

SUNNYBROOK RESEARCH INSTITUTE RESEARCH REPORT 2004–2006

INVENTING THE FUTURE OF HEALTH CARE

RIGHT TURNS:
IMMUNOLOGY RESEARCH

SOUND FOCUS:
THERAPEUTIC ULTRASOUND

CLINICAL EPIDEMIOLOGY:
TAKE THREE

IMAGES OF EXCELLENCE:
SENTINELLE DEVELOPS MRI

LEARNING TO REACH:
EDUCATION AT SRI



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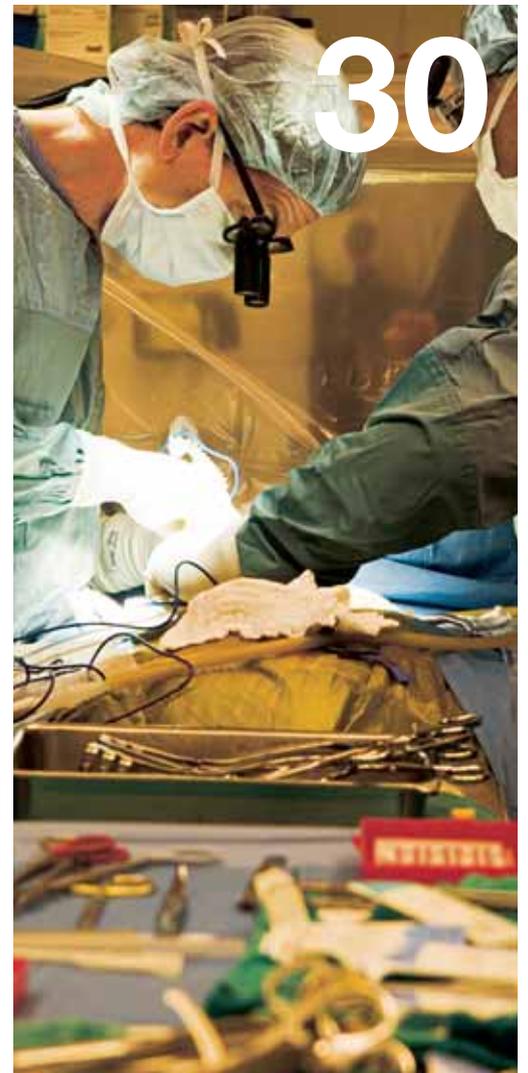


What's on the Cover

The polymethylmethacrylate (PMMA) beads you see on the cover are used in orthopaedic surgery at Sunnybrook Health Sciences Centre. PMMA is used clinically as a compound that, when prepared, cures into bone cement that helps devices and implants adhere to bone. It's commonly used, for example, to secure implants to bone during total hip replacement.

More recently, agents like PMMA that can be used to deliver biological therapies are being explored. The PMMA beads shown have been impregnated with antibiotics to help treat orthopaedic infections. Applying this principle toward the development of new treatments for musculoskeletal disorders is the cornerstone of the work in which some of our researchers are engaged.

This focus—to move discoveries into the clinic for the benefit of our patients—drives all that we do at Sunnybrook Research Institute, where we strive to understand and prevent disease, and develop treatments that enhance and extend life. These aims derive from a core vision: to achieve discovery and its translation into the clinic to set best practices.



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Message From Senior Leadership, Sunnybrook Health Sciences Centre

Our researchers are working to improve the quality of life for our patients and are achieving breakthroughs that are changing the face of health care



LEO STEVEN AND VIRGINIA MCLAUGHLIN

Sunnybrook Health Sciences Centre is proud of the significant accomplishments the research institute has achieved over the past two years. Although Sunnybrook Research Institute (SRI) is one of the youngest in the University of Toronto family, it has quickly become one of the most prominent. In the last few years SRI has nearly tripled its funding to become the second largest in Toronto, and has been home to a number of breakthroughs that have transformed health care.

Sunnybrook Research Institute has 600 world-class scientists and research staff who are tackling the most pressing problems in health care. Each day they work to prevent disease, improve patient care and develop life-enhancing treatments through their uniquely integrated “bench-to-bedside” approach to research.

Conducting more than a projected \$91 million in research last year alone, SRI is unearthing some of the most dramatic discoveries in health care. Proximity to the clinical activity and excellence in patient care at Sunnybrook are distinguishing features of the research institute. Learning from patients is key to SRI’s success, and the organization takes pride in this strong collaboration.

Over the last year, SRI researchers have explored methods of less invasive cardiovascular surgery, used leading-edge imaging techniques to improve diagnosis and treatment of cancer, uncovered significant findings to improve the treatment and prevention of mood disorders, and made next-stage critical discoveries in T cell development, which could potentially result in a therapy to treat patients with AIDS or other immune system deficiencies.

Our scientists are notable leaders in their fields, and as a result have been the recipients of numerous honours and awards from, among others, the Canada Research Chairs Program, Royal College of Physicians and Surgeons of Canada, Government of Ontario, Canadian Institutes of Health Research and the Canadian Cancer Society, over the past two years.

On behalf of the hospital and the many communities Sunnybrook serves, we offer congratulations to the research institute on another successful two years. We would also like to thank our funding partners, collaborators, and donors for their tremendous support and encouragement.

Virginia McLaughlin
Chair of the Board of Directors

Leo Steven
President and CEO

Message From the Vice-President of Research, Sunnybrook Health Sciences Centre

With our focus on the continuum of research at SRI—
from basic research to knowledge translation—we strive
to prevent disease and develop treatments that
enhance and extend life



DR. MICHAEL JULIUS

It is the best of times to be working in health research.

Over the last 10 years, the advances in our understanding of the human genetic code and how its products support health and contribute to disease have been breathtaking. Understanding the determinants of health and many diseases is either in hand or within our grasp. With our focus on the continuum of research at Sunnybrook Research Institute (SRI)—from basic research to knowledge translation—we strive to prevent disease and develop treatments that enhance and extend life. These aims derive from our core vision: to achieve discovery and its translation into the clinic to set best practices. We are dedicated to *inventing the future of health care*.

Central to achieving our vision is how we integrate research and clinical care. The research institute brings together scientists and clinician-scientists with diverse skills and backgrounds committed to excellence in their fields. Each scientist who calls SRI home is aligned with a research discipline—clinical epidemiology, clinical integrative biology, imaging, or molecular and cellular biology—and a strategic clinical program: aging and population health, cancer (Toronto Sunnybrook Regional Cancer Centre), cardiac (Schulich Heart Centre), musculoskeletal (Holland Orthopaedic & Arthritic Centre), perinatal and gynaecology, neurosciences, or trauma and critical care. Moreover, SRI is fully affiliated with the University of Toronto, a rich, enduring partnership. All of our scientists hold academic appointments there, and SRI and U of T are continually engaged in shared academic endeavours that extend beyond local borders to prominence on the international stage.

While this structure is critical to our success, it does not mean that every scientist at SRI concentrates on a specific disease. Rather, they are devoted to unraveling the mysteries of life processes, an undertaking simultaneously simpler and more complex. Because we cannot chart a cause-and-effect course of discovery, nor predict with any certainty the impact of a given discovery, researchers must embrace a level of uncertainty in their work. This calls for a research plan that is dynamic and responsive to discovery and its potential applications. Capturing and capitalizing on the potential for innovation inherent in this sometimes opportunistic path requires the most talented thinkers and an environment that fosters the free exchange of ideas.

In its 16-year history, SRI has built this environment. We are one of the fastest-growing research enterprises in Canada, with expected research expenditures of \$95 million in the coming year. While this is an important metric of success, the day-to-day integration of research and clinical care remains our proudest accomplishment, by providing an unparalleled setting in which to achieve breakthroughs, train the next generation of scientists and health care professionals, and, consequentially, do the best by our patients.

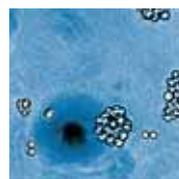
Our dedicated team of scientists, students, fellows, trainees and administrative staff makes this possible, as does the generous support of our funding partners and donors. As important is the staunch support from Sunnybrook's senior leadership team and Board of Directors. Led by Leo Steven, CEO and President, and Virginia McLaughlin, Chair of the Board, our vanguard ensures that our research does and will continue to transform health care.

Michael Julius
Vice-President, Research

Professor, Departments of Immunology
and Medical Biophysics
Faculty of Medicine, University of Toronto

AWARDS HONOURS

Below we spotlight some especially notable achievements of scientists at Sunnybrook Research Institute from 2004 to 2006



National and International Awards

During the last two years, four Sunnybrook researchers have been awarded Canada Research Chairs. The government of Canada created the Canada Research Chairs Program to attract and retain the best minds in science.

Dan Dumont takes up the Canada Research Chair in Angiogenesis and Lymphangiogenesis Signalling. **Juan Carlos Zúñiga-Pflücker** was awarded the Canada Research Chair in Developmental Immunology. Newly recruited **Kullervo Hynynen** received the Canada Research Chair in Imaging Systems and Image-Guided Therapy. **Ross Upshur** now holds the Canada Research Chair in Primary Care Research, and **Jack Tu's** renewal of his Tier 2 Canada Research Chair in Health Services Research was successful.

The Canadian Institutes of Health Research (CIHR) recognized **Richard Wells** with a Clinician Scientist Award and **Robert Nam** with a New Investigator Award, each of which is designed to support outstanding researchers. CIHR awarded **Jack Tu** its Knowledge Translation Award, which recognizes an exceptional individual or team involved in a collaborative project to advance the translation of knowledge from discovery to clinical application.

Sandro Rizoli has been awarded the Gold Medal in Surgery Award from the Royal College of Physicians and Surgeons of Canada. This award provides national recognition for original work by clinical investigators who have completed their training within the past 10 years.

Sponsored by the Canadian Cancer Society, the National Cancer Institute of Canada (NCIC) has awarded **Kathleen Pritchard** the O. Harold Warwick Prize. The NCIC awards this prize to a scientist whose work has had a major impact on cancer control in Canada.

The Myelodysplastic Foundation (U.S.) designated the myelodysplastic syndrome program led by **Richard Wells** as a Center of Excellence, one of only two in Canada.

Jack Tu also received the Robert E. Beamish Award from the Canadian Cardiovascular Society. This award is presented to the first author of an original research article published during the preceding three years in *The Canadian Journal of Cardiology* and judged to have the greatest (potential) impact on cardiovascular medicine.

The American Association of Physicists in Medicine awarded **John Rowlands** and co-authors the Sylvia Sorkin Greenfield Award for publishing the best paper in medical physics in 2005.

Provincial Awards

From the Ministry of Research and Innovation, **Dean Rowe-Magnus** received the Early Researcher Award. The aim of this award is to improve Ontario's ability to attract and retain the brightest research talent in priority economic sectors.

Lisa Barbera and **Rob Fowler** each received a Career Scientist Award from the Ministry of Health and Long-Term Care, given to enable promising researchers in the early stages of their careers to devote at least 75% of their time to health services research.

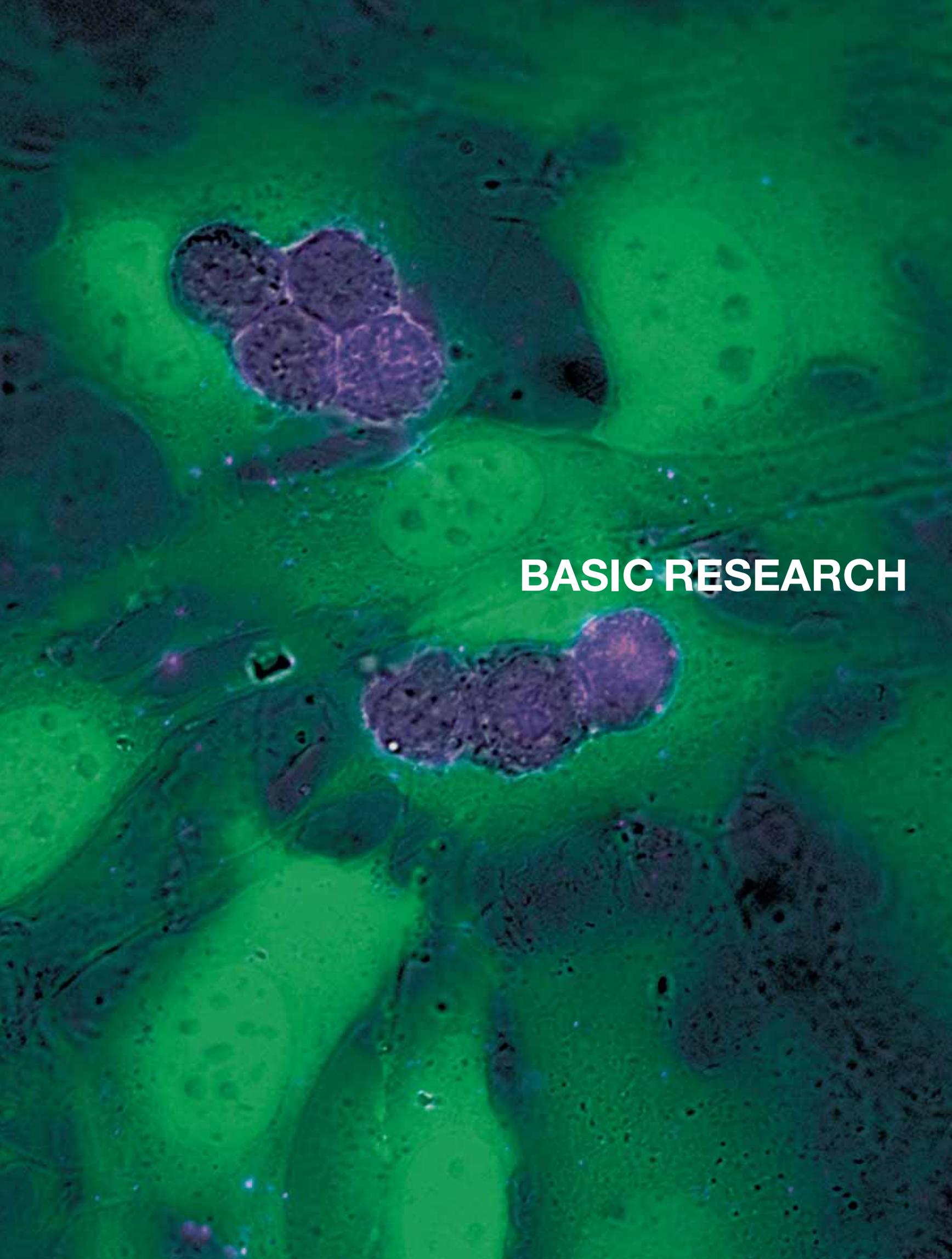
From the Heart and Stroke Foundation of Ontario, **David Gladstone** and **Dennis Ko** each have received a Clinician Scientist Award, and **Burton Yang** has been awarded a Career Investigator Award. From the Ontario Mental Health Foundation, **Krista Lancôt** and **Ayal Schaffer** each have received a New Investigator Fellowship, created for early-career-stage investigators.

Fellowships and Other Honours

The Canadian Academy of Health Sciences has elected **William Sibbald** and **Donald Stuss** as Fellows for their contributions to the promotion of health science. South of the border, the American Association for the Advancement of Science has elected **Donald Stuss** to Fellowship for his meritorious efforts to advance science or its applications.

The Department of Medicine at the University of Toronto awarded **Sandra Black** the Deborah Ivy Christian Brill Chair in Neurology, an endowed chair, for her excellent work in neurovascular disease.

Mark Henkelman has been elected as a Fellow to the Royal Society of Canada for his dedication to achieving excellence in his endeavours, thus enhancing Canada's competitiveness on a global basis. He has also been promoted to University Professor at the University of Toronto, the highest honour the university bestows upon its faculty.



BASIC RESEARCH



RIGHT

In 2002, Juan Carlos Zúñiga-Pflücker's lab changed immunology research by growing T cells in a Petri dish. Four years later, we're seeing the products of that change

TURNING

Sometimes, the correct turn is a 180. In 2002, Ciofani's PhD work wasn't going anywhere. She was trying to define genes and molecules that control T cell development in vivo—because T cell progenitors mature into T cells only inside the thymus. (The thymus is a small organ in the upper chest, to which T cell progenitors migrate from bone marrow.) But that year, Tom Schmitt and Zúñiga-Pflücker induced T cell development in a Petri dish by growing preclinical stem cells, with Delta-like-1 molecules, on supporting stroma. For the first time, scientists could view in molecular detail a process that had stymied them for 40 years. "It saved my degree," Ciofani says.

She and Zúñiga-Pflücker closed the book on her experiments and started down a new path.

Growing large numbers of previously hard-to-find early T cells in vitro, and with a new view into the signalling role of the Delta-like-1 molecule in differentiation (the crucial point when stem cells are directed to choose a lineage and become a specific cell type), Ciofani made a striking discovery about the receptor for Delta-like-1, known as Notch. Notch wasn't only instructing stem cells to become T cells, it was sustaining them after differentiation via another molecule inside the cells, called Akt, and ordering them to take up the nutrients required for their survival. In a fashion described by Zúñiga-Pflücker as typical of her—perfectly laid-out experiments and a rare ability to place them in a larger scientific context—Ciofani took a sharp turn from cell signalling to metabolism, literally looking into the microscope to recognize that removal of Delta-like-1 atrophied the T cells.

Beyond providing a critical piece in the T cell development puzzle, the discovery had clinical relevance for T cell acute leukemia (TALL), in which T cells turn cancerous. Notch is mutated in 50% of TALL patients, so pinpointing how and at what stage it promotes T cell growth opens a promising avenue for investigation into controlling its cell-sustaining effect during TALL. The discovery was featured on the cover of *Nature Immunology* in 2005.

In 2006, Zúñiga-Pflücker and Ciofani extended this finding. By selectively withdrawing Notch signals in vitro at various stages of T cell development, they determined at precisely what point the two main types of T cells—alpha-beta and gamma-delta, each with particular roles in protecting us

Science is discovery as storytelling. But the story unfolds along a nonlinear path. And, eventually, it veers in unexpected directions. "That's where being a good scientist comes in," says Dr. Juan Carlos Zúñiga-Pflücker. "You try to keep making correct turns." Zúñiga-Pflücker, senior scientist at Sunnybrook Research Institute and Canada Research Chair in Developmental Immunology, and Maria Ciofani, a PhD student in his lab, have a knack for right turns. The result is a string of discoveries on T cell development, and charting of new territory in developmental immunology.

T cells are fundamental to immunity; they identify and kill pathogens, including viruses and cancer cells. Understanding the genes and molecules that generate T cells could improve on existing—but largely experimental—types of cancer immunotherapy like vaccine therapies and adoptive T cell transfer (growing large numbers of T cells for injection, shown to eliminate some late-stage cancers). It could also unleash the enormous potential of T cell-targeted pharmaceutical cures for cancer and AIDS.

THE COLOUR OF FLOW

NEW TECHNOLOGY LIGHTS UP THE NATURE OF BIOLOGY

For the *Nature Immunology* paper on the role of Notch in sustaining T cell development, Maria Ciofani, though she could see the cells shrinking by comparing slides in the microscope, needed to quantify that change. She used Sunnybrook Research Institute's state-of-the-art Centre for Cytometry and Scanning Microscopy to produce the requisite numbers on decreasing cell size and volume. The centre is essential to the work done at SRI by several molecular and cellular biologists. One important new piece of equipment it houses is the LSRII by BD Biosciences, funded primarily by the Canada Foundation for Innovation and Ontario Innovation Trust.

The LSRII is a \$450,000 flow cytometer used to analyze and characterize cells and their environment after they've been sorted. It beams four independent laser lines onto cells suspended in liquid and stained with dyes to illuminate their various characteristics in up to 16 colours. A standard flow cytometer produces four colours with two lasers. Immunologists trying to characterize cell phenotypes, for example, use antibodies tagged with fluorescent dyes to look at proteins that are expressed by certain genes

inside and outside the cells. Advances in this technology have dramatically increased the rate of scientific discovery: cell analyses that took 45 minutes 15 years ago now take less than 10 seconds and give much more detail.

Several functions of the LSRII, the most advanced analyzer on the market, couldn't have been performed at all—even two years ago. The multiple fluorescence protein array, which allows for analysis of multiple genes at once that have been tagged with different fluorescent dyes, is an example. Genes are introduced into cells, either transiently or permanently, and tagged with red, green or yellow dye. Gisele Knowles, who runs the flow facility, says, "From the 1990s until 2004, only one dye—green—could be used for that type of analysis. Now we can use three with the LSRII only. It means we can see the effects of three different genes in a cell at once. That's huge."

As biologists shift their focus from identifying the presence or absence of individual genes in disease to looking at how various genes interact at specific points in time—genomics—the LSRII is enabling SRI to stay at the forefront of genetics research.

Having the equipment is essential, but using it effectively can take cellular research to another level. Knowles, the first in Canada to get a sorter and with 22 years of experience to draw on, provides the direction to make that happen. "I'll probably never work with another flow technician of Gisele's calibre," says Renée de Pooter, a frequent user. "She understands the physics of the machines and the biology of the cells you're trying to sort, and that's extremely rare. She's amazing." 



CONTINUED FROM PREVIOUS PAGE

from disease—bifurcate from a common T cell progenitor. Only gamma-delta cells will continue developing into mature T cells, despite the absence of Notch function beyond the early progenitor stage of development. While furthering the understanding of Notch, the finding also clarified how to generate the two types of T cells in the lab, thereby facilitating translational research on gamma-delta cells in adoptive T cell transfer therapy. Gamma-delta cells have robust, specific antitumour properties and are much less prone to autoimmunity, a common problem with adoptive transfer.

While Ciofani was mapping preclinical T cell development, Dr. Ross La Motte-Mohs, a postdoctoral fellow in Zúñiga-Pflücker's lab, added weight to her work by replicating their *in vitro* system with human stem cells drawn from cord blood. Zúñiga-Pflücker says, "It's critical to have the fundamental understanding of genes, molecules and cells, but it becomes a lot more important when you have the human correlate in place and shown playing a role." Published in *Blood*, the results translated to the human system and, says Zúñiga-Pflücker, "on some levels, provided a more complete sense of T cell development than in the preclinical experiments." La Motte-Mohs and Zúñiga-Pflücker

are now partnering with researchers and industry in the Advanced Regenerative Tissue Engineering Centre (see page 39) to explore the feasibility of constructing an artificial thymus for T cell transplantation.

In autumn 2006, Zúñiga-Pflücker confronted the reality that Ciofani will finish her PhD and leave the lab early in 2007. "It's the bittersweet aspect of this work," he says. Once students have developed their experience, worked through failed experiments and multiple forks in the road—just when the science is, one hopes, showing results—they leave. "All you can hope is that they go out and get what they're after," he says.

What is Ciofani after? She's moving to Manhattan to pursue T cell development as a postdoctoral fellow at Memorial Sloan-Kettering Cancer Center. "I want to know," she says. "I think that's probably a little part of every scientist—needing to know the answer. And this is a bit of ego-tism, but I want to know it first." It is that drive and curiosity that move the story of science forward. 

Ciofani's work was funded by the Canadian Institutes of Health Research.

Zúñiga-Pflücker's work is funded by the Canada Research Chairs Program, Canada Foundation for Innovation, Canadian Institutes of Health Research, Dana Foundation (U.S.), National Cancer Institute of Canada, Ontario HIV Treatment Network and Ontario Innovation Trust.

“To become the mentor and do science by proxy is very different. It can be difficult to let go and have an experiment done by someone else.”



LEFT TO RIGHT: GLADYS WONG, DZANA DERVOVIC AND DR. JUAN CARLOS ZÚÑIGA-PFLÜCKER

THERE'S ART IN THIS SCIENCE RUNNING A LAB IS AN EXPERIMENT IN BALANCE

As a future researcher at New York's Memorial Sloan-Kettering Cancer Center with a PhD behind her, Maria Ciofani doesn't expect interactions with Dr. Juan Carlos Zúñiga-Pflücker—which might include collaboration and competition—will feel any different from those they enjoyed when she was his student. That's because, she says, “He treats us as individuals with important ideas.” Interacting with students, postdoctoral fellows and technicians as collaborators is at the core of Zúñiga-Pflücker's management of the lab. As for the science, Ciofani says, “He'll never tell you not to do an experiment.”

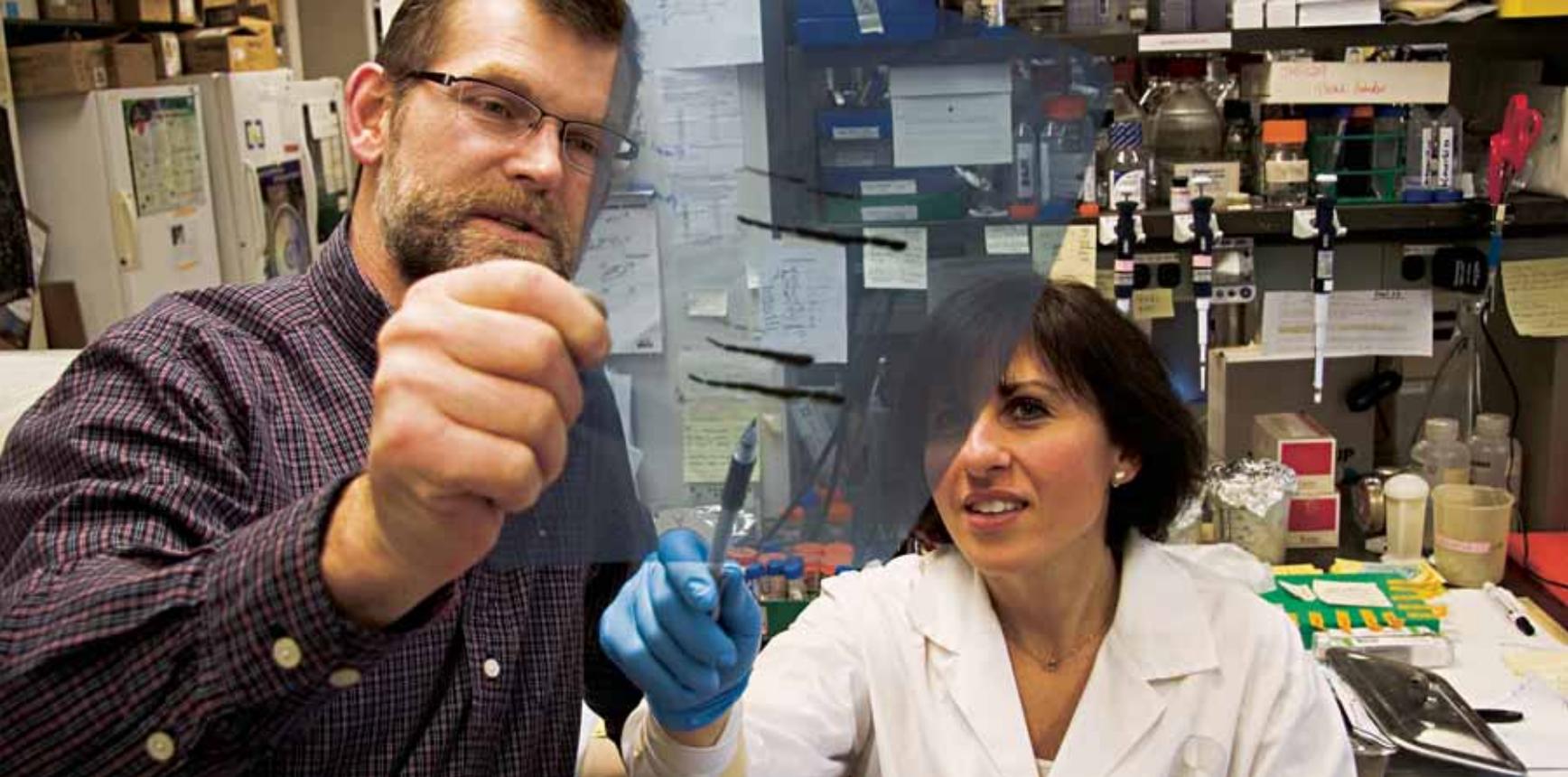
Indeed, Zúñiga-Pflücker has a certain fondness for failed experiments, from which he believes there's much to be learned. But, he says, “A badly conceived experiment doesn't teach you anything. We try to avoid that.”

While achieving that artful equilibrium with lab members across multiple projects is the goal, getting to the start of that process can be daunting. When Zúñiga-Pflücker arrived at the University of Toronto in 1994, he was given a big lab space, into which he walked and found nothing but a few benches. No equipment, no staff, no instructions. “Nobody tells you what to expect,” he says. “They don't take you aside and say, ‘This is how you run a lab.’” And that's how it has been done for decades, until recently. The National Institutes of Health in the U.S. now offers some postdocs training on starting and running a lab, and U of T is instituting a similar program. While Zúñiga-Pflücker believes this may help, he thinks it important that scientists develop their own opinions on running a lab, based on observing what different mentors did especially well. That approach also helps with the biggest change: moving from mentored to mentor.

“To become the mentor and do science by proxy is very different,” says Zúñiga-Pflücker. “It can be difficult to let go and have an experiment done by someone else.” Ciofani thinks Zúñiga-Pflücker still feels torn not being in the lab more, but that it's a natural progression that has allowed him to broaden his research. A constant temptation for an established scientist is to micromanage or impose a direction. But Zúñiga-Pflücker doesn't, and will get excited about ideas that aren't his. Renée de Pooter, another senior PhD student in the lab, says, “He's very supportive and hands-off, even if he doesn't agree with your hypothesis. I admire that.” At the same time, he is not at all shy about expressing dislike, even disgust, for a poorly done experiment. “He can be very direct, and I like that,” says Ciofani.

Zúñiga-Pflücker is less inclined toward blunt criticism now than early in his career, and he has refined his approach to choosing lab members. Students that have come from labs where their work wasn't necessarily going well are often more focused and better attuned to what research they want to pursue than someone successful from the start. They tend to fit well with Zúñiga-Pflücker's flexible style.

They also need to fit with the mix of personalities, skills and experience of existing lab members, and managing that mix is yet another challenge of running a lab, especially one focused mostly on T cell development. Though each lab member works on a specific part of T cell development, there is still movement within the projects. “We can think freely without stepping on someone's feet,” says Ciofani. They have occasional clashes; Zúñiga-Pflücker keeps a lid on them by refusing to get involved—an approach that goes against the prevailing wisdom in many labs. “There's really no one answer for getting the right mix,” says Zúñiga-Pflücker. “All the elements have to be there to make it happen, but it's like writing a good story—really hard to pin down. Happenstance, serendipity, coincidence, but all require a love of science.” ■



DRS. DAN DUMONT AND JENNIFER ALAMI

IN SICKNESS AND IN HEALTH SRI SCIENTISTS LIFT UP THE VEIL ON THE ENIGMA OF ANGIOGENESIS

Innovation, says Dr. Robert Kerbel, a trailblazer in the field of antiangiogenic therapy, is “something that is off the beaten path, thinking outside the box. It is not just new, but unexpected. Counterintuitive.”

Kerbel, along with Dr. Dan Dumont, a specialist in the genetic and molecular events that cause the vascular system to form, make up the vanguard of the science of angiogenesis at Sunnybrook Research Institute (SRI) and the translational applications it promises for people with cancer and other diseases. Together, these SRI senior scientists and Canada Research Chairs—Dumont in Angiogenic and Lymphangiogenic Signalling, and Kerbel in Tumour Angiogenesis and Antiangiogenic Therapy—are showing, time and again, what innovation looks like.

They co-lead the Toronto Angiogenesis Research Centre (TARC) at SRI, a unique-in-Canada virtual centre for the study of basic angiogenesis, antiangiogenic therapies and therapeutic angiogenesis. In their work there, they are striving toward a future in which cancer might be regarded as a chronic disease that can be managed, as diabetes is.

Each scientist brings his own œuvre of excellence to the enterprise. Dumont is celebrated for his advances studying the signalling processes controlling angiogenesis and lymphangiogenesis; Kerbel is renowned for his discoveries pertaining to novel antiangiogenic therapy strategies that are trained on making cancer therapy more effective and less arduous.

Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing ones. A natural process, it occurs in the healthy body for healing wounds and restoring blood flow to tissue after injury or insult, thanks to a series of “on” and “off” switches: angiogenesis-stimulating growth factors and angiogenesis inhibitors. The healthy body maintains a balance between the two.

Angiogenesis therapies are designed to control the switches—and, say some, are the next great wave in cancer care. Prior to the 1960s, there was barely a trickle. Indeed, researchers widely believed that blood supply reached tumours through the dilation of pre-existing blood vessels. Then, in 1971, a surgeon named Dr. Judah Folkman took a much-criticized stance with an article published in *The New England Journal of Medicine*, in which he hypothesized that tumour growth depends on angiogenesis. Angiogenesis-dependent diseases,

he conjectured, result when new blood vessels grow either excessively or insufficiently; effectively, the body loses control over the process. Four years later, Folkman co-discovered the first of many angiogenesis inhibitors; and, in the years to follow, the role of angiogenesis in the spread of tumours increasingly became accepted.

Today, it is one of the hottest areas in medical oncology, with three antiangiogenic drugs having been recently approved in the U.S., Canada and many other countries.

Dumont is director of molecular and cellular biology research at Sunnybrook. He was the first to identify, clone and map the Tie2 gene on the human and preclinical model genomes, work he started in 1988 as a postdoctoral fellow. “It’s been very much a niche for me because it’s been a difficult receptor and ligand pair to work with,” he says.

Inhabiting this niche has paid off. A recent success came when he created a mouse model with virtually all of the hallmarks of the human disease psoriasis—an ailment of the immune system involving interaction among skin, immune and blood vessel cells—by overexpressing the receptor Tie2 in the skin of genetically engineered mice. That they responded to immune system suppressor cyclosporine A, a classic human psoriasis treatment, paved the way for researchers to test other combination therapies prior to human clinical trials. The breakthrough was printed in March 2005 in *The American Journal of Pathology*.

Key was the identification of the interplay of angiogenesis, the immune system and a particular proliferation of the skin—three interdependent arms, each contributing to the disease. Dumont’s work revealed that if the expression of the angiogenic response is turned off, the disease—the skin phenotype (basically, how it presents)—goes away. And if the drug is withdrawn, it returns.

Also in 2005, Dumont discovered that Dok-R, a protein that his lab was one of the first to describe, had a crucial mediating role to play with the recruitment of other proteins, findings he published in *Molecular and Cellular Biology*. “It was one of the early papers showing [that] this class of sort of signalling or scaffolding does play a role in down-regulating signalling cascades from receptors,” he says. Several other groups then went on to show that knocking-out both Dok-R and Dok1 in mice leads to mild proliferative disease. “So, in essence, you knock out these negative regulators and you actually get a cancer.”

“This paper says we might be able to test angiogenesis by drawing a little bit of blood from the patients.”

While both Dumont and Kerbel do fundamental work in molecular and cell biology, Kerbel's work is closer to clinical application, by virtue of its translational nature. Kerbel is considered to be a pioneer in the study of antiangiogenic “metronomic” chemotherapy. This strategy—regular, long-term administration of low doses of cytotoxic drugs, with few or no breaks—is a complete departure from the way chemotherapy is usually given: at the highest doses possible, separated by long rest periods to recover from the toxic effects of this way of giving chemotherapy. Metronomic chemotherapy is thought to have an angiogenic basis.

Kerbel's work focuses on testing modified metronomic chemotherapy regimens in an effort to delay the relapses that he has seen in preclinical models. He and his lab have shown that repeated administration of cyclophosphamide every three or six weeks, combined with a daily, oral, low-dose metronomic regimen, improved efficacy and postponed relapses. Antiangiogenic activity, measured by reduction in circulating endothelial precursor cells in the bloodstream, revealed that the greatest degree of suppression occurred using the combination.

“For reasons that we still don't fully understand, low doses of chemotherapy in mice seem to have a powerful effect on these circulating endothelial progenitor cells, and even on the normal differentiated dividing endothelial cells in the tumour vascular bed. In other words, you're making chemotherapy a de facto antiangiogenic treatment strategy when you give it repetitively at close regular dosing, with no prolonged breaks.”

Kerbel has long been interested in this concept, he says, because of the possibility of reduced acute toxicity, lowered costs, increased convenience for patients when using oral drugs, and its possible role as an adjuvant therapy for early-stage disease.

This work has given rise to clinical trials worldwide. The results so far of some of these are “very encouraging,” he says.

In later work, Kerbel and postdoctoral fellow Dr. Yuval Shaked, who chose to work in Kerbel's lab because of the former's reputation and publishing record, attempted to zero in on the optimum biologic dose (OBD) for this treatment strategy.

The absence of OBD information, Kerbel says, is a major problem with the metronomic method. “Once you get away from the maximum tolerated dose concept, it becomes much fuzzier, much harder, to determine what is an optimal therapeutic dose.”

But they made some headway when they discovered that levels of circulating endothelial progenitor cells (CEPs) in peripheral blood can be used as surrogate biomarkers to help determine the best dose of antiangiogenic therapies. Shaked was the lead author of a study in which Kerbel and an A-list clutch of international colleagues found that levels of circulating endothelial cells (CECs) and CEPs vary, depending on the genetic background of a preclinical model. But within a particular strain, levels of these cells correlate with the ability to induce tumour blood vessel growth and the response to antiangiogenic therapy. He found that treatment with a drug that interferes with the major signalling receptor for a key regulator of blood vessel development caused a dose-dependent reduction in CEPs. This reduction closely reflected the previously established anti-tumour activity of this regulator, and the optimal decline in CECs and CEPs was reached at the optimal dose.

This article was published in January 2005 in *Cancer Cell*. In it, Shaked, the lead author, and colleagues, including Kerbel and Dumont, concluded that measuring peripheral blood cells could reliably indicate how well a therapy inhibits angiogenesis. “This paper says we might be able to test angiogenesis by drawing a little bit of blood from the patients,” explains Shaked.

Clinical application, if it comes to that, is a ways off, but clinical trials based on this work are in full swing. Shaked is doing testing for centres across North America, including six for clinical trials, because SRI is where the expertise is. The centres send their blood samples to Shaked, and he teaches others the technique. While he hasn't yet come full circle, he's starting to close in on it. He leaves in 2007 to start his own lab. He is, says Kerbel, one of the brightest. On his experience, Shaked is effusive: “I got much more than I wanted,” he says. “In my best dream, I never thought I would get this much.”

Angiogenesis is still a field in development, with relevance to cancer, other diseases and regenerative medicine. In this field, Dumont and Kerbel and their lab teams find themselves leading the chase, a pursuit that not so long ago would have been dismissed as folly, but today is increasingly recognized for what it is—a new way of thinking with unexpected impact: innovation. [16](#)

TARC is funded by the Canada Foundation for Innovation and Ontario Innovation Trust. Other funding for this research was provided by the Canada Research Chairs Program; Canadian Cancer Society; Canadian Institutes of Health Research; Heart and Stroke Foundation of Canada; National Cancer Institute of Canada; National Heart, Lung and Blood Institute; and National Institutes of Health (U.S.).

DRS. YUVAL SHAKED AND BOB KERBEL



PURPLE PROTAGONISTS

JONATHAN RAST LOOKS AT THE PURPLE SEA URCHIN AND FINDS THE PAST HINTS AT THE FUTURE OF IMMUNOLOGY

What can purple sea urchins tell us about the evolution of human immunity? A lot, it turns out. After a century of provoking questions as experimental subjects for developmental biologists, the spiny, tiny, globular sea animals are rousing interest in immunologists and have pricked a hole in prevailing work on the origin of human adaptive immunity.

A hallmark of the human immune response is diversity. Our immune system's ability to recognize and respond to antigens—a unique aspect of jawed vertebrates (animals with a backbone or spine)—depends on a process of gene rearrangement called V(D)J recombination. Scientists have known for years that the Rag1 and Rag2 proteins mediate this process. What has puzzled them is how it got started in jawed vertebrates like us.

As no significantly Rag-like genes had been discovered in sea urchins or other invertebrates, evolutionary biologists hypothesized that V(D)J recombination began when the Rag genes were co-opted after horizontal gene transfer and clustered together in a common jawed vertebrate ancestor—a kind of immunological big bang. Proponents of intelligent design pointed to V(D)J recombination as an example of something that suddenly appeared and couldn't be explained by evolution. While the former had more credibility, both explanations appear to be wrong, based on a discovery made by Jonathan Rast in the sea urchin.

Rast, a scientist in molecular and cellular biology at Sunnybrook Research Institute (SRI), found Rag1- and Rag2-like genes in the sea urchin genome and provided compelling evidence that they are homologues of vertebrate Rag1/2, meaning they share an evolutionary origin with them. “We were really surprised to find the Rag1/2-like cluster,” says Rast, “especially since nothing similar had been found in the sequenced genome of the sea squirt, which is closer to us evolutionarily.”

As more animal genomes are sequenced, scientists are finding that gene loss can explain the absence of a gene or sequence in an organism that is an intermediate between two in which they do appear. Rast says, “It's another case where, with an incomplete data set, it looks like something just popped into being, but as you get more information, you realize that it's much more ancient than previously thought.”

Comparing the sea urchin Rag 1/2-like genes with vertebrate Rag 1/2, Rast and graduate student Cynthia Messier built a persuasive case: both sets of genes share similarities in sequence and genomic organization and are coexpressed during development and in adult tissues. A collaborator in the United States was able to show that the sea urchin genes interact with each other and with Rag1/2 proteins from several vertebrates.

As well as undermining prevailing theories on the origin of V(D)J recombination, Rast's work has implications for understanding it and other aspects of adaptive immunity in humans. “This finding and other discoveries about the sea urchin immune system offer experimental opportunities that we didn't have before,” says Rast. In complex vertebrates like us, it is relatively difficult to characterize regulatory interactions. But by comparing that system to what's going on in a much simpler 1,500-cell organism like the sea urchin larva, scientists can parse out which elements of the system matter most.

Perhaps even more importantly, this discovery was only part of a larger screen of the sea urchin genome in which Rast's lab found other crucial similarities with vertebrates. They can now exploit these findings to see how other immune genes are controlled in urchins. “People say, ‘This gene causes leukemia,’ or ‘This gene causes these cells to become lymphocytes,’” says Rast. “But we know that genes don't do anything alone. They act as part of a larger program. And to understand how genes work, we've got to look at them globally.”

Rast's work was funded by the Canada Foundation for Innovation, Canadian Institutes of Health Research, Ontario Innovation Trust, National Science and Engineering Research Council, and Sunnybrook Research Institute.



DR. JONATHAN RAST AND CYNTHIA MESSIER

“This finding and other discoveries about the sea urchin immune system offer experimental opportunities that we didn't have before.”

GOING AGAINST THE GRAIN



DR. ROBERT JANKOV

ROBERT JANKOV BLOWS AIR INTO AN ENTRENCHED THEORY THAT CO₂ IS THE ENEMY OF HIGH BLOOD PRESSURE IN THE LUNGS OF BABIES

In theory, giving carbon dioxide (CO₂) to a baby with persistent pulmonary hypertension is an absurd notion. Studies in the 1960s and 1970s showed that, if you make the blood alkaline (i.e., increase the pH), the vessels in the lung open. If you make the blood acidic (i.e., decrease the pH), they tighten. Historically, then, doctors have worked to alkalize the blood to treat this condition by decreasing its exposure to CO₂. But the evidence supporting this approach, says Robert Jankov, a neonatologist and scientist at Sunnybrook Research Institute is, “not that strong. It’s really just become part of dogma. “I’m challenging that.”

Pulmonary hypertension is a common condition in newborns that results in response to the abrupt transition from womb to outside world. When a baby is born and necessarily cut off from her oxygen supply, her lungs must spring into action, and blood vessels must open to ease the entry of oxygen into the blood. In most cases, they do. For infants with this condition, they don’t.

What’s more, if a baby is suffering severely, her blood vessels will change their structure, going from thin-walled and flexible to a state that more closely resembles a corroded lead pipe. Along with it, her condition degrades from being possibly reversible to irreversible and potentially progressive. Jankov is concerned with understanding what makes the blood vessel “remodeling” occur so that it can be prevented or reversed.

New evidence—done on preclinical models in isolated vessel preparations—showed that injecting CO₂ into a blood vessel will automatically stimulate dilation. Carbon dioxide, it suddenly appeared, has two opposing consequences: It increases the acidity of the blood in the milieu, and it also chemically inspires dilation.

In an article published in 2006 in the *American Journal of Physiology*, Jankov not only showed that increased amounts of CO₂ would limit the development of chronic pulmonary hypertension, he confirmed that CO₂’s beneficial effect is tied to its power to limit oxidant stress. Finally, his research found a link between free radicals and the production of endothelin,

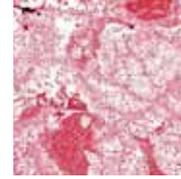
a molecule that constricts blood vessels and contributes to remodeling. If you decrease the free radicals content, he showed, you will reduce endothelin production in the lungs.

“This is completely opposite to what we would normally do,” Jankov says. “This suggests for the first time that, in the newborn, chronic exposure to CO₂ has beneficial effects.” The advantages of CO₂ are considerable: principally, that it’s cheap and easy to give.

There’s still a lot to be done. But in the meantime, says Jankov, “It’s nice to come up with something that might create a new paradigm.” 

Jankov’s work is funded by the Canada Foundation for Innovation, Canadian Institutes of Health Research, Ontario Innovation Trust and Ontario Thoracic Society.





Using preclinical models, **Yaacov Ben-David** tested if removing the spleens of mice with leukemia during the early phase of Friend disease would increase survival. Splenectomy was combined with antiangiogenic therapy, which works by halting the formation of new blood vessels that feed tumour growth. Overall, mice whose spleens had been removed survived for 95 days; those with their spleens intact survived 67 days. This research is the first to show that secretions of factors that relate to the immune system and promote formation of new blood vessels cause leukemic cells in the spleen to multiply. These results hint at the role the splenic environment has to play in the acceleration of Friend disease, and suggest that early removal of the spleen combined with antiangiogenic cancer therapy may halt the progression of leukemia and other cancers.

In a differential gene expression screen designed to find intracellular genes overexpressed in breast cancer, **Neil Berinstein** identified 15 genes, including one of the most prevalent: trichorhinophalangeal syndrome type 1. TRPS-1 is a gene shown to be associated with three rare autosomal dominant genetic disorders known as the trichorhinophalangeal syndromes. Immunohistochemistry analysis found TRPS-1 protein was expressed in more than 90% of early- and late-stage breast cancer, including ductal carcinoma in situ and invasive ductal, lobular and papillary carcinomas. Berinstein's research was to locate those genes that have potential as targets for immunotherapy, courtesy of a screen that was designed to detect high- and low-abundance targets, with the latter being of special interest because of its association with a lower likelihood of being subject to immune tolerance.



Based on the knowledge that cells are more radioresistant in a certain phase of the cell division cycle, **Georg Bjarnason** sought to determine if giving radiotherapy in the morning rather than the afternoon to patients with head and neck cancer would reduce the severity of mucositis (painful ulcerations in the mouth). Bjarnason found that fewer patients who received morning radiotherapy developed a severe grade of mucositis (43% vs. 67%) in a subgroup of patients receiving the highest doses of radiotherapy. Patients receiving the morning radiotherapy also stopped losing weight after therapy earlier. This research suggests that the timing of radiotherapy should be studied further in cancers in which gastrointestinal toxicity is dose-limiting, and that circadian rhythms should be considered in future studies.

Jorge Filmus demonstrated that glypican-3 (GPC3), a protein that is bound to the cell membrane and produced by most hepatocellular carcinomas, promotes the growth of these cancers. What's more, Filmus showed that the tumour-promoting activity of GPC3 is due to its capacity to stimulate the effect of certain growth factors that are present within tumours. He proposes that this stimulatory effect of GPC3 is a consequence of its ability to facilitate the binding of the growth factors to their cell surface receptors, and that GPC3 could be a target for novel therapies for hepatocellular carcinomas.

Type 1 (insulin-dependent) diabetes has been recognized since the 1980s as an autoimmune disease in which white blood cells, called T cells, attack and compromise the insulin-producing capacity of the pancreas. In healthy organisms, regulatory T cells prevent this process. Scientists had speculated that impaired function of regulatory T cell precursors played a central role in the pathogenesis of Type 1 diabetes. **Philippe Poussier** and colleagues demonstrated that *Ian5*, one of the few known disease-susceptibility genes in Type 1 diabetes, alters the survival and function of regulatory T cells in diabetes-prone individuals. This results in unchecked activation of diabetogenic T cells and antipancreatic autoimmunity.

B cell development normally requires expression of cell surface immunoglobulins on developing B cells. **Michael Ratcliffe** has demonstrated that this requirement can be bypassed by the expression of synthetic molecules that contain specific signalling

motifs. He has shown that the motifs required for optimal mobilization of calcium fluxes in B cells are not required to support B cell development. In contrast, a second motif, the Ig-alpha immunoreceptor tyrosine-based activation motif (ITAM) is dispensable for optimal calcium mobilization but required to support B cell development. These results begin to identify key signalling pathways required for the normal development of B lymphocytes.

Arun Seth found a new protein marker linked to positive outcome in patients with breast cancer. Seth was able to show that the overexpression of breast-cancer-associated gene 2 (BCA2) is a favourable factor in breast cancer in relation to occurrence of lymph node metastases and regional recurrence. BCA2 is a novel RING type E3 ligase protein—implicated in human cancers and genetic disorders—that inherently enhances ubiquitination activity. Ubiquitin is a small protein that marks other proteins by attaching itself to them and directing them to the proteasome for degradation. Seth showed that the BCA2 mediated such ubiquitin modification of the specific cancer-related proteins that affect breast cancer progression.

Burton Yang's group has cloned for the first time two important isoforms of a polysaccharide-modified protein called versican, the V1 (expressed in the early stages of tissue development) and V2 (expressed in mature tissues) isoforms. Beyond those already known from their previous studies of versican in mediating cell adhesion, migration, proliferation and differentiation, Yang and colleagues showed that V1 not only enhances cell proliferation but also modulates cell cycle progression and protects the cells from apoptosis. By contrast, the V2 isoform possesses opposite biological activities. This is relevant because it suggests distinct roles of two differentially expressed versican isoforms.

A microscopic view of numerous cells, likely red blood cells, with glowing red outlines against a dark background. The cells vary in size and are scattered across the frame. The text 'TRANSLATIONAL RESEARCH' is overlaid in white, bold, uppercase letters on the right side of the image.

**TRANSLATIONAL
RESEARCH**

A close-up, high-resolution portrait of a man's face, focusing on his eyes and the right side of his face. He has light green eyes and is looking slightly to the right. He is wearing a dark blue polo shirt. The background is plain white.

SOUND

THE PROMISE AND REALITY OF THERAPEUTIC ULTRASOUND ARE FINALLY IN HARMONY. KULLERVO HYNYNEN IS ONE REASON WHY

FOCUS

tumours; and low-intensity ultrasound to disrupt reversibly the blood-brain barrier, thereby enabling drug delivery and gene therapy in previously inaccessible parts of the brain; these and Hynynen's other discoveries have shaped the evolution of ultrasound from simple imaging tool to futuristic, noninvasive surgical paradigm, and helped push us to the cusp of a new era in medicine.

Use of ultrasound as a therapeutic technique predates its diagnostic application. Scientists began treatment studies in 1927 after finding that ultrasound could permanently alter bacteria, but these efforts were hindered in later decades by a limited ability to control application, and monitor temperature and tissue changes. Imaging capacity had improved a lot by the early 1990s, and in 1993 at the University of Arizona, Hynynen was the first to show that magnetic resonance imaging (MRI) could effectively monitor tissue death during ultrasound thermal coagulation (heating and destruction of cells) in a preclinical model. By 1996, he had moved to Harvard and expanded the use of MRI in this system to monitor precisely temperature elevation and cavitation (the occurrence of tiny gas bubbles)—two concerns for patient safety.

The same year, Hynynen sealed a renal artery with MRI-guided focused ultrasound in a preclinical model. Researchers are extending this technique to stop bleeding after internal organ damage, and to seal blood vessels following trauma. It has also shown potential as a cancer treatment, closing tumour-feeding vessels to starve tumours of oxygen.

Ultrasound appeared useful as a treatment for brain disorders including cancer as early as the 1950s, when scientists used focused beams to produce lesions in the central nervous system. But because sound waves distort on passing through bone, the need for invasive creation of a soft-tissue window limited further study. In 1998, Hynynen was among the first to show preclinically that ultrasound could produce a focused beam through an intact skull. He used two 64-element phased transducer arrays to deliver varying ultrasound frequencies, and then measured phase distortion caused by the skull for each element of the arrays and compensated for it through phase-control circuitry. "This requires," says Hynynen, "very detailed information on the skull structure, thickness and speed of sound, so you can model propagation of the sound field through the skull. In this way, beams come to a single focus inside the

Dr. Kullervo Hynynen is making time. Preparing to leave for the Sixth International Symposium on Therapeutic Ultrasound in Oxford, the new director of imaging research at Sunnybrook Research Institute (SRI) and Canada Research Chair in Imaging Systems and Image-Guided Therapy has pushed away from his LCD and settled into an armchair in his sixth-floor office to discuss research. Briefly.

"What frustrates," he says, "is slow clinical implementation." Hynynen speaks quietly and gently; his smile is infrequent but warm, and his face angular, precise. "Twenty years ago, there were lots of good ideas on using ultrasound for therapy, but developing them into treatments has been," he pauses. "Long and complicated."

It's a little surprising that Hynynen's greatest disappointment is the pace of translating physics into clinical ultrasound treatments. That he's frustrated speaks to a drive to help—to make sick people better—that has spurred several breakthroughs. High-intensity focused ultrasound to seal arteries and thermally destroy uterine fibroids, breast and brain

GETTING RESULTS SUCCESS IS A METHOD IN SCIENTIST'S LAB

Dr. Kullervo Hynynen is in the lab, but not for the reason he'd like to be. It's a photo shoot, and the photographer is encouraging him to look natural among vertical racks of green circuit boards. Hynynen uses the time to talk science with postdoctoral fellow Dr. Laura Curiel and scientist Dr. Rajiv Chopra, who will collaborate with him and share a newly renovated 3,600-square-foot lab on the seventh floor of Sunnybrook's C wing.

The lab is unique at Sunnybrook. Since arriving in January 2006, Hynynen has recruited 14 lab members, and expects to double that number in the next six months. By autumn 2007 there will be 35 students, postdocs, engineers, tissue culture assistants, animal technicians and research assistants—about the size of his previous lab at Harvard—engaged in 12 research projects.

Chopra, in his office down the hall, says, “The group gets so big because Kullervo focuses on a number of areas to get the work into the clinic.” For focused ultrasound therapy of brain tumours, he explains, one team calculates algorithms on wave distortion and refocusing inside the brain. Another handles electronics driver development—how to get signals to sound transducers in the MRI unit. Yet another makes the transducers. Then there is a major effort in preclinical evaluation of prototype devices. “It’s the whole spectrum of research,” says Chopra.

While the range of activity in Hynynen’s lab is unusual, his interaction with his staff is most striking. “One thing that sets Kullervo apart is communication,” says Chopra. “He doesn’t sit isolated from the students.” Students face agonizing forks in the road during experiments, and Chopra admits that there’s something to be learned from going down the wrong path, seeing it and coming back. But

at the same time, he says with some understatement, “You don’t want to make your career out of it. Kullervo really uses his experience to guide his students.”

Curiel, recently arrived from France, agrees. “It’s astonishing he finds time to speak with each person in the lab, often every day...to check progress and make suggestions.” She believes this unusual for an established scientist, but is grateful that he does so. “It saves a lot of lost time,” she says adamantly.

Hynynen’s short commute from his new home close to Sunnybrook helps him to find time, as does a daunting schedule of dawn-until-dusk work-days. But Hynynen nonchalantly regards the hours and the complex range of his work as requisite for his ultimate goal—clinical implementation. **10**



CONTINUED FROM PREVIOUS PAGE

skull.” Remarkably, these corrections produced enough focused heat to destroy tumour tissue.

By 2002, Hynynen and colleague Dr. Greg Clement had constructed a helmet-shaped 320-element array to achieve a more precise application in human skulls. They developed wavevector-frequency models to dictate sound delivery; these allowed for reconstruction of a more sharply focused beam after distortion. Hynynen is now starting clinical trials of these models at Toronto Sunnybrook Regional Cancer Centre (TSRCC) to treat brain tumours—no hair out of place.

MRI-guided ultrasound is adaptable to treat tumours in other areas of the body, and Hynynen was the first to show its potential in the breast. In 2001, Hynynen was a part of a group that eliminated benign tumours up to 6.5 cubic cm. Ablated tumour tissue was absorbed by the body with no adverse effects. He has since collaborated with other scientists in applying this technique to the more complex challenge of cancerous breast tumours. Results are promising, and Hynynen plans to start a clinical trial at TSRCC with SRI scientists Drs. Greg Czarnota and Peter Burns next year.

Three in four women will develop uterine fibroids at some point in their lifetimes, and one in four will experience symptoms, which include pain, bleeding and infertility; they’re also the main reason for hysterectomy. In 2003, Hynynen and collaborators zapped uterine fibroids up to 10cm in diameter in a clinical trial. The procedure took less than three hours, produced only mild discomfort, and patients were released immediately. The treatment is now federally approved in the United States and Canada. Despite the bureaucratic frustrations of pushing the treatment into the

marketplace, its success is the accomplishment that pleases Hynynen most. “I’m very happy ultrasound surgery is now in clinical practice — it will most likely make a huge difference in the lives of people,” he says.

While Hynynen is pleased ultrasound surgery is finally a clinical reality, he believes his work on disruption of the blood-brain barrier holds the most promise. The blood-brain barrier is a membrane that controls movement of substances between blood and the central nervous system. In 2001, Hynynen and his lab were the first to use MRI-guided ultrasound with microbubbles as cavitation nuclei to open specific parts of the barrier—a feat thought impossible by many scientists. The preclinical procedure required removal of skull bone, but was done at relatively low frequency, thus leaving surrounding tissue intact and ensuring the opening was transient. In 2004, by combining this technique with earlier work on algorithmic correction of distorted sound waves, the team achieved the same effect noninvasively. Clinical translation of this procedure could have profound implications in brain cancer and other diseases of the nervous system for which treatment is difficult or even impossible.

Hynynen is keen to get into the lab. End of interview in sight, he becomes almost expansive looking back at his career. On developing an interest in science during high school in Finland, he recalls, physics quickly became his strongest subject. At the University of Kuopio, he was accepted in all physics streams, but says, “Medical physics seemed to be the area which could most benefit others. That was a deciding factor, and it felt right.” Interview over. Standing up, Hynynen laughs, adding, “There are easier choices where you make more money, but I’m happy and have never looked back.” **10**

Translation in Collaboration

Kullervo Hynynen and Greg Czarnota will combine therapy and imaging in a new ultrasound treatment for breast cancer patients

Moving research results into the clinic requires collaboration between scientists and clinicians. But convincing busy MDs that basic research is interesting and potentially useful can be difficult. It's less challenging with clinician-scientists like Dr. Greg Czarnota, an imaging researcher at Sunnybrook Research Institute (SRI) and oncologist at Toronto Sunnybrook Regional Cancer Centre (TSRCC).

Clinician-scientists have a valuable perspective on what research advances are needed in the clinic and what science can offer to patients. They are desirable collaborators for scientists focused on translation, like Dr. Kullervo Hynynen, and can offer the kind of partnership—in Czarnota's case, using ultrasound imaging to monitor focused ultrasound surgery in breast cancer—that drew Hynynen to the multidisciplinary environment of Sunnybrook. Says Hynynen, "The clinical collaborations are key to what I want to do."

Czarnota took an unusual and difficult path to becoming a clinician-scientist. While completing his PhD at the University of Toronto in the mid-1990s, he made a bet over a round of beer that he could detect a special form of cell death using ultrasound (though ultrasound was outside his area). After some late-night experiments with equipment grabbed from a clinic and cells from a culture lab at the then

Ontario Cancer Institute (OCI), Czarnota and Dr. Michael Kolios found they could indeed detect cell death with high-frequency ultrasound. Surrounded by patients at OCI, Czarnota saw the potential of the discovery in tracking antitumour therapy, and he embarked on nine years of study with the aim of implementing his discovery. While most clinician-scientists complete an MD and then a PhD, often much later, Czarnota took the reverse route, thereby keeping his science active. Of returning to student life, he says, "The hardest thing was keeping the research going while in medical school and residency. I was stretched to the limits." Stretched, but he put in the hours and did the work.

In 2003, established at OCI and working with Kolios, Czarnota discovered he could detect cell death with low-frequency ranges of ultrasound, opening the possibility of widespread clinical implementation that wouldn't require expensive and complicated high-frequency equipment. The next year, Czarnota moved to Sunnybrook, attracted by its mix of biologists and physicists, and SRI's patient-focused relationship with TSRCC.

In 2006–2007, he plans to conduct a clinical trial with Hynynen, monitoring cell death during focused ultrasound surgery in patients with locally advanced and recurrent breast cancer. "These patients have

poor outcomes and so can potentially derive the most benefit from new treatments," Czarnota explains. "It's an ideal situation to marry what Kullervo is doing with therapeutic ultrasound with what we're doing monitoring cell death." The collaboration will also include SRI senior scientist Dr. Peter Burns; Burns's team will use microbubble techniques he pioneered to image tumour vessels dying at the same time Czarnota and his group monitor cells dying. Together, they hope to provide inexpensive, highly accurate, real-time monitoring of Hynynen's tumour ablation techniques in a large population that desperately needs better treatments. "It looks like it will be a very good collaboration," says Czarnota.

For Hynynen, there are two key elements in a good partnership: complementary scientific expertise and compatible personalities. He says, "There's no point collaborating with people who have expertise but no desire to do the work. I've seen plenty of that—lots of good ideas but no time to do the work." If Czarnota's history is a marker, his collaboration with Hynynen will be worth hearing about. 

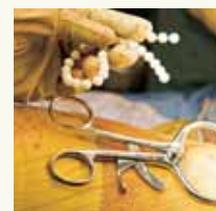
DR. GREG CZARNOTA

"These patients have poor outcomes and so can potentially derive the most benefit from new treatments."





DRS. ALBERT YEE AND HANS KREDER



REDUCING THE BURDEN

HOLLAND CENTRE RESEARCHERS WORK CLOSE TO THE BONE TO RESTORE QUALITY OF LIFE FOR PATIENTS

The woman lying on the operating room table is asleep, oblivious to the miracles about to unfold inside her body. They will be facilitated by a clutch of talented physicians who are bowed over her spotlight-lit hip bone intent on excavating the disease that poisons it. It is a display of surgical brilliance whose excellence is only partly tied to the way it seems to take place effortlessly. Musculoskeletal (MSK) research at Sunnybrook Research Institute (SRI) is on a path of progress, travelling along a network of avenues, each leading to new promise for a generation increasingly finding itself in need of MSK pioneers.

The *raison d'être* for the MSK research program at Sunnybrook's Holland Orthopaedic & Arthritic Centre, says Dr. Hans Kreder, Marvin Tile chair and chief of orthopaedic surgery, is to restore function and quality of life quickly to someone who has suffered sometimes-devastating injuries to the MSK system. Researchers at SRI focus on three groups of MSK problems: bone and soft tissue injury, arthritis and bone metastases. Superimposed over this are issues of access to care and an imperative to choose the least invasive option.

"We're approaching all of this," says Kreder, "by trying to understand the biology of these things, and make an impact in terms of interventions to understand the cellular mechanisms involved in these disease processes and hopefully improve primary and secondary prevention."

The first tool Kreder asks for in the OR is a pen. He uses it to draw an incision line along the front of the patient's hip and then traces the ink stroke with the blade of a scalpel. His actions are swift but precise. For Kreder and colleague Dr. Albert Yee, an associate scientist at SRI and surgeon-investigator, another day has just begun.

Demographics, says Kreder, are partly responsible for powering the activity of the research engine at the Holland Centre. An aging population means arthritis is increasingly prevalent. Moreover, better cancer treatment means patients are living longer and thus require more sophisticated care for their longer-lived, metastasis-ravaged bones. On top of that, the incidence of geriatric trauma is on the rise and more challenging for its

advancing onset of occurrence. "And it's patient demand," Kreder says. "Patients today demand to have a maximum quality of life until they drop dead."

Given this revised reality, Yee concerns himself with the beginnings of the biological continuum of orthopaedic care: people in their 20s and 30s whose bones, joints and tissues are suffering normal wear and tear. "A lot of what orthopaedic surgery does well is geared toward conditions in the end-stage," Yee says. "We really don't have a lot of good clinical therapies for treating this degenerative process early in the cascade."

For example, research on the spine shows that the earliest structural changes are not in the bone or facet joints (each vertebra is connected by two: one on each side of the spine) but in the intervening disc tissue between vertebrae. "There's less known about discal tissue and cells in the disc than is known about cartilage," says Yee, who spends his time in the lab studying the effects of abnormal loading of the disc.

To that end, much of his research considers the tissue-regenerative development of stem-cell-based materials that emulate a disc.

The surgeons focus their attention on the product of their incision. They take delivery of their instruments from their assistants with grace, receiving them in gloved hands, blade side down, and using them to work through the layers of tissue inside the patient's upper thigh. It is a lengthy process that plays out against an ironically upbeat soundtrack, courtesy of a crackling radio in the corner of the OR. They trade the lead back and forth, elegantly shifting surgical roles, always in pursuit of a common goal. At last, they reach their destination: the bone itself, awash in infected fluid. Now the real work begins.

One of the publications that has most recently sprung from the hospital showed that improving the system of care for hip fracture patients is essential. For each day a patient otherwise ready for surgery waits for treatment, the mortality rate climbs. Kreder points this out. "We need to build a system that gets patients to the operating room quicker."

Sunnybrook researchers have, over recent years, also shown that the least invasive surgery for wrist fractures leads to the best outcomes; that oft-prescribed blood thinners for patients with fractures below the knee are not as critical as they were once thought to be; that the highest risk of complications for hip and knee replacements is for patients operated on at a low-volume hospital; that collarbone fractures featuring completely displaced bones are better treated with surgery than a sling; that, depending on where you live, bone metastases surveillance varies wildly; and that there's a gender bias in terms of access to care for MSK patients, favouring men.

The surgeons are bent over the open wound. What they see inside it is something altogether different from what an inexperienced eye would see. Like trying to read a foreign language when you haven't got a clue. But the message for these doctors is clear, and they exchange few words as they set about deciphering it. They are thorough, and within 30 minutes they have entirely drained the bone of its toxin. For the patient whose body has been the subject of their careful ministrations during all of this time, the relief will be immediate.

At the end of the day, says Yee, the Holland MSK research program is committed to establishing a world-renowned centre of excellence in basic and clinical research discovery, health services research and policy development, and clinical care for musculoskeletal illness. Wherever possible, he says, prevention is the ideal, and excellent clinical care is the next best thing. Across the board, he says, orthopaedic surgery research at SRI aims to improve quality of life. "Through fostering emerging transdisciplinary research teams, our research efforts are integrally directed in research translation aimed at reducing the burden of illness in musculoskeletal conditions."

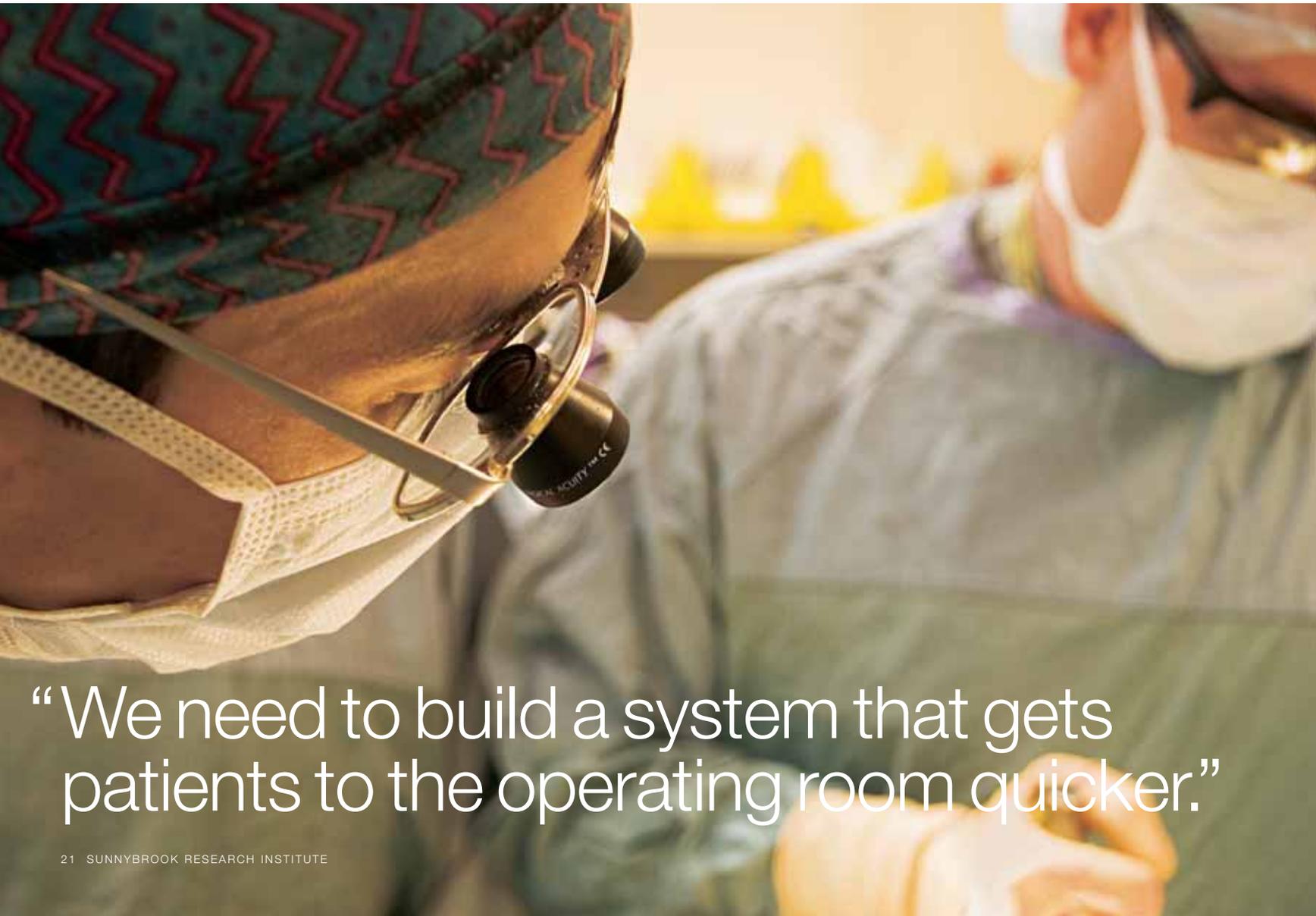
DRS. ALBERT YEE AND RICHARD JENKINSON

The patient will be revived shortly. All that remains is for her physicians to tuck into the pockets of her infected flesh 60 beads of polymethylmethacrylate, a type of bone cement that will serve as a carrier for antibiotics that will leach into her system over the next two days. The tissue from the innermost depths of her hip closes in around the spheres, and then a surgeon completes the closure with gliding finesse and a length of nylon thread. The staples that seal the deal leave a neat row of 25 metal teeth crawling up her leg.

"It is done," says Yee, stepping away from the scene and allowing the patient to be awoken.

But of course he—and Kreder, too—know this not to be the case; they know it couldn't be for a long time yet. On the map of MSK research, there are still many roads to be travelled. **LE**

The Holland MSK research program is funded by The Arthritis Society, Canadian Breast Cancer Foundation, Canadian Breast Cancer Research Alliance, Canadian Institutes of Health Research, National Institutes of Health (U.S.) and the North American Spine Society (along with SRI, University of Toronto and industry), and through the generous support of Bill and Suzanne Holland and other donors.



“We need to build a system that gets patients to the operating room quicker.”

Reigning in the Radical

The active surveillance strategy regards prostate cancer sufferers as individuals and treats them appropriately

Dr. Laurence Klotz, chief of urology at Toronto Sunnybrook Regional Cancer Centre (TSRCC) and an associate scientist at Sunnybrook Research Institute (SRI), thinks too many men with prostate cancer are treated more aggressively than the condition of their disease warrants. Indeed, statistics indicate that 93% of so-called favourable-risk patients in the United States in 2003 were treated radically with major surgery to remove the prostate gland and some surrounding tissue. “That’s bad,” says Klotz. “A radical prostatectomy is a serious operation. It can have an impact on a patient’s erectile and voiding function.”

He’s leading the charge to do something about it as the principal investigator of an international clinical trial that will seek to underline the benefits of a treatment strategy known as active surveillance.

This trial, which launched in September 2006 and has participants from Canada, the United States, the United Kingdom, the rest of Europe, Australia and New Zealand, will randomize patients with indolent, or slow-to-progress, prostate cancer in an effort to identify the extent of treatment needed. Of the one in six men who are diagnosed with prostate cancer every year, 40% may be candidates for this treatment. “That’s a big deal,” says Klotz. “We hope to demonstrate that you can reduce the impact of therapy with favourable-risk patients with this approach.”

Conventionally, prostate-specific antigens (PSAs) are identified in blood tests used to diagnose prostate cancer early and to monitor the disease after treatment is delivered. “But we’re using the rate of rise of PSA to determine whether a patient should be treated,” says Klotz. “This is a novel use.”

With active surveillance, doctors treat patients individually, limiting their therapy to just the 20% whose PSAs are on the rapid rise, or whose stage of cancer, on repeat biopsy, worsens. Favourable-risk patients who qualify for active surveillance are those who have PSA counts lower than 10, Gleason scores of six or less, and who are considered to have “low-stage cancer.”

Of the 500 people in Sunnybrook’s program, fewer than 1% have died of prostate cancer in the almost 10 years since they have joined it. And of the patients who did die of prostate cancer, all of them have died so rapidly, says Klotz, that they were clearly not curable at the time of diagnosis. “So far, we don’t have one patient who’s had a prostate cancer death that, in retrospect, we believe was preventable.”

Under the direction of Klotz, who is the leader of the GU site group at TSRCC, Sunnybrook has been using this novel strategy for almost 10 years in its treatment of prostate cancer patients. And the concept is catching on. “It started as a radical idea, this thought that you don’t treat cancer,” says Klotz. “But now it’s being widely adopted.”

The trial will involve 2,100 patients who will be accrued over the next five years and followed-up for 15 years after that. The organizing committee features one representative from each of six cooperative clinical trials groups (one each in Canada, the United Kingdom and Europe, and three groups in the United States). “The fact that we’ve been able to cobble together this consortium for a fairly complicated and expensive international trial is phenomenal,” says Klotz.

Each country’s group will finance its role in the study. In Canada, the research is being funded by the National Cancer Institute of Canada Clinical Trials Group.

“To be able to lead an initiative of this size is something you don’t get to do too often,” Klotz enthuses. “And to start with an idea that came out of a group 10 years ago and now has ... moved to the stage of an international clinic trial; well, that is just the chance of a lifetime.” ■

“So far, we don’t have one patient who’s had a prostate cancer death that, in retrospect, we believe was preventable.”



DR. LAURENCE KLOTZ



DR. MARTIN YAFFE AND MELISSA NOCK

ENTER ANOTHER DIMENSION DIGITAL TOMOSYNTHESIS ENHANCES BREAST CANCER DETECTION WITH A 3-D SNAPSHOT

Medical science has become increasingly dimensional in the last several years, good news for anyone who might have suffered from the flatter alternative.

Digital tomosynthesis (DT), an investigational breast imaging technique, creates a three-dimensional picture of the breast using multiple x-rays snapped from several angles. The information is sent to a computer, where it's assembled to produce clear, highly focused, 3-D portraits of a woman's breast.

Mammography usually takes two x-rays of each breast from different angles: top to bottom, side to side. Detecting a tumour inside it is a bit like finding the jelly in a donut with a couple of knife slices. Better to carve up the pastry, piece by piece, in search of the spot of jam.

The more accurate latter pursuit—exit bakery, enter lab—has been made easier over the years with increasing technical attention to mammography that has ushered its entrée into the digital field, replacing film with an electronic detector. This has enabled radiologists to acquire the image more precisely and enjoy the freedom to manipulate, enhance and share it digitally; to use computer-aided algorithms in cancer detection and diagnosis; to create functional contrast-enhanced images that display the effects of tumour angiogenesis; and to perform DT, among the most exciting applications on the improved digital mammography platform.

Where a mammographic image is a projection of the 3-D information in the breast onto a flat plane, DT creates 3-D images that explode the structures into a more lifelike materialization, a transformation, says Dr. Martin Yaffe, a senior scientist at Sunnybrook Research Institute (SRI) and co-principal investigator of the Breast Cancer Research Centre at SRI and Toronto Sunnybrook Regional Cancer Centre (TSRCC), that may help to detect breast cancer more accurately and avoid false positives.

Tomosynthesis uses a standard digital mammography machine, but angulates the x-ray tube at different angles to the stationary digital detector. The resultant set of 11 to 15 images is subject to calculations that combine the data to reconstruct a 3-D computer image. "When you look at it, it's as if you're looking through the breast, slice by slice," says Yaffe.

SRI's DT system, a \$750,000 miracle that's part of a research collaboration with GE Healthcare, is destined for three clinical research studies: With Yaffe, lead investigator Dr. Roberta Jong, director of breast imaging at Sunnybrook/TSRCC, will test the role of DT in screening; in diagnostic examinations; and as a new technique, contrast-enhanced tomosynthesis.

"Our overall goals," Yaffe says, "are to help improve the early detection of breast cancer for better outcomes. Digital tomosynthesis is a means of doing that." 

Yaffe's work in digital tomosynthesis is funded by the Canada Foundation for Innovation, Canadian Breast Cancer Research Alliance, Canadian Institutes of Health Research, National Cancer Institute, Ontario Innovation Trust, Ontario Research and Development Challenge Fund and GE Healthcare.

Sandra Black was the co-principal investigator in a study that revealed patients with early-stage Alzheimer's disease (AD) may benefit from the new drug Flurizan. The drug, tested over one year in Canada and the United Kingdom in a phase 2 clinical trial, is among the first to show potential to slow progression of AD in patients with the mild stage of the disease. Flurizan reduces the production of toxic amyloid, a sticky protein that becomes deposited between nerve cells in the brains of people with AD. The study also identified the optimum dose of the drug and highlighted the need to be patient in anticipation of its results.

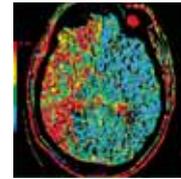
Anthony Feinstein determined that, in patients with mild to moderate traumatic brain injury, the e4 allele of the apolipoprotein E (APOE) gene does not have an adverse impact on outcome (a person's cognitive functioning). The patients were studied six months after injury. It has been suggested that the possession of at least one APOE-e4 allele may be linked to poor outcome in patients with predominantly severe traumatic brain injury.

Allan Fox and colleagues identified a linear relationship between carotid stenosis diameter and derived % stenosis that is less risky, more accurate and cheaper than its predecessor. Multidetector, high-speed, computed tomography angiography (CTA) now allows direct mm measurement of stenosis. Fox's results open up the possibility to substitute accurate mm stenosis measurements, yet still refer to % stenosis, a key finding because it allows prediction of North American Symptomatic Carotid Endarterectomy Trial results from 1991 that guide surgical management today. Accurate calculation of carotid stenosis degree can now be done from CTA, giving neck and brain artery images from one injection with contrast material over seconds. This replaces a full catheter angiogram, which takes an hour or more with risk of stroke (not present with CTA).

David Gladstone and colleagues published the results of a multicentre trial of stroke rehab therapy, investigating dextroamphetamine coupled with physiotherapy to treat patients with hemiparesis (paralysis of one side of the body). Despite animal studies showing enhanced stroke recovery with amphetamine administration, this trial—given during the first six weeks post-stroke, and featuring a 10 mg dose of amphetamine or placebo coupled with twice-weekly physiotherapy—showed no clinical benefit in this group of patients with mostly severe motor deficits. He recommended further study of neurorestorative approaches for patients with moderate severity hemiparesis using higher intensity and longer dosing regimens, and targeting the upper and lower limbs separately.

Glutamatergic synaptic transmission is crucial for brain function. **Wei-Yang Lu** discovered that excessive expression of acetylcholinesterase (AChE) impairs glutamatergic synaptogenesis in hippocampal neurons. He found that expression level of AChE was high during the early days of cultured embryonic neurons, but declined while other synaptic proteins increased. Chronic blockade of the peripheral anionic sites of AChE with specific inhibitors results in excess expression of AChE and impairments of glutamatergic synaptic structure and function, which were mostly preventable by antisense suppression of AChE expression. Further studies have suggested that excessive AChE interrupts the interaction between synaptic adhesion molecules.

Jean-Philippe Pignol produced the first report on the new technique of breast irradiation involving the permanent implantation of ¹⁰³Pd radioactive seeds under image guidance and local anaesthesia. Of the 16 patients with early-stage breast cancer who received the treatment, all were satisfied and none experienced a significant skin reaction. Permanent seed implantation is preferable to the current radiotherapy involving up to seven weeks of treatment to the whole breast, because women experience far less skin toxicity and the one-hour procedure is less of a burden. This is a major advance for partial breast irradiation.

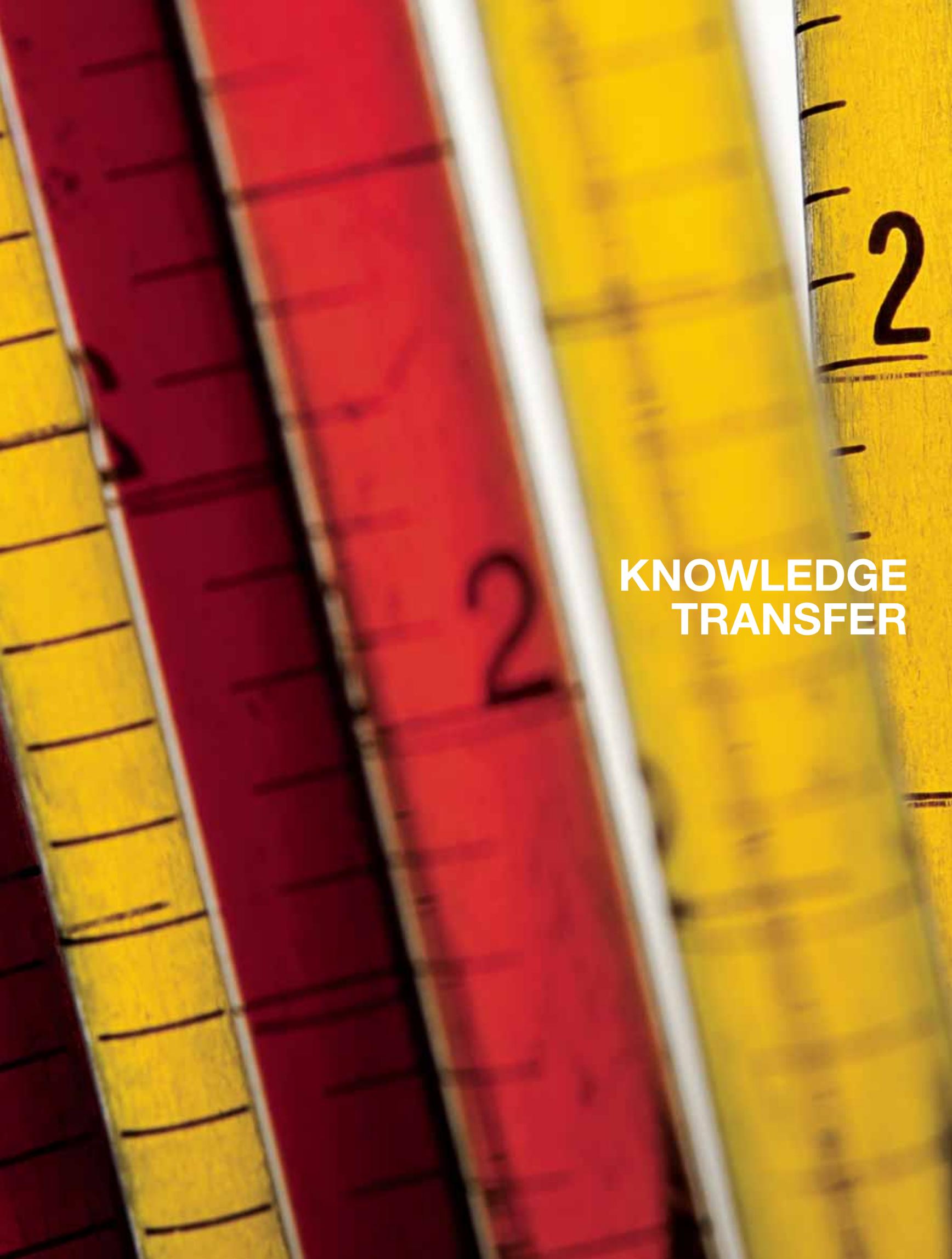


John Rowlands unveiled an electronic portal imaging device whose design features a quantum efficiency that is more than an order of magnitude higher and a spatial resolution equivalent to that of the flat panel systems that are used for portal imaging. This combination is unique. For an imaging system to have a higher level of x-ray absorption—desirable for applications such as a megavoltage cone-beam computed tomography and megavoltage fluoroscopy—usually means its spatial resolution has been sacrificed in the process. In this case, that imperative has been sidestepped.

Mary Tierney provided evidence that a few neuropsychological tests can identify who will progress to Alzheimer's disease (AD) within 10 years. Short delayed recall was found to be the most predictive test: it was the only one to identify progression to AD within 10 years. Tierney's was the first prospective study examining the prediction of AD over 10 years in a large sample in which the diagnostic outcomes were derived independently of the predictors. Her findings have implications for the early identification of AD in people without the disease. This information can be used to care for patients and will be helpful to researchers who are studying treatments for the disease in its earliest stages.

Using biphasic finite element modelling (modelling the solid and fluid phases of a material), **Cari Whyne** evaluated the effect of multiple loading conditions on a metastatically involved thoracic spine, with a view to defining better the level of compromise to which the vertebral bone's mechanical integrity is subjected when metastatic cancer cells migrate there. She found axial loading to be the main load type leading to increased risk of burst fracture. Rotational loading led to only moderate increases in risk. Inclusion of the ribcage was found to reduce the potential for burst fracture by 27%. These results may prove useful in informing activity recommendations for patients affected by lytic spinal metastases.



The image features four rulers arranged vertically, slightly overlapping. From left to right, the colors are yellow, red, yellow, and yellow. The number '2' is printed on the red ruler and the rightmost yellow ruler. The rulers have black markings and numbers. The text 'KNOWLEDGE TRANSFER' is overlaid in white on the right side of the image.

**KNOWLEDGE
TRANSFER**



CLINICAL
EPIDEMIOLOGY

TAKE THREE

A trio of researchers offers its take on a multidisciplinary branch of medical science with a broad reach

Dr. Don Redelmeier wants you to get real.

He wants you to realize that the work that gets him up every morning, that inspires him to grab a peach and a can of Diet Black Cherry Vanilla Coke and to step lightly over the papers stacked on his office floor so he can reach his chair and put his feet up on his desk, is sincere. No pinhead-dancing angels here. Not even any astrophysics or subatomic stuff. Nope. Clinical epidemiology, he'll tell you, is science anchored in the real world.

"It's got to do with washing your hands before surgery, or buckling up in an automobile so you won't need surgery in the first place," says Redelmeier, who is director of clinical epidemiology at Sunnybrook Research Institute (SRI). "My favourite definition of clinical epidemiology calls it the science that evaluates the causes and consequences of disease in humans. If you're a bunny rabbit, we don't care about you. If you're a person who is suffering, you've got our attention."

Most people, Dr. Kathleen Pritchard laments, don't know what clinical epidemiology is. Tracing a finger along the words, this other prominent member of SRI's clinical epidemiology team at the Toronto Sunnybrook Regional Cancer Centre (TSRCC) gives a textbook explanation a go. "The practice of epidemiology that begins in a clinical setting," she says, reading aloud from *A Dictionary of Epidemiology*.

But it's only become an established term in the last generation, this amorphous concept, taking shape as a formal discipline distinct from epidemiology as a whole. Receiving training in it, says Dr. Linda Rabeneck, a senior scientist at the TSRCC and Sunnybrook's vice-president of regional cancer services, means having a box whose tools are portable and applicable. "If you decide tomorrow that you want to work on HIV, you can, because you have the training and the concepts. It's a way of thinking."

“The mission statement around here is to make health care in the future better than it is today.”



RABENECK PUTS COLONOSCOPIES UNDER MICROSCOPE

The research in which Linda Rabeneck engages is what she likes to call “policy relevant,” a label that suggests it has very real-life consequences. “We set the bar very high here, and we’re trying to do research that’s not just, ‘Oh gosh, that’s intriguing.’” It is also, she says, identifiable for her level of involvement in its nuts and bolts. “I’ve always taken a dim view of folks who are making broad policy statements but not contributing to the area,” Rabeneck, who is also a senior scientist, says. “I think to fully understand the field you have to be working in it and contributing to it.”

Rabeneck has engaged in both recently, in the service of more accurately defining the limitations and applications of colorectal cancer research. A colonoscopy is the final common pathway for any abnormalities revealed through a colon cancer screening test. But while it may be the best tool available for detecting polyps and cancer in the colon, it’s still some distance from perfect. It was Rabeneck’s dismay over stories from colon cancer patients about colonoscopies that missed their diagnoses that spurred her to research investigating their accuracy.

Focusing on 2,654 patients newly diagnosed with cancer on the right side of their colon (the most technically difficult to reach) who had surgery for their cancer between 1997 and 2001 and a colonoscopy in the preceding three years, Rabeneck honed in on the last colonoscopy before the diagnosis, and considered the interval. If the colonoscopy was within six months of the diagnosis, she determined, it found the cancer. But for those diagnosed between six months and three years after their test, the “miss rate” was alarming. Specifically, it was 4%: the cancer in 105 of 2,654 patients had been overlooked by the very test undertaken to find it.

The results of this retrospective cohort study were published in *Gastroenterology* in 2004.

The translation of this grim fact to the reality of a patient’s life is easy, says Rabeneck. It means now, in addition to explaining the various physical risks of the procedure (e.g., bleeding, a punctured bowel), a doctor must include noting the possibility that, “If you have cancer, there’s a small chance I might miss it.”

Rabeneck, about whom SRI senior scientist Dr. Thérèse Stukel admires, “her intellectual curiosity, her absolute rigour in doing research and her openness to comments from [others],” has also investigated the issue of setting an upper-age cutoff for colonoscopy screenings. Currently, international recommendations say these tests should begin at age 50, but nobody’s ever put a ceiling on them. They should, believes Rabeneck, who has a strong family history of the disease. A person’s likelihood of developing colon cancer rises beyond the age of 50, but his life expectancy goes down. And, again, colonoscopies are not without risk.

Her study, published in *The Journal of the American Medical Association* in 2006, examines the trade-off, and concludes that a colonoscopy screening lends an 80-year-old only 15% of the expected gain in life expectancy that it does younger patients. This finding, says Rabeneck, “should be factored into decision-making about whether elderly patients should be screened.”

SRI SCIENTIST GIVES CHOLESTEROL-REDUCING DRUG NEW LIFE IN DEFENCE AGAINST SEPSIS

Don Redelmeier’s understanding of clinical epidemiology smacks of some dissatisfaction. “There really are many things wrong with current health care, and we want future health care to be better,” says the senior scientist, who holds a Canada Research Chair in Medical Decision Sciences and is cross-appointed to the Institute for Clinical Evaluative Sciences (ICES).

But Redelmeier, whom SRI senior scientist and colleague Dr. Michael Schull describes as “one of the few people who can manage to create broad interest in his research,” is not about to let the flaws go untreated. “The mission statement around here,” he says, “is to make health care in the future better than it is today.”

Examples of this early declaration in action are legion. Among the more recent is his research on the connection between statins and sepsis.

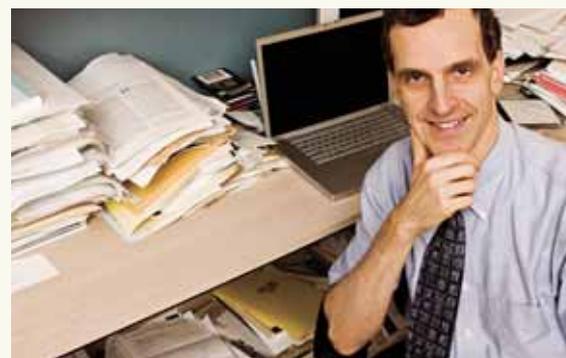
In general, people with hardening of the arteries take a statin, a drug that lowers fat levels in the blood, to reduce their cholesterol. A possible underlying predisposition to sepsis is not a consideration in its prescription. Similarly, the risk of contracting sepsis has nothing to do with cholesterol count. Sepsis, a rare but serious bacterial infection, visits its victims in response to other factors, like if they have cancer, compromised immune systems or just lousy luck, and develop pneumonia or a kidney infection.

Jumping to preclinical models from experiments outside of the clinical epidemiology realm, Redelmeier noted that pretreatment with statins extends survival and sometimes even promotes complete recovery from blood-poisoning sepsis.

He extended this research to people, considering 60,000 Ontarians with hardening of the arteries, some of whom were taking a statin, some of whom were not. Taking care to peer-match them in terms of other risk factors, Redelmeier followed-up these people—a mean age of 74, 56% men, 16% living in rural Ontario—for a median duration of five years between 1997 and 2002. Findings, published in *The Lancet* in 2006, were revealing. He observed that those who were taking statins had a 20% lower risk of developing or dying from sepsis than those who were not.

“That’s a big deal,” he says, closing his eyes for emphasis, leaning his long body back in his chair, “because sepsis can be a very unpleasant disease: lethal (the case fatality rate of sepsis is at least 20%) and expensive to treat.” What’s more, he notes that current clinical treatment for sepsis is “not always satisfactory.” Statins, he concluded, might prove a feasible method for preventing at least some cases.

That his work revealed a new use for drugs whose relevance was previously assigned to another application cements Redelmeier’s conviction that research of medications that are now being used more broadly under normal community circumstances, might reveal characteristics—surprising harms or benefits—that weren’t anticipated. This impulse makes sense to Schull, who calls Redelmeier “a very serious guy superficially,” but says, “deep down, Don and his research are like a kid in an amusement park: He sees all this opportunity to go on the rides.”



DR. DONALD REDELMEIER



“With a marker like Her-2/neu, you can spare the patient who doesn’t need the toxicity.”

DR. KATHLEEN PRITCHARD

CANCER DOC WORKS TO CUSTOMIZE TREATMENT— WITH A LITTLE HELP FROM HER FRIENDS

It was Easter 2004, and Kathleen Pritchard was putting all of her eggs into one basket.

The head of clinical trials and epidemiology at TSRCC was on the phone with a pathologist in New Brunswick, imploring her to delve back into a decade-old inventory to uncover a specimen whose new examination, in Pritchard’s hands, might reveal valuable information that was inaccessible when the samples were first pulled. Specifically, Pritchard needed her to sort through, prepare and mail some new “unstained” slides from a dozen women’s stored pathology specimens. It was five or six hours of work, and the pathologist had come in on the holiday weekend to address Pritchard’s request.

In the end, the study leader’s passion, which was spilled out over the country across phone lines every Friday morning for three years, was enough to persuade sympathetic pathologists to send along 639 old tumour specimens (over 90% of those she sought) for the new life she would give them as part of a National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial, whose Breast Cancer Site Group Pritchard co-chairs. (It’s not surprising, says Dr. Maureen Trudeau, head of the division of medical oncology and hematology, who says of her colleague: “She has a great personality, she’s fun loving, she’s hard working, she’s collegial and she’s collaborative.”)

Pritchard wanted to return to these specimens from the NCIC CTG Mammary.5 (MA.5) trial (archived in hospitals) in pursuit of her hypothesis that women with breast cancer with a positive incidence of a particular protein—Her-2/neu— would respond better to a certain kind of chemotherapy than women without.

Pritchard was able to prove that women with an overexpression of Her-2/neu (25% of those in the MA.5 trial) did much better if they received the dose-intensive anthracycline-containing regimens such as CEF (which uses a combination of cyclophosphamide, epirubicin and fluorouracil), while those without this overexpression seemed to do just as well with the less toxic CMF (cyclophosphamide, methotrexate and fluorouracil), the de facto standard. In those whose tumours overexpressed Her-2/neu, she showed that CEF was better for both disease-free and overall survival.

Her findings, published in *The New England Journal of Medicine* in 2006, are significant, because they mean treatment can be more exactly tailored. CEF is more expensive, more toxic, puts its recipients at risk of more infection and side effects, and, importantly, exposes patients to up to a 1% chance of contracting heart disease, and a 1% to 2% chance of getting leukemia. “With a marker like Her-2/neu,” Pritchard says, “you can spare the patient who doesn’t need the toxicity.”

One of the challenges of this study—solved, in great part, by the willingness of the pathologist volunteers—was that it required the measuring of a gene that wasn’t even known about when the patients consented to participate in the original. Partly as a result of this stumbling block, the national trials group has rewritten its privacy and ethics codes such that they now include a clear mechanism for allowing patients to give their permission for future tumour specimen reviews. “We’re going to have a gold mine of material for long-term follow-ups and specimens,” Pritchard says.

Her basket runneth over. **LP**

Redelmeier’s research was funded by the Canadian Institutes of Health Research, National Institutes of Health (U.S.) and Physicians’ Services Incorporated Foundation. He holds a Canada Research Chair.

Rabeneck’s miss rates research was funded by the Cancer Quality Council of Ontario, where she is a senior investigator, through salary support; the study on colonoscopy age caps was funded by her colleagues in the gastrointestinal section of the Virginia Mason Medical Center in Seattle, WA.

Pritchard’s research was funded by the Canadian Breast Cancer Research Alliance and the Canadian Cancer Society through the National Cancer Institute of Canada. Infrastructure support was provided by the Canada Foundation for Innovation, Ontario Innovation Trust, and industry and private investment.



“The results were very encouraging. They confirmed what we were doing in clinical practice, and will hopefully persuade others to look at that strategy, as well.”



DRS. STEPHEN FREMES AND ELSAYED ELMISTEKAWY

FINGERS ON THE PULSE CARDIAC SURGEONS CONSIDER THE RADIAL ARTERY AS A BYPASS GRAFT ALTERNATIVE

The beating heart is the constant for cardiac surgeons, the pulsating index of their success or failure, the animated background set piece to the unfolding drama of improving health care with technical excellence and a relentless pursuit of better ways to get things done. So it is with Drs. Stephen Fremes and Nimesh Desai, two Sunnybrook heart surgeons who regarded with interest the scripted evolution of bypass graft materials over the years—and never felt convinced that the plot had resolved itself to their satisfaction.

For all of its leaps-and-bounds advances, bypass surgery is a guarantee of nothing. The saphenous vein that typically bridges the faulty chasm for heart patients is notoriously short-lived. By 10 years after surgery, almost one-half of the grafts have failed. Their hosts may have suffered more angina, heart attacks or heart failure. Still, this ankle-to-thigh vein was the conduit of choice for more years of heart surgery's history than anything else. It's easy to access, the right size and, in most people, in decent enough shape for harvesting.

In the 1980s and 1990s, though, the saphenous vein's uncontested position was challenged by surgeons' increasingly regular use of an artery on the chest wall, initiating the age during which the saphenous standard was supplanted with the saphenous and internal thoracic artery combination.

On the face of it, an artery is an obvious improvement on a vein for bypass surgery. After all, arteries are used to systemize blood pressure,

and the blood inside veins only trickles—doesn't bound—back to the heart. Veins' failure rates are often pegged on this shortcoming. They're not accustomed to high blood pressure, and there is speculation that its demanding presence for this adapted application causes the veins to thicken and, over time, close.

It surprised no-one, then, to discover that, if used as a bypass graft, the thoracic artery lasts longer than the vein. In fact, it almost never breaks down. After 10 years, research has revealed that more than 95% of them are still functioning. But this chest-wall vessel is more delicate to work with and trickier to extract than its predecessor. It also carries with it the risk of bone infection in response to the necessary closing-off of circulation to the breastbone during surgery.

Surely, thought Fremes and Desai, the perfect bypass graft material was yet to be identified.

The radial artery, which carries the body's pulse through the forearm, was first engaged in bypass surgeries in the 1970s, but with limited success. Some 20 years later, a paper came from Paris inviting the medical community to reconsider it as an alternative to the saphenous vein, which was producing worrying results for the blockages that were developing late after surgery. Fast-forward to today, when tissue-handling techniques have progressed to where, physicians hypothesize, it may be entirely reasonable to celebrate this alternate artery's role in heart surgery. It looked promising for its speculative ability to offer

A RARE GLIMPSE

THE SPY SYSTEM OFFERS CARDIAC PHYSICIANS AN EXTRAORDINARY OPPORTUNITY FOR AN OF-THE-MOMENT QUALITY CHECK

The better the quality assurance in the operating room, the better a patient's chances for recovery and survival.

Or so the theory goes.

Historically, an absence of a particular kind of diagnostic imaging technology has meant coronary bypass surgery couldn't see the theory through. Surgeons' inability to look at the quality of a graft in the OR is a significant omission, considering the revelations of studies on postoperative patency and angiography: of grafts that fail, a number do so while the patient is on the table.

Enter the SPY system, a made-in-Canada angiography device that has revolutionized how—and, most significantly, when—grafts are assessed. The SPY system, which Sunnybrook cardiac doctors have been using since 2001, allows doctors to do an angiogram without using x-rays or a toxic-to-kidneys contrast dye. Instead, indocyanine green (a green pigment) injected into the vascular system is fluoresced with the near-infrared laser light of an imaging head that can penetrate up to two millimetres of soft tissue, and also houses a tiny

video camera. The result is an image that surgeons can view on a computer screen at the end of a procedure, before the patient is sewn up, to gauge the graft's effectiveness. Graft problems it reveals—a stitch taken too deep, a vessel kinked off, a clot at the junction between two channels—can then be repaired in the OR. Its influence now extends to between 5% and 10% of the patients it monitors.

"It's real-time, real-life, clinically applicable research," enthuses Dr. Nimesh Desai, a research fellow and chief resident in cardiac surgery at Sunnybrook. "That's very gratifying, especially if you take a SPY angiogram of someone, find a problem and fix it right there. You've prevented a whole pile of grief in the long term."

Research on the SPY system was funded by the Canada Foundation for Innovation, Ontario Innovation Trust, and industry and private investment through the Imaging Research Centre for Cardiac Intervention. The Heart and Stroke Foundation of Ontario and Physicians' Services Incorporated Foundation provided operating grants.



the same longevity as the internal thoracic artery without the surgical demands or attendant side effects.

Moreover, Fremes, who is a senior scientist at Sunnybrook Research Institute, had a personal interest in the subject. "Most surgeons have something they're known for," he says. "I had a reputation for being a very good coronary surgeon." He was troubled, though, by the coincidence of the risk of vein-graft disease and late cardiac events among the two-thirds of patients who die beyond the first one to 12 months following coronary surgery. "That's the scientific rationale for looking at other bypasses."

At the time of the study's launch, the radial artery was acknowledged for various intrinsic advantages, but was also suffering variable reports about whether its results could be characterized as excellent or mediocre. Ultimately, there was equipoise, meaning that the information relating to the question was balanced: there was no good evidence in favour or not of the radial artery.

Recruitment for the study took place between 1996 and 2001. It was a multicentre trial that spanned the country and included one international site. Results were published in *The New England Journal of Medicine* in 2004.

One year postoperatively, tests of the 561 participants revealed a significantly greater proportion of the radial arteries were functioning

better than the saphenous veins. What's more, the radials were 40% less likely to fail at one year.

The research also spoke convincingly of the link between radial patency—the state of being open and unblocked, and a key predictor of long-term survival—and the extent of disease within the target vessel. If a vessel had a 90% or higher obstruction, the radial artery would remain patent; if the obstruction was between 70% and 90%, patency declined. "That's something that surprised us," says Fremes.

All told, says Desai, who is a research fellow and chief cardiac surgery resident at Sunnybrook, "the results were very encouraging. They confirmed what we were doing in clinical practice, and will hopefully persuade others to look at that strategy, as well."

In practical terms, it means cardiac surgeons at Sunnybrook—and those throughout the world, particularly in Australia and Europe—are expanding their use of the radial artery on the strength of this evidence that it will eventually surpass the saphenous vein in effectiveness.

Up next for Fremes and Desai: a five-year examination of postoperative outcomes, along with studies that seek to understand why bypass grafts fail over the long term.

The drama continues. **LP**

Fremes' and Desai's research was funded by the Canadian Institutes of Health Research.

THE SKEPTICS

IF A FEDERAL REGULATORY BODY GIVES ITS STAMP OF APPROVAL TO—OR RAISES THE SPECTRE OF DOUBT ABOUT—A CLASS OF ON-THE-MARKET DRUGS, IS IT A DONE DEAL? DON'T YOU BELIEVE IT

Question everything; trust nothing.

It is the maxim across which Sunnybrook Research Institute (SRI) neuroscientists Nathan Herrmann and Krista Lanctôt have slung their lab coats in the years since embarking on research to uncover the reality behind a declared association between a certain class of drugs and an unfavourable reaction the drugs are said to produce sometimes.

The subject spiked concerns—first in the medical community, then in the general population—in 2002, when randomized controlled trials of an atypical antipsychotic's use with Alzheimer's patients suggested a higher risk of strokes and other cerebrovascular events, and subsequent increased rates of mortality. In response, Health Canada, along with other regulatory agencies including the FDA in the United States, issued a warning.

The tailspin into which the clinical community was then thrown was what Herrmann and Lanctôt undertook to stabilize. "When the warnings came out," says Herrmann, "we feared they might create a false impression of safety with [regards] to the older class of antipsychotics."

Atypical antipsychotics are the newer iteration of this class of drugs. They were introduced in the early 1990s as a more efficacious and less side-effect-prone replacement to the "typical" treatment for psychosis and related symptoms that's been prescribed since the 1950s.

"Clinicians were left not knowing what to do," says Lanctôt.

The researchers took aim at what they considered to be significant shortcomings within the original research, which sprang from four

randomized controlled trials (comprising 1,230 elderly dementia patients) that revealed an increased rate of strokes and transient ischemic attacks among patients taking risperidone compared with those taking a placebo. Herrmann and Lanctôt were dismayed by the modest number of subjects enrolled in the study and the small absolute numbers of subjects who experienced adverse cerebrovascular events. Indeed, they submitted, it was unclear whether there even was a true association. Finally, they pointed out that this research said nothing about whether this apparent reaction was limited to risperidone or if it might extend to other atypical antipsychotics.

The pair launched a study that compared stroke rates among patients taking atypical antipsychotics against those taking their predecessors. The analysis used a retrospective population-based cohort of some 1.4 million patients in Ontario aged over 65 years. One group was taking typical antipsychotics; the other, atypical antipsychotics: either risperidone or olanzapine.

In 2004, Herrmann, who's an associate scientist at SRI, and Lanctôt, a scientist at SRI, had their results published in *The American Journal of Psychiatry*. They reported there was no statistically significant increase in the risk of stroke between the typical and atypical classes of drugs. The article did two things: reassured clinicians that the absolute rates of strokes in patients treated with both types of antipsychotics are low; and warned clinicians that if they thought they were protecting their patients from adverse cerebrovascular events by using the older typical antipsychotics, they were wrong.

This article is the first in a trio that examines the link between atypical antipsychotics and the risk of cerebrovascular accidents, all of which scrutinize some aspect of the safety of these drugs. The second study is a meta-analysis of the trials that prompted Health Canada's warnings; the third looks at more adverse events associated with the drugs (including mortality, movement disorders, weight gain and diabetes) and attempts to put all that preceded it into perspective.

This research, say the scientists, has only served to strengthen their conviction that skepticism in all things scientific is a good thing. "I was surprised by how little we know about the true safety of these drugs, even after they've been approved and on the market for several years," says Herrmann.

The world, says Lanctôt, has known to be dubious about drug research—whether it validates or undermines it—since the thalidomide disaster. "We shouldn't be surprised," says Lanctôt. "But we always are." **19**

DRS. NATHAN HERRMANN AND KRISTA LANCTÔT



Raising the Volume on a Silent Killer

Sheldon Tobe brings a unique blood-pressure-control strategy to a First Nations community then finds some surprises in a community of his own

Hypertension (high blood pressure) is the second-leading cause of end-stage kidney disease (ESKD), a life-threatening condition requiring dialysis or transplantation; the first is diabetes. Diabetes is a risk factor for hypertension and vice-versa. Together, they dramatically increase risk for ESKD. And for every person with ESKD from diabetes, 20 have already died from heart attack or stroke. Controlling hypertension in people with diabetes, therefore, is crucial. Here's where it gets complicated.

Doctors know how to treat hypertension. "It's not rocket science," says Sheldon Tobe, an associate scientist at Sunnybrook Research Institute. "We have the knowledge, technology and drugs. The issue is implementation."

As a nephrologist treating patients with kidney failure, Tobe butted up against that reality for years. As a researcher, he found the solution in the DREAM 3 study (Diabetes Risk Evaluation and Microalbuminuria). In this study, he tested the effectiveness of a community-based strategy, in which home care nurses implemented a treatment program of antihypertensive medication in First Nations people with diabetes.

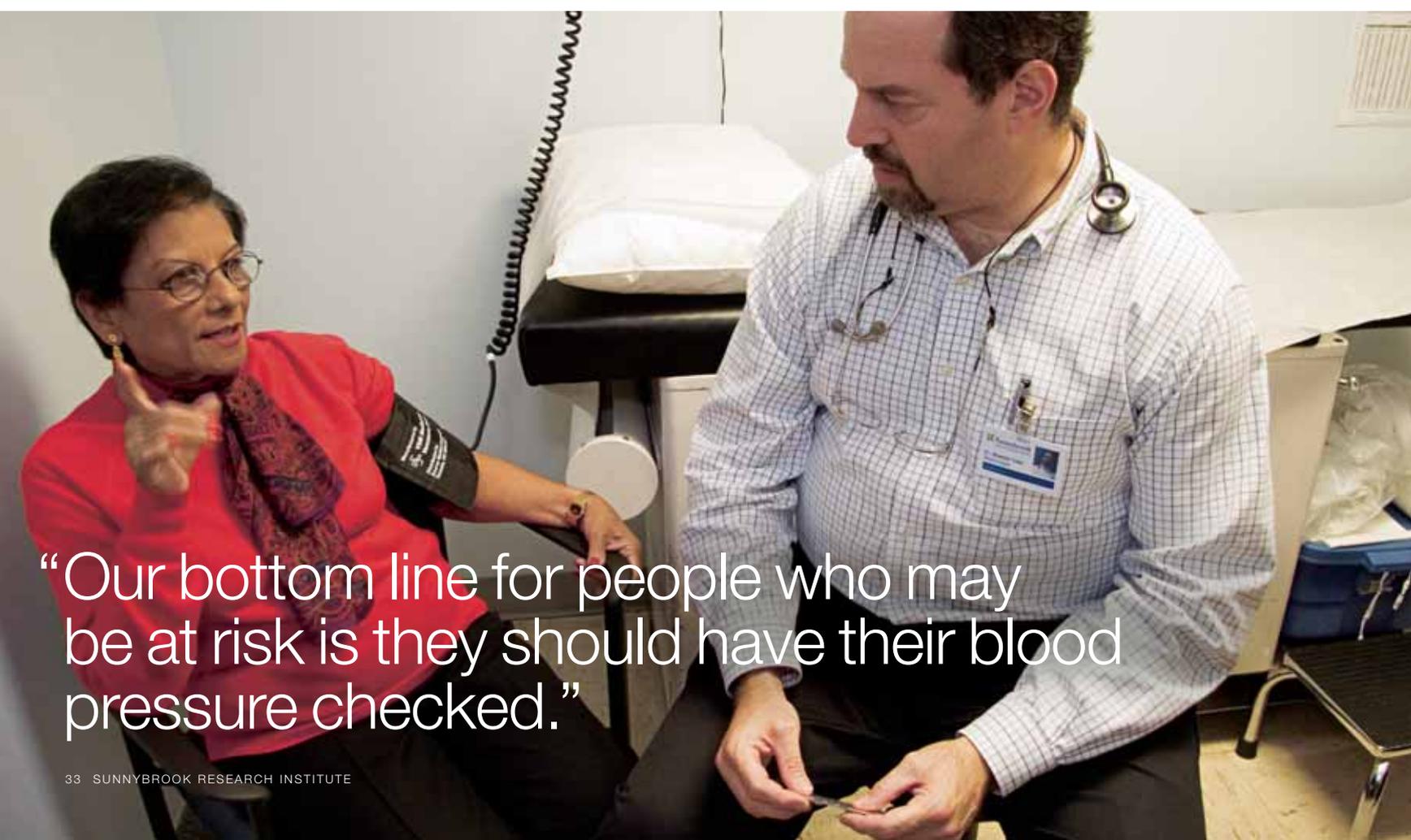
The results: participants receiving treatment saw a 24-point reduction in systolic blood pressure (BP) (the top number in a BP reading, taken as the heart contracts) and an 11.6-point reduction in diastolic BP (the bottom number, measured between contractions). The strategy brought BP to the target in 50% of people. The Canadian average for BP control of people with diabetes is 9%. Two years after the completion of the study, their BP was still under control. "We left a lasting impact in that community," says Tobe.

In addition to impacting First Nations communities facing barriers to health services, Tobe found clues to the development of hypertension closer to home. In the 2005 "Double Exposure" study, in which he measured BP in 248 employees at Sunnybrook Health Sciences Centre (SHSC), Tobe determined that marital cohesion was associated with lower systolic BP in subjects experiencing job strain. Later that year, he examined the relationship among drinking alcohol, gender and BP in the same cohort. As expected, he found elevated BP among drinkers; unexpectedly, females had higher BP than did males, especially during times spouses spent together. "Across the board, women tend to have lower BP than men, so it was a striking finding," says Tobe.

Also surprisingly, the study revealed that 22% of 352 additional SHSC employees screened as potential participants had hypertension, and 40% of those didn't know it—just like the general population. It's a reminder that education and easy access to health care don't always bring implementation and treatment. Two people's readings were so high that they would have had a stroke within weeks. Tobe says, "Our bottom line for people who may be at risk is they should have their blood pressure checked." And that's a wake-up call for us all. [10](#)

Tobe's studies were funded by the Canadian Institutes of Health Research in partnership with Pfizer Inc. and the Heart and Stroke Foundation of Ontario.

DR. SHELDON TOBE AND PATIENT



"Our bottom line for people who may be at risk is they should have their blood pressure checked."



William Geerts summarized main recommendations of the American College of Chest Physicians' guidelines on how to prevent venous thromboembolism (which includes blood clots in the veins of the legs that can travel to the lungs). For the past 10 years, Geerts has led this international guideline process. Among them: hospitals should develop and implement a strategy to prevent blood clots; patients having major surgery or admitted with a serious illness should receive thromboprophylaxis; do not use aspirin alone to prevent venous thromboembolism for any patient group; for moderate-risk surgery or medical patients, use either low-dose heparin or low-molecular-weight heparin (LMWH); for high-risk surgery patients, use one of three anticoagulants (LMWH, fondaparinux or adjusted-dose warfarin).

Curious about the on-the-street response to a drug's recall, **Gillian Hawker** investigated the fallout from the recall of Vioxx, the anti-inflammatory drug rofecoxib recalled in September 2004 after studies showed that long-term use increased the risk of heart attack and stroke. Many of the 968 elderly patients who participated in the survey—all of them with hip/knee osteoarthritis, and over one-half of them with a history of rofecoxib use—were unaware of, or overestimated, the absolute risk of adverse events associated with the drug. Hawker's research highlights the need for clarity in the communication of a therapy's risks and benefits.

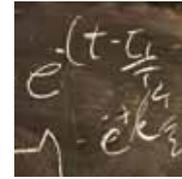
Acting on the hypothesis that the September 11, 2001, attacks in the United States influenced rates of self-harm around the world, **David Juurlink** was the primary author on an ecological analysis of poisonings in the days immediately after the attack. Juurlink and colleagues found that the terrorist attacks were associated with a transient but dramatic reduction (62%) in deliberate self-poisoning in Ontario. He speculated that the unexpectedness and enormity of the attacks led to mass distraction at the population level, causing the usual precipitants of self-harm behaviour (financial and work stressors, for example) to assume, transiently, less importance.

Beta blockers substantially improve survival in chronic heart failure (HF) patients with left ventricular systolic dysfunction, but concerns about cardiovascular side effects may deter physicians from prescribing this therapy. **Dennis Ko** performed an overview of randomized β -blocker trials in HF patients to quantify the risks of these effects in order to guide physicians during implementation. While an overview of randomized β -blocker trials in patients with HF revealed annual increases in risks of hypotension, dizziness and bradycardia, the absolute increases in risk were small. β -blocker therapy was associated with reductions in all-cause withdrawal of medication, all-cause mortality, HF hospitalizations and worsening HF.

Anthony Levitt and colleagues concluded that light therapy and antidepressants—the two remedies most commonly reached for to treat seasonal affective disorder—are equally effective and tolerated. Light treatment resulted in earlier response onset and a lower rate of some of the adverse events that resulted from the antidepressant drug fluoxetine, but there were no other significant differences in outcome. As such, other clinical factors, such as patient preference, should be taken into consideration when selecting first-line treatment for seasonal affective disorder.

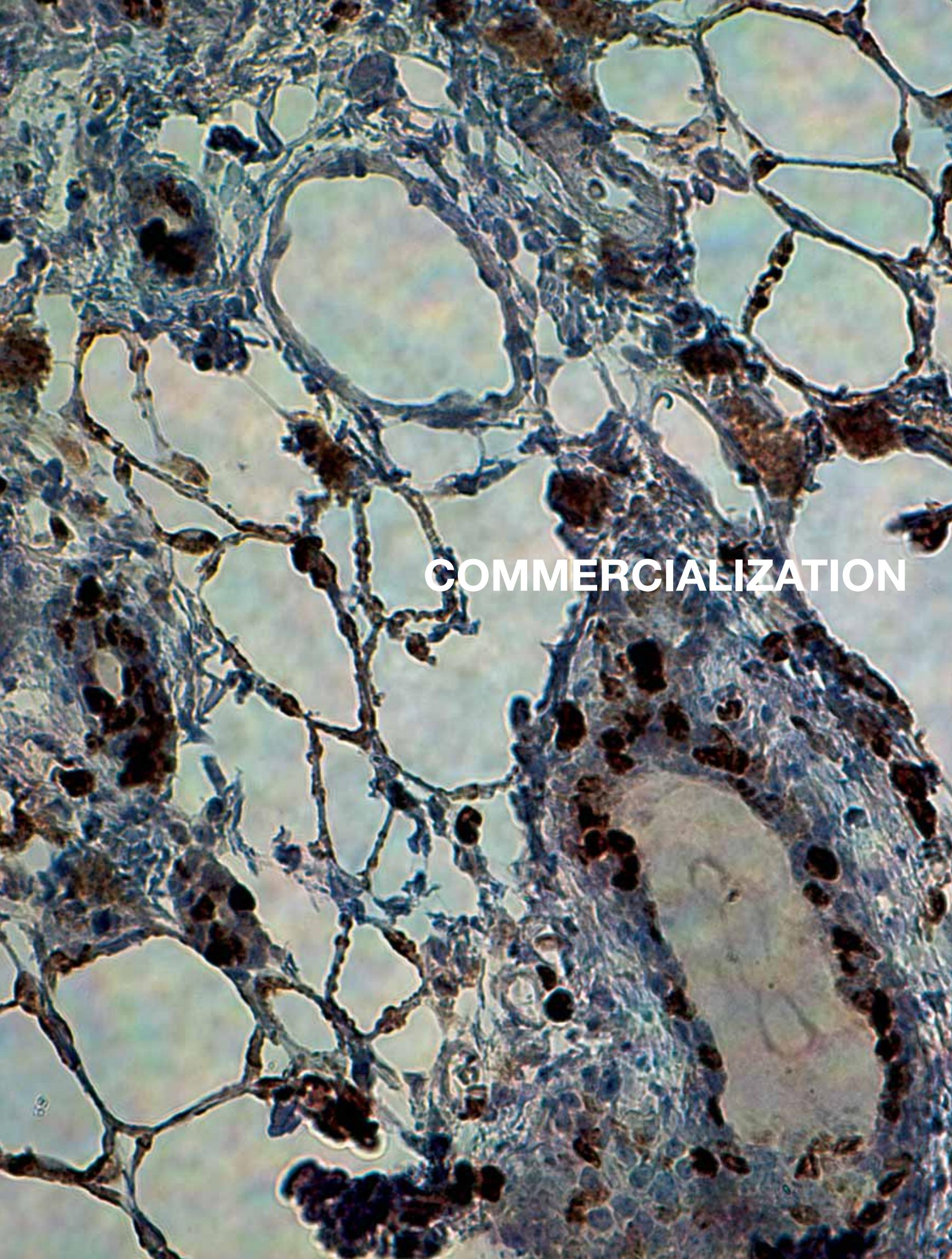
Donald Redelmeier found evidence that withholding warfarin from elderly patients after major trauma—a common practice in anticipation of hemorrhage risk—was not associated with an increased possibility of arterial thrombotic events, stroke or myocardial infarction, but was associated with a significantly increased risk of venous thromboembolism (when a vein is blocked or partially blocked by a blood clot that originates somewhere else in the body). This study is a cautionary tale for physicians who prescribe this long-term oral anticoagulant to patients with a history of trauma, urging them to consider the competing risks of hemorrhage and venous thromboembolism.

Considering long-term outcomes of regional variations in intensity of invasive versus medical management of Medicare patients with acute myocardial infarction, **Thérèse Stukel** found that a more intensive medical management style was associated with improved survival regardless of the level of invasive management in the region. But in regions that espoused a policy of high medical management intensity, there was little or no improvement associated with additional invasive treatment. Her research warned that routine use of more costly and invasive treatment strategies may not be linked with an overall population benefit beyond that seen with excellent medical management.



In a trial studying the effect of dairy products on human immunodeficiency virus (HIV) illness, **Jill Tinmouth** concluded that modern lactose ingestion doesn't worsen chronic diarrhea as has long been believed. In the study, lactose's influence on diarrhea was measured according to stool weight, and lactose was judged not to worsen diarrhea if the weight difference between two separate study periods (during one, study participants drank low-fat milk; during another, they drank lactose-free milk) did not exceed 167 g in eight hours with 95% certainty. These results challenge common practice, which dissuades dairy product ingestion on the assumption that it will worsen this aspect of HIV sufferers' illness.

In comparing gender differences in outcomes after hospital discharge after undergoing coronary artery bypass grafting, **Jack Tu** and colleagues determined that women are more likely to be readmitted to hospital with unstable angina and congestive heart failure, but that they experience survival rates similar to men. Women also have a more complex clinical preoperative presentation. Gender differences in outcomes, Tu noted, may be improved through durable revascularization strategies and close post-operative follow-up care targeting women.



COMMERCIALIZATION

IMAGES OF



SUNNYBROOK RESEARCH INSTITUTE SPIN-OFF SENTINELLE DOES DOUBLE-DUTY WITH AN MRI BED THAT IMPROVES WOMEN'S COMFORT WHILE MAKING MORE EFFICIENT USE OF TECHNOLOGY

EXCELLENCE

Mammography has long been the standard for breast cancer detection. But it is failing women who carry the BRCA1 or BRCA2 gene. The breast tissue of these women, at risk for contracting cancer at a much earlier age, is quite different from that of postmenopausal women. It tends to exhibit an abundance of cycling fibroglandular tissue, a characteristic that complicates a mammogram's ability to pick up subtle differences for their similar appearance to tumours.

MRI is a three-dimensional technology that uses the nuclear properties of hydrogen protons in body tissues—which offer rich signatures—and the dramatic contrasts among them to highlight breast tumours. It has the advantage of not using ionizing radiation, which has a proven—if extremely small—carcinogenic risk. And MRI bypasses the fibroglandular issue thanks to the intravenous injection of a contrast agent that ultimately sequesters in tumours as a result of tumour angiogenesis, a biological process whereby cancer cells recruit and create new blood vessels to support their need for tumour growth. These blood vessels are different from normal blood vessels in that their permeability to this contrast agent is somewhat higher.

Research is ongoing, but the emerging conclusion is that MRI is the best bet for early detection of breast cancer in this population—about 84% versus 36% for mammography and 33% for ultrasound, based on findings from a large Sunnybrook study headed by Dr. Ellen Warner at the Toronto Sunnybrook Regional Cancer Centre. It is, says Dr. Don Plewes, a senior scientist at SRI, co-principal investigator of the study and founding member of Sentinelle, “just a spectacularly ingenious and fantastic imaging method.” That MRI—traditionally used mostly for neurological applications—is now acknowledged as an optimal breast-cancer detection tool makes perfect sense to him.

Soon after Sentinelle launched, exploding onto an MRI scene dominated by big players like GE, Philips and Siemens, its founders became aware of an inherent challenge to their field. Breast MRI is limited in its ability to facilitate the next logical step after breast cancer has been detected: intervention.

In the conventional unfolding of events, a patient undergoes an imaging procedure and, if evidence of a suspicious mass is discovered, the next

The image Cameron Piron pulls up on his laptop computer is as disturbing as it is beautiful. It is a mammogram of a woman's breast, its cloudy appearance obscuring a deadly secret: a tumour nestles inside the white swirls. Piron, who is president of Sentinelle Medical, a Toronto company spun off from Sunnybrook Research Institute (SRI) to produce breast magnetic resonance imaging (MRI) devices, along with supporting electronics and software, knows it's there because he knows it's there—not because the blotch of disease is visible to the naked eye. Which is just the point.

Alongside this shot is an MRI of the same breast. In this one, the cancer is unmistakable: a glowing white pool at an intersection of a dozen spidery tributaries.

Sentinelle celebrates the superiority of the latter over the former, particularly for a segment of the breast cancer population. And the celebration is made material with Sentinelle's development of a breast MRI biopsy system that extends a conventional MRI scanner's application to places previously unimagined. Sentinelle's innovation is one of the first medical devices developed at Sunnybrook that has secured United States Food and Drug Administration (FDA) approval.



But the most remarkable thing about the bed is that it adapts the old standard such that it can accommodate not only an MRI session but a biopsy, as well.

DR. DON PLEWES AND CAMERON PIRON

step is to draw a tissue sample for histopathology. But for those scenarios in which only MRI can detect the tumour, this unfolding can be problematic. Undertaking a biopsy under the influence of a powerful magnet in the tight confines of an MR unit is often unrealistic, and only in an ultrasound setting can a technician draw a tissue sample and feel reliably ensured, thanks to the visual touchstone, that the tip of the needle is in the tumour, and that it's capable of slicing out a sample for microscopic analysis.

What if, Plewes conjectured, you could take MR images of a patient, wheel her out of the magnet room and into another room, still in the bed, coordinate the 3-D MRI images with an ultrasound probe and extract the tissue—even though the radiologist may not see the tumour?

In 1992, Plewes handed the project of developing technology that could handle MRI-guided biopsies to Piron, then a medical biophysics graduate student at the University of Toronto, where Plewes is a professor. It was June 2004 before the pair cast their eyes across the technology they'd produced and decided that it, in conjunction with the experience they'd amassed in its creation, might provide the basis for the formation of a commercial enterprise.

"We were presenting this technology at conferences," says Piron, "and we had world-class researchers and clinicians saying, 'When can we get one of these tables?' It occurred to us that there might be an opportunity, or even an obligation, to take this to the next stage."

The modular design of Sentinelle's stretcher allows better access to the breast than does the typical MRI bed, which, says Piron, "has terrible ergonomics with only a small window to get at the breast." If a patient's tumour is medial—in the middle of her breast—radiologists using Sentinelle's bed can biopsy from the middle, meaning they needn't cross as much tissue as if they had approached it laterally, which they would have to do with a conventional system.

But the most remarkable thing about the bed is that it adapts the old standard such that it can accommodate not only an MRI session but a biopsy, as well. A patient in it—lying prone, her breasts pendant and snug against the coils in the sophisticated boxes designed to house them—needn't change her position for MR and ultrasound imaging.

It is, says Plewes, a more efficient use of all the imaging modalities. "Now you're using ultrasound and MRI for what they're both best suited: ultrasound for real-time guidance and MRI for initially detecting the tumours and then quickly releasing the magnet for the next patient. By fusing these imaging modalities, you get the best of both worlds and maximize the utilization of expensive MRI resources."

Just the same, the scientists don't demur from an admission that going commercial was a leap that came with hurdles. It was all tied into a mentality shift, says Piron, from being "perfectionists in R&D" to negotiating a new range of tasks previously outside their purview.

The future for Sentinelle, says Piron, is all about improving accessibility to MRI for cancer detection and management. Indications for MRI have opened up like a hand in the time since Sentinelle first nudged into the picture, and the company has plans to go beyond breast cancer.

"We talk up the notion at Sunnybrook of bench-to-bedside research," says Plewes, currently on sabbatical from U of T at UBC. "That's true, but in order for things to reach the bedside in a general way, it really needs to be bench to bedside to commercialization. Unless some other entity can acquire the technology you've used to get from bench to bedside, it's useless. We tend not to talk much about that third piece, but it's actually critical for the first two to be meaningful." ■

Plewes' research was funded by the Canada Foundation for Innovation, Canadian Breast Cancer Research Alliance, Ontario Innovation Trust, Ontario Research and Development Challenge Fund, and industry and private funding.

MODEL REGENERATION

ARTEC IS HELPING TO SHAPE THE QUICK-SHIFTING COMMERCIAL REALITY AND DAZZLING FUTURE OF TISSUE ENGINEERING

Regenerative medicine—repairing or replacing damaged or diseased tissue and organs—is a research field with massive potential. Triggered by advances in the understanding of stem cells, it is an explosive nexus of cell biology, genetics, chemical engineering, materials science and surgery. Expectations have fluctuated wildly, from hope for easing the transplant organ shortage and curing Parkinson's, to despair over unchecked, cancerous cell growth, a common problem in regenerative medicine experiments. But progress has been real.

One model for innovation in the field is the Advanced Regenerative Tissue Engineering Centre (ARTEC) based at Sunnybrook Research Institute (SRI). Anchored by the commercial focus of four industrial partners and investment from the Ontario Research and Development Challenge Fund, ARTEC scientists at the University of Toronto and SRI have been solving tissue-engineering challenges since 2002. They're now looking to the future with a new focus thanks to incoming director Dr. Juan Carlos Zúñiga-Pflücker. Dr. Kimberly Woodhouse, associate director of ARTEC, says, "Juan Carlos brings the immunology expertise that will help move us forward. Immunology is a very important part of tissue engineering and regenerative medicine."

Beyond working on immune rejection in tissue and organ recipients, Zúñiga-Pflücker, a senior scientist at SRI, has an ambitious goal for ARTEC: he plans to engineer an artificial thymus. Located in the

upper chest, the thymus produces T cells, white blood cells that enable the immune system to target and destroy disease-causing pathogens. "If you want to recreate T cell development within an organ, within a person, you need structural components: the nutrients, oxygen and blood vessels," explains Zúñiga-Pflücker, who holds a Canada Research Chair in Developmental Immunology. In vitro, these requirements are foregone, because serum media and reagents supplant them. In a living organism, he says, "You need a scaffold-containing environment to make the system transplantable."

Woodhouse, a scientist at SRI cross-appointed to the department of chemical engineering and applied chemistry at U of T, constructs such scaffolds and other materials for soft tissue development. While continuing to develop new skin products for wound healing with ARTEC partner ApoPharma and fat tissue for reconstructive surgery after trauma, she'll work with Zúñiga-Pflücker to design and test products that could support vasculature in T cell development, including an artificial thymus. Additionally, with SRI researchers Drs. Albert Yee and Cari Whyne, and in conjunction with Elastin Specialties, Woodhouse's lab is developing materials that will support stem cell proliferation to repair degenerative spinal discs.

ARTEC excels at creating commercial synergy between academia and industry, but Woodhouse notes it also encourages industry-to-industry partnership. "ARTEC has been a nurturing environment for the companies to work with each other as well. Two of the corporate partners have combined technologies and are working collaboratively on a new project under the ARTEC umbrella," she says.



DRS. KIMBERLY WOODHOUSE AND CHRIS HRABCHAK

Though optimistic about ARTEC and tissue engineering, Woodhouse is realistic. Some regenerative medicine products take decades to develop. She and Rimon Therapeutics, an ARTEC partner with which she works, understand the need to bring products to market on a shorter timeline. Rimon's therapeutic wound dressing polymer, MI Theramer, took just four years to develop from conception to clinical trial.

Woodhouse appreciates the leveling effect of ARTEC's industrial partners: "They keep us grounded in terms of what's reasonable and what work may produce marketable products." At the same time, those companies encourage fundamental research and ask important scientific questions. Says Woodhouse, "We need to support basic research and commercialization; ARTEC has been fortunate in working with forward-thinking companies interested in both. If we don't encourage the continuum between the two, the next generation of scientific discovery—and industry-driven distribution of its products to patients—will be missing."

ARTEC excels at creating commercial synergy between academia and industry, but Woodhouse notes it also encourages industry-to-industry partnership.

TO MARKET, TO MARKET

SRI DELIVERS THE BENEFITS OF ITS RESEARCH AND TECHNOLOGY DEVELOPMENT TO THE WORLD THROUGH A DEDICATED FOCUS ON COMMERCIALIZATION



DR. STUART FOSTER AND TOM LITTLE, PRESIDENT AND CEO, VISUALSONICS

Commercialization is an important part of research at Sunnybrook Research Institute (SRI), driven by a straightforward aim: to bring research breakthroughs to patients. Commercialization at SRI is focused primarily on clinical trials, technology transfer, venture capital and industry partnerships.

Clinical trials are fundamental to the work of researchers at SRI. They are the means by which researchers test new drugs and devices with a view to their eventual unveiling at the clinical level. The research ethics board at SRI reviews some 500 clinical trials protocols every year, and then monitors the trials as they unfold. When the results from this research are translated into the clinic, the net benefit is safer, more effective patient care and evidence-based practices and policies.

Technology transfer is a process that identifies, explores and develops strategies to take promising research to the market. Researchers at SRI are heavily involved in technology transfer that is focused on making drugs and technologies better. Recent success stories include the formation of spin-off companies VisualSonics Inc. and Sentinel Medical Inc., which emerged from the research of senior scientists Drs. Stuart Foster and Donald Plewes, respectively.

Sunnybrook Research Institute retains the University of Toronto to direct its technology transfer activities through Innovations at U of T (IUT), whose representatives, dually versed in commercialization and science (a unique distinction at Sunnybrook), provide on-site experts who are available to discuss ideas and help scientists to navigate the process.

For too long, Ontario researchers were challenged by the absence of the capital they needed to take ideas to the next stage, owing to the perceived high risk associated with these ventures in Canada. In 1998, Sunnybrook registered Ontario's first community small business investment fund (CSBIF) with the provincial government's CSBIF program. That injection provided early-stage money for the first generation of SRI spin-off companies. The research institute has two CSBIFs: the Sunnybrook Working Ventures Medical Breakthrough Fund and the Medical Ventures Fund.

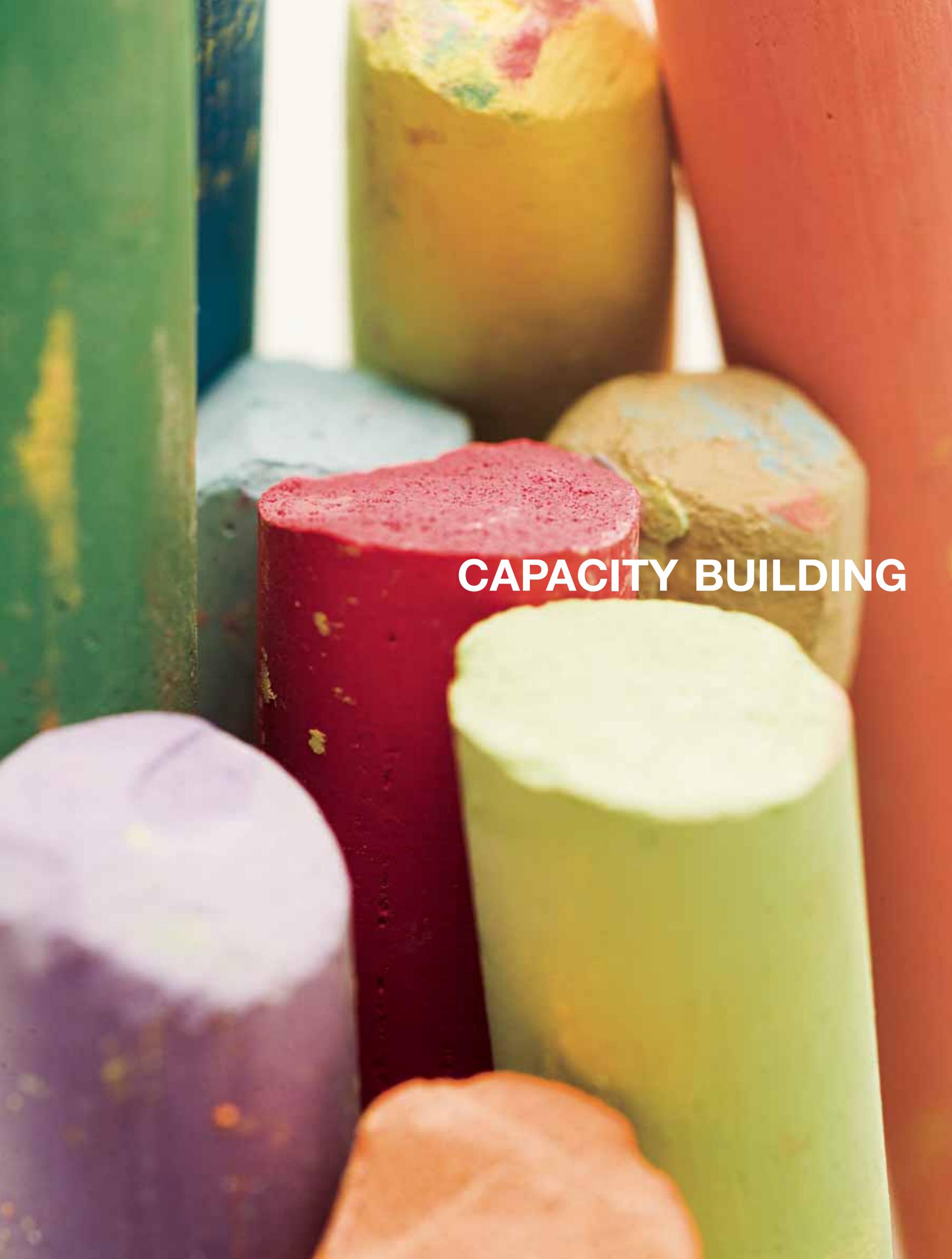
The funds—which are committed to enhancing Canada's research and development infrastructure, and contributing to high-quality medical entrepreneurship in Canada—offer access to professionals with extensive knowledge and experience in science, technology and business development.

Increasingly, research institutes are partnering with companies in joint research endeavours. Sunnybrook Research Institute was one of the first to venture down this road and today participates in many such partnerships. Some of our industrial partners are Amgen, Apotex Inc., Bristol-Myers Squibb, Elan Pharmaceutical, Elastin Specialties,

Exact Sciences Corp., GE Healthcare, Novartis Pharma Canada Inc., Pfizer Canada Inc., PRA International, Ortho Biotech, Quintiles Canada Inc., Rimon Therapeutics, sanofi pasteur, Siemens and Zoll Medical Corp.

Indeed, sanofi pasteur has located the world headquarters of its cancer vaccine program here, across 40,000 square feet at the research institute. As part of this, the company formed the Pan-Canadian Cancer Vaccine Network to fund different academic centres for cancer vaccine research; SRI is the largest single site of the Pan-Canadian program.

Moreover, SRI has been instrumental in helping to form strategic alliances to help commercialize Canadian technology. It is a founding member of Yorkbiotech and BioDiscovery Toronto. It also holds several commercialization-specific grants. And just this past year, it formed a partnership with Thunder Bay Regional Health Sciences Centre to form the Molecular Medicine Research Centre. The objective of these types of initiatives is to form alliances and partnerships to amass the needed expertise to develop and market new Canadian intellectual property.



CAPACITY BUILDING



LEARNING TO

EDUCATION AT SRI MOVES FROM THE INSIDE OUT TO INSPIRE A NEW GENERATION OF POTENTIAL SCIENTISTS

REACH

Dr. Mira Puri, a scientist at Sunnybrook Research Institute (SRI), is passionate about education. “I think it’s really important to have outreach to the public about science,” she says. “In Canada, we need to be aware that the public’s support is crucial. There’s a gap between awareness of health issues and awareness of what scientists are doing.”

Puri, who studies the cardiovascular and hematopoietic development of mammals, is working to narrow that gap. Several times a year she visits schools to educate children about what scientists do. She encourages her graduate students to do the same. She has also attended science fairs as a judge, where most kids appreciate having a real scientist evaluate their projects. Puri targets elementary schools because she has found that’s where kids get most excited about science.

While primarily showcasing science as a potential career, Puri notes that those children and their parents may also be future donors to research funding agencies. “I think a lot of our issues in funding research fall back to what the public perceives as our productivity, and our utility in society. And that comes down to scientists going out and teaching the public,” she says. “We shouldn’t have an attitude of entitlement, and we should be accountable to the taxpayers who fund us.”

To that end, Puri is encouraging other SRI scientists to participate in a program set up by the Canadian Institutes of Health Research. Called Synapse, it’s a youth outreach fund for scientists and their trainees to give public talks, attend science competitions and provide mentored lab experiences for high-school students.

Other funding bodies have also discerned the importance of connecting scientists with students. For example, Ontario’s Ministry of Research and Innovation has recognized the need for youth outreach by making it either the central or a mandatory component of several programs it runs, including the Youth and Science Technology Outreach Program and Early Researcher Award (ERA) Program. It recently awarded SRI scientist Dr. Jonathan Rast an ERA award. As part of his research program, Rast will visit grade 10 and 11 biology students in their classrooms to talk about his work on the sea urchin genome and run in-class experiments whereby the students will grow their own sea urchin embryos.

Rast, however, is not the only researcher involved in outreach at SRI. There are others, including Puri, each focusing on what he or she thinks will have the most impact.

Puri is positive about education within SRI. “There’s a real sense of a peer group here. My students had a smooth transition to finding out who could help them with techniques they didn’t know, and to meeting colleagues who encouraged them to think differently about their research.” Sunnybrook’s open lab structure, where researchers share space, facilitates the sharing of techniques and ideas, as do seminars, social events and retreats.

Scientists participate in these knowledge-sharing events and help trainees navigate the career aspects of the system, particularly proposal writing and the peer-review grant submission process. Puri involves her postdoctoral fellow in the review of other scientists’ papers that have been submitted for publication to journals, thereby familiarizing her with the process she would engage in as a scientist and the scrutiny she can expect her papers to undergo.

Not all trainees, however, want to become scientists. Students, and technicians in particular, may want only advanced scientific knowledge, or to gain experience in a technique. Some will go on to work in industry. Puri says, “People are here for different reasons, and we have an obligation to teach them, to get them where they want to go, because we are an educational institution.” ■

GIVING WITH PASSION

PRIVATE DONORS, INDIVIDUALS WHO UNDERSTAND THE IMPORTANCE OF RESEARCH AND DONATE TO IT, ARE IMPORTANT PARTNERS IN INVENTING THE FUTURE OF HEALTH CARE AT SUNNYBROOK RESEARCH INSTITUTE

Donor gifts often form the seed money around which an external grant application may be developed, fund the acquisition of equipment and support base salary costs of new researchers.

Iain and Cristina Ronald are two such donors. Iain, a retired CIBC executive, served on the Board of Sunnybrook Foundation from 1992 to 2002, and as Chair of the Board from 1994 to 1997. He and Cristina have worked tirelessly to support Sunnybrook in various ways, currently as donors and volunteers for the Campaign for Sunnybrook. Both feel that their experiences as volunteers here have allowed them to gain an understanding of the challenges that face health care, get to know the people dedicated to patient care and research, and understand firsthand the impact that donor funding can have.

The Ronalds' ongoing association with the Governing Council of the Foundation allows them to keep up-to-date on foundation and health care issues, and contribute regularly to promoting the hospital as a centre of valued caregivers, sources of research discovery and a worthy recipient of philanthropic dollars.

Cristina and Iain's health philanthropy is driven by a deep, long-term understanding of the workings of the hospital, its challenges and what might be achieved by private giving. Cristina's brush with colorectal cancer and Iain's recent stroke have focused their giving in these areas. They are particularly struck by the impact that research and early diagnosis and treatment of colon cancer can have on survival rates: if caught and treated early, survival rates are profoundly improved. For Iain, a long road to recovery from stroke has heightened his awareness of the need for more research and understanding of the causes of stroke, and particularly how warnings of stroke, such as some transient ischemic attacks, need to be understood and diagnosed better, and then used to put patients on a path to avoid a full stroke.

The patient-care experiences that Cristina and Iain have had, combined with a knowledge of the work being done at Sunnybrook, have led them to become passionate supporters of research in these areas. They are impressed with the focused research being conducted at Sunnybrook Research Institute and the hospital's philosophy of rapidly translating research findings into improved clinical practice.

Both derive immense personal satisfaction from learning more about health care, and seeing their donation help to improve the care provided to others.

When asked why more people don't give to support hospital-based research, Iain and Cristina responded: "Most people aren't aware of the research being conducted in our hospitals, and the importance of that research to changing the care we receive." The Ronalds hope the legacy of their donations is one step toward a cure for their diseases and that, in the meantime, Sunnybrook research will improve patient care. Their ultimate dream is to prevent disease in the first place, perhaps the greatest hope associated with their act of giving.

By guest writer Kevin Goldthorp,
CEO, Sunnybrook Foundation

"Most people aren't aware of the research being conducted in our hospitals, and the importance of that research to changing the care we receive."

IAIN AND CRISTINA RONALD



Q&A

SRI CHATS WITH A CLINICIAN-SCIENTIST DOING GLOBALLY RELEVANT RESEARCH ON BIOTERRORISM

DR. ROB FOWLER

Rob Fowler is a critical care physician at Sunnybrook and an associate scientist at Sunnybrook Research Institute (SRI). In 2005, the Ontario Ministry of Health and Long-Term Care awarded him a career scientist award. This award recognizes promising scientists in the early stages of their careers.

Fowler's focus is on clinical epidemiology and outcomes for critically ill patients. In 2005, *Annals of Internal Medicine* published his study, *Cost-Effectiveness of Defending Against Bioterrorism: a Comparison of Vaccination and Antibiotic Prophylaxis Against Anthrax*, in which he investigated the options for a metropolitan city facing a bioterrorism attack. Fowler spends about 75% of his time on research. Dropping a stethoscope and an empty chocolate milk carton on the table beside him, the 37-year-old shared his thoughts on the study, which included the work of researchers from Toronto, Stanford University, Duke University and the US Centers for Disease Control.

What's your interest in bioterrorism? There are limited resources to care for large numbers of patients who are critically ill or who have the potential to become critically ill. I want to look at what to do when health care systems are faced with more demand than they can supply. I was in California when 9-11 hit and when the anthrax scare was going through the States. After that, a lot of stakeholders in various levels of U.S. government started asking, "What if?"

What are the big bioterrorism threats? In the U.S., they are smallpox, anthrax, *Yersinia pestis* (the infectious agent of bubonic plague) and tularemia (a severe infectious bacterial disease). Anthrax can be aerosolized and you could potentially fly an airplane and douse a city with spores, which are extremely difficult to get rid of. It might sound farfetched, but with the things that happen these days, it's not so much.

What outcomes were you after? There were two. One is effects (lives and quality of life saved) and the other is cost. We had to put into this model both of these considerations to see what looked better.

What did you find? The strategy of vaccinating everybody in a population ahead of time doesn't make a lot of sense. You've got no anthrax

and a portion of the people suffering side effects. And it costs a lot: hundreds of dollars per person over the course of the vaccination. (It takes six months to a year to fully inoculate someone.) So we determined that the most attractive strategy—the one associated with the greatest effects and the fewest costs—was to wait until an attack took place, then give the population preventive antibiotics very quickly, along with a vaccine.

Can we feel confident with this plan? Not at all. A lot hinges on a system's ability to handle a mass tragedy. If we go back to the SARS experience—and I was quarantined at Sunnybrook during that ordeal—clearly our health care system wasn't prepared. In the last three years, have we done a lot to try and prepare? Yes. But are we prepared? Absolutely not.

So what should we be doing? That's the question. It's very hard to justify preparing for very unlikely terrorist threats when they may never happen, and you end up diverting energy and funds from worthy near-term causes like AIDS, poverty and tuberculosis. I would say we should probably get into place a system where you could distribute vaccines for something like this in short order, an infrastructure that's pretty flexible.

What's appealing about this kind of research? From a mental-adrenaline perspective the idea that, in 2006, there are still lots of things out there that can wipe out big chunks of us in an instant, and the idea that our sense of security is at risk is, to me, interesting, exciting and potentially very important. ■

Fowler's work was funded by the University of Toronto, Sunnybrook Research Institute and the Department of Medicine at Sunnybrook Health Sciences Centre.

WIND AT THEIR BACK THE PARTNERSHIP BETWEEN SRI AND GE HEALTHCARE CHARTS A COURSE FOR EXCELLENT WATERS

Dr. Martin Yaffe, a senior scientist at Sunnybrook Research Institute (SRI), invokes a nautical theme in considering the relationship between SRI and GE Healthcare. Each has their strengths, he says. The former is a speedster, celebrated for its maneuverability and alacrity; the latter is a battleship, remarkable for its size and strength. By and large, he says, the combination has enjoyed smooth sailing since setting out on its tandem journey.

The tradition of academia sharing the waters with industry is a long one. At SRI, under research agreements, scientists have access to GE Healthcare's systems—software and hardware—including the right to program. Dr. Graham Wright, a senior scientist at SRI, says the affiliation between the pair is “very close.” Sunnybrook Research Institute and the Imaging Research Centre for Cardiac Intervention (IRCCI), a unique-to-Canada facility that opened in November 2006, have a 3-Tesla and two 1.5-Tesla magnetic resonance imaging systems, as well as a flat-panel Innova x-ray system, all from GE and dedicated to research. That the equipment is kept state-of-the-art, Wright, a co-principal investigator (PI) in the IRCCI says, “so we're pretty much always on the leading edge of the platform,” is essential. In the absence of such tools, he notes, scientists would simply be solving already solved problems.

GE Healthcare also figured in SRI's participation in the international Digital Mammography Imaging Screening Trial (DMIST). Sunnybrook was the sole Canadian participant in this landmark study that compared digital mammography (DM) with film mammography and found that DM detects more cancers in women who are 50 or younger, premenopausal, or who have dense breasts. Sunnybrook's DM machine was a GE Healthcare unit, funded by federal and provincial government investment.

In his current work in digital tomosynthesis (DT), Yaffe, who is co-PI of the Breast Cancer Research Centre at SRI and Toronto Sunnybrook Regional Cancer Centre (TSRCC), is also working closely with GE. The company supports technical aspects of Yaffe's DT research, including providing the equipment needed to make the simulator that allows scientists to try ideas in the lab. GE has provided Yaffe with the second-in-the-world clinical prototype DT system, a \$750,000 unit that can be used with patients, and which will be used in clinical trials soon. Dr. Roberta Jong, director of breast imaging and associate scientist at SRI/TSRCC, will lead the clinical tomosynthesis study.

And venturing into new areas, which IRCCI is—with scientists developing technologies for cardiovascular imaging to improve early detection and treatment for heart conditions—necessitates equipment not

available commercially. An alliance with a commercial partner that provides the basic infrastructure and the sea charts needed to be able to go beyond what's available commercially, says Wright, is critical.

“There are things that we're building for them that just don't exist,” says Peter Robertson, general manager of GE Healthcare Canada. Moreover, GE provides SRI researchers with protection from obsolescence over a project's term. For GE's part, says Robertson, the Sunnybrook connection is a boon to a company whose pockets have bottoms, after all, in spite of what so many think when considering this massive corporation. As such, he appreciates the judicious and clinically relevant management of GE resources in the hands of SRI, “a global player on the research stage.” 

Anchors aweigh.

The Breast Cancer Research Centre and IRCCI are funded by the Canada Foundation for Innovation, Ontario Innovation Trust, and industry and private sponsorship.

JOHN LORBIECKI, GE HEALTHCARE, AND DR. GRAHAM WRIGHT



“There are things that we're building for them that just don't exist.”

Core Facilities at SRI

The core facilities and related services available at Sunnybrook Research Institute (SRI) are comprehensive. Housed in our cores is cutting-edge equipment whose application to a broad spectrum of research spans a range of disciplines



1.5T and 3T MRI Facility

Imaging research has three whole-body magnetic resonance imaging (MRI) systems dedicated to research. The adjacent 1.5T and 3T research systems feature state-of-the-art hardware and software. The newly installed cardiac MRI system in the Imaging Research Centre for Cardiac Intervention is coupled with an advanced catheterization lab for research in cardiac disease diagnosis and interventional therapies. In addition, SRI's MRI labs include a clean room and complete electronic-shop and machine-shop facilities, including a computer-controlled lathe, and milling and prototyping machines. Finally, the 3T MRI facility, a multi-institutional resource, has a GE Healthcare long-bore, 16-channel MRI system with EXCITE HD technology.

Antibody Core Facility

This facility offers researchers purified and conjugated antibodies specific for differentiation markers and signalling molecules expressed in hematopoietic and endothelial cells of various species. Here, antibodies are conjugated to various fluorochromes, to biotin and to microbeads for cell surface immunofluorescence, immunohistochemistry, functional assays and biochemical analyses. Following purification and conjugation of an antibody, the optimal titer for various applications is determined. In addition to antibodies, the facility produces other molecular biology reagents, and offers genotyping services for mice and rats.

Transgenic Facility

The transgenic facility provides the technical expertise, equipment and pathogen-free animal quarters necessary for various services, including blastocyst injection, pronucleus microinjection, rederivation and cryopreservation.

Hybridoma Facility

SRI's hybridoma facility is set up to generate hybridomas that produce monoclonal antibodies of desired specificity. Services include immunization of preclinical models, fusion of spleen with myeloma cells to create hybridomas, assay hybridoma supernatant by ELISA and western blots, selection and expansion of clones, and cryopreservation of hybridomas, antibody-positive hybridomas and supernatant. This core provides a high-throughput monoclonal antibody production for developing antibodies to specific antigens of interest.

Histology Facility

The histology facility at SRI offers the following services: tissue processing, decalcification, paraffin embedding, microtoming, routine staining (H&E), special stainings (available on an individual basis), cryosectioning and vibratoming.

Cytometry and Scanning Facility

The Centre for Cytometry and Scanning Microscopy houses two BD multilaser, multiapplication, digital, high-velocity cell sorters. Up to four separate target populations can be extracted at the same time into tubes at speeds of 25,000 cells/second. Trained users can access three four-colour bench-top BD facs analyzers and a customized four-laser 16-colour digital BD LSRII analyzer. There is also a Zeiss confocal laser scanning system with five laser lines and a Zeiss wide-field fluorescence deconvolution microscope with Apotome and heating insert.

Genomics Facility

SRI's genomic facility can accommodate a range of services, including high-density DNA microarrays that contain Qiagen's 70-mer oligonucleotides representing every gene in the mouse and human genomes, multi-tumour tissue microarrays, laser-capture microdissection, automated DNA sequencing, QRT-PCR analysis and laboratory robotics. It also offers rapid and economical services to create custom oligo microarrays and access to equipment for automated DNA chip hybridization, microarray scanning and GeneSpring data analysis software.

Proteomics Facility

This facility is capable of several functions, including differential proteomics, protein/peptide fractionation, protein identification and characterization by liquid chromatography tandem mass spectrometry (LC-MS/MS), and peptide synthesis. The lab is equipped with modern chromatography fractionation systems to ensure the deepest possible analysis of the proteome.

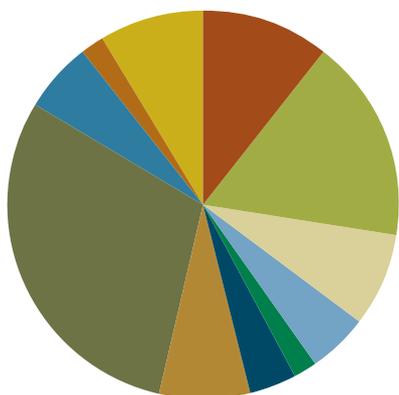


GISELE KNOWLES

QUICKSTATISTICS

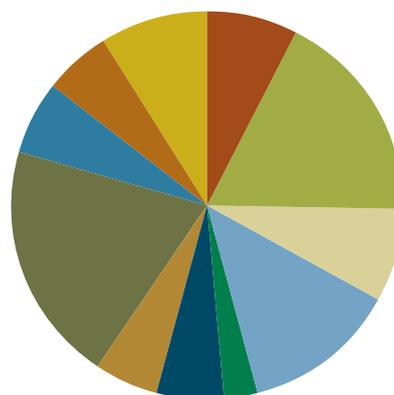
MAJOR SOURCES OF EXTERNAL FUNDING

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\$74.5 million (2004–2005)

- Canada Foundation for Innovation 11%
- Canadian Institutes of Health Research 17%
- Donations and Trust Income 8%
- Industry 5%
- Ministry of Health and Long-Term Care 2%
- National Cancer Institute of Canada 4%
- Ontario Innovation Trust 7%
- Ontario Research and Development Challenge Fund 30%
- Other Foundations 6%
- Other Funding Sources 2%
- Other Government Sources 8%

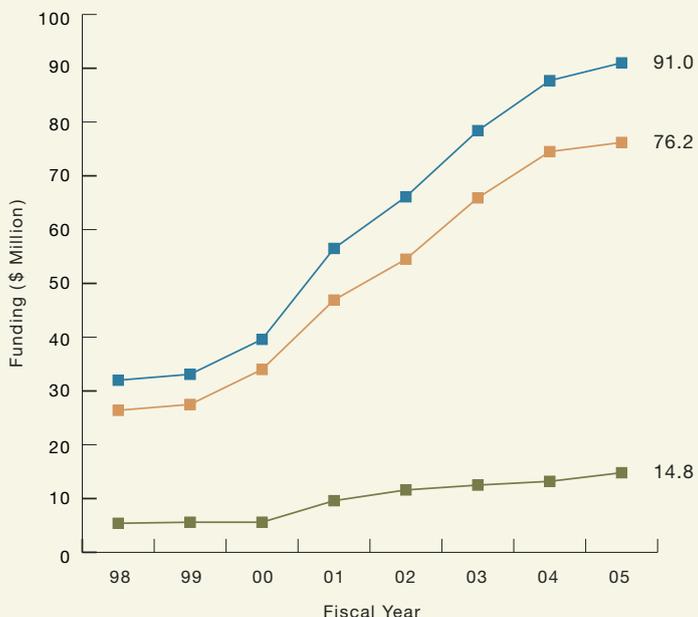


\$76.2 million (2005–2006)

- Canada Foundation for Innovation 8%
- Canadian Institutes of Health Research 18%
- Donations and Trust Income 8%
- Industry 13%
- Ministry of Health and Long-Term Care 3%
- National Cancer Institute of Canada 6%
- Ontario Innovation Trust 5%
- Ontario Research and Development Challenge Fund 20%
- Foundations 6%
- Other Funding Sources 6%
- Other Government Sources 9%

HISTORY OF RESEARCH EXPENDITURES AT SUNNYBROOK RESEARCH INSTITUTE

- Total Funding
- External Funding
- Internal Core Funding



RESEARCH STAFF

Senior scientists and scientists	91
Associate scientists	85
Research associates, engineers and physicists	68
Laboratory technicians and research assistants	149
Research fellows and graduate students	200
Total	593



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Your help is needed to ensure we continue to provide the best care in the best facilities. We are raising funds for capital expansion that will build for the future and transform these key areas:

Perinatal & Gynaecology:	\$40 million
Trauma & Critical Care:	\$21 million
Breast Cancer Research:	\$27 million
Holland Musculoskeletal Program:	\$24 million
Schulich Heart Centre: Research:	\$24 million \$56 million

The \$300 million Campaign for Sunnybrook will also sustain our world-class medical leadership, our pace-setting research and education, and our innovative technologies for patient treatment. It will make certain that Sunnybrook will always be here for you and your family when it matters most.

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