and Students	
Senior Scientists	45
Scientists	19
Affiliate Scientists	5
CRU Members	89
Total Researchers	158
Fellows	158
Graduate Students	159
Total Trainees	317
Technical and Support Staff	432

Research Council

DIRECTOR
Christopher Paige (current)
Benjamin Neel
(effective January 2007)

DIVISION HEADS
Applied Molecular Oncology
Fei-Fei Liu

Biophysics & Bioimaging
Brian Wilson

Cancer Genomics & Proteomics
Linda Penn

Psychosocial Oncology & Palliative Care
Gary Rodin

Signaling Biology
Mitsu Ikura

Stem Cells & Developmental Biology
Robert Rottapel

SITE REPRESENTATIVES
Mary Gospodarowicz
Armand Keating
Jonathan Irish
Malcolm Moore

CLINICAL RESEARCH UNIT
Padraig Warde

THE CAMPBELL FAMILY INSTITUTE FOR BREAST CANCER RESEARCH
Tak Mak

CENTRE FOR RESEARCH EDUCATION AND TRAINING
David Rose

OCI includes the Advanced Medical Discovery Institute and The Campbell Family Institute for Breast Cancer Research

Recent Findings

Cancer Metastasis: Molecule Critical

Drs. Tak Mak and Rama Khokha have discovered that the molecular switch RhoC is crucial for tumour metastasis—the spread of cancer from one part of the body to another.

The researchers showed that in mice that lack RhoC, cancer cells are less likely to spread, as they are smaller, less mobile and fewer in number than cancer cells from normal mice.

"Notably, the absence of RhoC in mice does not affect other normal cell functions or immune responses," says Dr. Mak. "This implies that the RhoC pathway may be a suitable target for cancer therapies."

Genes Dev. 2005 Sep 1;19(17):1974-9.
Supported by Canadian Institutes of Health Research and Amgen Inc.

Lung Cancer: Drug Prolongs Survival in International Study

A National Cancer Institute of Canada Clinical Trials Group study, led by Dr. Frances Shepherd in collaboration with Dr. Andrea Bezjak and 17 other researchers from eight different countries, showed that erlotinib—a drug that curbs cells from growing and multiplying—can prolong survival for some non-small cell lung cancer (NSCLC) patients who have been treated previously.

The study, evaluating 731 patients, showed

that there was a 42.5 percent improvement in the average survival of patients who were treated with erlotinib compared to patients who were given a placebo. The patients who received erlotinib also had an improved quality of life: their symptoms of pain, shortness of breath and cough were decreased, and their physical function was significantly better.

"Lung cancer is the leading cause of cancer death among men and women in North America," says Dr. Shepherd. "Once NSCLC patients have been given one or two rounds of chemotherapy their treatment options become limited. This drug now offers a new alternative for patients who previously had no other options for therapy."

Applied Molecular Oncology
Senior Scientists
Asa, Sylvia
Bristow, Robert
Ezzat, Shereen
Gallie, Brenda
Hedley, David
Hill, Richard
Liu, Fei-Fei
Moore, Malcolm
Squire, Jeremy
Tannock, Ian
Tsao, Ming-Sound
Scientists
Done, Susan
Liu, Geoffrey
Trudel, Suzanne
Affiliate Scientist
Kamel-Reid, Suzanne

Biophysics & Bioimaging
Senior Scientists
Chakrabartty, Avijit
Hunt, John
Jaffray, David
Sherar, Michael
Vitkin, Alex
Wilson, Brian
Scientists
Lilge, Lothar
Siewerdsen, Jeffrey

Cancer Genomics & Proteomics
Senior Scientists
Arrowsmith, Cheryl
Gariépy, Jean
Harrington, Lea
Pai, Emil
Penn, Linda
Privé, Gilbert
Rose, David
Scientists
Kislinger, Thomas
Raught, Brian
Schimmer, Aaron
Tillier, Elisabeth
Affiliate Scientist
Bradley, Grace

Epidemiology, Statistics & Behaviour
Senior Scientists
Boyd, Norman
Cunningham, Alastair
Minkin, Salomon
Till, James
Tritchler, David
Affiliate Scientist
Ritvo, Paul

Psychosocial Oncology & Palliative Care
Senior Scientists
Devins, Gerald
Gagliese, Lucia
Rodin, Gary
Scientists
Edelstein, Kim
Howell, Doris
Zimmermann, Camilla
Affiliate Scientists
Esplen, Mary Jane
Stewart, Donna

Signaling Biology
Senior Scientists
Ikura, Mitsu
Khokha, Rama
Manoukian, Armen
Ohashi, Pam
Scientists
Cheung, Peter
Hakem, Razqallah
Jurisica, Igor
Koch, Anne
Okada, Hitoshi
Stambolic, Vuk
Vaziri, Homayoun

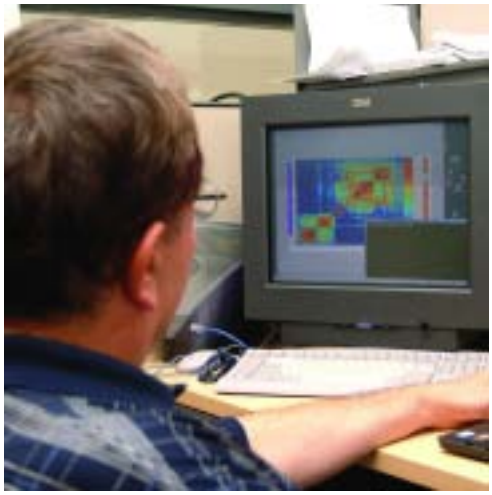
Stem Cell & Developmental Biology
Senior Scientists
Barber, Dwayne
Iscove, Norman
Mak, Tak
McCulloch, Ernest
Medin, Jeffrey
Messner, Hans
Minden, Mark
Paige, Christopher
Rottapel, Robert

Clinical Research Unit (CRU)
Bayley, Andrew
Bell, Bob
Bezjak, Andrea
Boerner, Scott
Brandwein, Joseph
Brierley, James
Brown, Dale
Catton, Charles
Catton, Pamela
Chang, Hong
Chapman, William
Chen, Christine
Chen, Xueyu
Chetty, Runjan
Cho, John
Chung, Peter
Crook, Juanita
Croul, Sidney
Crump, Michael
Cummings, Bernard
Darling, Gail
Dawson, Laura
Dodge, Jason
Easson, Alexandra
Elliott, Mary
Evans, Andrew
Feld, Ronald
Finelli, Antonio
Fleshner, Neil
Fyles, Anthony
Gallinger, Steven
Geddie, William
Ghazarian, Danny
Gospodarowicz, Mary
Greig, Paul
Gryfe, Robert
Hodgson, David
Irish, Jonathan
Jones, Jennifer
Kane, Gabrielle
Kim, John
Knox, Jennifer
Krzyzanowska, Monika
Laperriere, Normand
Leighl, Natasha
Levin, Wildred

N Engl J Med. 2005 Jul 14;353(2):123-32. Supported in part by a grant from OSI Pharmaceuticals to National Cancer Institute of Canada Clinical Trials Group

Heart Disease: Eliminating a Dynamic Duo May Provide New Treatment

Research by Zamaneh Kassiri, a postdoctoral fellow in Dr. Rama Khokha's lab, in collaboration with TGRI researchers Drs. Gavin Oudit, Peter Backx and Peter Liu, has provided some key clues into why the heart becomes enlarged in heart disease patients.



In a mouse model of heart failure, the researchers blocked two molecules—matrix metalloproteinases (which regulate the structures that support tissues) and TNF∝ (which is elevated in patients with heart disease)—completely preventing heart enlargement in these mice. These researchers further established a novel connection between the two pathways through a physiological inhibitor of metalloproteinase called TIMP-3.

"From previous research we knew that TNF∝ was involved in heart disease, but targeting it alone has been shown to be an ineffective treatment for patients," says Dr. Khokha. "By investigating other avenues, our findings have provided a basis for a new combination therapy for treating patients with heart disease—a leading cause of death in North America."

Circ Res. 2005 Aug 19; 97(4):380-90. Supported by Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, National Science Foundation and National Institutes of Health (US)

Cell Structure: Microtubule Machinery Unmasked

Using crystallography, NMR and mutational analysis, a team led by Dr. Mitsu Ikura and postdoctoral fellow Ikuko Hayashi has discovered the structural basis for microtubule activation by two plus-end tracking proteins—the carboxy-terminal dimerization domain of EB1 and the microtubule binding domain of a dynactin subunit p150Glued. Microtubules are structures that play an essential role in cytoskeleton remodeling such as chromosomal segregation events during mitosis. They have intrinsic polarity with plus-ends that grow quickly towards the outside edge of the cell and minus-ends that are anchored at the centrosome, the microtubule organizing centre.

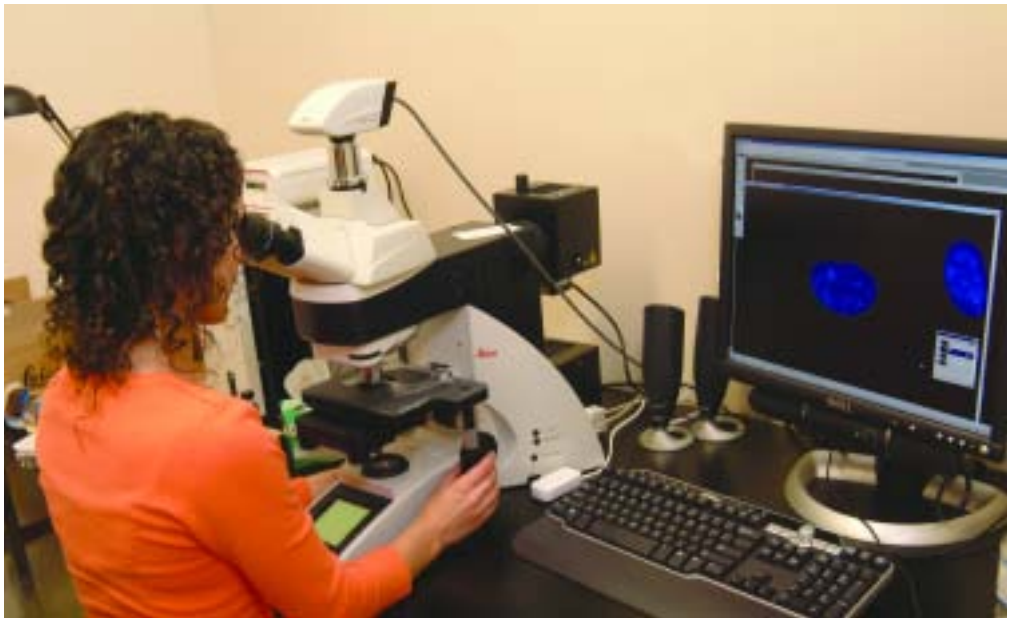
"We found that microtubule assembly is dependent on the interaction between the flexible tail region of EB1 and the binding sites of p150Glued, changing the way we model this process," says Dr. Ikura. "Now, we think that EB1 is the key regulator and that other proteins, such as p150Glued, are coming together with EB1 to activate this process."

Mol Cell. 2005 Aug 19;19(4):449-60. Supported by National Cancer Institute of Canada, Canadian Institutes of Health Research and Canada Research Chairs Program

Cancer Genetics: Breaking News at DNA Break Sites

UHN researchers Drs. Robert Bristow and Lothar Lilge, in collaboration with researchers in Toronto, the US and the UK, recently found evidence that damaged DNA in a cell binds a specific form of the tumour suppressor protein p53—a molecule essential to the cell's ability to sense and repair damaged DNA.

Using novel microscopy methods developed within UHN, the team recorded where p53 was found in the cell following different types of DNA damage. They discovered that only a



phosphorylated form of p53 (modified by the addition of phosphate groups) interacted with DNA repair proteins and accumulated at sites of DNA damage.

Mutation and altered phosphorylation of p53 proteins are common in cancer cells and can reduce the response to cancer therapy.

Damaged DNA binds to a specific form of the tumour suppressor molecule p53, opening new possibilities for cancer therapies

"Determining what specific forms of p53 direct DNA repair opens up new possibilities for cancer therapies that work by targeting the cancer cell's response to DNA damage," says Dr. Bristow.

Cancer Res. 2005 Dec 1;65(23):10810-21.

Supported by Canada Foundation for Innovation, Princess Margaret Hospital Foundation, National Cancer Institute of Canada, Canadian Institutes of Health Research, US Department of Energy and Cancer Research UK

Chemotherapy: Drug "Pressures" Tumours to Respond

A drug that disrupts blood vessels in tumours may improve the effectiveness of anti-cancer drugs according to a recent study by UHN researchers Drs. Richard Hill, Alex Vitkin and Michael Milosevic. The team investigated how the fluid pressure level in a tumour—known as the interstitial fluid pressure (IFP) level—was impacted by this drug in in vivo studies.

Tumours with high IFP levels have been linked to poor prognosis for cancer patients, perhaps because high pressure hinders therapeutic drugs from penetrating the tumour. The research team showed that a blood vessel disrupting drug, ZD6126, reduces the IFP level and kills almost all the tumour cells in the centre of the tumour but its efficacy depends on the IFP level.

"Our research gave the surprising result that even drugs which disrupt blood vessels within tumours have reduced efficacy when the tumour has a high IFP level. The results suggest that careful scheduling of the use of such drugs in conjunction with other anti-cancer drugs will be needed to obtain the maximum benefit in the treatment of cancer patients," says Dr. Hill.

Cancer Res. 2006 Feb 15;66(4):2074-80.

Supported by National Cancer Institute and Terry Fox Foundation

Lipa, Joan
Lipton, Jeffrey
Manchul, Lee
Mason, Warren
McCready, David
McLean, Linda
McLean, Michael
Menard, Cynthia
Mikhael, Joseph
Millar, Barbara-Ann
Miller, Naomi
Milosevic, Michael
Neligan, Peter
O'Sullivan, Brian
Oza, Amit
Paul, Narinder
Payne, David
Perez-Ordonez, Bayardo
Pierre, Andrew
Quirt, Ian
Reece, Donna
Ringash, Jolie
Rosen, Barry
Rotstein, Lorne
Shaw, Patricia
Shepherd, Frances
Simpson, Rand
Siu, Lillian
Sturgeon, Jeremy
Sun, Alexander
Sutherland, Robert
Swallow, Carol
Tkachuk, Douglas
Trachtenberg, John
Tsang, Richard
van der Kwast, Theodorus
Waldron, John
Warde, Padraig
Warr, David
Wei, Alice
Wells, Woodrow
Wong, Rebecca
Youngson, Bruce

Appointments as of June 30, 2006. Where members have more than one affiliation, only one is indicated; see www.uhnresearch.ca for full details

TORONTO GENERAL HOSPITAL

Toronto General Research Institute

Research Space	203,000 sq ft
Publications	571
Total External Funding	$45,618,000

Staff and Students	
Senior Scientists	66
Scientists	26
Affiliate Scientists	33
CSRC Members	69
Total Researchers	194
Fellows	152
Graduate Students	110
Total Trainees	262
Technical and Support Staff	424

Research Council

DIRECTOR
Richard Weisel

DIVISION HEADS
Behavioral Sciences & Health
Gary Rodin
Cell & Molecular Biology
Eleanor Fish
Clinical Decision-Making & Health Care
Claire Bombardier
Clinical Investigation & Human Physiology
Richard Weisel
Experimental Therapeutics
David Kelvin
Genomic Medicine
Katherine Siminovitch

CLINICAL STUDIES RESOURCE CENTRE
John Parker

VICE PRESIDENT, RESEARCH
Christopher J. Paige

CLINICAL REPRESENTATIVES
Carl Cardella
Christopher Feindel
Gary Levy
Valérie Sales

SITE REPRESENTATIVE
Catherine Zahn

EX OFFICIO MEMBERS
Vivek Rao (Medical Technology Innovation)
Thomas Waddell (Regenerative Medicine)
Ren-Ke Li (TGRI Space Committee)
Mingyao Liu (Graduate Education Committee, CREDIT)
Shaf Keshavjee (TGRI Appointments Committee)
Reginald Gorczynski (MBRC Facilities Management Committee)
Li Zhang (Flow Cytometry Facility)
Lowell Langille (Microscopy Facility)
George Fantus (Diabetes Program and the Human Physiology Division)

Recent Findings

Central Sleep Apnea and Heart Failure: Treatment Shows Improvement

A team of researchers led by Drs. Douglas Bradley, Alexander Logan and John Floras recently showed that treatment with continuous positive airway pressure (CPAP) in patients with both central sleep apnea and heart failure reduced the frequency of central sleep apnea episodes and improved other health factors.

Central sleep apnea is caused by disordered signaling in the brain, leading to interruptions in breathing during sleep. The disorder lowers quality of life and is linked to increased death rates in patients with chronic heart failure.

CPAP devices have benefited patients with obstructive sleep apnea, but this study, involving 258 patients and lasting from 1998 to 2004, was the first to prove a beneficial effect in patients with both central sleep apnea and heart failure. Patients treated with CPAP had greater alleviation of central sleep apnea, and greater improvements in cardiac function and exercise capacity, and greater reductions in sympathetic nervous system activity, than patients who did not receive CPAP.

"Surprisingly, the trial revealed that while

Behavioural Sciences & Health
Senior Scientists
Flint, Alastair
Kaplan, Allan
Katz, Joel
Olmsted, Marion
Rodin, Gary
Scientists
Carter, Jacqueline
Hamstra, Stanley
Jones, Jennifer
Nolan, Robert
Regehr, Glenn
Affiliate Scientists
Abbey, Susan
Baker, Brian
Davis, Caroline
de Groot, Janet
Grace, Sherry
Heslegrave, Ron
Hodges, Brian
Irvine, Jane
Katz, Mark
McVey, Gail
Reid, Graham
Ritvo, Paul
Robinson, Gail
Styra, Rima
Woodside, Blake

Cell & Molecular Biology
Senior Scientists
Backx, Peter
Berger, Stuart
Cardella, Carl
Cybulsky, Myron
Dick, John
Drucker, Daniel
Elsholtz, Harry
Fantus, George
Fish, Eleanor
Gorczynski, Reginald
Gotlieb, Avrum
Grant, David
Johnston, Wayne
Langille, Lowell
Levy, Gary
Liles, Conrad
Liu, Mingyao
Phillips, James
Rotstein, Ori
Rubin, Barry
Schuh, Andre
Whiteside, Catharine
Zacksenhaus, Eldad
Zhang, Li
Scientists
Cattral, Mark
Husain, Mansoor
Irwin, David
Jin, Tianru
Kotra, Lakshmi
Lam, Tony
Volchuk, Allen
Waddell, Thomas
Affiliate Scientists
Branch, Donald
Clark, David
Cole, Edward
Ojha, Matadial
Wen, Xiao-Yan
Wilson, Gregory

Clinical Decision-Making & Health Care
Senior Scientists
Bombardier, Claire
Eysenbach, Gunther

Jadad, Alex
Naglie, Gary
Scientists
Alibhai, Shabbir
Cheung, Angela
Krahn, Murray
Urbach, David
Wilson, Kumanan
CSRC Members
Daly, Paul
Jewett, Michael
Kapral, Moira
Singer, Lianne
Affiliate Scientists
Goel, Vivek
Lok, Charmaine
Tomlinson, George

Clinical Investigation & Human Physiology
Senior Scientists
Allard, Johane
Bradley, Douglas
Cattran, Daniel
Detsky, Allan
Downar, Eugene
Floras, John
Kucharczyk, Walter
Lewis, Gary
Logan, Alexander
Marshall, John
Miller, Judith
Olivieri, Nancy
Steiner, George
Walmsley, Sharon
Zamel, Noe
Scientists
Perkins, Bruce
Reilly, Raymond
Wong, Florence
CSRC Members
Bril, Vera
Cameron, Douglas
Chan, Charles
Chan, Christopher
Chauhan, Vijay
Cooper, Richard
Djaiani, George
Fedorko, Ludwik
Fisher, Joseph
Harris, Louise
Herridge, Margaret
Ing, Douglas
Jassal, Vanita
Johnston, Michael
Karkouti, Keyvan
Karski, Jacek
McCluskey, Stuart
McRae, Karen
Parker, John
Ross, Heather
Salit, Irving
Schwartz, Len
Seidelin, Peter
Sherman, Morris
Siu, Samuel
Slinger, Peter
Affiliate Scientists
Easty, Anthony
Raboud, Janet
Sawka, Anna

Experimental Therapeutics
Senior Scientists
Keating, Armand
Kelvin, David
Keshavjee, Shaf

CPAP improves several physiological outcomes for patients with both conditions, it does not significantly improve their long-term survival rates. This may be due to the relatively small number of patients involved that did not allow a difference in death rates to emerge," says Dr. Bradley.

"This points to the need for further research into appropriate treatment options for patients with both disorders. However, we did show that CPAP is effective in improving cardiovascular function and exercise capacity, which are important outcomes for heart failure patients."

N Engl J Med. 2005 Nov 10; 353(19): 2025-33.
Supported by Canadian Institutes of Health Research, Healthdyne, Respironics, ResMed, Tyco Healthcare, Canada Research Chair Program and Heart and Stroke Foundation of Ontario

Inflammatory Diseases: Missing Molecule Stops Signals in Their Tracks

Drs. Gregory Downey and Patrick Shannon led a team that discovered that the Meg2 protein has a crucial role in the early development of mice and the activation of white blood cells in adult mice. Meg2 is an enzyme that helps cells develop properly and communicate with each other by regulation secretion.

By transplanting embryonic liver stem cells lacking Meg2 into a strain of mice, the researchers discovered that Meg2 is important to the correct functioning of lymphocytes and platelets. Lymphocytes that lacked Meg2 could not properly respond to the immune system's activation signals.

"These findings could help to understand diseases related to defects in the activation of white blood cells during innate and inflammatory responses," says Dr. Downey. "Further research into Meg2's role in cell signalling could lead to treatments for inflammatory diseases."

J Exp Med. 2005 Dec 5;202(11):1587-97.
Supported by Canadian Institutes of Health Research, Ontario Thoracic Society and National Institutes of Health (US)

Anorexia Nervosa: Study Suggests Antidepressant Does Not Prevent Relapse

A recent study led by UHN's Dr. Allan S. Kaplan and Columbia University's Dr. B. Timothy Walsh found that taking the commonly prescribed antidepressant fluoxetine does not reduce the risk of relapse for patients with anorexia nervosa—an eating disorder where individuals have a distorted body image and are obsessed with maintaining a low, and often unhealthy, body weight.

Many patients with anorexia nervosa relapse following treatment. The research team—which included UHN's Drs. Marion Olmsted, Jacqueline Carter, Blake Woodside and Ms Wendi Rockert—examined the effects of taking the antidepressant fluoxetine on the time-to-relapse for patients with anorexia nervosa.

> "This finding calls into question the current practice of prescribing antidepressants for anorexia and stresses the need for alternative therapies including psychotherapy and innovative medications"

"Surprisingly, our study discovered no difference in time-to-relapse rates between patients who took fluoxetine and those who took the

placebo," says Dr. Kaplan. "This finding calls into question the current practice of prescribing antidepressants for this disease and stresses the need for alternative therapies including psychotherapy and innovative medications."

JAMA. 2006 Jun 14; 295(22):2605-12. Supported by National Institutes of Health (US)

Heart Failure: Enzymes at the "Heart" of Structural Changes

The discovery by UHN researchers Drs. Ren-Ke Li and Richard Weisel that a family of enzymes called the disintegrin metalloproteases is associated with structural changes in the heart could lead to new treatment options for congestive heart failure.

Says Dr. Li, "We discovered that the levels of disintegrin metalloproteases in heart tissues of congestive heart failure mirror the pattern of structural changes, indicating that there is a relationship of some type. There is a good possibility that these enzymes could prove to be targets for therapies to prevent congestive heart failure."

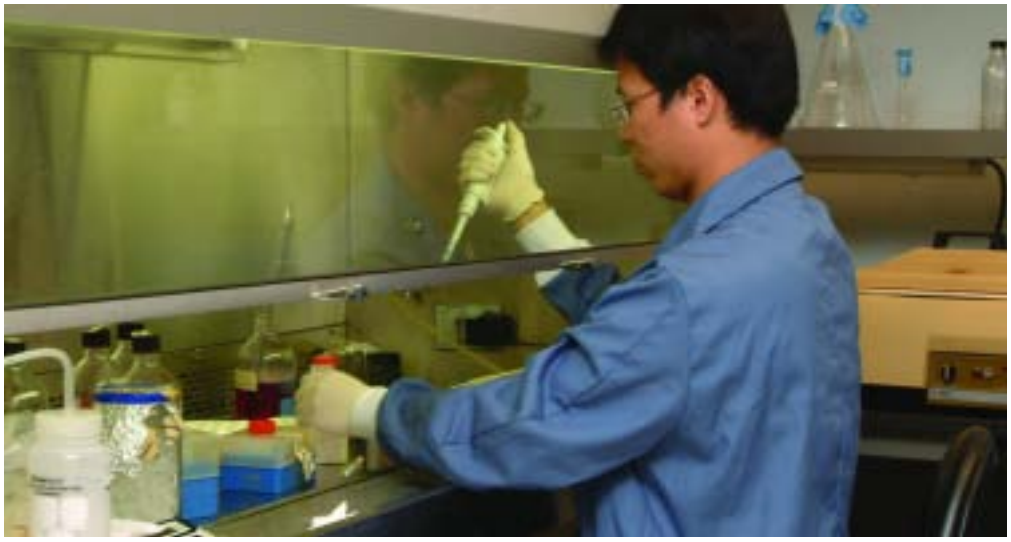
Over 200,000 Canadians are affected by congestive heart failure and it is the leading cause of hospital admission among the elderly.

Circulation. 2006 Jan 17;113(2):238-245. Supported by Canadian Institutes of Health Research and Heart and Stroke Foundation of Ontario

Coronary Artery Disease: Discovery "Stresses" New Direction for Blood Vessel Repair

A recent finding from the laboratory of UHN's Dr. Lowell Langille sheds light on blood vessel disorders, including the narrowing of blood vessels that occurs with coronary artery disease and when therapies to correct this disease fail.

Cells that line the interior of blood vessels are able to change their shape in response to the shear stress of blood flowing over their surfaces. As these cells—vascular endothelial cells—stretch and flatten in response to shear stress, the cell's internal machinery becomes organized in a single direction—a phenomenon called planar cell polarity. Blood vessel repair is influenced by the direction in which the cells are polarized. The team found that the molecule GSK-3ß is critical to this process.



"By manipulating the activity of GSK-3ß we have, for the first time, shown that a single cell type can reverse the direction of its polarity," says Dr. Langille. "This capacity to manipulate cellular polarity may lead to improvements in the treatment of blood vessel diseases, and other disorders, by enhancing the cell's own repair mechanisms."

Circ Res. 2006 Apr 14;98(7):939-46. Supported by Canadian Institutes of Health Research and Canadian Hypertension Society

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Reznick, Richard
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Ross, John
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Sutton, David
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Wilson, Stephanie
Wolman, Stephen
Yeo, Erik

Toronto Western Research Institute

Research Space	105,000 sq ft
Publications	326
Total External Funding	$23,679,000

Staff and Students	
Senior Scientists	46
Scientists	6
Affiliate Scientists	11
CSRC Members	65
Total Researchers	128
Fellows	95
Graduate Students	72
Total Trainees	167
Technical and Support Staff	216

Research Council

DIRECTOR
Peter St George-Hyslop

DIVISION HEADS
Applied & Interventional Research
Andres Lozano
Cell & Molecular Biology
Rod Bremner/Cathy Barr
(acting co-heads)
Outcomes & Population Health
Elizabeth Badley

CLINICAL STUDIES RESOURCE CENTRE
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VICE PRESIDENT, RESEARCH
Christopher J. Paige

CLINICAL REPRESENTATIVES
Michael Fehlings
Nizar Mahomed
Martin Steinbach

SITE REPRESENTATIVE
Catherine Zahn

CENTRE FOR RESEARCH EDUCATION AND TRAINING
Frances Skinner

Recent Findings

Alzheimer's Disease: Finding Offers New Therapeutic Targets

The discovery that a molecule—TMP21—is involved in the accumulation of a toxin in the brain could have a profound impact on the treatment of Alzheimer's disease (AD). AD is the most common cause of dementia in older people and an estimated 290,000 Canadians currently have the condition.

UHN's Dr. Peter St George-Hyslop led a research team that determined TMP21 is a key molecule in the biological processes that produce a toxic compound called amyloid beta. This toxin accumulates around nerve cells in the brain, causing them to die and the brain to degenerate.

Nature. 2006 Apr 27;440(7088):1208-12. Supported by Canadian Institutes of Health Research, Howard Hughes Medical Institute, Canadian Institutes of Health Research-Japan Science and Technology Trust, Alzheimer's Society of Ontario, Ontario Research & Development Challenge Fund and Canada Foundation for Innovation

Eye Development: Gene Bars Rod Development in the Retina

A team headed by UHN researcher Dr. Rod Bremner found that the gene Chx10 directly controls retinal cell development by discouraging cells from becoming 'rods'—a type of photoreceptor cell.

Rods and cones are the two types of retinal cells that capture and process light, helping us to see. A number of eye diseases are caused by the loss of rod cells, including retinitis pigmentosa, a progressive degenerative eye disease affecting one in 4000 people.

By manipulating Chx10 expression in the

Applied & Interventional Research

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Fehlings, Michael
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Skinner, Frances
Stanley, Elise
Tator, Charles
Tsui, Florence
Wan, Qi
Wither, Joan

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Chung, Frances
Davey, Roderick
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Escallon, Jaime
Etlin, David
Evans, Michael
Farb, Richard
Fung, Ken
Gentili, Fred
Graham, Brent
Hawa, Raed
Heathcote, Jenny
Iwanochko, Mark
Lam, Robert
Lam, Wai-Ching
Manninen, Pirjo
Massicotte, Eric
McCartney, Colin
McGuire, Glenn
McIntyre, Roger
Melvin, Kenneth
Miyasaki, Janis
Montanera, Walter
Moro, Elena
Nasmith, James
Oandasan, Ivy
Ogilvie, Richard
Ogilvie-Harris, Darrell
Panisko, Daniel
Parikh, Sagar
Peng, Philip
Radomski, Sidney
Rampersaud, Yoga
Rootman, David
Rosen, Cheryl
Saltzman-Benaiah, Jennifer
Seyone, Chanth
Shannon, Patrick
Shaw, James
Silver, Frank
Simons, Martin
Singer, Shaun
Slomovic, Allan
St George-Hyslop, Peter
Stanbrook, Matthew
Tarlo, Susan
Terbrugge, Karel
Tu, Karen
Tumber, Paul
von Schroeder, Herbert
Voon, Valerie
Wherrett, John
Willinsky, Robert
Wong, David
Wong, Jean
Yogendran, Suntheralingam
Yu, Eric

retina, the researchers discovered that the gene promotes progenitor cells to become bipolar neuron cells—the first in a series of nerve cells that transmit visual information to the brain—diverting them from becoming rods.

"In the early stage of retinal development, Chx10 is required for retinal cells to multiply. We found that, later on, retinal cells multiply even without Chx10. However, at this stage Chx10 is required to control what type of cells are produced. Thus Chx10 changes jobs in mid-career," explains Dr. Bremner, a member of UHN's Vision Science Research Program. "Our findings could help in discovering new treatments for eye disease, such as using stem cells to produce new rods."

PNAS. 2006 Mar 28;103(13):4988-93. Supported by Canadian Institutes of Health Research

Spinal Cord Injury: Adult Stem Cells Offer Growing Hope

The discovery that transplantation of adult brain stem cells into the sites of spinal cord injuries (SCI) in rats helps restore mobility could lead to improved treatment for SCI in humans. SCI can affect the body's ability to send signals to and from the brain, leading to paralysis.

In a study led by UHN's Dr. Michael Fehlings and postdoctoral fellow Soheila Karimi, the adult brain stem cells were able to multiply and replace missing spinal cord cells as well as partially regrow the missing myelin sheath—a coating around nerve cells that permits them to carry signals to and from the brain.

"The treatment actually improved movement and coordination in rats with SCI. Although further research is needed, our work confirms that adult brain stem cells show strong potential for treating SCI," says Dr. Fehlings.

J Neurosci. 2006 Mar 29;26(13):3377-3389. Supported by Canadian Institutes of Health Research, Stem Cell Network, Ontario Neurotrauma Foundation, Christopher Reeve Paralysis Foundation and Sam Schmidt Paralysis Foundation

Brain Injury: Killer Molecule Identified in Immune Cells

Dr. Lyanne Schlichter's lab has shown that a gate on the surface of microglia called Kv1.3 allows these immune cells of the brain to kill neurons following brain injury and in disease states.

Many central nervous system disorders involve inflammation, a process that is orchestrated by microglia. Thus there is considerable interest in anti-inflammatory strategies that target microglia. Microglia wreak their destruction

by producing oxygen free radicals—a dangerously reactive form of oxygen.

"This discovery offers a new strategy for controlling microglia and hence reducing neuronal death," says Dr. Schlichter. "We are now testing drugs that inhibit Kv1.3 in animal models for stroke and neurotrauma."

J Neurosci. 2005 Aug 3;25(31):7139-49.
Supported by Canadian Institutes of Health Research and Heart and Stroke Foundation of Canada

Understanding Brain Function: New Method Produces Active Neurotoxins

A new production method developed by Dr. Shuzo Sugita and colleagues that will enable neuroscientists to study the structure-function relationships of molecules involved in neurotransmission has already led to insights into the process of exocytosis.

Using a new prokaryotic expression system, Dr. Sugita succeeded in generating a series of active alpha-latrotoxins, a powerful neurotoxin isolated from black widow spider venom and studied for its ability to induce exocytosis in cells.

"The new method allowed us to truncate alpha-latrotoxin to test the effect of structural variants on calcium-dependent exocytosis," says Dr. Sugita. "Using it we showed that the toxin requires a free N-terminus and C-terminal ankyrin-like repeats to form pores, and that receptor binding alone was insufficient to stimulate calcium-dependent exocytosis. We anticipate this method will be useful in studying the mechanisms of other active molecules and possibly in developing new research or clinical tools."

J Neurosci. 2005 Nov 2;25(44):10188-97.
Supported by Canada Research Chairs Program, Canadian Institutes of Health Research and Premier's Research Excellence Program (Ontario)

Arthritis: Sleep Problems Linked to Joint Pain

Pain is a major cause of sleep difficulties in individuals with arthritis, according to a large-scale study that analyzed data from more than 130,000 people across Canada.

Little was previously known about the role of pain in the relationship between arthritis and sleep problems, leading UHN's Dr. Elizabeth Badley and her research team to analyze data from the 2000/2001 Canadian Community Health Survey (CCHS), which includes data on individuals representing all demographics of Canadian society.

"The rate of sleep problems for individuals with arthritis was found to be approximately double that of the general population," says Dr. Badley. "Most sleep problems in arthritis sufferers were due to pain," she continued. "Our results suggest that it is important for Canadians to manage pain appropriately."

Arthritis and insomnia symptoms are common disorders, afflicting approximately one in six and one in seven Canadians respectively. Sleep problems have far-reaching consequences that extend into other aspects of quality of life, including work and academic performance.

Arthritis Rheum. 2005 Dec 15; 53(6): 911-9.
Supported by Ontario Ministry of Health and Long Term Care

Analyzing data from a survey including 130,000 Canadians, the TWRI team found that the rate of sleep problems in individuals with arthritis was twice that of the general population

Opening the Doors to Discovery

UHN's New Research Tower Takes Off in 2005/06

It takes vision, teamwork, and resources to create a research tower, and 2005/06 saw the realization of 5 years of sustained effort. A critical piece of UHN's strategic plan, the creation of the Toronto Medical Discovery Tower (TMDT) located on College and Elizabeth streets, is the first major expansion of UHN research space in more than a decade.

This fifteen-floor, 400,000 sq ft building has been designed to house state-of-the-art biomedical research facilities including some of Toronto's most advanced programs in genomics, proteomics, integrative biology, infectious disease, image-guided therapy, structural biology, regenerative medicine, stem cell research and drug discovery.

UHN has been a key player in the TMDT development from day one. The MaRS complex is on lands formerly owned by UHN and contiguous to the UHN campus. UHN has signed a thirty-year lease on the tower space and, along with ABE, formed a joint venture group to design, build and operate the facility.

Thanks to donors and federal and provincial grants won by UHN research teams, a substantial propotion of the fit out costs are already paid for. Currently UHN labs occupy nine floors, with five additional floors rented by neighbouring hospitals and one public floor with retail tenants.

Tenants also enjoy the social aspects of the new building. "It is a great opportunity to be with a group of like-minded colleagues, and offers many new avenues for collaboration," says Dr. John Dick, TGRI Senior Scientist and part of the stem cell group on the eighth floor.

The impact on UHN overall has been significant. " We allocated space in TMDT using a 'programmatic' approach that has led to some very innovative groupings including new centres and programs," says Dr. Christopher J. Paige, Vice President, Research. "It's allowed us to hire new talent as well as provide better space utilization for our established research teams. And of course it's freed up space in other buildings to create and consolidate other programs—for example, the new translational research area in OCI/PMH."

UHN's expansion into the Toronto Medical Discovery Tower was made possible by Canada Foundation for Innovation and the Province of Ontario and generous donors: the Campbell Family; Weekend to End Breast Cancer Walkers for Breast Cancer Research; Robert & Cheryl McEwen; Sandra Rotman; and the WB Family Foundation. Ongoing support provided by the Princess Margaret Hospital Foundation, the Toronto General & Western Hospital Foundation and the Arthritis & Autoimmunity Research Centre Foundation.

Toronto Medical Discovery Tower: Timeline

May 2000
MaRS incorporates as a not-for-profit founded by leaders from academic/scientific and business sectors

Dec 2000
First monies received

June 2001
UHN Board approves agreement of sale of lands

December 2002
MaRS in partnership with UHN completes successful bond financing of $100M

January 2003
Construction on base building commences

October 2003
Concept design of interior finish

"It is a great opportunity to be with a group of like-minded colleagues, and offers many new avenues for collaboration."
Dr. John Dick

"It's allowed us to hire new talent as well as provide better space utilization for our established research teams."
Dr. Christopher J. Paige

May 2004
Concrete structure of base building complete

October 2004
Glass enclosure complete

December 2004
Detail design complete

January 2005
Base building systems complete

May 2005
MaRS Centre opens

August 2005
RBDO and GV move into MaRS Centre

September 2005
Official MaRS opening

October 2005
First UHN Research tenants move into TMDT; moves continue in late 2005 and early 2006.

November 2005
Launch of UHN programs in TMDT

"Magnetic North":

Attracting the World's Research Talent to Canada

Being a research hospital means hiring the best researchers and scientist-clinicians. In recent years UHN has attracted a substantial number of highly-qualified new investigators—many from leading institutes internationally.

"UHN is creating a magnetic attraction in health sciences, bringing some of the most promising and renowned scientists and clinicians from around the world to Toronto," said Dr. Bob Bell, President and CEO. "These leaders are choosing to come here largely because of the rich and supportive environment we've created through the success of our fundraising campaign and the deep pool of talent already in place."

"The ability of UHN to recruit talent of this kind underscores our role as a leading research hospital. But it really is a tribute to the excellence of our existing research staff," said Dr. Christopher J. Paige, Vice President, Research. "Their expertise and commitment—and the rising investment in Canada's human capital—fuels innovation that is leading to better understanding of disease."

UHN's precedent-setting fundraising campaign has enabled UHN to attract and retain leading talent, as well as purchase new capital equipment, increase research space including building the new Toronto Medical Discovery Tower at MaRS, and establish 40 new research chairs bringing the total to 60.

Launched in November 2002, the campaign had an initial goal of $400-million, ultimately raising a total of $554 million by June 2006 — a Canadian record for hospital fundraising.

> "UHN is creating a magnetic attraction in health sciences, bringing some of the most promising and renowned scientists and clinicians from around the world to Toronto."
> Dr. Bob Bell.

Rudiger von Harsdorf, MD
Charité University Hospitals, Germany
Holds the inaugural Robert McEwen Chair in Cardiac Regenerative Medicine at UHN

Tony Lam, PhD
Albert Einstein College of Medicine, New York
Appointed to the John Kitson McIvor (1915-1942) Chair in Diabetes Research

Thomas Kislinger, PhD
University of Toronto
Proteomics expert researching biomarkers for early detection of cancer

Benjamin Neel, MD, PhD
Harvard Medical School
Renowned cancer cell researcher recruited to UHN as Director of the Ontario Cancer Institute (OCI) at PMH

Lakshmi Kotra, PhD
University of Toronto
Medicinal chemist using 3-D computer modelling, biochemistry and structural biology to design new drugs

Brian Raught
Institute for Systems Biology, Seattle, Washington
Holds a Canada Research Chair in Proteomics and Molecular Medicine

Geoffrey Liu, MD
Harvard School of Public Health
Medical oncologist and holder of the Alan B. Brown Chair of Molecular Genomics of Lung Cancer at UHN

Conrad Liles, MD, PhD
University of Washington
Head of Infectious Diseases at the University of Toronto

Gordon Keller, MD, PhD
Mount Sinai Hospital, New York
A leading stem cell researcher recruited as the Founding Director of the McEwen Centre for Regenerative Medicine at UHN

Gang Zheng, PhD
University of Pennsylvania
Molecular imaging expert and recipient of the Tanenbaum/Brazilian Ball Chair in Prostate Cancer Research at UHN

New Directors Bring International Reputations

Two New Senior Research Leaders Appointed in 2005/06

> "This spirit of collegiality was among the most powerful incentives for me to take this position."
> DR. BENJAMIN NEEL

Director-Elect Brings Strong Credentials and Visionary Leadership to Leading Cancer Institute

American signalling biologist Dr. Benjamin Neel will join the Ontario Cancer Institute as its new director, an appointment announced in spring 2006.

Dr. Neel, who studies cell signalling by protein tyrosine phosphatases in mouse models, is recognized as a world leader in the field of cancer biology and signal transduction. He has received several awards, including the first American Association for Cancer Research Gertrude Elion Award and an NIH Merit Award.

Formerly a Professor at Harvard Medical School, he was also Director of the Cancer Biology Program and Deputy Director, Basic Research, Hematology/Oncology Division at the Beth Israel Deaconess Medical Center, a major Harvard teaching hospital.

"I have been extremely gratified by the many expressions of support that I have already received from OCI investigators," wrote Dr. Neel in a welcome email to OCI investigators. "This spirit of collegiality was among the most powerful incentives for me to take this position."

"Dr. Neel is a dynamic researcher and an inspirational leader. He combines outstanding scientific productivity with a strong advocacy for the ultimate clinical application of cancer research. He's a powerful addition to the internationally-recognized OCI team," says Dr. Christopher J. Paige, Vice President, Research, UHN.

"There is an enormous pool of talented regenerative medicine researchers in Toronto"
DR. GORDON KELLER

Inaugural Director Launches Regenerative Medicine Centre with Stem Cell Focus

Dr. Gordon M. Keller—a pioneer in embryonic stem cell research—has been named the first Director of the McEwen Centre for Regenerative Medicine (MCRM) at UHN.

"This is truly an exciting opportunity," says Dr. Keller. "There is an enormous pool of talented regenerative medicine researchers in Toronto. My goal as the Director of the MCRM is to create an environment that will foster cross-disciplinary interactions and encourage investigators to work synergistically towards the development of innovative regenerative medicine approaches."

Dr. Keller is past president of the International Society for Stem Cell Research and the immediate past director of the Black Family Stem Cell Institute at Mount Sinai School of Medicine (New York City). He was selected following an international search to further the McEwen Centre's strengths in the field of regenerative medicine.

"The recruitment of Dr. Keller is a tremendous coup for UHN and the McEwen Centre. His reputation for scientific excellence, his vision and his leadership will greatly contribute to the establishment of the MCRM as a Canadian hub for regenerative medicine," says Dr. Paige

The McEwen Centre for Regenerative Medicine

The McEwen Centre for Regenerative Medicine was established at UHN in 2003 with a generous donation from Robert and Cheryl McEwen. Its mission is to be a catalyst for regenerative medicine research by facilitating collaborations and promoting research and awareness to accelerate the development of better, more effective treatments for life-threatening conditions such as cancer, heart disease, diabetes, respiratory disease and spinal cord injury. The McEwen Centre launch is scheduled for October 25, 2006.

Hitting the Bull's Eye by Combining Imaging with Therapy

The UHN Guided Therapeutics (GTx) team recognizes that you can't hit a target days after you've seen it. They are working to accurately administer therapies in real time by combining them with medical imaging technologies.

PMH/OCI physicists Dr. David Jaffray, leader of the GTx initiative, and Dr. Jeffrey Siewerdsen are part of a team of researchers who were the first to test a new technology called the cone-beam CT—a sophisticated form of computed tomography, or CT, scanning that helps direct radiation treatment.

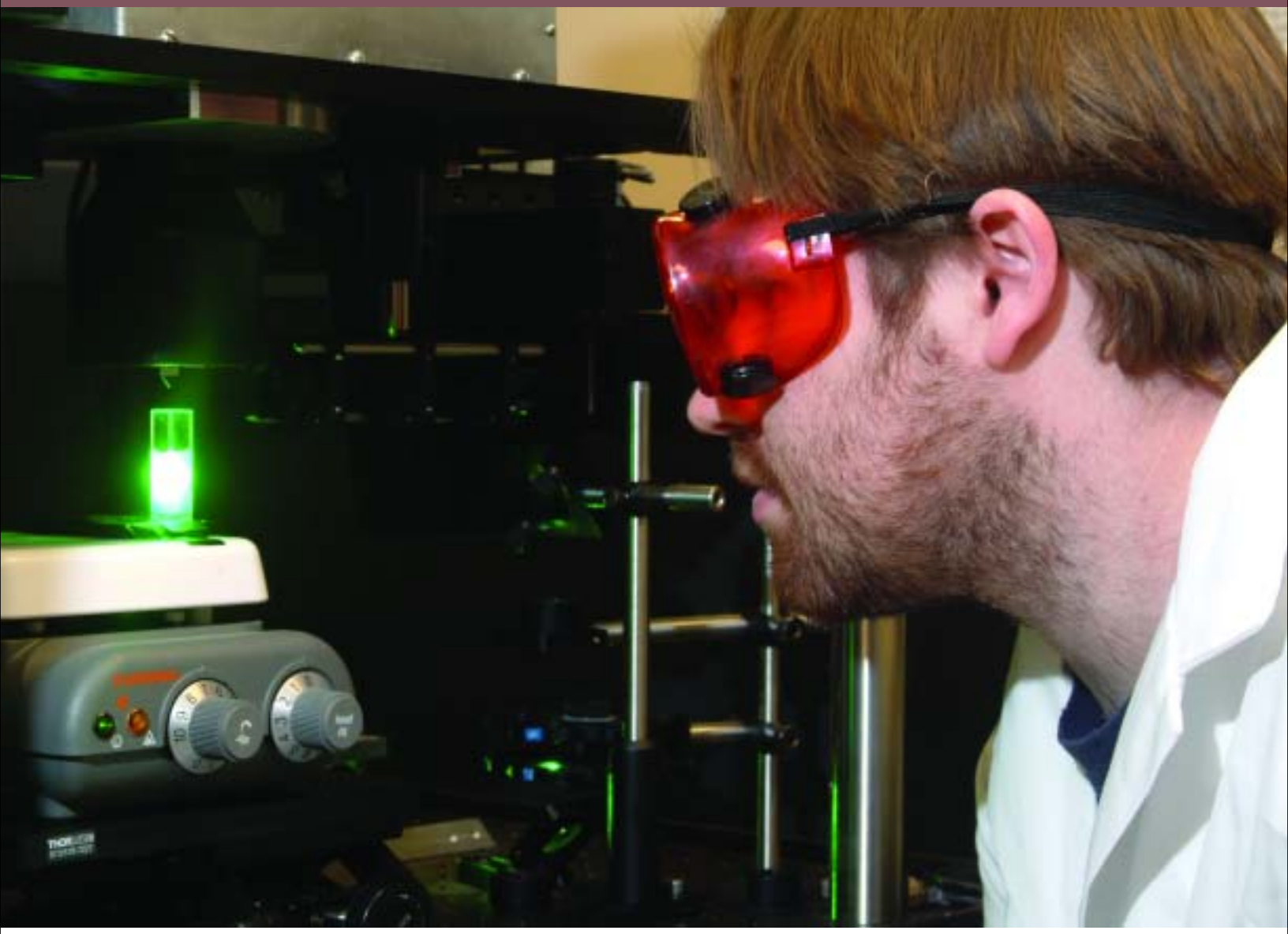
Explains Dr. Jaffray, "Before, radiation oncologists were dependent on imaging information from days ahead of the radiation treatment. This system uses minimal amounts of radiation to target and then irradiate in the same session."

A Common Desire for Increased Precision

Since this first step, the GTx initiative has grown out of a common desire to translate the use of guided therapeutics to other imaging technologies and clinical problems outside the realm of radiation therapy.

The physicists have teamed up with head and neck cancer surgeon Dr. Jonathan Irish (OCI/PMH) to combine the cone-beam CT imaging systems with a surgical tool called a C-arm that takes

> "It provides improved surgical confidence in a complicated terrain, such as the skull, making it extremely useful for assessing our work and for training new surgeons."
> Dr. Jonathan Irish



images during surgery, providing a map for the surgeon.

"It provides improved surgical confidence in a complicated terrain, such as the skull, making it extremely useful for assessing our work and for training new surgeons," says Dr. Irish.

Along the same lines, UHN's Drs. Walter Kucharczyk, John Trachtenberg, Masoom Haider and others are combining magnetic resonance (MR) imaging with robotic devices to create new ways to treat solid organ tumours, which are otherwise difficult to image.

UHN neuroscientists also make use of these technologies for their innovative work in spinal cord repair. "By combining MR and CT imaging to target delivery of our stem cell therapies to specific injury sites in the spinal cord, we hope to maximize the potential of these new therapies and improve results in the clinic," says Dr. Michael Fehlings (TWRI/TWH).

Healing with a "Toxic" Light

Also contributing to GTx's arsenal of imaging technologies are OCI/PMH's Drs. Brian Wilson and John Trachtenberg. Instead of radiation, they use lasers to image tumours in a less toxic way and are working towards combining their imaging capabilities with photodynamic therapies that make use of light-activated drugs.

"Bringing together all these groups, it's clear GTx will be a seed for the development of other new and interesting collaborative research projects in the future. Applying the research and technology know-how to the complex clinical problems that are part of UHN's clinical mandate helps keep us on the cutting edge as a research hospital," says Dr. Jaffray.

Drug Discovery Takes UHN on Global Journey

AS a research hospital UHN goes to the ends of the earth in order to understand how drugs work and get them into the hands of clinicians.

An important research focus at UHN is studying disease mechanisms to find treatments which can be moved quickly and safely through the drug discovery pipeline.

Partners in Discovery

One drug discovery initiative takes UHN to the other side of the world—specifically to Shanghai, home of the new Shanghai-Toronto Institute for Health Research. A partnership between UHN and two members of the Chinese Academy of Sciences—the Institute of Health Sciences and Shanghai Institute of Organic Chemistry—this facility is a research hub of biomarker and medicinal chemistry laboratories.

But sometimes UHN just goes across the street to find expertise in this area. New TGRI/TGH recruit Dr. Lakshmi Kotra, a former UT professor, is a medicinal chemist who collaborates with UHN structural biologist Dr. Emil Pai and infectious disease scientists Drs. Kevin Kain and Eleanor Fish, among others.

"By combining computer modelling with biochemistry and state-of-the-art strategies, we can design new drugs and then test them in the lab," says Dr. Kotra. "Right now we are working on developing new drugs against malaria, other infectious diseases and cancer."

Disruptive Behaviour Beneficial

A few blocks away at TWRI/TWH, Dr. Michael Tymianski has been exploring innovative approaches to developing drugs to curb the effects of stroke and head injuries.

"Stroke is a devastating neurological condition that results in a

Dr. Jingwu Zhang, Director, Institute for Health Science, Premier McGuinty and his wife Terri and Dr. Paige at the opening of the Shanghai-Toronto Institute for Health Research in Shanghai.

serious socioeconomic burden. Preventing brain damage in stroke is key to maintaining functions such as speech, balance, walking and one's independence. We're developing new molecules that disrupt certain interactions between brain proteins that cause stroke damage instead of attacking the brain molecules themselves, so as to prevent side effects," says Dr. Tymianski. "A compound called Tat-NR2B9c is particularly promising and is in early stage testing."

> By combining computer modelling with biochemistry and state-of-the-art strategies, we can design new drugs and then test them in the lab.
> Dr. Lakshmi Kotra

Unique Program Recognized Internationally

Moving these discoveries into testing after they have been proven safe and effective requires clinical trials expertise, which is well established over at PMH. Oncologists Drs. Malcolm Moore, Amit Oza and Lillian Siu are the driving forces behind the Bras Family Drug Development Program at OCI/PMH. This flagship program holds the only NIH/NCI contract for Phase II trials in Canada, giving PMH access to and funding for new investigational cancer drugs.

"This contract gives us an opportunity to provide Toronto cancer patients with access to treatments that would otherwise be unobtainable for them," explains Dr. Moore. It's research like this alongside the other elements of the drug discovery program that helps make UHN a great place for patients.

The Future is Now

for Regenerative Medicine Research at UHN

Imagine this scenario: A fifty-eight year old man presents with his first heart attack which injures the front of the heart. He is treated with clot-busting medication and he undergoes stent implantation into the artery supplying the damaged region.

However, the function of that part of his heart does not recover and he is at high risk to develop progressive heart failure which can be fatal. His own stem cells are harvested from his bone marrow (by needle puncture in the hip bone). The cells are grown in the laboratory, enhanced with specific genes and then administered to the patient. The cells help the heart recover and the man goes on to live a long and healthy life.

Sound like science fiction? It's not as far off as you might think, and UHN researchers are looking into this visionary future with an area of research called regenerative medicine, unique because it harnesses the body's own biology—cells, tissues and organs—to heal.

Predicting Lung Transplant Success

UHN is known for historical firsts in regenerative medicine dating back to before the field existed. A pair of important 'firsts' in tissue replacements took place at UHN: the successful single and double lung transplants performed by Dr. Joel Cooper in 1983 and 1986.

The tradition continues at UHN to this day. One of the biggest hurdles in transplantation is finding a compatible donor. TGRI/TGH researchers Drs. Shaf Keshavjee, Marc de Perrot, Mingyao Liu and Thomas Waddell are optimizing this process by improving donor lung selection and utilization before surgery.

"Recently we showed that by checking the gene expression of several immune molecules we can more accurately assess whether the transplantation will be a success. Using this information, hopefully, we can improve donor organ utilization in lung transplants," explains Dr. Keshavjee.

Harnessing the Body's Healing Power

UHN researchers are also investigating how to transplant healthy cells and tissues into patients. TGRI/TGH cardiovascular researchers Drs. Ren-Ke Li, Richard Weisel, Terrence Yau and Donald Mickle are trying to improve cell therapy by combining it with gene therapy—working towards the future scenario described above.

> Manipulating embryonic stem cells may give us the tools to manufacture large numbers of cells for potential therapies as well as for testing toxicity and efficacy of new drugs.
> Dr. Gordon Keller

"Cell survival is a major problem in cell therapy," says Dr. Li. "When we use gene therapy to add growth factors to the mix, there is increased blood vessel growth at the site of injury, which is key for increased cell survival."

Stem Cells: Raw Material for Transformation

Stem cells are an important part of many regenerative medicine strategies since they are the "chameleons" of the cell world: under the right circumstances a stem cell can develop into one of many different types of cells. In 1961, OCI/PMH researchers Drs. Ernest McCulloch and James Till were the first to prove the existence of bone marrow stem cells and colleague Dr. Norman Iscove has been an innovator in the field for more than thirty years. So you could say UHN's deep "roots" in the "stem" cell field continue to "flower"!

Many UHN researchers are following in their footsteps. Dr. Gordon Keller, the newly recruited Director of the McEwen Centre for Regenerative Medicine, is investigating how embryonic stem cells mature into different cell types. "Manipulating embryonic stem cells may give us the tools to manufacture large numbers of cells for potential therapies as well as for testing toxicity and efficacy of new drugs," Dr. Keller explains.

Another stem cell leader at UHN is Dr. John Dick, who has been at the cutting edge of the re-emerging cancer stem cell field. His lab was the first to pinpoint cancer stem cells—cells that have the potential to trigger cancer—from tumours and show that they could initiate leukemia in animal models.

It's often said that today's science is tomorrow's medicine: that today's discoveries in the lab will, in the future, be available in the clinic and pharmacy as treatment options. As a research hospital UHN is making the inventive concepts a reality and our patients will clearly benefit.

Research Funding Revenues

UHN RESEARCH CORE FUNDING
(thousands of dollars)

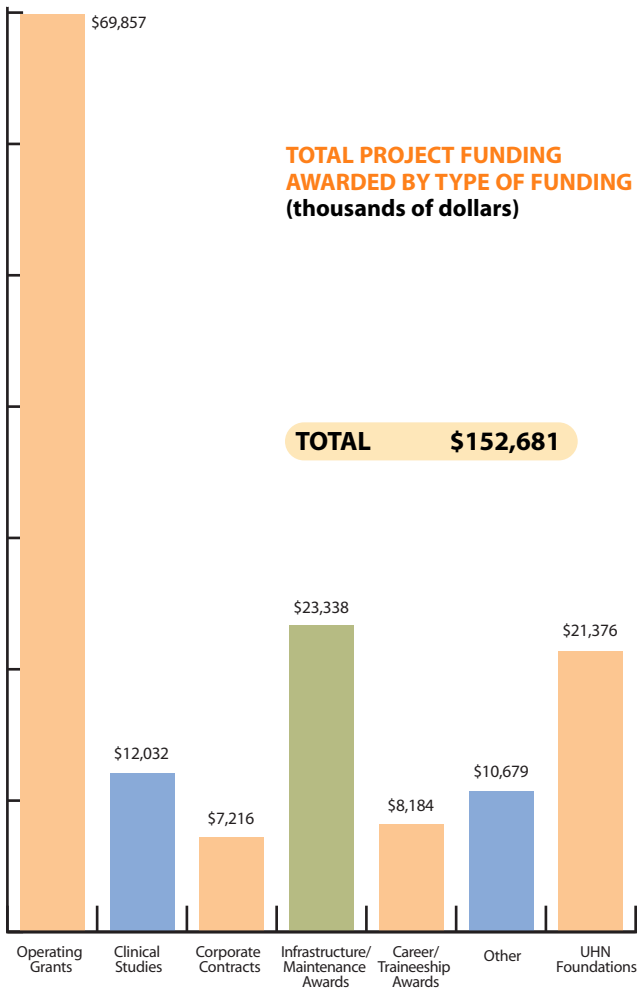
Princess Margaret Hospital Foundation	$12,986
Toronto General & Western Hospital Foundation	$2,500
Arthritis & Autoimmunity Research Centre Foundation	$1,250
Ministry of Health & Long Term Care	$2,816
Recoveries	$6,496
Investment income	$4,441
Includes $900k interest provided by the Toronto General & Western Hospital Foundation	
Other	$6,087
TOTAL	**$36,576**

MAJOR SOURCES OF EXTERNAL FUNDING
(thousands of dollars)

Canadian Institutes of Health Research	$23,127
Canada Foundation for Innovation	$11,716
Ontario Innovation Trust	$9,086
National Cancer Institute of Canada	$8,316
Ontario R&D Challenge Fund	$5,582
National Institutes of Health (US)	$5,200
Heart and Stroke Foundations	$4,236
Ontario Cancer Research Network	$3,498
Ontario Genomics Institute	$2,594
Canada Research Chairs Program	$2,173

TOTAL PROJECT FUNDING AWARDED BY TYPE OF FUNDING
(thousands of dollars)

TOTAL $152,681



All figures represent fiscal year 2005/06 and include Ontario Cancer Institute (Princess Margaret Hospital); Toronto General Research Institute (Toronto General Hospital); and Toronto Western Research Institute (Toronto Western Hospital). Figures are rounded.

These figures have been provided by UHN Research Financial Services and Research Grant and Contract Services. These figures have not been audited. However, they have been included in the overall UHN statements and, as a result, have been subjected to audit procedures deemed appropriate by auditors in order to determine their overall reasonableness.

External Agencies Funding UHN Research

Abbott Laboratories
Aegera Therapeutics
Agouron Pharma
American Heart Association
Alberta Heritage Foundation
Allergan
Allos Therapeutics
Alzheimer Society of Canada
Alzheimer's Disease and Related Disorders Association
American Association for Thoracic Surgery
American Association of Neurological Surgeons and Congress of Neurological Surgeons
American Cytoscope Makers
American Digestive Health Foundation
Amgen
Amyotrophic Lateral Sclerosis Society of Canada
AnorMED
ArgiNOx Pharmaceuticals
Argos Therapeutics
Arius Research
Arthritis & Autoimmunity Research Centre Foundation
Arthritis Community Research & Evaluation Unit
Arthritis Society
Assoc. of Med Micobiological & Infectious Disease Canada
Association Française contre les Myopathies
Astellas Pharma Canada
Astra Pharma
AstraZeneca Canada
Aventis Pasteur Limited
Banting and Best Diabetes Centre
Bausch and Lomb
Baxter Healthcare Corporation
Beckman Coulter
Berlex Canada
Berlex Laboratories
BioAxone, Stryker Biotech
Biogen IDEC
Biosite
Biotrofix
Boehringer Ingelheim
Boston Scientific
Bristol-Myers Squibb
Canada Foundation for Innovation
Canada Health Infoway
Canadian Anesthesiologists Society
Canadian Arthritis Network
Canadian Breast Cancer Foundation
Canadian Breast Cancer Research Alliance
Canadian Breast Cancer Research Initiative
Canadian Coordinating Office for Health Technology Assessment
Canadian Cystic Fibrosis Foundation
Canadian Diabetes Association
Canadian Foundation for Aids Research
Canadian Health Services Research Foundation
Canadian Institutes of Health Research
Canadian Society of Atherosclerosis, Thrombosis and Vascular Biology
Canadian Space Agency
Canadian Urologic Oncology Group
Canadian Urology Research Consortium
Cancer Care Ontario
Cancer Research Institute
Cancer Research Society
Celgene Corporation
Cell Genesys
Cervical Spine Research Society
Change Foundation
Christopher Reeve Paralysis Foundation
CLP Research
Coley Pharmaceutical Group
Cyanamid
Delex Therapeutics
Department of Justice Canada
Dompe S.p.A.
Eastman Kodak
ECHO Research
Edwards Lifesciences
EISAI Medical Research
Elekta Instrument AB
Elekta Oncology Systems
Eli Lilly
Eli Lilly Canada
Enzon Pharmaceuticals
Epilepsy Canada
Expression Diagnostics
Eye Research Institute of Canada
Fisher Scientific
Foundation Fighting Blindness
Foundation for Lung Cancer
Fragile X Research Foundation of Canada
Gemin X Biotechnologies
Genome Canada
Genzyme
Gilead Sciences
GlaxoSmithKline
GTx
Guidant/Advanced Cardiovascular Systems
Health Canada
Heart and Stroke Foundation of Canada
Heart and Stroke Foundation of Ontario
Hoffman-La Roche
Hoosier Oncology Group
Howard Hughes Medical Institute
Human Genome Sciences
IBM
Idenix Pharmaceuticals
Ilex Oncology
Immunex Corporation
In Motion Investments Ltd
International Society for Clinical Densitometry
James S. McDonnell Foundation
Janssen-Ortho
Johnson & Johnson
Juvenile Diabetes Foundation
Kidney Foundation of Canada
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Leukemia & Lymphoma Society
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Leukemia Research Fund of Canada
Light Sciences Corporation
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Lundbeck
Lupus Clinical Trials Consortium
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Medicure
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Metrigenix
Michael J. Fox Foundation for Parkinson's Research
Miikana Therapeutics
Ministry of Health and Long Term Care
Multiple Myeloma Research Foundation
Muscular Dystrophy Association of Canada
National Alliance for Research on Schizophrenia and Depression
National Cancer Institute of Canada
National Colorectal Cancer Campaign
National Institutes of Health
Natural Sciences and Engineering Research Council
NCE: Canadian Institute for Photonics Innovation
NCE: Canadian Network for Improved Outcomes in SLE
NCE: Canadian Network for Vaccines and Immunotherapeutics
NCE: Canadian Stroke Network
NCE: PENCE
NCE: Photonics Research Ontario
NCE: Stem Cell Network
NCE: Arthritis Center of Excellence
NMT Medical
Northern Therapeutics
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Novartis Pharma AG
Novartis Pharmaceuticals Canada
Novo Nordisk A/S
NPS Allelix
Nyocemed Amersham
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Ontario Clinical Oncology Group
Ontario Genomics Institute
Ontario Health Institute Research Corporation
Ontario HIV Treatment Network
Ontario Innovation Trust
Ontario Mental Health Foundation
Ontario Neurotrauma Foundation
Ontario R&D Challenge Fund
Ontario Thoracic Society
Ontario Women's Health Council
Ortho Biotech
Parexel
Parkinson Society Canada
Parkinson Study Group
PDL BioPharma
Pediatric Oncology Group of Ontario
Peninsula Pharmaceuticals
Pfizer Canada
Pharmacia
Pharmacyclics
Physicians' Research and Education Network
Physicians' Services Incorporated Foundation
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PMH Foundation
Possis Medical
Photonics Research Ontario
Procter & Gamble/Alexion Pharmaceuticals
Prostate Cancer Research Foundation of Canada
Purdue-Pharma
R. Samuel McLaughlin Foundation
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SAIC Frederick
Sangamo Biosciences
Sanofi -Synthelabo Canada
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Schering Canada
Senesco Technologies
Sepsis
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Snell Medical Communication
Society of Chinese Bio-Scientists in America
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Spiration
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SuperGen
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Tourette Syndrome Association
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