



NET RESULTS

Report on research at University Health Network

W I N T E R • 2 0 0 2

Strategic Planning for Research

Research Business Development explained

New Canada Research Chairs named

All inside...

The Immense Promise of Regenerative Medicine

UHN scientists investigate innovative treatments for organ failure, organ rejection, injury and disease

Dr. Shaf Keshavjee was in the operating room during the world's first successful double-lung transplant in 1986. "I was fortunate enough to have been the resident who closed the incision," he explains. Now a Senior Scientist in the TGRI, Dr. Keshavjee researches ways to improve lung function after transplant. "In our lab, we are looking at ways of using molecular and genetic strategies to express immunomodulatory proteins in donor organs before transplant. In pre-clinical studies we have shown that the cytokine interleukin-10 can significantly enhance the function of donor lungs post-transplant. Our hope is to bring this therapy to the clinical setting to improve the outcomes of transplantation in our patients."

One of four key trends

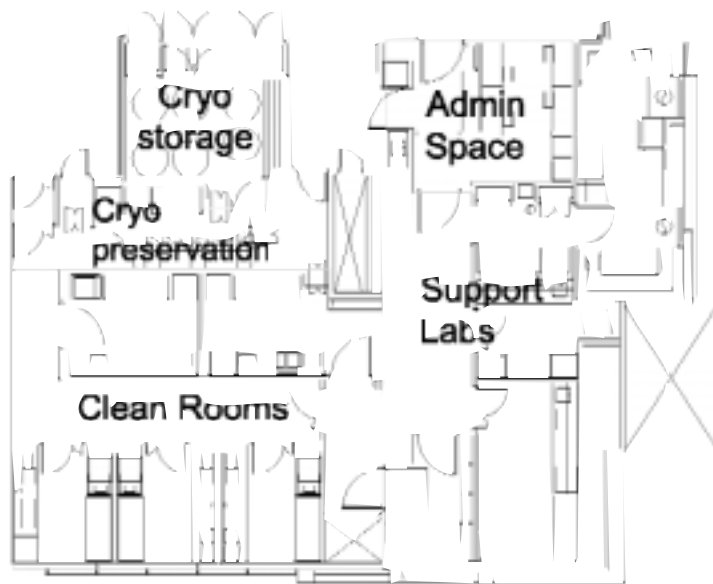
Dr. Keshavjee's research is one facet of UHN's program in regenerative medicine. Regenerative medicine uses the body's own cells and growth factors to repair or grow tissues, organs and cells. It encompasses organ transplantation, molecular therapy, gene therapy, stem cell therapeutics, cell therapy and tissue engineering.

Regenerative Medicine was one of the four trends selected by the UHN Task Force on New Diagnostic Tools and Treatments as the "most significant and potentially transformative" for UHN in the next decade. It has also been selected as a priority program within the TGRI.

Its selection as a key trend reflects the strength of UHN's current position in regenerative medicine—in terms of both our clinical and our research activities. UHN research successes in this field are many and varied, in fields as diverse as cardiovascular research and cancer.

Repairing the heart

For example, a TGRI research program led by Drs. Richard Weisel, Donald Mickle, Terrence Yau, and Ren-Ke Li focuses on molecular and cell therapy to treat ailing hearts. Their team has already shown that implanting cardiomyocytes into scar tissue in the heart can improve the heart's ability to pump blood after heart attack. Recently they have had success with an innovative approach that involves expressing a growth factor in these cells prior to implant. "VEGF increases angiogenesis or growth of blood vessels in the area of the implant," explains Dr. Li, "which increases the blood flow to these cells by about 70% as compared to implanted cells not expressing this growth factor." /continued on page 3



The new UHN Research Cell Processing Centre (2,900 sq ft) is being developed by a team led by Dr. Hans Messner and will be a vital part of the infrastructure established for research in regenerative medicine.

Hospital Research Makes Its Voice Heard

There are clear advantages to uniting with others to advance common interests. Whether the issues are research ethics, commercial relationships, or the necessity of stable research funding, it is crucial that we influence policies that have impact on us. UHN is involved with external bodies—locally, provincially, and federally—which do just this.

In 2001, the Toronto Academic Health Sciences Council, made up of the 8 CEOs from Toronto academic hospitals and three senior executives of the U of T, formed a Research Committee to advise them on issues relating to research. The Research Committee is composed of the Vice Presidents or Directors of the academic hospitals and is chaired by the Dean of Medicine.

One of the first tasks facing the TAHSC Research Committee was to examine various research policies across all UT-affiliated institutions with the aim of

harmonizing them where possible. Among the policies under examination are the intellectual property policies, guidelines concerning clinical trials agreements and use of animals in research, and grants and contracts administration. The purpose of harmonization is to identify best practices and to adopt, as much as possible, common policies, and streamline inter-institutional relationships and interactions.

At the provincial level, we launched the Council of Ontario Research Directors (CORD) in 2001. Its formation recognizes that teaching hospitals are working towards comprehensive research administration systems to manage the complex world of research infrastructure and funding. With over 6400 research staff and trainees, the 19 CORD member institutions spend more than \$450M/yr on research.

CORD will lobby for issues of importance to hospital-based and stand-alone research institutes, including full support

for indirect costs. The recent federal budget announcement promised a \$200M down-payment on indirect costs, but this is only a small portion of the true costs of doing research. CORD is also working with the Change Foundation and the Ontario Health Alliance to establish an Ontario Health Research Council to increase the base of provincially derived research funding.

On national issues, CORD is working with the Association of Canadian Academic Healthcare Organizations (ACAHO) to form an effective lobby for research issues that affect the entire Canadian research community.

Biomedical and health care research is a driving force in the economy at all levels—in this city, in Ontario and in Canada. The time is ripe for us to remind our politicians that an investment in our work produces tangible benefits for our country and its citizens.

Christopher J. Paige

Research Strategic Planning on Agenda for 2002

Joint Research Councils meet, agree to undertake strategic planning

Research leaders from TGRI, TWRI and OCI met with UHN senior management and the UHN Board of Trustees, members of the Boards of our Foundations and Research Support Services at the second annual Joint Research Council Meeting on October 1, 2001.

The purpose of the meeting was to review existing planning documents used to determine strategic directions in Research. In light of the recent UHN-wide planning process and the upcoming launch of the International Research Advisory Board for UHN, they decided to re-examine UHN Research strategic plans in order to better integrate with the existing planning environment.

“We are pleased that the hospital has recognized the importance of having global impact. To maintain our impact, Research will look at adopting a focused approach. Our focus will be determined through the strategic planning process,” explains Dr. Christopher Paige, Vice President, Research.

“The UHN Strategic Planning process also identified four new trends in tools and treatments. We now want to take a closer look at how these four trends fit with our plans for Research in the future,” he continues.

Research leadership is currently meeting to decide issues for planning, with a Strategic Planning retreat scheduled for this year.

Focus on Allied Health Research

The first annual Allied Health Research Day was held at UHN on Friday November 9, 2001. The Allied Health directorate was established in 2000. It encompasses chaplaincy, clinical nutrition, occupational therapy, pharmacy, physiotherapy, psychology, respiratory therapy, social work and speech language pathology. The Research Day was intended to profile research being conducted in allied health areas and to provide a forum for researchers to share results.

Regenerative Medicine...continued from page 1 / Preventing organ rejection

In another part of TGRI, Dr. Li Zhang is following a line of research that may eventually produce a way of avoiding transplant rejection without weakening the immune system. In the year 2000 her team discovered the CD4CD8 double-negative regulatory T-cell. These cells can act as a decoy for killer T-cells, thus protecting foreign

(OCI) are performing research that should lead to clinical trials of long-term gene replacement strategies within the next three years. “Hematopoietic stem cells can be easily isolated from the bone marrow of adults. Outside of the body, we can introduce genes into these cells using viruses as delivery vehicles: for example, the factor VIII gene that is defective in hemophilia. Once reimplanted, these cells will produce

lem. Dr. Charles Tator’s lab (TWRI), in collaboration with a team from the UT Bioengineering Department, showed that neurons in an injured spinal cord could be made to grow along an implanted plastic tube, resulting in increased mobility of lower limbs. “We are pursuing several strategies to enhance regeneration of nerve fibers through the tubes, including growth factors and matrix substrates which are embedded in the walls of the tubes,” explains Dr. Tator.

UHN Contributions to Regenerative Medicine Research

Landmark discovery of hematopoietic stem cells - 1956

World's first single and double lung transplants - 1983 and 1986

Canada's first molecular therapy trial in myeloma - 1995

tissue from destruction by the immune system. “In pre-clinical testing, we have shown that injecting these cells can increase the success of organ transplant,” she says, “and so we are hopeful that our ongoing work may eventually produce a cell therapy treatment for graft rejection, autoimmune diseases and cancer.”

Replacing missing genes

Building on UHN’s early successes in stem cell and molecular therapy research, a team of scientists at UHN led by Dr. Keith Stewart (Director, TGRI) and including Drs. Andre Schuh (TGRI) and Jeff Medin

the missing protein and thus, we hope, correct the problem over the long term,” explains Dr. Stewart. Since adult hematopoietic stem cells may indeed be plastic, or capable of developing into differentiated tissue other than blood cells, they may also eventually be applied to the repair of damaged organs.

Fixing the spinal cord

The spinal cord contains a universe of nerves which, once severed, are impossible to repair. But scientists at UHN are conducting preliminary studies in tissue engineering that may overcome this prob-

Bringing discoveries to the clinic

The examples above are only a small portion of the regenerative medicine research which is already thriving in individual laboratories. But UHN has also made a significant institutional commitment to the program.

Testing and validating new treatments requires specialized research infrastructure. In 2002 UHN will open a new cell processing facility dedicated to research in bone marrow transplant, built with federal, provincial and PMH Foundation funding. We have also launched a scientific recruitment campaign in regenerative medicine: this initiative has so far resulted in the recruitment of scientists such as Drs. David Kelvin and Jeff Medin.

“Our ultimate goal is to create and maintain a critical mass of scientists, and provide them with the tools to bring new technologies to clinical practice. Given our current successes there is every reason to expect UHN should lead this field, and we are committed to seeing that happen,” says Dr. Stewart.

IRAB Meeting Scheduled for June

The first meeting of the UHN International Research Advisory Board has been set for June 6-7, 2002. The new IRAB brings together six internationally-recognized scientists in high-impact areas to meet with UHN Research leadership and to advise on Research policy, governance and management. IRAB members include Joseph Fraumeni, Jr, MD, Director, NCI Division of Cancer Epidemiology and

Genetics; Victor Ling, PhD, Vice-President, Research, British Columbia Cancer Agency; Ferid Murad, MD, PhD, Director, University of Texas Institute of Molecular Medicine; John A. Parrish MD, Chair of Dermatology, Harvard Medical School; and Leena Peltonen MD, PhD, Chair of UCLA School of Medicine Department of Human Genetics (one member TBA).

TWRI Annual Research Day

Approximately 150 people turned out to see posters, attend talks and hear a keynote address delivered by noted stem cell researcher Dr. Ron McKay of the NIH. The Research Day was held November 1, 2001.

Recruitment

at UHN Research

Jeffrey A. Medin, PhD

Gene therapy has always been Dr. Jeff Medin's first love. Since his earliest days in science—his PhD studies of the enzymology of adenosine deaminase (one of the first products considered for a gene therapy trial) and terminal transferase—he has been focused on genetic approaches to disease treatment and cure. Before being recruited to OCI's Division of Experimental Therapeutics in 2001, he worked in two separate areas of gene therapy research: gene therapy



Jeffrey A. Medin, PhD

approaches for hematopoietic cells and for Fabry disease (in which impaired catabolism of alpha-galactosyl-terminal lipids causes vessel occlusions and ultimately cardiovascular, cerebrovascular and renal disease).

Cancer vaccines and suicide gene therapy

Today, in addition to continuing his earlier work in hematopoietic cells and Fabry disease, Dr. Medin is embarking on a study to create vaccines or immunotherapy-based treatment schemes for acquired diseases,

with a specific focus on prostate cancer. "The body has mechanisms to clear prostate cancer cells but these mechanisms are not always efficient," he says. "Our approach is to try and 'jump-start' the immune system into rapidly recognizing cancerous cells as foreign and to eliminate them." This approach will be broadly applicable against a number of known malignancies and human pathogens.

Another project in Dr. Medin's laboratory, in collaboration with Dr. Daniel Fowler of NIH, focuses on improvement in "suicide" gene therapy. "In bone marrow transplantation, graft versus host disease is still a major issue and causes a relatively high frequency of patient morbidity and mortality. We are currently optimizing methods to selectively kill graft cells following their important anti-tumour effects. Prior to transplantation into the host, cells are infected with a gene that renders them uniquely susceptible to a class of specifically cytolytic drugs. If rejection symptoms do develop, the cells can be cleanly and efficiently killed before the patient develops chronic graft-versus-host illness."

A "roller coaster" history

According to Dr. Medin, the challenge is to harness this immensely promising technique while at the same time ensuring the highest standards of safety. "Gene therapy has had a roller coaster ride over its history. It was first presented as a cure for any possible disorder either acquired or inherited, but the science proved much more complicated than expected. Recently, however, landmark research papers which demonstrate the

usefulness of this approach, combined with improved gene transfer technologies, have again demonstrated the power of gene therapy."

Monique Gignac, PhD

The Arthritis and Autoimmunity Research Centre at UHN is the largest of its kind in Canada. It comprises more than 100 scientists, staff and students working in five separate research centres. One of these centres, the Arthritis Community Research



Monique Gignac, PhD

& Evaluation Unit or ACREU, is led by Dr. Elizabeth Badley and has as its mission the study of the impact of arthritis and how it is managed, and to identify needs and gaps in treatment and support for people with arthritis in order to contribute to policy and program development in this area.

Coping and adaptation

One of the newest scientists in ACREU is Dr. Monique Gignac, a social psychologist and Scientist in the Division of Outcomes &

Population Health at TWRI. Dr. Gignac completed her Ph.D. at the University of Waterloo in social psychology focusing on adaptation of older adults to the aging process, and did a postdoctoral fellowship as part of the Canadian Aging Research Network.

At UHN, Dr. Gignac's research focuses on individuals with physically disabling illnesses, how they cope and how they have managed to adapt to chronic stress. One area of research looks specifically at older adult groups with osteoporosis and osteoarthritis, and the impact of such illnesses on the achievement of an independent lifestyle.

OA strikes at a critical time

Dr. Gignac's research also involves a longitudinal study of middle-aged adults who suffer from arthritis, and she is exploring the methods of adaptation individuals apply in order to effectively manage their condition and remain profitably employed. "This study is extremely important as people aged 40 and up are usually in their prime earning years and actively saving for retirement," she notes. "Unfortunately, these are also the years when arthritis symptoms can begin for many individuals and, as a consequence, people may be forced to make changes to or even give up their employment."

Precise measurement tools necessary

"We try, wherever possible, to develop precise measurement tools, including conducting psychometric statistical analyses, when developing and measuring key constructs. These analyses, which can include complex modeling and multivariate statistics, take into account individual differences but will

also identify any consistencies within the collected information," says Dr. Gignac.

In the future, Dr. Gignac will work with physicians, employers and ergonomics specialists to develop and test interventions directed to reduce the adverse impact of chronically disabling health conditions.

Vivek Rao, MD, PhD

Dr. Vivek Rao, a cardiovascular surgeon and Scientist at the Toronto General Research Institute, first became interested



Vivek Rao, MD, PhD

in recent developments and new techniques to preserve the heart during surgical transplantation while he was training to be a surgeon at the University of Toronto.

Brings heart pump to Toronto

"We recognized that one of the major tools available to surgeons around the world was the heart pump, but unfortunately this technology was not available in Toronto." Soon after obtaining private support to establish a heart pump program at TGRI, Dr. Rao

traveled to Columbia University, New York, to gain the surgical expertise required for successful heart pump transplantation. He returned to Toronto in July 2001.

The Left Ventricular Assist Device, the device used in the TGRI program, is designed to temporarily take over the primary functions of the heart, but not to permanently replace the heart itself. "This pump is used simply as a tool to support the patient's blood pressure and vital organs, on an interim basis, until a donor heart becomes available." This device has been successfully used in thousands of patients worldwide and is a well-established, standardized therapy for chronic heart failure.

Plastic surgery of the heart increases efficiency

Dr. Rao has also studied several other surgical procedures commonly used in the treatment of heart failure, including the modified DOR procedure, a technique in which the shape of the left ventricle is 'remodeled'. "This is basically 'plastic surgery' of the heart. We actually alter the shape of the heart in order to make it work much more efficiently."

Dr. Rao's research program includes preservation of the heart during transplantation, with a specific focus on prevention of graft coronary artery disease. In addition, he is collaborating with Dr. Richard Weisel to develop novel heart preservation techniques such as cell transplantation and cell therapy. "Eventually, we hope to establish a surgical clinic for the treatment of advanced heart disease that goes well beyond present-day conventional bypass or valve surgery."

"Relationships Are Our Business"

The Research Business Development Office at UHN

A typical day of the UHN Research Business Development Office (RBDO) might include a meeting with a large pharmaceutical company to develop a proposal; a practice run of a presentation being prepared for an upcoming talk to visitors from the Ontario Ministry of Finance; urgent review of several draft contracts and materials transfer agreements; and a meeting with a scientist to lay groundwork for a spin-off company being formed around his work.

More than technology transfer

The breakneck pace of the office is a clue to the scope of its activities. "People might know us as the technology transfer office," explains Bob McArthur, Director of the RBDO. "And while technology transfer is still an important part of what we do, we changed our name to reflect that we undertake a much wider range of business development functions on behalf of UHN Research." This means, in addition to the patenting and licensing activities that constitute technology transfer, the office is involved in forming spin-off companies to commercialize promising new technologies, funding these ventures through venture capital and angel investors, and incubating these companies within UHN.

TGRI Annual Research Day

A day-long series of talks and poster presentations was held October 31, 2001 to highlight research at TGRI. Over 180 people attended.



To do this, the RBDO engages in a directed effort towards building relationships and marketing UHN Research and the expertise of our scientists. "Relationships

"But through commercialization, we are able to draw on the resources of a partner to accelerate development of a promising technology..."

-Bob McArthur

are our business, and everything we do is geared towards creating relationships between the UHN community and the commercial world," Mr. McArthur stresses.

New intellectual property policy shares profits

In December 2001, the UHN Board of Trustees approved a new IP policy for UHN Research. "This past spring we commissioned a study that compared our draft policy to IP policies in other Canadian institutions and in American and international institutions," says Mr. McArthur. "Our policy compared favourably to these, and we are proud of the fact that ours addresses the formation of spin-off companies—an issue not yet addressed in other policies."

The UHN policy is an "institution-owns" policy, which means that if an invention is favourably evaluated, UHN will undertake to protect and commercialize it through appropriate mechanisms. After costs are recovered, profits are shared among the inventors, the division/department, UHN, and the UHN Foundations. This formula seeks to reward the discoverer and his collaborators as well as the organizations that support research.

Alternative funding a necessity

The RBDO figures prominently in UHN's plans to generate research funding in the future, and the new IP policy is a key piece of this. The new UHN strategic plan cites IP and business development revenues as an important means of increasing research revenue. Notes Dr. Christopher Paige, Vice President, Research, "As alternative funding sources become more important, we are establishing a culture of innovation and entrepreneurship among scientists, and we are equipping the RBDO to capitalize on commercialization opportunities our researchers generate."

Achieving global impact through commercialization

But enhanced funding is only part of the RBDO's mission. "Ultimately UHN's goal is to achieve global impact, and increased funding is only one step toward that goal," says Mr. McArthur. "But through commercialization, we are able to draw on the resources of a partner to accelerate development of a promising technology, to surmount regulatory hurdles more quickly

RBDO Statistics 2000/01:

**New discoveries disclosed: 31 •
New patents filed/in preparation: 14 • Trademarks/copyrights filed: 3
• License or options signed/under evaluation: 17 • Material transfer agreements signed: 235 • Spin-off companies formed/in development: 4 • Value of research contracts signed: >\$1M**

and to market a product world-wide. When this product is a drug or treatment that could help people suffering from disease or injury, the impact is immediate, tangible, and, we would like to think, global."

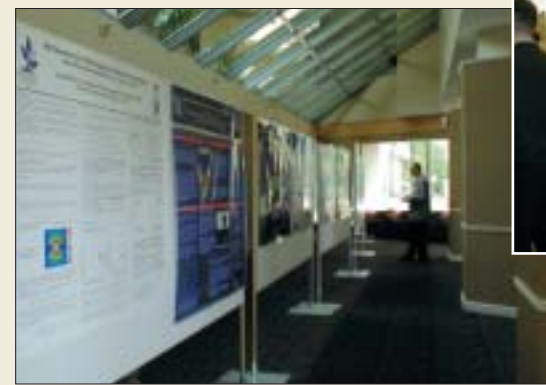
Access the new RBD IP policy on the Research Intranet at Support Services > Business Development > IP Policy

First Annual Imaging Symposium Held

The UHN-based Ontario Consortium for Image-Guided Therapy and Surgery (OCITS) joined with other members of the Imaging Network Ontario to co-host the first Annual Imaging Symposium October 19-20, 2001. OCITS researchers spoke on recent developments in image-guided therapy in oncology and urology as well as applications of image guidance in neurosurgery and orthopedic surgery. Over 20 UHN researchers are

involved in OCITS and other Ontario imaging consortia.

OCITS has also been successful in bringing MICCAI, the Medical Image Computing and Computer-Assisted Intervention Conference, to Toronto in 2003. This conference is the major annual international gathering in the areas of computer-assisted interventions, medical robotics and image processing.



The Symposium was sponsored by the Ontario R&D Challenge Fund and private sector partners.

Microarray Symposium a Hit

The second annual Microarray Symposium, presented by the UHN Microarray Centre, was held Oct 23-25, 2001. The sold-out affair attracted over 80 attendees from as far away as Australia and Finland. Its sponsors included the Ontario R&D Challenge Fund, the PMH Foundation, and 14 private sector sponsors.

New Medical Director at CSRC

Dr. John Parker, a noted cardiologist, has been appointed as Medical Director, TGH, for the UHN Clinical Studies Resource Centre. Dr. Parker will work with Dr. Jenny Heathcote, Medical Director, TWH, and CSRC management and staff to provide direction and support to their efforts to enhance clinical trials at UHN.

HONOUR ROLL

UHN Research extends its congratulations to the following researchers:

Drs. Claire Bombardier, Alex Jadad, and Kevin Kain (TGRI), who won Tier I Canada Research Chairs, which are awarded to experienced investigators recognized internationally for their achievements; and to **Dr. Shuzo Sugita** (TWRI), who won a Tier II Canada Research Chair as a promising new investigator. These announcements were made in December 2001.

Dr. Robert Bristow (OCI), who led a successful proposal to the Canadian Prostate Cancer Research Initiative establishing a five-year, inter-institutional prostate cancer network

Dr. Gerald Devins (OCI), one of two new CIHR Senior Investigators named across Canada in June 2001.

Drs. John Floras, Gary Lewis and Ren-Ke Li (TGRI), all named Career Investigators by the Heart and Stroke Foundation of Ontario

Dr. Ren-Ke Li (TGRI), who won a Premier's Research Excellence Award from the Province of Ontario

Dr. Fei-Fei Liu (OCI), who was named to the new UT/PMH Elia Chair in Head and Neck Oncology Research

Dr. Tak Mak, Director of the Amgen Institute at OCI, who was selected to give this year's UK-Canada Rutherford Lecture, a prize jointly established by the Royal Society of London and the Royal Society of Canada

Dr. David Mikulis (TWRI), UHN lead investigator on the \$48.6M Behavioural Research and Imaging Network (BRAIN) grant awarded by the Ontario R&D Challenge Fund

New Diagnostic Tools and Treatments at UHN

Four Future Trends Defined

As part of the *Strategic Directions* process, a Task Force was convened to investigate 30 high impact trends in biomedicine. During the consultation process, they evaluated current clinical and research activities in each area, established a target position for UHN and estimated the amount of effort it would take to get there. Based on these deliberations, the Task Force made the following recommendations, which were used by UHN in formulating its tactical plan for the next decade.

“The task force has identified four significant and potentially transformative trends that should drive UHN strategic planning. The selected trends are those that will significantly impact on patient care within the next decade, and are those in which UHN is best positioned to be an international leader.”

Quoted from Report of the New Diagnostic Tools and Treatments Task Force

GENOMICS/PROTEOMICS AND PATIENTS Encompassing the use of genetic/molecular profiles to identify risk, determine diagnosis and target treatments	CLINICAL INFORMATICS Encompassing the integration of electronic patient records with clinical and biological variables through computer-assisted technologies, eHealth initiatives and system-wide information systems
REGENERATIVE MEDICINE Encompassing gene-, cell-, tissue- and organ-based regenerative medicine	ADVANCED CLINICAL TECHNOLOGIES Encompassing minimally invasive, robot-assisted and image-guided procedures

Net Results is a magazine which reports on developments in Research at UHN. It is published by the Office of the Vice President, Research.

Your questions or comments can be directed to braunton@uhnres.utoronto.ca.



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