DRIVING HEALTH INNOVATION

Research Report 2010

University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

University Health Network (UHN) consists of Toronto General, Toronto Western and Princess Margaret Hospitals. The scope of research and complexity of cases at University Health Network have made it a national and international source for discovery, education and patient care. It has the largest hospital-based research program in Canada, with major research in transplantation, cardiology, neurosciences, oncology, surgical innovation, infectious diseases and genomic medicine. University Health Network is a research hospital affiliated with the University of Toronto.

University Health Network Research Report 2010 / Published by the Office of the Vice President, Research, UHN / Produced by Research Communications, UHN / Data provided by Research Support Services, UHN. Respective data types are accurate as of December 31, 2009 (publication count year-end), March 31, 2010 (fiscal year-end) and June 30, 2010 (academic year-end) / Graphic design by Clear Space Design & Communications Inc. / Photographs courtesy of Yuan Lew, UHN and various sources including John Loper, Woodbine Entertainment Group and AARCF, Ride to Conquer Cancer and Sandler Photography. Some figures may be rounded and/or may include data not represented in institute-specific data. Publications jointly authored by investigators at multiple UHN institutes are counted once in UHN Research total.

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UHN Research: A Snapshot

Senior Scientists	150
Scientists	44
Affiliate Scientists	74
Assistant Scientists	4
CSRC/CRU Members	263
TOTAL RESEARCHERS	**535**
Fellows	435
Graduate Students	469
TOTAL TRAINEES	**904**
TECHNICAL AND SUPPORT STAFF	**1,637**
RESEARCH SPACE	**745,000 SQ FT**
PUBLICATIONS	**1,781**
TOTAL FUNDING	**$267,655,000**

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WELCOME

Quality patient care is enriched by innovative research—something we are proud to embody at UHN.

Every day, our scientists search for solutions to medical mysteries and, in doing so, push the boundaries of our knowledge of human health and disease. These scientific discoveries pave the way for novel technologies and enhanced therapeutics, which ultimately allow for improved care for our patients, our community and the world. Please read on to learn more about some of the fascinating discoveries that are enabled at UHN every day and are set to help change our future.

Robert S. Bell

Christopher J. Paige, PhD
Vice President, Research
University Health Network

Some of the best medical researchers in the world work at UHN. They seek to understand health at the cellular, biochemical and genetic level to prevent diseases from arising, as well as to offer targets for potential treatment.

They invent better tools to diagnose disease and monitor response to therapeutic interventions. They study how best to deliver treatment and improve both outcomes and quality of life. And they study how the health care system itself works, hoping to make it more efficient and effective. They work at UHN because at UHN they have top flight laboratory facilities, the latest research equipment, a large and stimulating biomedical research environment anchored by the University of Toronto and the affiliated research hospitals, excellent trainees, supportive fundraising foundations, leading hospitals treating the most challenging medical problems and, most of all, colleagues whose research accomplishments and international stature match their own. Having a large and diversified research staff offers the opportunity for UHN researchers to form multidisciplinary teams—teams which have the diversity of expertise to tackle the toughest research questions. In parallel, UHN preserves an environment that also fosters individual creativity allowing researchers the freedom to follow their own inventive instincts, a well-proven approach that leads to major medical breakthroughs.

Sustained research success requires that all of these individual elements flourish as part of an integrated program, thus building a vibrant community of scholarship with a common mission of improving health. However, sustained positive impact on health requires even more: the integration of research and health care. It requires that all members of the hospital community including health care professionals, administrators, researchers, support staff and patients and their families share a common commitment to working together to improve health. At UHN, these elements coalesce into what we have termed the *Creative Domain.* It is one of UHN's five strategic planning domains–*We, Caring, Accountable, Creative,* and *Academic*. Over the last year, as we have worked to update the Creative Domain's strategic plan, it is exciting to see the Research Hospital of the Future emerge. We invite you to share in this excitement and to join us in the further development and implementation of these plans over the next few years.

Christopher J. Paige

YEAR IN REVIEW

OGI INVESTS IN UHN-SICKKIDS FINDING

The Ontario Genomics Institute (OGI)—through the Pre-Commercialization Business Development Fund—has invested in a research project led by UHN's Drs. John Dick and Jean Wang and SickKids investigator Dr. Jayne Danska.

The team is working towards improving patient outcomes for hematopoietic stem cell (HSC) transplants, commonly referred to as bone marrow transplants. Together, they have identified variants in a protein called SIRPalpha that contribute to the interaction between transplanted blood stem cells and the recipient's bone marrow environment. Based on these findings, the team has begun a retrospective genetic analysis to identify an association between SIRPalpha genetic variants and the outcomes of HSC transplants in 200 pairs of donors and recipients. Using the panel of new genetic tests that they have established, Dr. Dick and his colleagues will continue to develop and validate new prognostic genetic tests in HSC transplant donors and recipients, and will evaluate how accurately newly identified protein variations are able to predict patient outcomes.

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UT-UHN TEAM AWARDED CFI FUNDS

Dr. Herbert Gaisano—with colleagues at Toronto General and Toronto Western Hospitals, Mount Sinai Hospital and the Faculty of Medicine's Department of Nutritional Sciences group—and lead investigators from the University of Toronto's (UT) Gastrointestinal Research Group, were awarded $5.4M in new funding from the Canada Foundation for Innovation towards the "Centre for Research on Diet, Digestive Tract and Disease" or the "3D Centre".

Dr. Gaisano will lead the Molecular, Cellular & Whole Animal Research Core Facility that will oversee the development of animal and cellular disease models. The mechanistic studies performed using these disease models will provide improved information for designing human clinical studies. The team will use the awarded infrastructure funds to advance state-of-the-art imaging and high-throughput technologies.

APPOINTMENT OF THE NEW RESEARCH ETHICS BOARD CO-CHAIRS

On April 1, 2010, three members of the UHN Research community took on new Co-Chair appointments with the Research Ethics Board.

Dr. Karen McRae, a long-time member and Vice-Chair of Board A, and an Associate Professor in the Department of Anaesthesia, became Co-Chair of the Multidisciplinary Board. Dr. Ronald Feld became Acting Co-Chair of the Oncology Board, giving Dr. Jack Holland—a pediatric endocrinologist with extensive experience in research ethics at the local, national and international levels—time to move his academic base from Hamilton to Toronto. Dr. Anna Gagliardi, who is a Canadian Institutes of Health Research New Investigator in Knowledge Translation and a member of the Clinical Decision-Making and Health Care Division of the Toronto General Research Institute, accepted the Co-Chair/Minimal Risk position.

(L-R) TDC Senior Business Development Officer Mark Taylor presents Drs. Mohammad Islam and Michael Sharpe with the Inventor of the Year Award

INVENTOR OF THE YEAR ANNOUNCED

UHN's 2009 Inventor of the Year Award was presented to Drs. Mohammad Islam and Michael Sharpe of Princess Margaret Hospital's Radiation Medicine Program.

The Inventor of the Year Award recognizes the UHN inventor or team best exemplifying the spirit of inventiveness, entrepreneurial culture and commercialization. It is sponsored by UHN's Technology Development & Commercialization (TDC) Office. Drs. Islam and Sharpe have added 16 inventions to their portfolio since 2004, half of which are from last year alone. Building on a platform of radiation safety and quality assurance technologies, 40 percent of their inventions are already licensed to Ontario and multinational companies through UHN's TDC Office. Their web-based treatment plan approval software has been licensed to Philips and is in use in 20 hospitals worldwide, while a patient immobilization device and an image-guided radiation therapy phantom have been licensed to Bionix and Modus Medical Devices, respectively.

MCLAUGHLIN-ROTMAN CENTRE UP FOR GRAND CHALLENGE

UHN's McLaughlin-Rotman Centre for Global Health will be the host organization of Grand Challenges Canada, a national initiative helping to redefine Canada's role in solving persistent health challenges facing poor countries.

Led by a world-class Scientific Advisory Board and Board of Directors—including Chairman Joseph L. Rotman and UHN's Dr. Peter Singer—and working with the International Development Research Centre and the Canadian Institutes of Health Research, the group will identify challenges that, if solved, will significantly improve global health. The goal of the organization is to improve the diagnosis of diseases afflicting millions in the developing world by bringing diagnostic tools to the patient's bedside. The Government of Canada has committed $225M over five years to the Development Innovation Fund, to be delivered by Grand Challenges Canada, to support this goal.

Trainees view poster presentations at TWRI Research Day

10TH ANNUAL TWRI RESEARCH DAY—A BIG SUCCESS!

May 12, 2010 marked an important milestone as the Toronto Western Research Institute (TWRI) community came together to celebrate a decade of achievements within the Research Institute and the Toronto Western Hospital.

This year, there were a large number of outstanding oral and poster presentations representing a wide spectrum of interests and disciplines at TWRI. Graduate and post-graduate trainees presented their accomplishments, describing the basic and clinical research that is performed across TWRI divisions. In addition to the presentations, keynote speaker Dr. Ann Graybiel from the McGovern Institute for Brain Research at the Massachusetts Institute of Technology gave a fascinating lecture entitled "Learning and Memory Mechanisms of the Basal Ganglia".

ELLICSR OPENS ITS DOORS

The Electronic Living Laboratory for Interdisciplinary Cancer Survivorship Research (ELLICSR) celebrated its official opening on June 4, 2010, an event that was attended by UHN and surrounding community members.

The 12,000 square foot research centre is located at the Toronto General Hospital and is led by Dr. Pamela Catton, Medical Director of the Cancer Survivorship Program, and Founding Director of ELLICSR. This unique facility was made possible by grants from the Canada Foundation for Innovation ($1.2M) and the Ministry of Research and Innovation ($1.2M), along with additional support that brought the total project budget to $3.7M. The goal of ELLICSR is to improve the cancer experience by exploring novel ways to learn from survivors, to develop new survivorship communities and to study how cancer survivors can be engaged, empowered and active in adopting healthier behaviours that minimize the negative impact of cancer and its treatment. It is a spacious community centre with teaching and self-management areas for patients and survivors and is fully wired to support virtual programming, community connections and global collaborations.

Dr. Pamela Catton speaks at the opening of ELLICSR

HONOUR ROLL

Dr. John Dick
Clifford Prize for Cancer Research, Fourth Barossa Meeting on Cell Signalling in Cancer and Development; Canada Research Chair in Stem Cell Biology (Tier I)

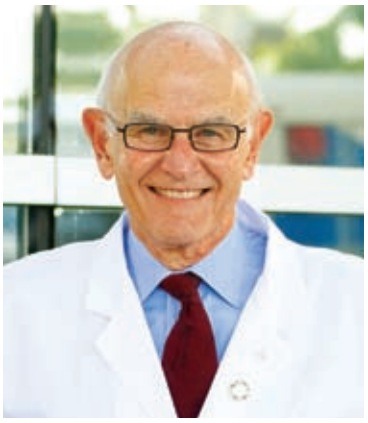
Dr. Michael Fehlings
Leon Wiltse Award, North American Spine Society; Olivecrona Medal, Karolinska Institutet

Dr. Tony Lam
Canada Research Chair in Obesity (Tier II)

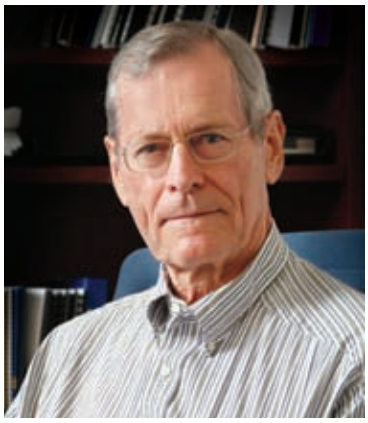
Dr. Nizar Mahomed
Top Canadian Achievements in Health Research Award, Canadian Institutes of Health Research - Canadian Medical Association Journal

Dr. Nancy Olivieri
Scientific Freedom and Responsibility Award, American Association for the Advancement of Science

Dr. Christopher Paige
Bernhard Cinader Award, Canadian Society for Immunology

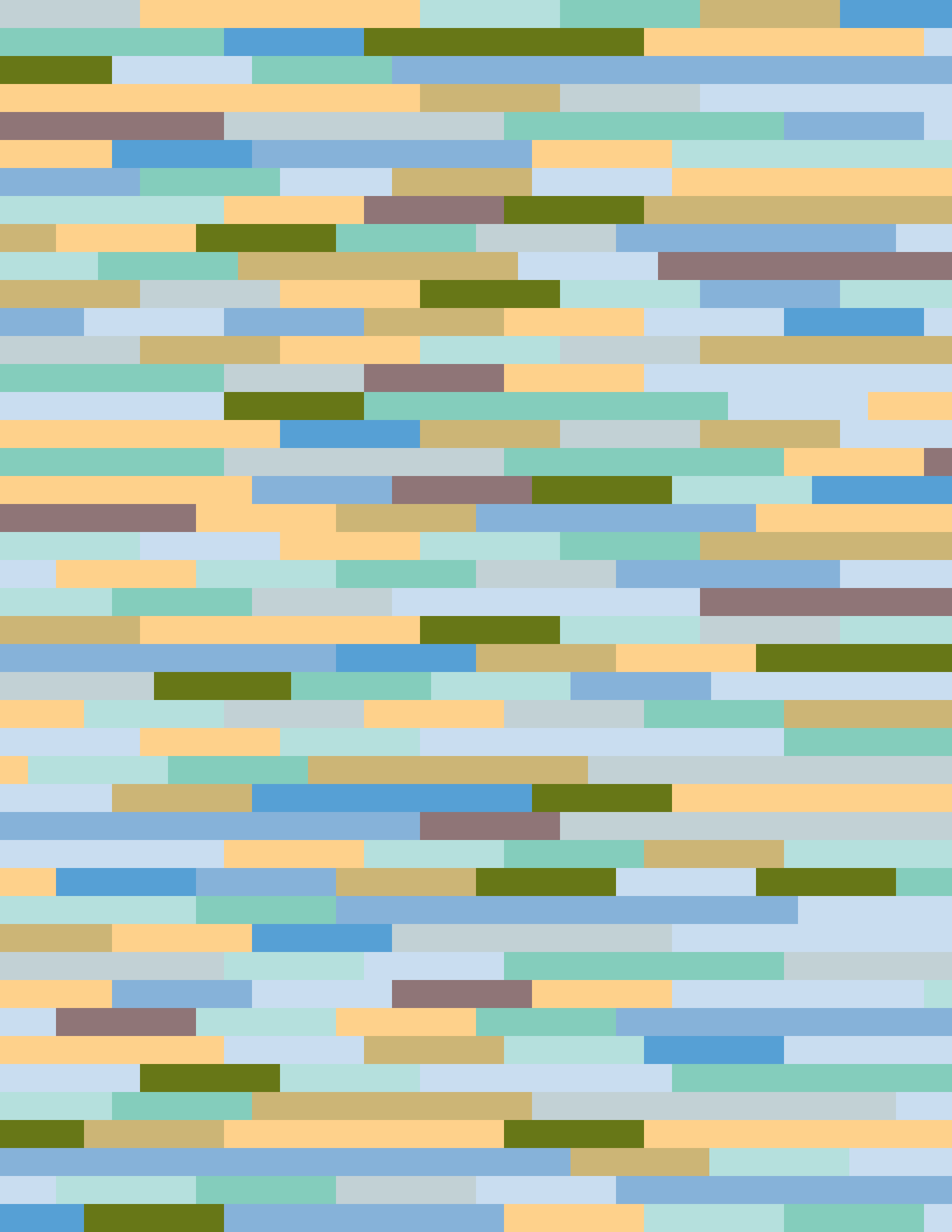


Dr. Charles Tator
Lifetime Achievement Award, Canadian Neurosurgical Society



Dr. James Till
Inducted into the Innovators Hall of Fame, University of Saskatchewan

Dr. Richard Weisel
Scientific Achievement Award, American Association for Thoracic Surgery



DRIVERS OF INNOVATION

The following pages highlight some of the factors identified as recent drivers of innovation within UHN Research Institutes.

STRATEGIC PLANNING

INFRASTRUCTURE

NEW FUNDING

INDUSTRY PARTNERSHIPS

COLLABORATIONS

COMMERCIALIZATION

OUR FOUNDATIONS

STRATEGIC PLANNING

A Blueprint for the Future

Every organization requires a strategy: a plan that outlines a desired future course based on its own strengths and capabilities, environment and opportunities for growth. In a research hospital setting, sound strategic planning ensures that resources are allocated to optimize the potential to enable discoveries that will ultimately benefit patients around the world.

Strategic planning ideas were presented at the 2010 UHN Board of Trustees Retreat

The strategic planning efforts have led to a UHN-wide commitment to build "The Research Hospital of the Future". UHN itself will become a 'living laboratory' for determining the best avenues to achieve optimal health outcomes.

University Health Network's (UHN) *Creative Domain* builds on a foundation of research and innovation that leverages strong integration and partnership to improve health outcomes and patient care. UHN Research brings together leading medical researchers and clinicians and fosters a comprehensive environment with programs that span the full spectrum—from discovery research in elucidating the mechanisms of health and disease, to applied and translational research, to community-based population health and health care delivery. Across UHN a strong commitment to excellence leads to the continual generation of research questions: how can a disease be better understood; how can we optimize treatment outcomes; how can quality care be delivered more efficiently?

In late 2009, UHN Research embarked on a new strategic planning process spearheaded by Dr. Christopher Paige, Vice President, Research, to find a way to capture these important research questions and to funnel them along pathways leading to breakthrough solutions. This process included an exploration of the research aspirations from 15 strategic plans assembled from UHN's clinical and research programs. From this exercise, 'clusters of excellence'—common research priorities—emerged. As expected, these clusters were frequently rooted in the four platforms that guided the last decade of UHN's growth, which were embodied in *Strategic Plan 2011* and *The Future Project:* "Genes, Proteins & People", "Medical Technology", "Regenerative Medicine" and "Health Informatics". They also corresponded well with institutional infrastructure grants, including the seven Themes that formed the Advanced Therapeutics Research Platform (UHN's largest infrastructure grant awarded to date).

A key element that emerged from the strategic planning efforts of the last year was that information capture and integration were essential factors in realizing the research goals of the clinical programs, centres, institutes and hospitals: their goals all depend on the ability to collect and use the vast stores of data that emerge from UHN every day. Thus, a prime focus of the next five years will be to enhance the information technology capacity to ensure the seamless integration of clinical and research information to fundamentally maximize UHN's ability to provide optimal patient care and a rich resource for research mining.

The strategic planning efforts have led to a UHN-wide commitment to build "The Research Hospital of the Future". UHN itself will become a 'living laboratory' for determining the best avenues to achieve optimal health outcomes, and the data integration will provide the backbone for discovering new insights, testing novel ideas and implementing best practice. Five domains have been identified that are critical to accomplishing these goals: "Biology" and "Technology" platforms (to understand the basis of health and disease), "Health Services" and "Experimental Therapeutics" (to determine the best way to implement the knowledge from the previous two platforms to impact patients' lives) and "Informatics" (to enable the gathering, analysis and utilization of information).

Comments Dr. Paige, "UHN is home to a remarkable group of extremely accomplished individuals. Working collectively through our planning process, a dynamic and ambitious strategy has emerged, which will accelerate medical advances and greatly improve health outcomes."

INFRASTRUCTURE

The Krembil Discovery Centre Ushers in a New Era of Discovery

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Novel equipment, innovative technologies and state-of-the-art laboratories: these are a few examples of the infrastructure required to perform research that pushes the boundaries of our knowledge. Medical discoveries are facilitated through the use of these resources. Soft infrastructure, such as informatics systems, which enable integration and analysis of clinical data, biomarker expression, tissue assessment and outcome measurement, is equally important.

UHN has taken another major step in expanding its capacity for research at the Toronto Western Research Institute (TWRI). Set to open in 2013, the Krembil Discovery Centre (KDC)—a mixed use tower that will be a key building for the Toronto Western Hospital and that will house central components of TWRI—is one of the most exciting projects in UHN's history. On March 4, 2010, the UHN community and supporters gathered at the site of the highly anticipated $151M research facility for the official groundbreaking ceremony. Philanthropists Robert and Linda Krembil, who provided the initial lead donation of $30M towards the Centre, spoke of the urgent need to provide TWRI's top scientists with a state-of-the-art facility to solve the next generation of health questions affecting Canadians and the world.

The ceremony also recognized the efforts of other key project backers, including $60M raised by the combined efforts of the Toronto General and Western Hospital Foundation and donors; and the $119M grant awarded to UHN by the Canada Foundation for Innovation in 2008—the largest award in UHN history—which included $29M for outfitting space at the KDC and TWRI.

Bob and Linda Krembil speak at the Krembil Discovery Centre ground-breaking ceremony

An architectural rendering of the Krembil Discovery Centre

The 325,000 square foot KDC facility will span nine floors with 150,000 square feet of laboratory space. Five and a half floors of state-of-the-art research space will house world-renowned research programs in arthritis and rheumatism, autoimmune diseases, spinal cord injury, stroke, Parkinson's disease, epilepsy, Alzheimer's disease, brain tumours and aneurysms, pain disorders, eye diseases and orthopedics. In addition, one and a half floors will be dedicated to UHN's Rehabilitation Solutions, a provider of innovative health and disability management solutions.

The building also features some innovative design aspects, including a Healing Garden and a Sky Lobby. The Healing Garden will be located on the lower floors and will provide an outdoor patio for yoga and other rehabilitation exercises not traditionally performed within a gymnasium. Located on the upper floors, the Sky Lobby will be a two-storey space that will encourage gathering and collaboration among various research groups.

TWRI is a world leader in neurosciences, vision, orthopedics and arthritis research and treatment. Currently home to over 125 researchers and more than 168 trainees from around the globe, TWRI attracted over $32M in external funding in 2009/10. As Ian McDermott, Senior Director, UHN Research Facilities Planning, notes, "We are steadily progressing with the plans for the KDC that, when completed, will offer a world-class research space enabling us to retain and attract the very best and brightest researchers."

NEW FUNDING

Ontario Ministry Makes Major Investments in UHN-led Research Projects

Funding, whether through government agencies, companies, foundations or associations, has a key role in driving discovery. These awards provide the means for scientists to recruit and retain laboratory staff and trainees, purchase research supplies, obtain new equipment and technologies, and build new office and laboratory space—all to advance medical knowledge.

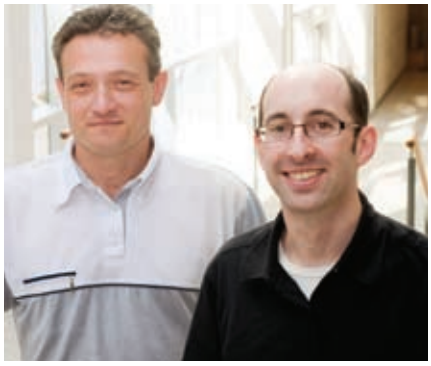
The end of April marked an exciting time for UHN Research, with multiple announcements from the Ontario Ministry of Research and Innovation (MRI) providing support for seven UHN-led projects totaling $40M in new funding. These leading investments by the Ministry—through the Ontario Research Fund Research Excellence and the Global Leadership in Genomics & Life Sciences programs—will enable important new scientific discoveries in areas of research spanning cancer, cardiology, lung transplant, vision sciences and computational biology. These MRI investments will help to support the training of Ontario's next generation of scientific leaders, nurture existing collaborations and foster new global academic and private sector partnerships.

Dr. David Jaffray was awarded $7M towards the "Ontario Consortium for Adaptive Interventions in Radiation Oncology." This cross-Ontario project, also known as OCAIRO, includes 22 scientists, physicists and engineers across seven institutions. OCAIRO also established partnerships with 16 private sector companies who will invest $7M over the next five years. OCAIRO's mission is to advance innovative adaptive radiation therapy, a new approach that involves creating hardware, software, imaging and database systems. This new approach will help oncologists to adapt radiation to each individual patient and their response during the course of therapy.

RESEARCH EXCELLENCE ROUND 4 AWARDEES

Dr. Christopher Hudson and nine colleagues from the University of Waterloo and the University of Toronto were awarded $2.4M for the "Retinal Oxygen Saturation, Blood Flow, Vascular Function and High Resolution Morphometric Imaging in the Living Human Eye" project. This team will develop retinal imaging instruments to allow for the early detection and improved management of the three most common causes of age-related vision loss: macular degeneration, glaucoma and diabetic retinopathy. Together, they will build, develop and validate new quantitative non-invasive imaging technologies to assess the blood supply to the back of the eye, a diagnostic capability that is currently severely limited; and oxygen transport to the back of the eye, a diagnostic capability that currently does not exist.

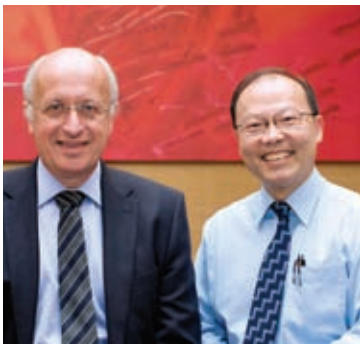
GLOBAL LEADERSHIP ROUND IN GENOMICS & LIFE SCIENCES (GL2) AWARDEES



Drs. Igor Jurisica and Gary Bader were awarded $10M for the "Cancer Gene Encyclopedia (CGEP): Computationally Optimized Characterization of Cancer Genes, Proteins, Their Structure, Function and Interactions" project. The Toronto-led project, which spans 20 institutions across eight countries, will establish an integrated database for the systematic characterization of cancer proteins and their interactions and pathways. This integrated resource will allow scientists to identify new cancer targets, which will be the basis for new diagnostics and therapeutics, improving outcomes for patients with lung, ovary, prostate, and head and neck cancers.

Drs. Benjamin Neel and Bradly Wouters will receive $10.1M for the "Functional Genomics of Solid Tumours for Discovery and Development of New Biologics and Biomarkers" project. With collaborators at the University of Toronto, the team will use state-of-the-art genetic screens, next-generation genome sequencing and high-throughput synthetic antibody development to accelerate the discovery of novel cancer therapies and biomarkers.

Drs. Gordon Keller and Peter Liu will receive $6.6M in support of the "Cardiovascular Biomarker Discovery in Disease and Development through Predictive Precision Proteomics (CBD3P3)" project. Their team will work towards developing new screening and diagnostic tools to identify patients in the early stages of heart disease and to determine the most effective treatment on an individual basis.



Dr. Rama Khokha was awarded $2.1M towards her proposed "Functional Oncogenomics for the Discovery of Cancer Drivers and Unique Subclasses (FOCUS)" project that aims to understand how certain genes affect the development of osteosarcoma, a devastating form of bone cancer brought to the world's attention by Terry Fox thirty years ago during his Miracle of Hope campaign.

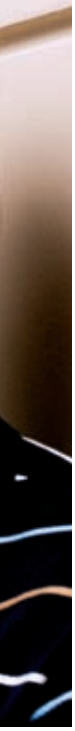
Drs. Shaf Keshavjee and Mingyao Liu were awarded $1.75M for the "Molecular and Genomic Diagnostics to Improve Outcomes in Lung Transplantation" project that will work towards developing novel and accurate diagnostic strategies for donor lung injury and for the prediction and diagnosis of recipient rejection.

(L-R) Drs. Lillian Siu, Amit Oza, Benjamin Neel and Malcolm Moore

INDUSTRY PARTNERSHIPS

UHN and Merck Join Forces in Global Cancer Clinical Trials Network

Working with industry partners is essential to bring research discoveries into clinical practice. Furthermore, these partnerships can strengthen the UHN brand among organizations in the health industry and provide access to additional resources that can help foster research discoveries.



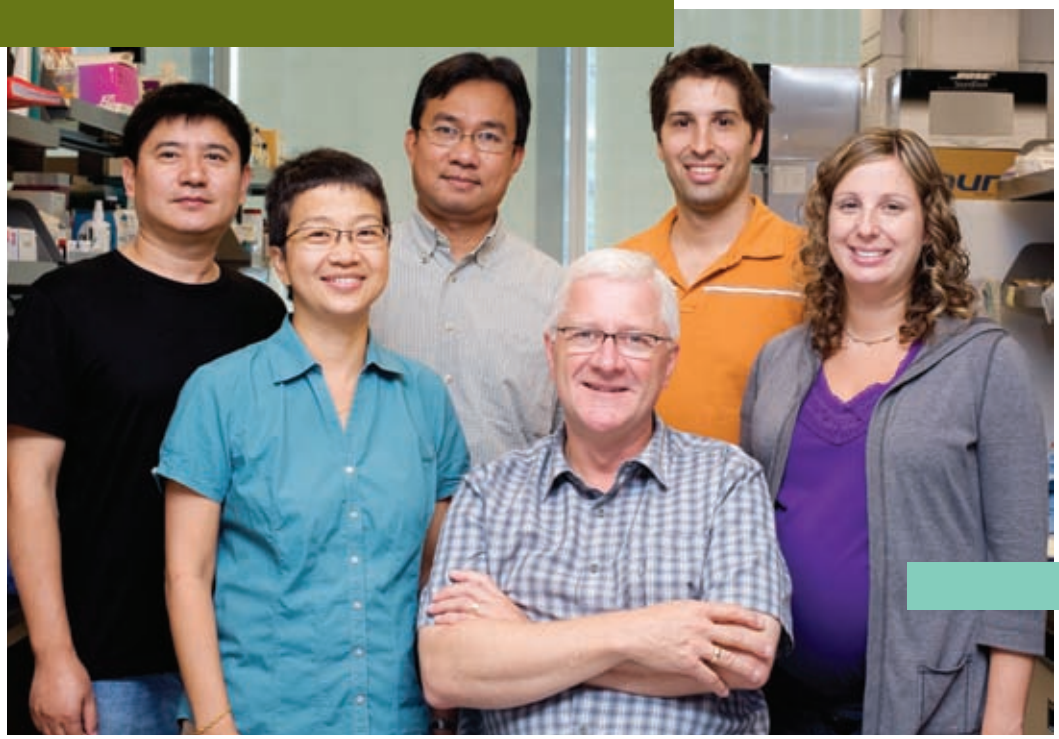
On April 15, 2010, UHN entered into a groundbreaking partnership with pharmaceutical giant Merck as one of 15 sites across the Americas, Europe, Asia and Israel taking part in the "Merck Oncology Collaborative Trials Network" (Onconet). This pioneering alliance will focus on developing Merck drug and vaccine candidates for cancer treatment and prevention. Participating sites will lead the design and conduct of Phase 0-2a clinical studies of Merck's investigational oncology candidates and, each year, Onconet will enroll about 1,200 patients in 30-40 investigator- and company-sponsored trials. UHN's Princess Margaret Hospital (PMH)/Ontario Cancer Institute (OCI) is Onconet's only Canadian site. With the largest and most active drug development program in Canada, PMH is the only site outside of the United States that hosts a Phase I grant and Phase II contract with the US National Cancer Institute for adult cancers. It has also developed a strong multi-institution collaboration, the PMH Consortium, which focuses on early phase clinical and translational research. PMH has consistently led the way in Ontario and Canada for innovative early phase clinical trials. Cancer Care Ontario statistics show that 20-25% of its patients participate in clinical trials—a number that is considerably higher than most academic centres across Canada and the US. In addition, OCI and the Ontario Institute for Cancer Research have collaborated to increase the strength of their clinical and translational research programs and have together created a unique environment for complex clinical trials.

Key to the $17.3M venture between UHN and Merck is the support of the Ontario Biopharmaceutical Investment Program, which has committed $2.6M over five years to this partnership. On-site at PMH/OCI, this initiative is led by Drs. Malcolm Moore (Lead and Co-Chair of the Merck Onconet Steering Committee; Director, PMH Bras Family New Drug Development Program), Lillian Siu (Co-Director, PMH Bras Family New Drug Development Program), Amit Oza (Director, Cancer Clinical Research Unit and Co-Director, PMH Bras Family New Drug Development Program) and Benjamin Neel (Director, OCI and Campbell Family Cancer Research Institute). Onconet at UHN will also build on current in-house infrastructure; PMH has a robust clinical trials enterprise through the Cancer Clinical Research Unit, the Bras Family New Drug Development Program and departmental clinical trials groups that enable coordinated investigation of the latest clinical hypotheses in cancer research.

"There is still an overwhelmingly urgent need to have effective treatments for patients with cancer, and the momentum of traditional drug development often lags far behind the latest scientific discoveries," states Dr. Oza. "This exciting pioneering collaboration could serve as an important model for how industry and academia can work together more efficiently and effectively to expedite the delivery of innovative cancer therapies to patients."

COLLABORATIONS

New California Partnership Spurs Stem Cell Research

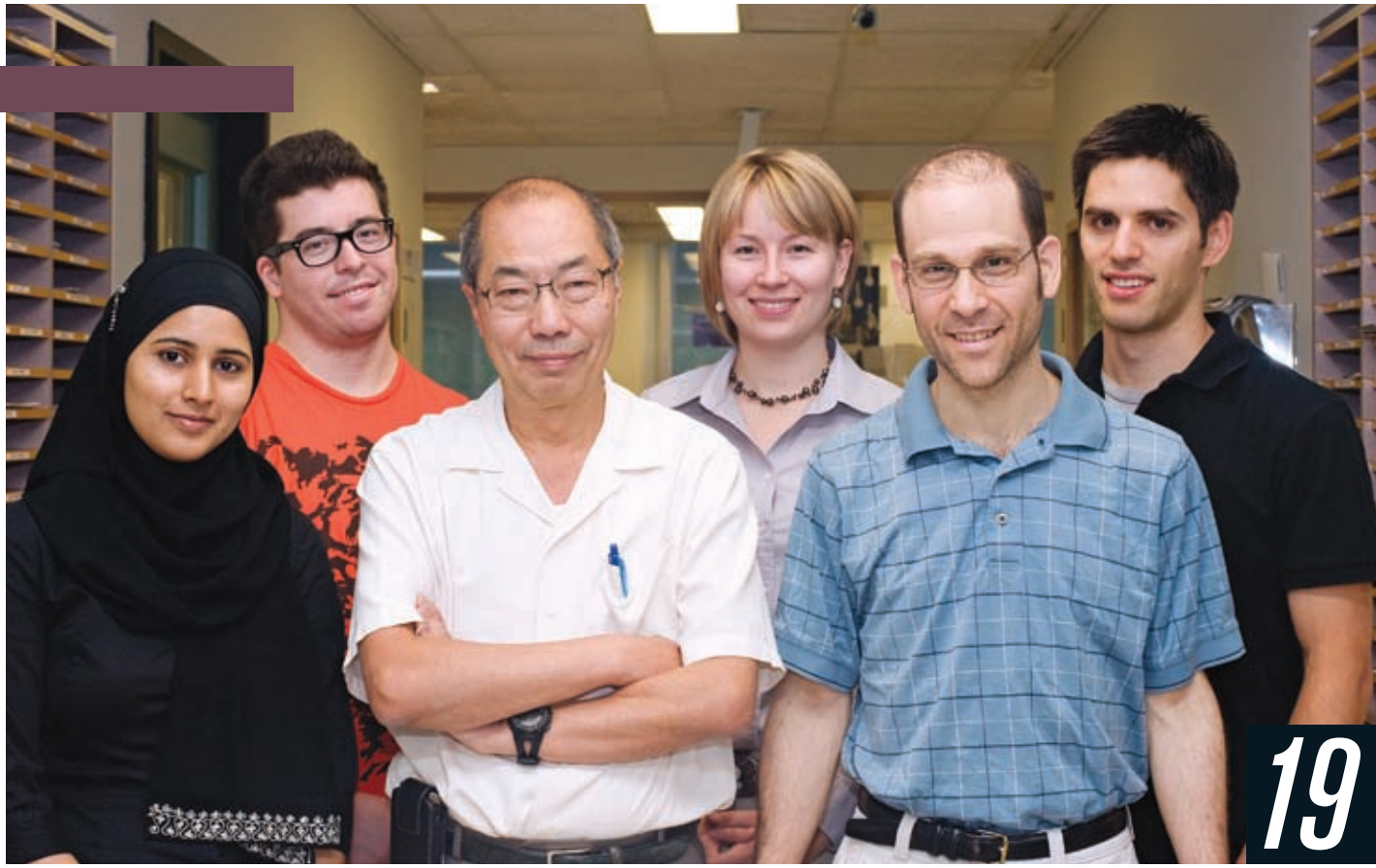


Dr. John Dick (seated) with (L–R) staff member Liqing Jin, Affiliate Scientist Dr. Jean Wang, and staff members Jaime Claudio, Armando Poeppl and Amanda Mitchell

Collaborations with scientists at other institutions are critical to advancing research, as they offer additional viewpoints, capabilities and resources. Together with local, national and international colleagues, our investigators—who are all faculty at the University of Toronto and participants in the vibrant research culture of the Toronto Academic Health Science Network of research hospitals affiliated with the University—are able to define and solve some of the most complex medical issues of our day.

On October 28, 2009, OCI researchers Drs. John Dick and Tak Mak were each awarded almost $20M in funding over four years from the Collaborative Partnership Program between the Cancer Stem Cell Consortium (CSCC) and the California Institute for Regenerative Medicine (CIRM).

The Program was initiated by CSCC, a not-for-profit corporation developed to coordinate an international strategy for cancer stem cell research and translational research activities, and CIRM, which was established in 2004 with over $3B in funding for stem cell research at California universities and research institutions. Its mission is to support international collaborations that bring together the best scientists in the world to focus on research leading to cancer stem cell-based therapies, with the goal of improving cancer treatment.



Dr. Tak Mak (third from left) with graduate students (L–R) Samia Afzal, Isaac Harris, Val Lapin, Brian Herschenfield and Dave Cescon

Dr. Dick, who is recognized worldwide for identifying stem cells in human leukemia, will work together with the University of California, San Diego's Dr. Dennis Carson to develop new drugs targeting leukemic stem cells (LSCs).

"The treatment for many types of leukemia is not effective because LSCs are resistant to the drugs that are currently available," explains Dr. Dick. "Therefore, developing new drugs that specifically target LSCs could have an important impact on the success of leukemia treatments."

Dr. Mak, in collaboration with University of California, Los Angeles researcher Dr. Dennis Slamon, will develop new drugs targeting cancer-initiating cells in solid tumour cancers. Dr. Mak is renowned for cloning the human T-cell receptor and has played a key role in developing genetically altered mice that have led to important scientific breakthroughs.

Says Dr. Mak, "Our hope is that this collaboration will lead to significant clinical benefit to cancer patients through the identification and development of new drugs."

These two Canada-California collaborative projects were selected from 31 applications. Funding for the Canadian research teams will be provided by the Canadian Institutes of Health Research and Genome Canada, two members of the CSCC. The California teams also received similar levels of funding, provided by CIRM.

COMMERCIALIZATION

Med BioGene and LungExpress Dx

(L-R) TDC Director Brian Barber with Drs. Igor Jurisica, Ming-Sound Tsao and Frances Shepherd

The translation of researchers' ideas into marketable products, services and practices is crucial to achieving the ultimate goal of improving patient health. UHN's Technology Development & Commercialization (TDC) Office protects UHN intellectual property, facilitates the interaction between UHN researchers and private investors and companies, and enables research discoveries to enhance their market value.

The decision to undergo adjuvant chemotherapy after surgery is a significant one. While numerous factors undoubtedly play a role in a patient's decision-making process, a prognostic test called LungExpress Dx—licensed by UHN to Med BioGene, a biotechnology company based in Vancouver—may offer guidance.

This test, a proprietary gene expression-based assay for patients with early-stage non-small-cell lung cancer (NSCLC) who have had their tumours removed by surgery, may predict the extent to which patients could benefit from adjuvant chemotherapy. The science at the root of this test can be traced back to research performed over a four year period by a team including Drs. Ming-Sound Tsao, Frances Shepherd and Igor Jurisica—all internationally renowned OCI investigators. Working with collaborators at the National Cancer Institute of Canada Clinical Trials Group at Queen's University and supported by funding from the Canadian Cancer Society, the team performed genomic analysis of lung tumour samples collected from patients across Canada. From this analysis the team identified a genetic signature for patients with significantly different survival outcomes.

Since the collaboration between UHN and Med BioGene was first announced in April 2008, several key milestones have been achieved, each of which has brought LungExpress Dx closer to the marketplace for use by oncologists. In 2009, the original collaboration was expanded to include additional new gene expression-based markers for NSCLC, further refining the scope and accuracy of this prognostic test. Subsequently, a 2009 validation study confirmed that the 15-gene expression-based assay underlying the test is an independent prognostic marker in NSCLC that can provide additional clinical value beyond standard measures of risk.

"From the work that we have done, and through our collaborators and with Med BioGene, we see that LungExpress Dx can contribute to more clearly informed treatment decisions for those with early-stage NSCLC," explains Dr. Tsao. Adds Dr. Shepherd, "The ability to tell whether a particular patient is a good candidate for adjuvant chemotherapy will bring us closer to our goals of improving patient care through personalized medicine."

Med BioGene is continuing with its commercialization plans to make LungExpress Dx available initially to physicians and patients in the United States in 2010. Their future plans include working with companies to distribute LungExpress Dx in Asia and Europe, and also offering LungExpress Dx as a diagnostic tool to be used alongside FDA-approved or development-stage targeted therapies created by pharmaceutical company partners.

OUR FOUNDATIONS
Supporting Research

Our three foundations are, literally, the foundation for UHN Research. The Arthritis & Autoimmunity Research Centre Foundation, the Princess Margaret Hospital Foundation and the Toronto General & Western Hospital Foundation work with generous donors who are eager to make a difference in health care. Their collective efforts contribute to raising more than $250M each year to drive health and research innovation at UHN.

AARC FOUNDATION: DAY AT THE RACES
Celebrating a Decade of Progress and the Future of Research

On October 4, 2009, the Arthritis & Autoimmunity Research Centre (AARC) Foundation proudly held the tenth annual *Day at the Races*, the Foundation's signature fundraising event in support of arthritis and autoimmune disease research at UHN and Mount Sinai Hospital. Over 200 attendees gathered at the Trackside Marquis Tent at Woodbine Racetrack in Toronto to enjoy an afternoon of thrilling horse races, gourmet food, champagne and festivities, including wagering and a silent auction.

"*Day at the Races* is truly a horse of a different colour in comparison to other fundraising events such as galas," explains AARC Foundation Events Manager Jennifer Marczak. The trackside setting allows unparalleled social interaction, and the casual atmosphere is well-loved and highly anticipated each year by the event's sponsors, donors, organizers and volunteers. Adds Dr. Eleanor Fish, Director of AARC, "*Day at the Races* allows individuals who attend to mingle with the scientists and learn more about the research and become inspired by the young rising stars who are dedicated to beating arthritis."

Since its inception in 2000, *Day at the Races* has generated over $1.37M for arthritis and related autoimmune disease research. Notable attendees at the tenth anniversary event included Hall of Fame Jockey and Honourary Event Patron Sandy Hawley and Honourary Chair Dr. Ed Keystone, who was recognized for his outstanding research contributions in the areas of rheumatoid arthritis and clinical therapeutics.

A large part of the ongoing success of *Day at the Races* has been the tremendous commitment of many of its continued supporters, including Woodbine Racetrack, event partner for ten years, and board member Don O'Born, the current Event Chair, who has volunteered for the past six years. "As Chair—and someone personally affected by arthritis-related conditions—I realize how important it is to raise funds for this vitally important research. I hope in some small way my contribution helps to beat arthritis," notes O'Born.

Building on a decade of achievement, *Day at the Races* looks ahead with excitement to 2010 when it will launch its new theme "Fillies and Fellows." Explains Marczak, "Next year we will cheer on the young champions on the track as we introduce our Fellows, the next generation of rising stars at AARC!"

At the track at the *Day at the Races*

PRINCESS MARGARET HOSPITAL FOUNDATION: THE RIDE TO CONQUER CANCER

Cycling for a Cure

A sea of riders participate in the *Ride to Conquer Cancer*

Steve Merker knows the power of determination. As the Chief Cycling Officer and Director of Business Development for the Princess Margaret Hospital Foundation's (PMHF) *Ride to Conquer Cancer,* he has seen first hand the determination of riders, volunteers and donors that make the *Ride* one of PMHF's most successful fundraisers.

"From the first *Ride* in 2008, our supporters have consistently helped us exceed our wildest expectations. Our original goal that first year was to have 2,100 riders raise $8M and we ended up having 2,800 riders who raised $14M for world-class cancer research. It was amazing to know that all of these people were as determined as we were to defeat cancer."

Three years later, that determination is still very much present. The 2010 *Ride to Conquer Cancer,* a two-day cycling event that started in Toronto and ended in Niagara Falls, has been the most successful *Ride* to date, with over 4,000 riders raising a total of $16.1M. These funds, which benefit the Princess Margaret Hospital—one of the world's top five cancer research centres—have a strong impact on areas such as breast and prostate cancer research, image-guided therapy and surgery, tumour microenvironment, cancer stem cells and immunotherapy.

"It's been said that nearly 40% of Canadian women and 45% of men will develop cancer during their lifetimes," explains Merker. "This is why we have the *Ride*—for our families and our friends. Many cancer survivors also participate. There's an amazing sense of camaraderie along the routes and at the overnight camps, because no matter how different we all are, the way we have all fought against cancer—and are still fighting it by taking part in the *Ride*—is shared among us."

Perhaps the best way to sum up the spirit of the *Ride* can be seen at the finish line. "It's an amazing sight to see the range of emotions that people have at the end," recalls Merker. "Some are laughing, some crying. Others just look exhausted. I remember a particularly memorable time when after the *Ride* finished, a cyclist—who was a cancer survivor—said to me that while his body had already been treated, it was his mind that was healed as he crossed the finish line."

TORONTO GENERAL & WESTERN HOSPITAL FOUNDATION: HATS OFF TO HARRY

Supporting Regenerative Medicine and Diabetes Research

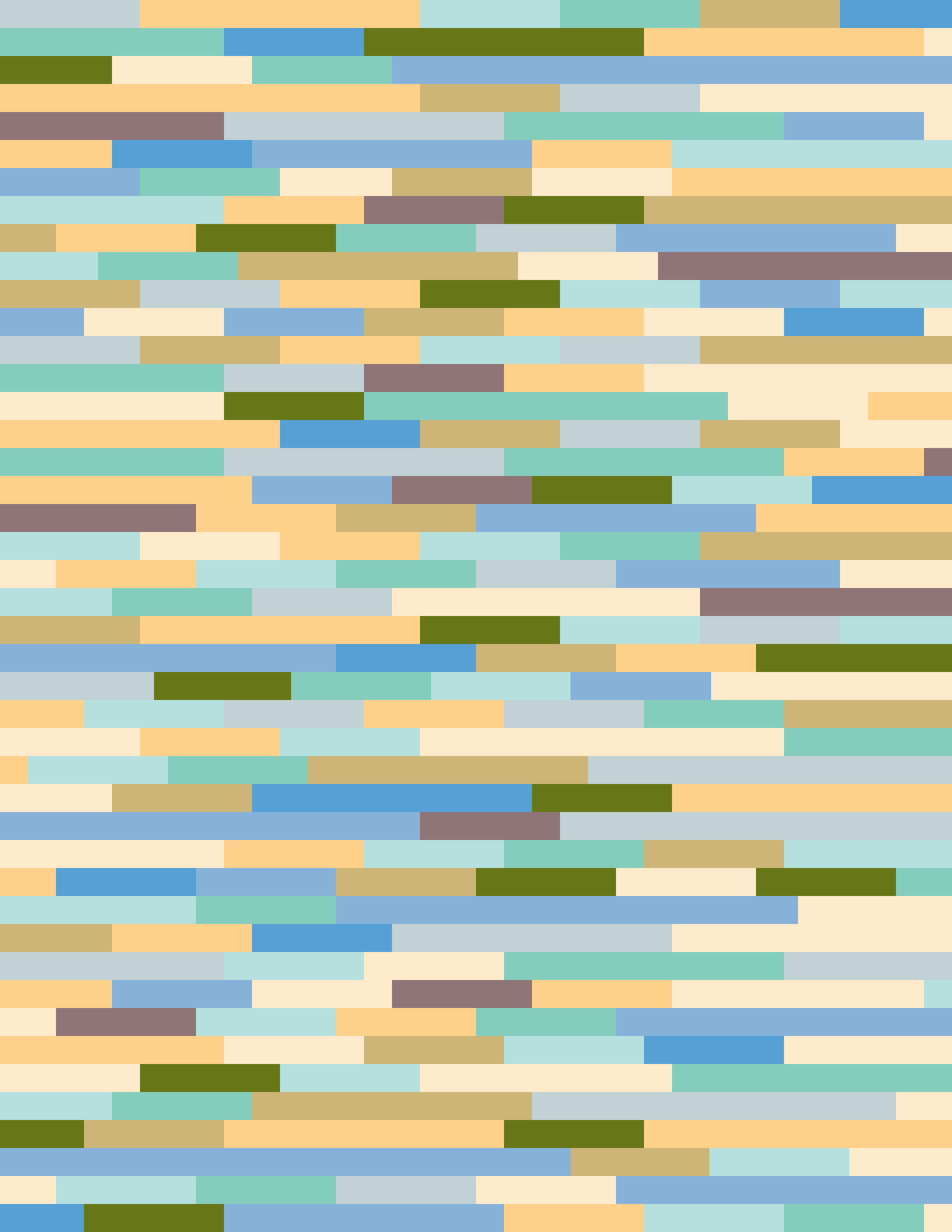
(L-R) Harry Rosen, Cheryl McEwen and Larry Rosen at *Hats Off to Harry*

The Toronto General & Western Hospital Foundation holds several key fundraising events each year to raise money to enable research, education and the enhancement of patient care at the Toronto General and Toronto Western Hospitals, and their respective Research Institutes.

This year, an event that had everyone buzzing was *Hats Off to Harry*, a tribute dinner to Canadian menswear icon Harry Rosen, which raised $1.8M to establish The Harry Rosen Diabetes Chair in Stem Cell Research at the McEwen Centre for Regenerative Medicine at UHN.

As Tennys Hanson, President and CEO of the Foundation, explains, "Proceeds from this event will support the recruitment of a high-calibre scientist who will focus on applying stem cell biology and regenerative medicine approaches towards a greater understanding and potential cure for diabetes." This research is critically needed, as 285 million people worldwide are affected by diabetes, with an additional seven million people developing the disease each year. Toronto's strong history of groundbreaking discoveries in diabetes and stem cell research, from the discovery of insulin by Frederick Banting and Charles Best in 1921 and the discovery of blood-forming stem cells by James Till and Ernest McCulloch in 1961, to the pioneering stem cell research taking place at the McEwen Centre today, makes UHN the ideal setting to undertake this important research.

The *Hats Off to Harry* evening took place at the Four Seasons Hotel and included a tribute video to Harry Rosen along with speeches from UHN President and CEO Dr. Robert Bell, McEwen Centre Director Dr. Gordon Keller, and renowned diabetes researchers Drs. Derek van der Kooy and Gary Lewis, who spoke about the important advances taking place at the McEwen Centre. Canadian singer Matt Dusk provided the evening's entertainment, particularly when he was joined onstage for a duet with Harry Rosen himself. Special guests included McEwen Centre co-founders Robert and Cheryl McEwen, Canadian Olympic rower and gold medalist of the Pan Am Games Chris Jarvis, who outlined his struggles and successes competing with type 1 diabetes, and many celebrated figures from the fashion world.



RESEARCH

UHN's principal investigators undertake the full spectrum of research, from basic research into the fundamental mechanisms of disease and health, to translational research that demonstrates the basic relevance of findings to human health application, to clinical research and its direct application to patients. Their foci span a range of programs including those in cancer, cardiovascular sciences, transplantation, diabetes, neural and sensory sciences, arthritis and autoimmunity, infectious disease and community and population health.

BASIC RESEARCH

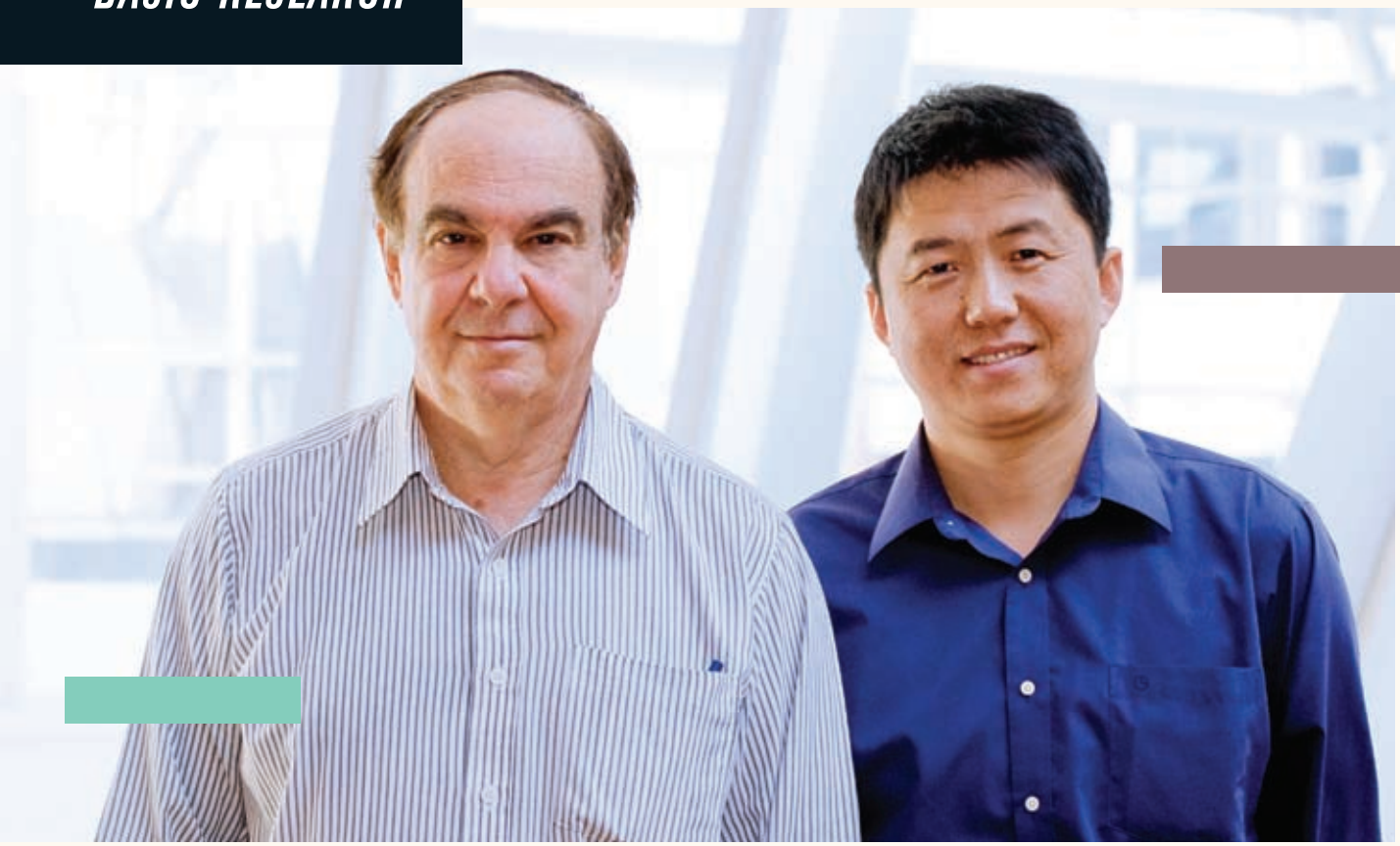
Basic research is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts.

TRANSLATIONAL RESEARCH

Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce disease incidence, morbidity and mortality.

CLINICAL RESEARCH

Clinical research is patient-oriented and includes clinical trials to evaluate new medications, procedures or medical devices by monitoring their effects on people, as well as surveys, behavioural studies, epidemiological studies, and health services/outcomes research.



Drs. Peter Carlen and Hui Ye

BRAIN INJURY

Learning What Contributes to Damage

A shortage of oxygen and blood supply, respectively known as hypoxia and ischemia, can cause serious injury in the brain. TWRI Senior Scientist Dr. Peter Carlen and his team have discovered a previously unknown means of signaling that may contribute to, or promote, long-term brain injury.

As explained by Dr. Carlen, brain cells (neurons) communicate with one another by transmitting 'impulses', also called action potentials (APs). These can be stimulated by the amino acid glutamate, which supports the transmission of impulses from cell to cell through its release into the extracellular space between neurons (known as synaptic release) and subsequent stimulation of the adjacent neuron. When glutamate levels are abnormally high in the extracellular space, it can contribute to brain injury.

With colleague Dr. Hui Ye, the team examined the AP-dependent and -independent release of glutamate by measuring nerve impulses in rodent brain tissue. Their findings revealed that under hypoxic/ischemic conditions 74% of glutamate-induced impulses could be attributed to AP-dependent release, and that the neurons releasing the glutamate were 'hyper-excited'—meaning that they experienced more impulses than those under normal conditions.

"The kind of AP-dependent release we observed could occur almost immediately in an animal after a critical decrease in oxygenated blood supply," says Dr. Carlen. "This outpouring of glutamate could play a significant role in contributing to later irreversible damage in the brain. Our future studies will look to pinpoint where, and how, to stop injury before it even begins, which could significantly impact our knowledge of brain injuries stemming from diseases such as stroke."

Ye H, Jalini S, Zhang L, Charlton M, Carlen PL. Early ischemia enhances action potential-dependent, spontaneous glutamatergic responses in CA1 neurons. J Cereb Blood Flow Metab. 2010 Mar;30(3):555-65. Research supported by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Alzheimer Society of Canada and Pfizer Canada.

SEPSIS

Applying Cell Therapy to Combat Infectious Disease

Dr. Conrad Liles

Sepsis (generalized inflammation caused by infection) and complications arising from sepsis, including acute respiratory failure and organ dysfunction, are among the leading causes of death in critically ill patients. Currently, sepsis remains without an effective treatment strategy; however, research findings out of UHN, St. Michael's Hospital and the University of Ottawa point to an innovative treatment strategy that controls inflammation while increasing clearance of infection to improve outcome in sepsis.

Co-led by TGRI's Dr. Conrad Liles and the University of Ottawa's Dr. Duncan Stewart, a series of molecular investigations found that administration of mesenchymal stem cells (MSCs)—stem cells derived from bone marrow—to mice with sepsis that were receiving appropriate antimicrobial therapy significantly reduced mortality in comparison to mice who did not receive MSC treatment. MSC administration also prevented organ failure and significantly reduced levels of inflammation-promoting proteins (cytokines), which are a critical contributing factor to sepsis-related complications. Collectively, these findings demonstrate the potential for therapeutic use of MSCs for sepsis and provide the basis for launching a clinical trial in patients with sepsis.

"MSCs were able to improve eradication of invading bacteria while effectively harnessing harmful systemic inflammation," explains Dr. Liles. "We've shown that by reducing inflammation and promoting the eradication of bacteria, MSC therapy may be an effective tool, combined with antibiotics and current supportive care, to reduce sepsis-related morbidity and death."

Mei SH, Haitsma JJ, Dos Santos CC, Deng Y, Lai PF, Slutsky AS, Liles WC, Stewart DJ. Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. Am J Respir Crit Care Med. 2010 Oct 15;182(8):1047-57. Research supported by the Canadian Institutes of Health Research, Northern Therapeutics, NSERC Doctoral Canada Graduate Scholarship and Ontario Graduate Scholarship, the Weston Foundation, the McLaughlin Centre for Molecular Medicine, the McLaughlin-Rotman Centre for Global Health and the Canada Research Chairs Program.

Dr. Eleanor Fish

INFLUENZA A

Identifying a New Cell Population to Battle Infection

An Arthritis & Autoimmunity Research Centre (AARC) and TGRI team have uncovered a new population of immune cells that may play a pivotal role in regulating resistance against pulmonary influenza A virus infections. The influenza A virus primarily affects organs and tissues that are associated with breathing; once infected, these viruses grow rapidly in number (within hours of first exposure), impacting the immune system.

As explained by study lead and AARC Director Dr. Eleanor Fish, "For influenza virus infections, our bodies are equipped with two very distinct responses, known as T1 and T2 immunity. Our study specifically looked at T2 immunity within the context of disease cause and progression, primarily because our understanding of the workings behind this T2 response is still in its infancy."

Using an animal model of influenza A infection, the group revealed the novel late-activator antigen presenting cell (LAPC) population, and showed how these cells differ and are unique from other well-known immune cells. The study then went one step further, demonstrating how LAPCs regulate influenza A infection to coax our T2 immune response into action.

"We've shown that LAPCs have widespread involvement in different virus infections and that they appear to have distinct roles in the immune response to virus infections. For flu infection, LAPCs leave the lungs much later than other virus-fighting cells and trigger different responses," reports Dr. Fish. "Future studies looking at the function of LAPCs in different virus infections and how they respond to different pathogens may provide us with new therapeutic targets for the treatment of a host of infections, including influenza A virus."

Yoo JK, Galligan CL, Virtanen C, Fish EN. Identification of a novel antigen-presenting cell population modulating antiinfluenza type 2 immunity. J Exp Med. 2010 Jul 5;207(7):1435-51. Research supported by the Canadian Institutes of Health Research and the Canada Research Chairs Program.

BREAST CANCER

Evidence Points Towards Hormone-Driven Cell Growth

Graduate student Purna Joshi and Dr. Rama Khokha

Reproductive history is one of the strongest risk factors for breast cancer after age, genetics and breast density. Thanks to findings from an OCI-led study, we now know that progesterone—an ovarian hormone that helps to prepare the uterus to receive a fertilized egg—plays a critical role in changing breast stem cells.

Breast stem cells have the potential to become any type of breast cell and can create multiple copies of themselves; however, until now, they were believed to remain inactive except during puberty and pregnancy. Study lead Dr. Rama Khokha and her team have now shown a direct link between hormones and breast stem cells, adding important new knowledge to our understanding of breast cancer risk.

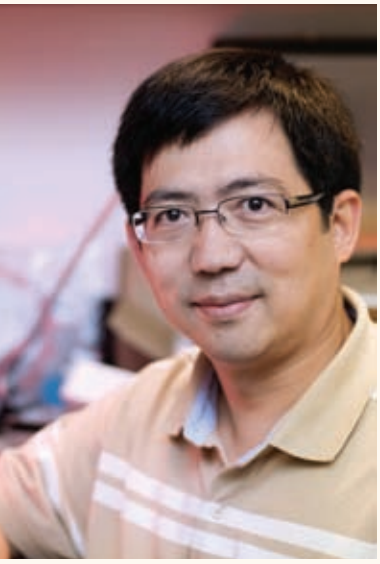
Using an animal model system, the team discovered how and when hormones affect breast stem cells during the natural reproductive cycle. Through a series of experiments, the team mimicked the human menstrual cycle to show that, as progesterone peaks in the second half of the menstrual cycle, it affects breast stem cells and neighboring cells, causing normal breast stem cells to expand in number. It is this rapid cell expansion that could trigger an environment in which cancer could begin, a finding that has sparked new areas of future research targeting stem cells and treatment.

Dr. Khokha explains that these are significant findings because they demonstrate, for the first time, progesterone-driven shifts in the breast stem cell pool. Understanding how hormones change these stem cells provides important new information about how breast cancer growth begins and how, in the future, it may be prevented.

Joshi PA, Jackson HW, Beristain AG, Di Grappa MA, Mote PA, Clarke CL, Stingl J, Waterhouse PD, Khokha R. Progesterone induces adult mammary stem cell expansion. Nature. 2010 Jun 10;465(7299):803-7. Research supported by the Canadian Cancer Society Research Institute and the Canadian Breast Cancer Foundation.

IMAGING

Developing the Underpinnings of a New Era of Imaging Technologies



Dr. Gang Zheng

A new era of diagnosis and treatment may be possible thanks to new developments in probe design from the lab of OCI's Dr. Gang Zheng. Probes are small molecules designed to interact with specific proteins for the purposes of exploring the role of the protein in cells. With Dr. Brian Wilson (OCI), the team developed and tested an improved superior probe system that can be used to enhance imaging and therapeutics for numerous diseases including cancer.

Several challenges need to be overcome when designing fluorescent probes, including problems of poor targeting—where the probe may target areas not under study—and high background levels that make it difficult to study a specific site. The team created a probe, the Zipper Molecular Beacon (ZMB), to overcome these challenges by incorporating a fluorescent dye at one end of the molecule and a "quencher" (to prevent fluorescence) at the opposite end of the molecule, brought close together as a result of the variety of charges and shapes of the molecule.

"When a protein of interest is found, the molecule changes shape and moves the quencher away from the dye," describes Dr. Zheng. "The fluorescent signal then becomes visible and the probe becomes activated. We have also optimized other aspects of the ZMB so that the fluorescent probe can easily enter specific cell types to become activated."

As noted by Dr. Zheng, if scientists could tailor ZMB probes to target specific cancer proteins, these cells could be detected by fluorescence and forced to become sensitive to irradiation. Health care teams would be able to see the exact location of cancer cells sensitive to irradiation and apply treatment directly to the sensitized area to kill the cancerous cells. Alternatively, the same zipper approach could be used for many specific disease biomarker targets.

Chen J, Liu TW, Lo PC, Wilson BC, Zheng G. "Zipper" molecular beacons: A generalized strategy to optimize the performance of activatable protease probes. Bioconjug Chem. 2009 Sep 14. Research supported by the Canadian Institutes of Health Research, the Ontario Institute for Cancer Research through funding provided by the Government of Ontario, the Canadian Cancer Society Research Institute and the Joey and Toby Tanenbaum/Brazilian Ball Chair in Prostate Cancer Research.

Dr. Michael Fehlings

REGENERATIVE MEDICINE

Repairing the Injured Spinal Cord

A TWRI investigation of spinal cord injuries (SCI) has revealed how to prepare sites of spinal cord damage for cell transplantation. Importantly, they have also determined the particular combination of specific growth proteins promoting function and repair of injured spinal cords—findings which could bring scientists one step closer to the application of neuronal precursor cell (NPC), or stem cell, therapy for these patients.

Dr. Michael Fehlings, Medical Director of the Krembil Neurosciences Centre, along with Dr. Soheila Karimi-Abdolrezaee and colleagues, used an animal model of SCI to show that damaged areas of the spinal cord could be primed for cell transplant with the application of chondroitinase ABC (ChABC), which works to keep the area around the scar from negatively influencing the long-term survival and integration of transplanted NPCs. Injecting NPCs into the spine with a particular trio of growth proteins, the team promoted the integration of NPCs with other spinal cord cells and allowed NPCs to mature into oligodendrocytes, a type of nerve cell.

"When we used ChABC to ready the site of damage, supplemented our NPC transfusion with this particular 'cocktail' of specific growth proteins and applied it to the injured spinal cord, it markedly increased the long-term survival of transplanted cells and greatly optimized their migration and integration in the chronically injured spinal cord," says Dr. Fehlings. "We have also shown that this particular combination did not enhance the growth of pain nerves in the spine either. These are important findings, which may facilitate the clinical application of stem cells for patients suffering from chronic SCI."

Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Schut D, Fehlings MG. Synergistic effects of transplanted adult neural stem/progenitor cells, chondroitinase, and growth factors promote functional repair and plasticity of the chronically injured spinal cord. J Neurosci. 2010 Feb 3;30(5):1657-76. Research supported by the Christopher and Dana Reeve Foundation and the Sam Schmidt Paralysis Foundation, the AOSpine North America, the Canadian Institutes of Health Research and the Krembil Foundation.

STROKE

How Suppressing a Protein Can Prevent Brain Cell Death

During cardiac arrest, the brain is deprived of oxygen, which can cause brain cells to die typically within a few minutes. TWRI's Dr. Michael Tymianski and his team are aggressively working to learn how to prevent the death of brain cells, lessening the likelihood of permanent damage.

As reported in the journal *Nature Neuroscience,* the team used gene therapy in an animal model to specifically block the production of TRPM7—a protein responsible for causing cell death—in the hippocampus, a region of the brain responsible for high level functions such as learning, memory and emotion and also very sensitive to oxygen deprivation. Through this, the team was able to prevent irreversible brain cell death following a stroke.

"We are excited by this very promising research as it leads us one step closer to better care for the millions of people worldwide affected by stroke," comments Dr. Tymianski. "If we can better understand how to prevent this cell death, we could help reduce or remove disabilities associated with stroke. These findings are not only important for stroke victims but potentially also for patients with Alzheimer's and Parkinson's disease, conditions where brain cells are often deprived of oxygen, resulting in their death."

Sun HS, Jackson MF, Martin LJ, Jansen K, Teves L, Cui H, Kiyonaka S, Mori Y, Jones M, Forder JP, Golde TE, Orser BA, Macdonald JF, Tymianski M. Suppression of hippocampal TRPM7 protein prevents delayed neuronal death in brain ischemia. Nat Neurosci. 2009 Oct;12(10):1300-7. Research supported by the Canadian Institutes of Health Research, the US National Institutes of Health, the Canadian Stroke Network and the Krembil Seed Fund.

Dr. Michael Tymianski

MALIGNANT MESOTHELIOMA

Identifying New Investigative Tools Against Disease

Dr. Geoffrey Liu

The OCI-UHN Mesothelioma Research Program Team has identified a substance in blood that helps to predict treatment response in patients with malignant mesothelioma (MM), a rare tumour in the thin lining around the lungs and inner walls of the chest (pleura) related to asbestos exposure that occurred many years prior to cancer development.

Explains senior author Dr. Geoffrey Liu, "By using a simple blood test that looks for changes in specific proteins known to be associated with MM, we can better understand how the tumour is responding to treatment early on, and plan the remaining course of a patient's treatment accordingly."

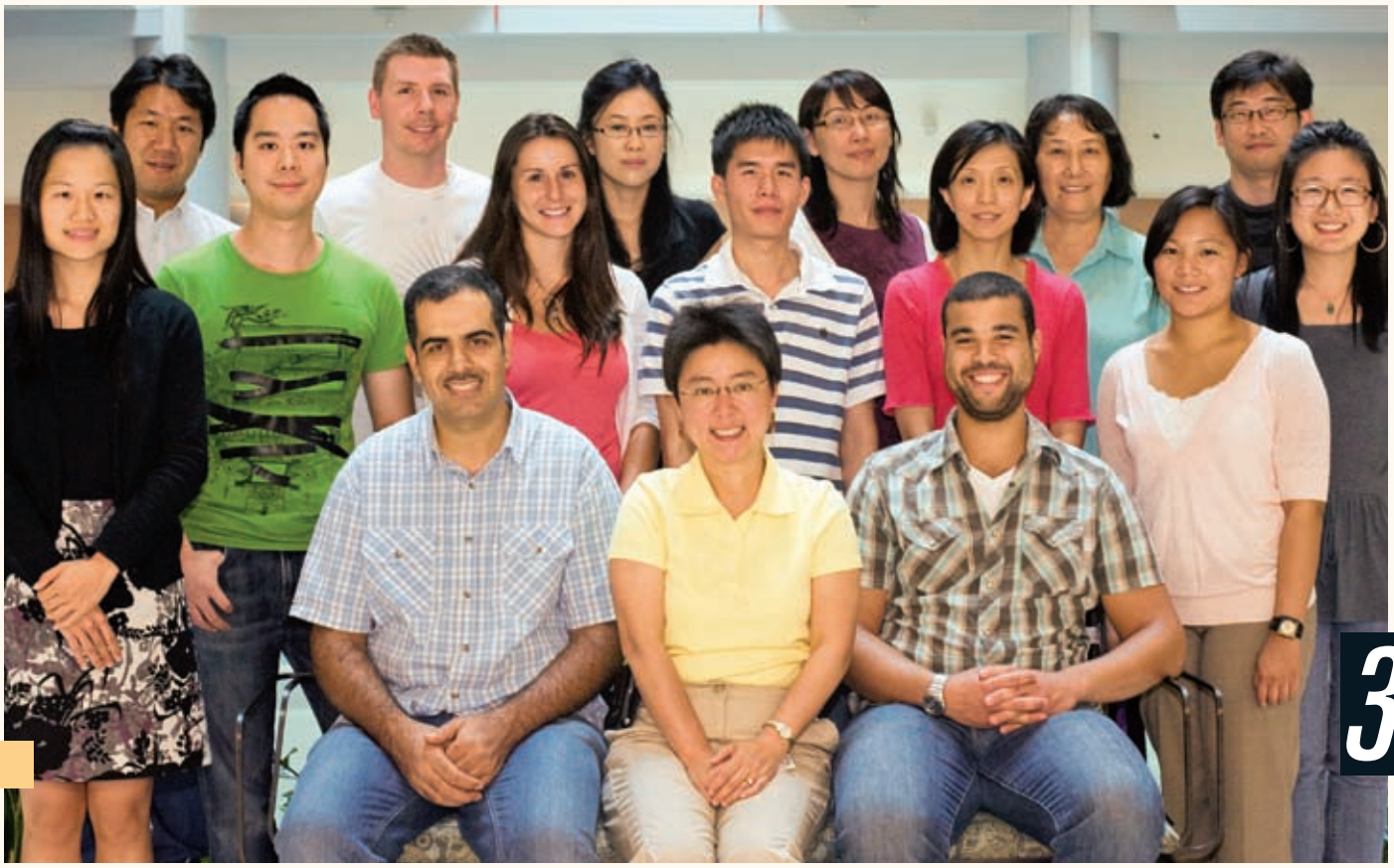
With Drs. Natasha Leighl, Ron Feld, Demetris Patsios, Ming-Sound Tsao and Marc de Perrot and colleagues from across Ontario, the team ran extensive tests on blood samples from 41 MM patients to screen for changes in the proteins SMRP (soluble mesothelin-related peptide) and OP (osteopontin). Findings show that rising SMRP levels were observed in all patients whose disease had progressed, and that patients responding to treatment had decreasing SMRP levels. Similarly, patients with stable disease had stable SMRP levels.

"When we used existing radiology tools to determine treatment response, we were unable to detect any significant association between relative changes in OP levels and disease course in the patients we examined," says Dr. Liu. "However, there was a significant association between SMRP changes and clinical outcome observed in patients receiving systemic therapy. With ongoing studies, SMRP could be a useful tool for physicians to detect changes in disease course that is more effective than the standard radiologic methods used today."

Wheatley-Price P, Yang B, Patsios D, Patel D, Ma C, Xu W, Leighl N, Feld R, Cho BC, O'Sullivan B, Roberts H, Tsao MS, Tammemagi M, Anraku M, Chen Z, de Perrot M, Liu G. Soluble mesothelin-related peptide and osteopontin as markers of response in malignant mesothelioma. J Clin Oncol. 2010 Jul 10;28(20):3316-22. Research supported by the Ontario Ministry of Health and Long-Term Care, a Cancer Care Ontario Chair in Experimental Therapeutics and Population Studies, and by the Alan B. Brown Chair in Molecular Genomics through the PMH Foundation. The Mesothelioma Research Program is supported by the Masters Insulators Association of Ontario, International Association of Heat and Frost Insulators and Asbestos Workers, Local 793 and other Unions and the Imperial Oil Charitable Foundation.

HEAD AND NECK CANCER

Global Screen Identifies Future Therapy Targets



Dr. Fei-Fei Liu (seated, centre) and her lab

For patients with head and neck squamous cell cancer (HNSCC), there is an urgent need to identify molecular changes that can predict the outcome of these cancers. Findings out of the laboratory of OCI's Dr. Fei-Fei Liu will contribute to this aim.

"Patients with locally advanced HNSCC have a 30% five year overall survival rate, which translates into a major opportunity to improve outcome for patients based on the molecular abnormalities of their disease," comments Dr. Liu. "Specifically, by developing predictive tests, health care teams could significantly improve patient selection for appropriate treatment and guide the development and evaluation of new therapies."

With Drs. Bayardo Perez-Ordonez, Igor Jurisica, Brian O'Sullivan, John Waldron and Bernard Cummings, Dr. Liu's team, led by Dr. Angela Hui, conducted a series of molecular tests to survey the global expression of microRNAs (miRNAs)—important molecules involved in the regulation of gene expression—in HNSCC versus normal or non-cancerous tissues. In total, the levels of 38 of the 117 detected miRNAs (33%) were significantly changed in these malignant tissues. Specifically, low levels of miR-375 and high levels of miR-106b-25 might play cancer-promoting roles in HNSCC.

Future studies will look to further dissect the complex molecular activities that underlie this disease in an effort to develop a molecular disease signature and, ultimately, to help to design future treatment strategies.

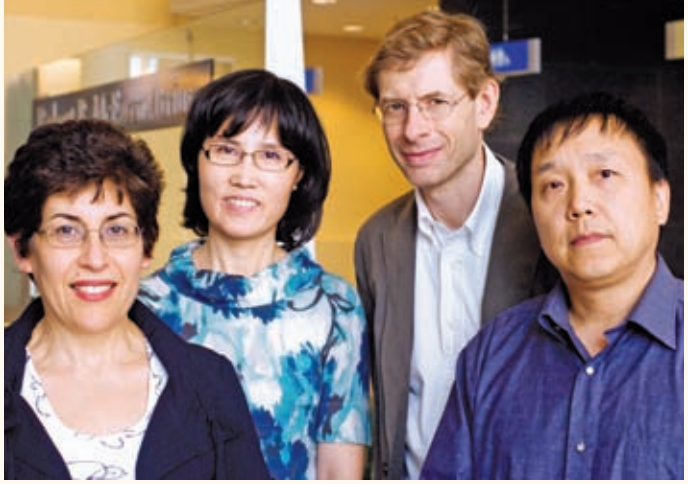
Hui AB, Lenarduzzi M, Krushel T, Waldron L, Pintilie M, Shi W, Perez-Ordonez B, Jurisica I, O'Sullivan B, Waldron J, Gullane P, Cummings B, Liu F-F. Comprehensive microRNA profiling for head and neck squamous cell carcinomas. Clin Cancer Res. 2010 Feb 15;16(4):1129-39. Research supported by the Ontario Institute for Cancer Research, the Canadian Institutes of Health Research, the Dr. Mariano Elia Chair in Head and Neck Cancer Research, the Wharton family, Joe's Team, Gordon Tozer, the Canada Research Chairs Program, the Canada Foundation for Innovation, IBM, the Campbell Family Cancer Research Institute and the Ministry of Health and Long-Term Planning.

ATHEROSCLEROSIS

Understanding the Beginnings of Disease

Atherosclerosis is the build-up of cells and fatty materials, such as cholesterol, on the inside of blood vessels and leads to the development of lesions that thicken artery walls. The exact workings behind how atherosclerotic lesions form is currently unknown; however, a TGRI group is providing new evidence that may help change this.

Dr. Myron Cybulsky and his team paired a specific cell labeling technique with state-of-the-art microscopy to inspect how immune cells accumulate in artery walls to form the initial lesions of atherosclerosis. What they found was quite significant: in response to a high-fat diet, immune cells in the artery wall divide and recruit more immune cells from the blood into the artery wall. Over time, these cells accumulate in the artery and ingest fatty materials, thus thickening the wall. Arterial cell proliferation was dependent on a protein called granulocyte/macrophage colony stimulating factor (GM-CSF). Previously, it was not appreciated that immune cells divide in the early stages of atherosclerosis, and that GM-CSF is an important regulator of this process.



Dr. Myron Cybulsky (third from left) with lab staff members (L-R) Jenny Jongstra-Bilen, Mian Chen and Suning Zhu

"Through an additional molecular layer of investigation to the previously mentioned imaging studies, we were able to show that the GM-CSF protein, which is normally involved in several immune cell functions, is responsible for immune cell division in early lesions," explains Dr. Cybulsky. "These findings may be critical in implementing new strategies for future treatments targeting GM-CSF to specifically prevent the immune cell division that contributes to the development of atherosclerosis."

Zhu SN, Chen M, Jongstra-Bilen J, Cybulsky MI. GM-CSF regulates intimal cell proliferation in nascent atherosclerotic lesions. J Exp Med. 2009 Sep 28;206(10):2141-9. Research supported by the Heart and Stroke Foundation of Ontario.

LUNG TRANSPLANTATION

Gene Therapy Repairs Injured Lungs

Dr. Shaf Keshavjee

Dr. Shaf Keshavjee and a team of internationally respected collaborators have successfully used gene therapy to repair previously unsuitable donor lungs for transplantation. The eloquent series of investigations, conducted outside the body, were performed to examine inflammation and organ rejection, two main complications after transplant surgery.

Studies were conducted in large animal and human models of end-stage lung disease. Using an innovative procedure that was developed by the team, donor lungs were maintained at normal body temperature and were administered IL-10 gene therapy. IL-10 was the gene therapy candidate chosen specifically for its anti-inflammatory capabilities.

"We are very excited," says Dr. Keshavjee. "It is as if gene therapy stimulates each individual cell to manufacture many more proteins in its own IL-10 factory. This protein decreases the inflammatory potential of cells injured before and during the transplant process. It also has the capacity to suppress the recipient's immune system, which rejects the transplanted organ."

Findings showed that lungs treated with IL-10 gene therapy had significantly improved blood flow throughout the organ and were considerably better at taking in fresh oxygen and removing carbon dioxide. In fact, the effect was so significant it lasted up to 30 days post-surgery. Dr. Marcelo Cypel, the study's first author, explains, "Anything we can do to prevent lung injury, especially in the first 72 critical hours after surgery, would have a significant impact on survival and quality of life after transplantation."

Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, Anraku M, Sato M, Medin J, Davidson BL, de Perrot M, Waddell TK, Slutsky AS, Keshavjee S. Functional repair of human donor lungs by IL-10 gene therapy. Sci Transl Med. 2009 Oct 28;1(4):4ra9. Research supported by the Canadian Institutes of Health Research and the Center for Gene Therapy National Institutes of Health.

Dr. Elena Moro

PARKINSON'S DISEASE

Researching the Long-Term Effects of Deep Brain Stimulation

Findings from an international team of investigators led by TWRI researchers provide strong evidence confirming the long-term efficacy of deep brain stimulation (DBS) in particular regions of the brain for patients with advanced Parkinson's disease (PD).

TWRI's Drs. Elena Moro, Andres Lozano and Anthony Lang and collaborators from France, Sweden, Germany, Spain, Italy, the Netherlands and the UK undertook a review of 51 patients who received either subthalamic nucleus (STN) or globus pallidus internus (GPi) DBS following a minimum of five years of treatment. Overall, study findings showed improvements in the patients' motor skills with either STN- or GPi-DBS. Both groups of patients also experienced marked decreases in the frequency of involuntary movements due to anti-PD medications (dyskinesias).

"Although this study was not a comparison between the two brain targets, patients who underwent GPi-DBS experienced less adverse effects, whereas STN-DBS provided more motor improvement," comments Dr. Moro. "We have confirmed that DBS in both regions of the brain are effective in improving motor PD signs with sustained benefit at the five to six year follow-up mark. Future studies will work towards understanding why STN-DBS patients may experience better outcome of motor signs while GPi-DBS patients experience fewer adverse effects."

Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, Kulisevsky J, Obeso JA, Albanese A, Hariz MI, Quinn NP, Speelman JD, Benabid AL, Fraix V, Mendes A, Welter ML, Houeto JL, Cornu P, Dormont D, Tornqvist AL, Ekberg R, Schnitzler A, Timmermann L, Wojtecki L, Gironell A, Rodriguez-Oroz MC, Guridi J, Bentivoglio AR, Contarino MF, Romito L, Scerrati M, Janssens M, Lang AE. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord. 2010 Apr 15;25(5):578-86.
Research supported by Medtronic.

LUPUS

Modeling Flare and Active Disease to Help Define Clinical Trial Inclusion

Systemic lupus erythematosus (SLE)—an autoimmune disease affecting primarily women in their reproductive years and which results in damage to internal organs, joints and skin—has provided a challenge to health care teams considering the design and recruitment of patients for clinical trials, due to the uniqueness of symptom severity and organ involvement for individual patients. A group of TWRI investigators has been working to overcome this challenge by examining the frequency and determinants of flare (clinically significant increase in disease activity) and persistently active disease (PAD).

As explained by Dr. Dafna Gladman, "Based on clinical data, our team has developed and tested models that attempt to predict flare and PAD. We believe this new model may help pave the way in determining clinical models for the prediction of these outcomes and providing a guideline describing how future SLE clinical trials can be organized."

With Dr. Murray Urowitz, the team prospectively collected data from the Toronto Lupus Cohort to determine the incidence of flare and PAD in 2004 and 2005. Findings show the annual incidence of flare and PAD were similar in both years, with 33% of patients experiencing more than one flare per year, and nearly half experiencing greater than one PAD per year. This suggests that using flare as the primary outcome variable in clinical trials fails to capture clinically important outcomes like PAD.

Dr. Gladman elaborates, stating, "PAD may be an important criterion to include when designing clinical trials in order to determine the therapeutic efficacy of a drug based on its ability to improve PAD, as well as in the interest of preventing PAD. The expected frequencies of flare and PAD during the year may serve a useful role in guiding the design of clinical trials, and, in particular, when selecting the duration of treatment or follow-up required."

(L-R) Drs. Dafna Gladman and Murray Urowitz with biostatistician Dominique Ibañez

Nikpour M, Urowitz MB, Ibañez D, Gladman DD. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. Arthritis Rheum. 2009 Sep 15;61(9):1152-8. Arthritis Rheum. 2009 Sep 15;61(9):1152-8. Research supported by the Centre for Prognosis Studies in the Rheumatic Diseases, the Smythe Foundation, the Ontario Lupus Association, the Lupus Society of Alberta, the Arthritis Centre of Excellence and the Geoff Carr Lupus Fellowship.

Dr. Natasha Leighl

LUNG CANCER

Targeting Therapy at the Early Stages of Disease

According to a Phase II clinical study finding from the laboratories of OCI's Dr. Natasha Leighl and TGRI's Dr. Thomas Waddell, gefitinib—a drug used to treat cancer that acts to inhibit the activity of a growth-causing protein (epidermal growth factor receptor, or EGFR) in cancer cells—may be a safe and feasible regimen for patients diagnosed with early (stage I) non-small-cell lung cancer (NSCLC).

Patients received 250mg/day of gefitinib for 28 days, and then had surgical removal of their tumours. High resolution computed tomography scanning immediately before the surgeries revealed that 43% of the patients had some tumour shrinkage and, interestingly, this was seen more often in females and non-smokers. The study also went on to show that gefitinib posed no additional surgical risk in patients with clinical stage I NSCLC and that 78% of these patients remained disease-free two years after surgery.

"Except for mutations in the EGFR gene, we did not find any other factors that were predictive of major response ," says Dr. Leighl. "As stage I NSCLC is potentially treatable by curative surgery, with a five year survival rate of 60-70%, it's important that future research is focused on finding and refining treatment options in selected patients, to allow medical teams to treat patients earlier and in a more molecularly-targeted manner. Our study design is an excellent way to identify markers that may predict response or resistance to novel therapies in lung cancer."

Lara-Guerra H, Waddell TK, Salvarrey MA, Joshua AM, Chung CT, Paul N, Boerner S, Sakurada A, Ludkovski O, Ma C, Squire J, Liu G, Shepherd FA, Tsao MS, Leighl NB. Phase II study of preoperative gefitinib in clinical stage I non-small-cell lung cancer. J Clin Oncol. 2009 Dec 20;27(36):6229-36. Research supported by the Junior Investigator Awards from Princess Margaret Hospital/University Health Network, AstraZeneca, the Canadian Cancer Society/National Cancer Institute of Canada and the Jacqueline Seroussi Memorial Foundation for Cancer Research Award.

LIVER TRANSPLANT

Determining When and Why to Apply the Brakes

Dr. Ian McGilvray

Living donor liver transplantation (LDLT) is a globally accepted method to treat end-stage liver disease. Now, a TGRI-led study is examining the reasons why donor liver surgeries may be stopped in the operating room—also known as a 'no go' operation.

When asked, study lead Dr. Ian McGilvray explains that while LDLT currently comprises less than 5% of adult liver transplants in North America, the implications of this research are key to potentially increasing the rates of LDLT one day. For example, a more widespread use of the procedure would depend on the definition of optimal recipient and donor characteristics. It is also important to understand why some patients who go into the operating room are not suitable to donate, so that health teams can improve upon and further develop this practice in the future.

The research group conducted a retrospective review of all patients brought to the operating room for donor hepatectomy (right liver lobe removal) between October 2000 and November 2008 and found that out of 257 of these patients, the donor operation was aborted in 12 (4.7%) cases. Operations were aborted due to unusual liver ductal or vascular anatomy, unsuitable liver quality or unexpected intraoperative events that placed donors at unacceptably high risk.

"To maintain the highest degree of patient safety, it is imperative to understand the elements that prevent surgeries from being completed and this study is an important step in optimizing procedures," comments Dr. McGilvray. "These findings have changed our imaging protocol to improve preoperative organ detection and complement our increased appreciation of which cases to avoid based on unique organ structure. With continued improvements to preoperative imaging and assessment criteria, the rate of 'no go' donor liver surgeries should decrease, but will never be zero because unpredictable factors are always a possibility."

Guba M, Adcock L, MacLeod C, Cattral M, Greig P, Levy G, Grant D, Khalili K, McGilvray ID. Intraoperative 'no go' donor hepatectomies in living donor liver transplantation. Am J Transplant. 2010 Mar;10(3):612-8.

Dr. Gary Rodin

CANCER

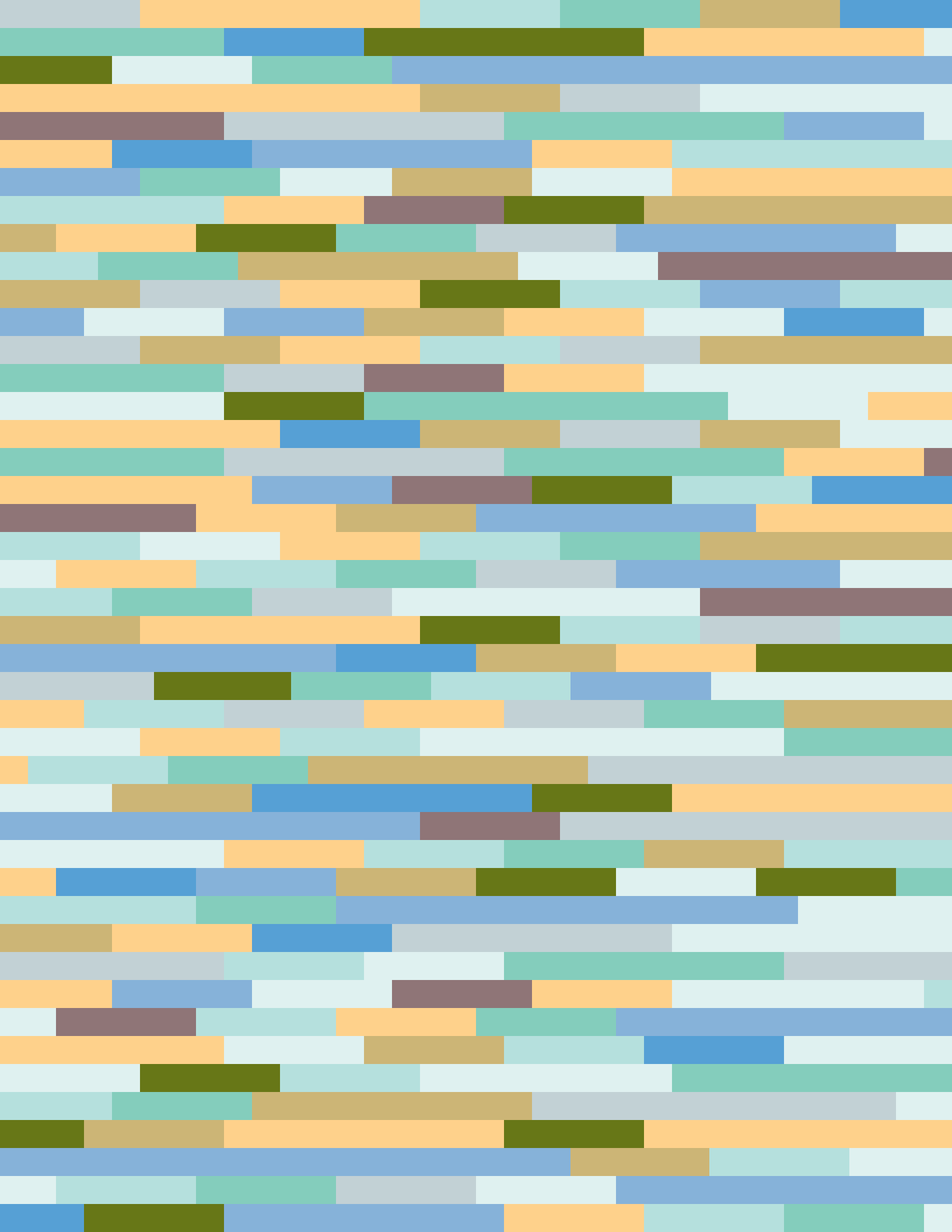
Getting to the Root of Depression in Patients with Advanced Disease

UHN's Dr. Gary Rodin and colleagues are providing strong evidence that emphasizes the need for integrated approaches to address emotional and physical distress in patients with advanced metastatic gastrointestinal and lung cancer. Similar to other medical illnesses, cancer is a risk factor for depression, which can weaken treatment compliance and cause higher rates of health care utilization.

Dr. Rodin, with a team of UHN researchers, conducted the first longitudinal predictive study of depression in patients with metastatic cancer. They recruited 365 patients with metastatic lung or gastrointestinal cancer to complete, at two monthly intervals, measures of physical distress and psychosocial functioning, including self-esteem, attachment security, spiritual well-being, social support, hopelessness and depression. Of those surveyed, 35% reported at least mild depressive symptoms, with 16% reporting moderate to severe depressive symptoms, which were three times more common in the final three months of life than in the year before. A constellation of physical suffering and psychosocial vulnerability was found to predict depression near the end of life.

"Our findings further confirm that depressive symptoms in advanced cancer patients are relatively common and may occur as a final 'common pathway' of distresses in response to the proximity to death, physical suffering and individual psychosocial vulnerabilities," explains Dr. Rodin. "Future studies are needed to evaluate the benefit of preventive and therapeutic options for these patients, including integrated psychosocial and palliative interventions to address the emotional and physical suffering experienced by these patients."

Lo C, Zimmermann C, Rydall A, Walsh A, Jones JM, Moore MJ, Shepherd FA, Gagliese L, Rodin G. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J Clin Oncol. 2010 Jun 20;28(18):3084-9. Research supported by the Canadian Institutes of Health Research, York University and the Edith Kirchmann Fellowship at Princess Margaret Hospital.



INSTITUTES

UHN Research is organized on a three-institute model. Each hospital has an affiliated research institute. Institutes have separate governance structures but all three are under the direction of UHN's Vice President, Research. The following pages describe our Institutes.

ONTARIO CANCER INSTITUTE

TORONTO GENERAL RESEARCH INSTITUTE

TORONTO WESTERN RESEARCH INSTITUTE

Ontario Cancer Institute

38

Research Space
373,000 sq ft

Publications
815

Total External Funding
$122,557,000

Senior Scientists	49
Scientists	18
Affiliate Scientists	10
Assistant Scientists	3
CRU Members	165
TOTAL RESEARCHERS	245
Fellows	217
Graduate Students	216
TOTAL TRAINEES	433
TOTAL STAFF*	613

*Where researchers have more than one affiliation within each institute, only one is indicated. See www.uhnresearch.ca for more information on affiliations. Staff figure accounts for administrative and technical employees based at OCI and does not include Research Support Services staff, who support researchers at all three institutes.

Senior Scientists

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Chung, Peter
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Oza, Amit
Payne, David
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Pierre, Andrew
Rasty, Golnar
Reece, Donna
Ringash, Jolie
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Sahgal, Arjun
Santos, Gilda
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Sridhar, Srikala
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Sutherland, D. Robert
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Youngson, Bruce
Zhong, Toni
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Vice President, PMH
Sarah Downey

Executive Director, Research Operations
Lisa Alcia

Vice President, Research
Christopher Paige

Toronto General Research Institute

40

Research Space
267,000 sq ft

Publications
726

Total External Funding
$65,570,000

Senior Scientists	57
Scientists	19
Affiliate Scientists	53
Assistant Scientists	1
CSRC Members	56
TOTAL RESEARCHERS	186
Fellows	158
Graduate Students	108
TOTAL TRAINEES	266
TOTAL STAFF*	378

*Where researchers have more than one affiliation within each institute, only one is indicated. See www.uhnresearch.ca for more information on affiliations. Staff figure accounts for administrative and technical employees based at TGRI and does not include Research Support Services staff, who support researchers at all three institutes.

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Cellular & Molecular Biology

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Slinger, Peter

Experimental Therapeutics

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Ross, Heather
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Goldszmidt, Eric
Granton, John
Grigoriadis, Sophie
Kachura, John R
Kennedy, Sidney
Keystone, Edward
Lilly, Leslie
Loke, Julian
Neary, Mary Ann
O'Malley, Martin
Rajan, Dheeraj
Rakowski, Harry
Ralph-Edwards, Anthony
Reznick, Richard
Richardson, Robert
Roberts, Heidi
Ross, John
Straus, Sharon
Sutton, David
Sweet, Joan
Wolman, Stephen
Yeo, Erik

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Division Head, Cell and Molecular Biology
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Richard Weisel

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Gary Levy/Ian McGilvray

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Thomas Waddell
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Lisa Alcia

Vice President, Research
Christopher Paige

Toronto Western Research Institute

42

Research Space
105,000 sq ft

Publications
504

Total External Funding
$32,166,000

Senior Scientists	46
Scientists	7
Affiliate Scientists	15
CSRC Members	57
TOTAL RESEARCHERS	125
Fellows	73
Graduate Students	95
TOTAL TRAINEES	168
TOTAL STAFF*	216

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Brain, Imaging & Behaviour - Systems Neuroscience

Senior Scientists
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Saint-Cyr, Jean

Fundamental Neurobiology

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Genetics & Development

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Wither, Joan

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Health Care & Outcomes Research

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Patient Based Clinical Research

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Shapiro, Colin
Sharpe, James

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Vision Science

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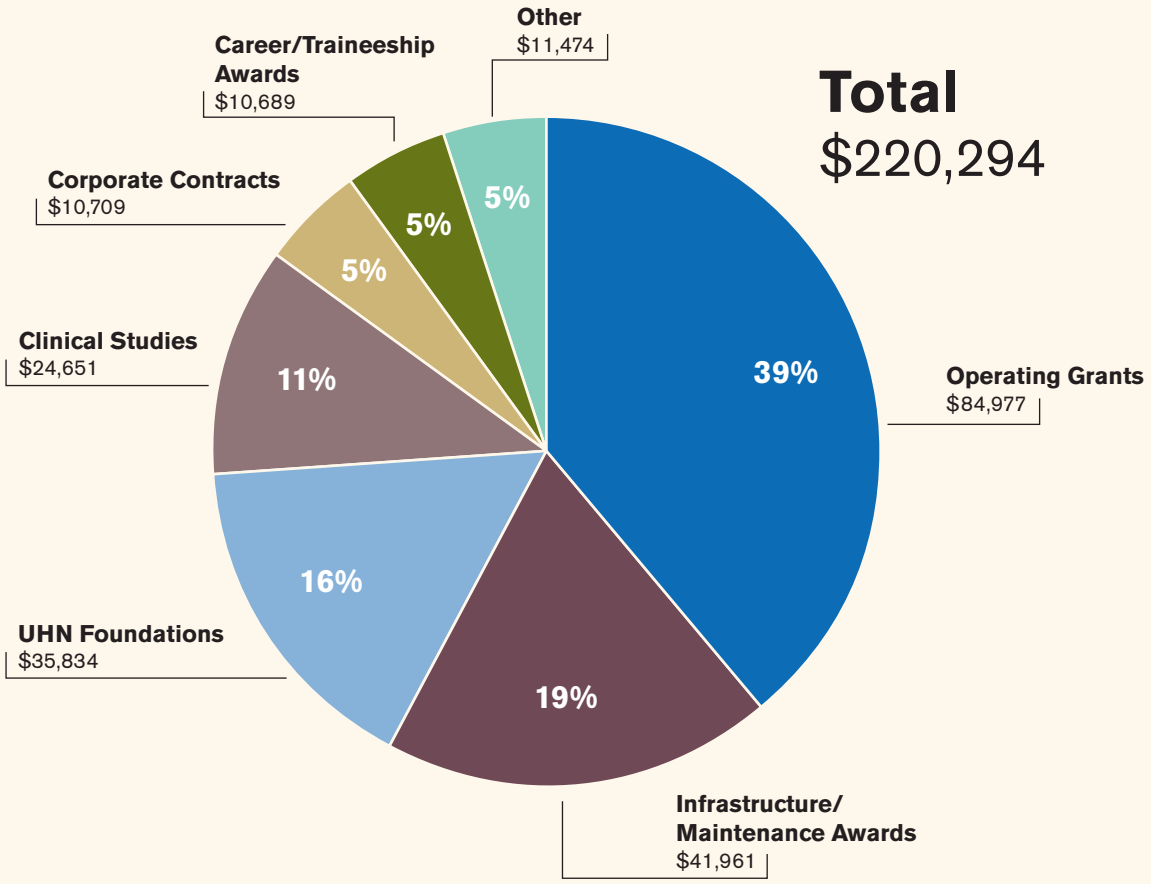
Financial Information

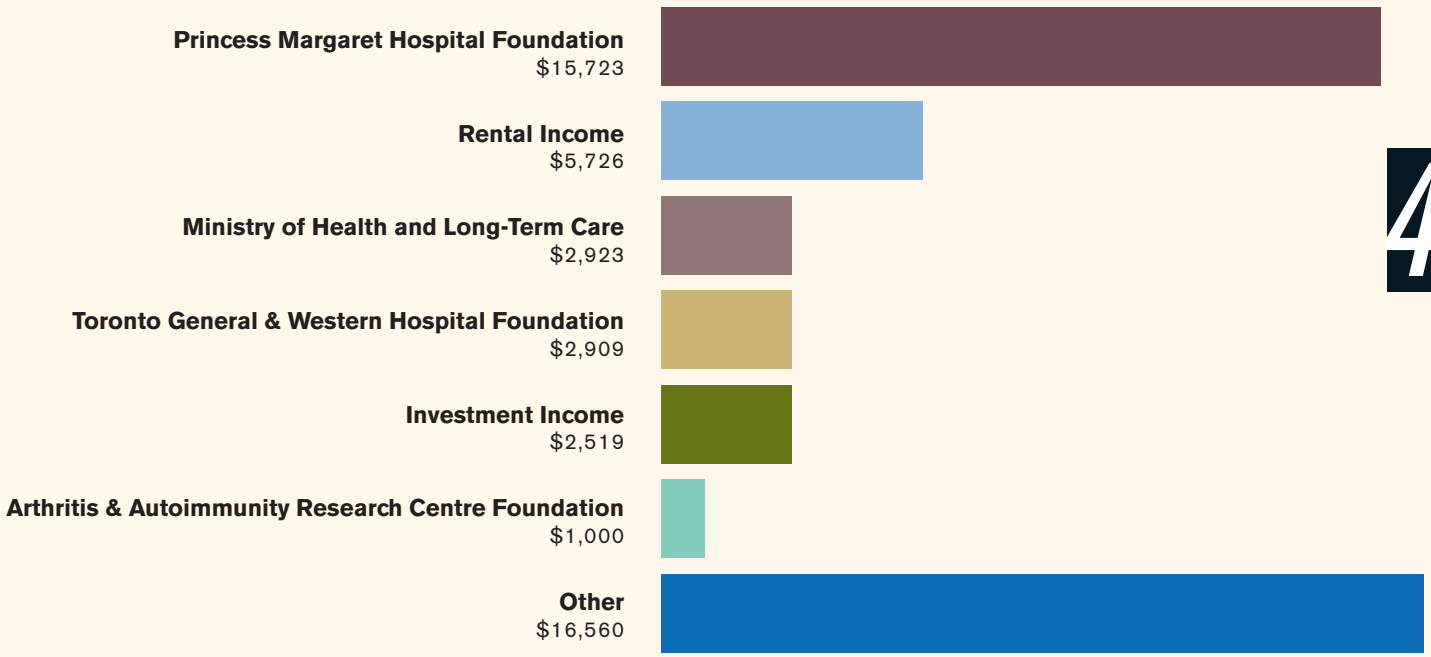
TOTAL PROJECT FUNDING AWARDED

(by type, in thousands)



RESEARCH CORE/TMDT OPERATING FUNDING

(in thousands)



Total
$47,360

All figures represent fiscal year 2009/10 and include Ontario Cancer Institute (Princess Margaret Hospital); Toronto General Research Institute (Toronto General Hospital); Toronto Western Research Institute (Toronto Western Hospital); Toronto Medical Discovery Tower (TMDT). Figures may not sum due to rounding.

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