INVENTING THE FUTURE OF HEALTH CARE

SRI

MAGAZINE

Sunnybrook Research Institute

2008

Hot Fusion

A behind-the-genes look at a promising new way to predict prostate cancer risk and progression

Managing Multiples

The quest to rewrite the rules of obstetric practice, two babies at a time

Think Again

Neuroscientists dig deep to understand and treat Alzheimer's disease

Balancing Act

Double trouble: the long, long path to becoming a PhD/MD—and why it's worth it

Sunnybrook
HEALTH SCIENCES CENTRE

Inventing the Future of Health Care
Sunnybrook Research Institute, 2006–2008

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TRANSLATING KNOWLEDGE, INFLUENCING POLICY AND CHANGING PRACTICE

COMMERCIALIZING RESEARCH AND BRINGING BREAKTHROUGHS TO PATIENTS

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MESSAGE FROM SENIOR LEADERSHIP

SUNNYBROOK HEALTH SCIENCES CENTRE

Dr. Barry A. McLellan and David A. Leslie

Sunnybrook has a vision to invent the future of healthcare, and the Hospital's successful research institute is the engine that powers innovation throughout our entire organization. We are proud of the extraordinary achievements of our more than 600 scientists who have made breakthroughs in preventing, detecting and treating some of our society's most debilitating health issues.

Conducting $100 million in research last year alone, Sunnybrook Research Institute uniquely reduces the distance between brilliant idea and its practical application to improve patient care by connecting researchers to staff at the bedside. By working side-by-side and collaborating on questions that are of immediate concern to the care we provide, our researchers and clinicians form a team that is dedicated to discovering new methods of improving the lives of our patients.

Over the last year, our teams have developed, for example, a promising new minimally invasive therapy to treat a common cardiovascular condition called coronary chronic total occlusion, which will help improve blood flow to the heart. Our researchers have explored the expression of a certain gene and established that it is a strong predictor of prostate cancer relapse in patients previously treated with surgery.

Our clinical and scientific investigators have also provided evidence of a unique molecular interaction in immunity to infection that suggests longer-term clinical implications for the treatment of patients with viruses such as HIV.

This year, we were also bolstered by the incredible support from the Canada Foundation for Innovation with an impressive $74.6 million grant, the single largest in the Hospital's history, to establish the Sunnybrook Centre for Research in Image-Guided Therapeutics.

This first-of-its-kind centre in Canada will develop and test state-of-the-art medical imaging technologies and therapeutics, including new vaccines, drugs, biological agents and imaging devices, and translate them into clinical practice primarily in the areas of cancer, cardiac, musculoskeletal and neurosciences.

In deep appreciation for making this world-leading research possible, we would like to thank our community, government, industry collaborators, fellow research hospitals and our generous donors.

Your support has enabled the creation of new approaches to care that are improving the lives of patients around the world. Sunnybrook is grateful for the support of our award-winning and dedicated faculty who have received recognition for their efforts from some of the most prestigious funding and granting agencies in the world.

Congratulations to our Sunnybrook Research Institute on its many accomplishments, which contribute to the achievement of our academic mission and build on our international reputation for leading in health sciences research.

David A. Leslie
Chair, Board of Directors

Barry A. McLellan
President and CEO

MESSAGE FROM THE VICE-PRESIDENT OF RESEARCH

SUNNYBROOK HEALTH SCIENCES CENTRE

Dr. Michael Julius

It has been a remarkable two years at SRI.

This last year we celebrated the largest grant in the history of Sunnybrook from the Canada Foundation for Innovation Research Hospital Fund: $74.6 million for the creation of the $160-million Centre for Research in Image-Guided Therapeutics, to be housed in 100,000 square feet of the M wing vertical expansion at Sunnybrook.

We also celebrated exceptional success provincially, receiving more than $23 million from the Ministry of Research and Innovation through its Ontario Research Fund for Research Excellence, matched in full by private-sector investment. This means that 25 cents on every dollar distributed in the 2007 round of the province-wide competition is coming to SRI.

Our success is rooted in our faculty: their dedication to discovery and its application to preventing and diagnosing disease early, and to creating new ways to treat the previously untreatable. Our recruitment of internationally acclaimed scientists and our nurturing of the upcoming generation of the world's best has not only secured our position as one of the fastest growing research enterprises in Canada, it has also galvanized our research efforts at the vanguard of *inventing the future of health care*, our vision.

It is the day-to-day integration of research and clinical care that is 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 leadership and success extend beyond local borders. We struck several key alliances over the last two years. Scientists at SRI have taken prominent roles in the new Ontario Institute for Cancer Research; the Heart and Stroke Foundation's Centre for Stroke Recovery; and the newly incorporated Thunder Bay Regional Research Institute. These partnerships will support more than $50 million of research at SRI over the next five years.

Moving discovery to clinical impact is certainly about harnessing new insights derived from basic and applied science. But it's also about people: those with the skills needed for knowledge translation. How best to accomplish the process by which we ensure that we capitalize on our discoveries and can develop—and use—the next set of best clinical practices itself requires research. Toward this end, we launched the Centre for Health Services Sciences. This centre is unprecedented in its partnership of senior hospital administrators and clinical and scientific leaders. Having this support in the many dimensions of the decision-making process in as complex a structure as a hospital will ensure that we lead in changing the way health care is delivered at Sunnybrook and beyond.

To invent the future of health care is an ever-unreachable goal. The stories selected for this edition of our research magazine nonetheless underscore our breathtaking success toward achieving this aim today, and show the even greater promise for tomorrow.

Our success would not be possible without our dedicated teams of scientists, trainees and administrative staff; the support of funding agency and industry partners and donors; and the University of Toronto, with which we are fully affiliated.

And all of these essential components would not bear fruit were it not for the tenacious support of Sunnybrook's senior leadership team, led by Dr. Barry McLellan; and its Board of Directors, led by David Leslie.

We are privileged in our position to invent the future of health care—and we're doing it.

Michael Julius
Vice-President, Research

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

AWARDS AND HONOURS

We spotlight some especially notable achievements of scientists at Sunnybrook Research Institute (SRI) from 2006 to 2008.

National and International Awards

The government of Canada awarded two SRI scientists Tier 1 Canada Research Chairs, one of the highest honours it bestows on researchers. **Stuart Foster** now holds the Canada Research Chair in Ultrasound Imaging. **Jack Tu** was awarded the Canada Research Chair in Health Services Research. (He previously held a Tier 2 Chair.)

The Canadian Institutes of Health Research (CIHR) recognized each of **James Carlyle**, **Charles Cunningham**, **Anna Gagliardi**, **Robert Jankov**, **Alex Mihailidis** and **Sandro Rizoli** with a New Investigator Award, designed to support outstanding researchers. CIHR also awarded **Amy Cheung**, **Baiju Shah**, **Tasnim Sinuff** and **Richard Wells** each with a Clinician-Scientist Award; in addition, **Amy Cheung** received the CIHR Randomized Control Trial Mentoring Program award. Also from CIHR, **Michelle Hladunewich** received a CIHR/Canadian Hypertension Society Clinical Scholarship Research Award.

Robert Nam received the 2008 Medal in Surgery Award from the Royal College of Physicians and Surgeons of Canada. This award provides national recognition for work by clinical investigators who have completed their training within the past 10 years.

Hans Kreder received the Canadian Orthopaedic Association's Presidential Award for Excellence. From the Canadian Society of Internal Medicine, **David Juurlink** received a Young Investigator Award.

South of the border, the International Pediatric/Neurosurgery Medtronic Corp. (U.S.) bestowed the 2007 Pudenz Award of Excellence for Research in Cerebrospinal Fluid Physiology on **Miles Johnston**. Additionally, **James Carlyle** received the Investigator in Pathogenesis of Infectious Disease Award by the U.S.-based Burroughs Wellcome Fund.

Provincial Awards

From the Ministry of Research and Innovation, **Robert Nam** and **Jonathan Rast** each received an Early Researcher Award, the aim of which is to improve Ontario's ability to attract and retain the brightest research talent. The Ministry of Research and Innovation also presented the prestigious Premier's Discovery Award to **Stuart Foster**.

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 received a Clinician Scientist Award, as did **Alexander Dick**, and **Burton Yang** was awarded a Career Investigator Award.

From the Ontario Mental Health Foundation (OMHF), **Amy Cheung** and **Ayal Schaffer** each received a New Investigator Fellowship. **Ayal Schaffer** also received the John Dewan Prize from the OMHF, which recognizes an outstanding researcher whose work has been, or is now, supported by the foundation.

Endowed Chairs

The University of Toronto and Sunnybrook Health Sciences Centre jointly awarded **Bradley Strauss** the Reichmann Chair in Cardiovascular Sciences for his excellent work in this field. **James Perry** was awarded the Crolla Chair in Brain Tumour Research, and **Sandro Rizoli** was appointed to the de Souza Chair in Trauma Research. Finally, **Martin Yaffe** took up the Tory Family Chair in Oncology, to further academic enquiry into the cure and treatment for cancer.

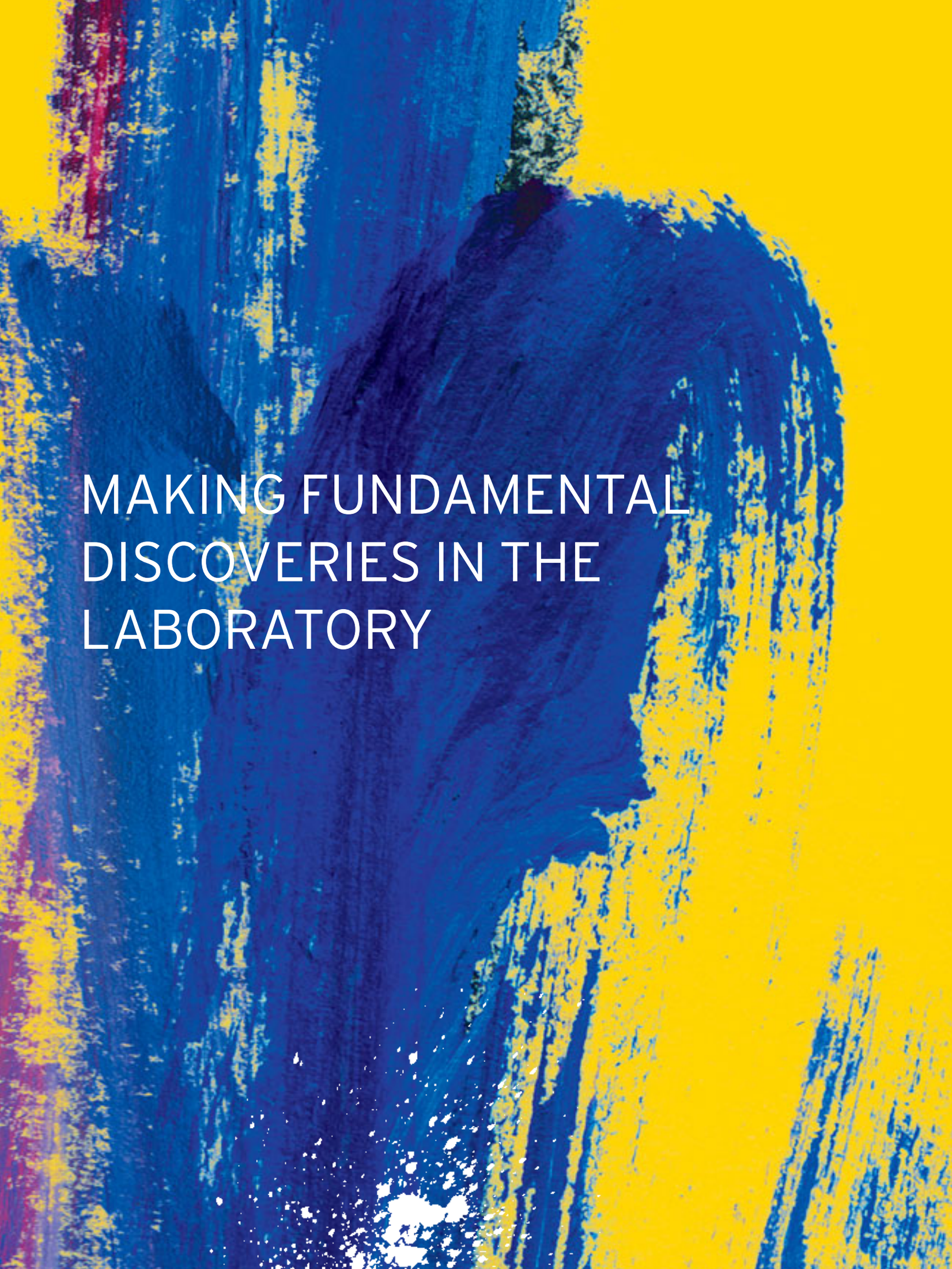
Fellowships and Other Honours

Yosef Barrett has been appointed by the World Health Organization as an advisor on maternal health.

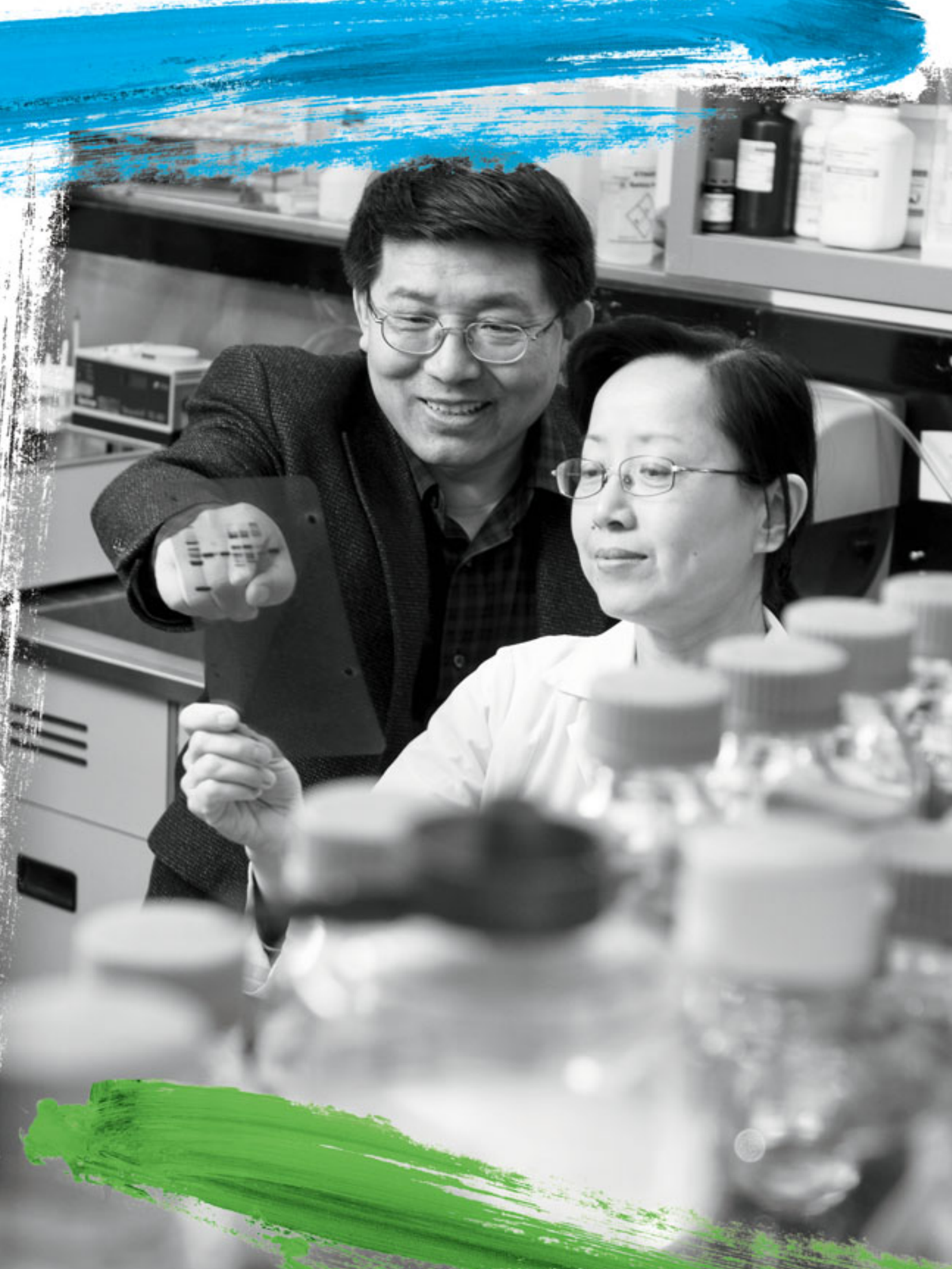
Anthony Levitt received the 2008 Mood Disorders Association of Ontario's Hope Award, given to a person who works in treatment or research to inspire hope for recovery from a mood disorder.

Several SRI researchers were appointed as fellows by various academies and associations. **Roberta Jong** was appointed as a Fellow to the Society of Breast Imaging. **David Juurlink** was appointed as a Fellow to the American Academy of Clinical Toxicology. **Thérèse Stukel** has been appointed as a Fellow to the American Statistical Association.

In other honours, the American Institute of Ultrasound in Imaging awarded **Peter Burns** the William Frye Memorial Award. He also received a Distinguished Lecturer Award from The Institute of Electrical and Electronics Engineers. Finally, the Canadian Society for Immunology awarded **Juan Carlos Zúñiga-Pflücker** its 2008 Investigator Award in recognition of his excellence in the field.



MAKING FUNDAMENTAL DISCOVERIES IN THE LABORATORY



PLUGGED

An SRI neuroscientist flicks a switch on the link between an unusual neurotransmitter and severe asthma

They call him the electrician. Dr. Wei-Yang Lu, a senior scientist at Sunnybrook Research Institute (SRI) whose latest laboratory preoccupations may yet make a wheezing segment of the population breathe easier, has his finger on the master switch controlling the body's mucous production. That the neuroscientist is surprised to find himself there—"I never thought I would study asthma, not in a thousand years," he says—dims not at all his passion for the subject. Indeed, Lu's own neurons are more fired than ever for his participation in a recent bioelectrical expedition whose intricate buzzing pathways led to the identification of a signalling system that promotes mucous overproduction during an asthma attack, an extraordinary consideration for a body of study heretofore consumed with inflammation and constriction—not blockage.

Drs. Wei-Yang Lu and Yanna Xiang

The asthma story is much more complex than it was once thought.

This discovery, elaborated on by Lu and his collaborators in a 2007 *Nature Medicine* article, is significant both for its groundbreaking scientific novelty and its end-stage applications in encouraging the medical community to shift radically the focus of its treatment research.

Asthma—a chronic inflammatory disease of the airway that causes shortness of breath, tightness in the chest, coughing and wheezing—claims about 500 Canadian lives every year. Extensive study in this field has resulted satisfyingly in a treatment course highlighted by bronchodilating medications, which swiftly alleviate the breathless suffering of the asthmatic by reversing the squeezing that's taken grip of his airways. But atypical asthma attacks threaten the life of their victims for their lack of responsiveness—or at least their delayed responsiveness—to this conventional therapy. Autopsies have revealed the cause of death in most asthma-related fatalities to be blockage, not constriction. "If you reduce the mucous secretion, you would save the life of those people having severe asthma attacks," says Lu.

The news, he explains, is that the asthma story is much more complex than it was once thought, and that it includes not one but two plots—the first, quick and reversible; the second, sleepy and slow to react.

Up until his lurching into the airway, Lu had spent his scientific energies wandering the hallways of the brain. And it was within these winding pathways that the scientist fastened onto the miracles of the neurotransmitter and was hooked. In response to the tug of self-reproach Lu suffered whenever he reflected on his primary University of Toronto appointment being with the department of anesthesia ("My research has nothing to do with anesthesia, and I felt a bit guilty. I said I would do something about it."), he honed in on the Gamma-aminobutyric acid (often abbreviated to GABAa) receptor, the body's target for most anesthetics.

Inside the body, there are secret conversations taking place all of the time. Neuronal cells form connections with one another, and they communicate through the synthesis, release and reception of chemicals: neurotransmitters. Gamma-aminobutyric acid is a neurotransmitter found in the nervous systems of a wide range of species that has historically been thought only to be synthesized and released by neurons in the brain. There, it is responsible for regulating the body's inhibitory response. But its apparent lodging in cubbies outside the central nervous system is what fascinates Lu, who first stumbled upon this anomaly when he uncovered a GABA-enhanced non-neuronal cell in pancreatic beta cells. He kept on looking. "I thought: let's see whether the long epithelial cells have it, too," he says. It was a calculated line of inquiry. Airway epithelial cells, after all, are the frontline receptors to inhaled anesthetics. If any cells were going to emerge spectacularly with GABA receptors in active swing, says Lu, it would be these vanguard targets.

They did.

"Now I've found a non-neuronal cell in the airway synthesizing the release of a so-called neurotransmitter," he says. (Previous studies had indicated the existence of GABA receptors on epithelial cells inside an airway, but no one had identified what they were for.) "That's the first unique thing."

The next is that Lu identified that this extraordinary GABAergic system (neurons that produce GABA as their output are called GABAergic neurons) induces an excitatory, rather than inhibitory, response. Extensively using preclinical models, Lu found that the expression of both GABAa receptors (one of two ligand-gated ion channels responsible for mediating the effects of GABA) and glutamic acid decarboxylase, a major GABA synthetic enzyme in the lining of epithelial cells, increased dramatically when animals were sensitized and then challenged with ovalbumin (a major protein constituent of egg white, and a method of spontaneously inducing allergic reactions). So, too, did they when human subjects endured an allergen inhalation challenge. "That means," says Lu, "that this GABA airway epithelial system is associated with asthmatic reactions." In other words, under the asthmatic condition, this system was upregulated: more GABA receptors were found in these

Drs. Yanna Xiang and Wei-Yang Lu

cells. What's more, these cells, under the influence of this stimulation, actually changed their morphology and function. Upregulated, they produce more mucous, releasing these great bolus strings of gelatinous risk for their host. "That's the second unique finding."

Having identified neurotransmitters in epithelial cells, and having begun to understand the role they play in an asthma patient's serious episodes, Lu was keen to forge a path of investigation into the effects of anesthetics on these and all non-neuronal cells.

Lu and his colleagues toil in a scientist's kitchen: two dozen jars of clear fluid, capped with ribbed orange lids and labeled with neat strips of yellow tape on which cryptic intelligence is scrawled—10% SDS, 0.5 M EDTA, DW (DEPC)—sit prominently on one shelf in the laboratory. In an adjacent glass-door cabinet, find more mixes: sucrose, sodium citrate tribasic, potassium chloride. And in the midst of all of this scientific industry, a simple sticky-note reminder, dangling from an overhead shelf. "Be careful!" it says.

Dr. Yanna Xiang, a research associate in Lu's lab, says she always is. And she was particularly so, four years ago, when she chose Lu as her supervisor. "It's been really good," she says, of the time she's spent under his guidance. "There's so much going on." And then, by way of proof, Xiang opens the door to an incubator spilling over with dishes of cultured cells, and gingerly removes one. Underneath the microscope, she regards the living focus of her and her supervisor's years of research: epithelial cells from the tracheal lining of a mouse, looking for all the world—microscopically speaking—like a bright green landscape as viewed from the sky. "Look," she enthuses, stepping away from the viewfinder. "You can see the glutamic acid decarboxylase is increased."

The best thing about working with Lu, Xiang says, is that he's "nice." A close second is that he's a value-added kind of scientist. Ask him a question, says Xiang, and you'll get more than you bargained for in return. "He doesn't just answer what you've asked," she says. "He takes your question right back to the basics and really explains things to you. I like that."

It was in sifting through the basics that Lu discovered the brilliant third piece of his epithelial puzzle. Grinning with its remembered identification, the scientist explains that he has learned that the mucous protein's synthesis in preclinical models is diminished significantly when scientists introduce an antagonist or inhibitor compound to the receptor. "If we block this GABA signalling system," Lu says, "we find that the mucous synthesis in the cell is much reduced."

The research, says Lu, is kind of a big deal. The GABAergic system is the current darling of the cell biology world, under the microscope for a lot of reasons, not the least of which is the part it has to play in controlling stem cell differentiation. At the clinical end, the promise of treating the most serious strains of asthma is very real and, says Lu, almost material. He has applied for a U.S. patent for the potential usage of a GABAa receptor inhibitor/antagonist that has been proven to curtail mucous production in asthmatics.

In the meantime, Lu, whose lab is working in conjunction with three others—at McMaster, the University of Manitoba and University of Toronto—has turned his attention to stripping the wires further. "We need," says the scientist they call the electrician, "to know how this happened." LP

Lu's research was funded by the Canadian Institutes of Health Research.

Pushing Back

SOMETIMES, LONG-SUFFERING CANCER PATIENTS DESPAIR TO LEARN THAT THEIR DISEASE HAS SPREAD TO THEIR SPINE. DR. CARI WHYNE WORKS TO OFFER THEM THE COMFORT OF PREDICTING WHEN AND WHY

Dr. Cari Whyne, David Wright, Asmaa Maloul and Meghan Crookshank

Dr. Cari Whyne, a senior scientist and director of the Holland musculoskeletal research program at Sunnybrook Research Institute, is keen to tap into the mysteries of the spine as they relate to its role in a cancer patient's journey through his disease. Whyne's research has resulted in a kind of guidebook for clinicians on how to predict the likelihood of this critical column of bone succumbing, in a cancer sufferer, to the kind of affiliated devastation that sometimes lies in wait.

Up to one-third of all cancer patients develop metastatic tumours in the spine. It's not entirely clear why, says Whyne, although a couple of theories attempt to explain it. One notes there's a physical link between the bones of the spine and common cancer sites, most notably the breast. The breast and the spine are actually connected by a venous network: a series of spidery roadways of toxic delivery. Another points out that the spine is a fertile environment for tumour growth. The site of abundant blood cell production, this bony garden offers a soil whose rich nutrients are as welcomed by the bad as the good cells.

In any event, that cancer does travel to the spine presents a serious clinical issue for the impact it has on a person's quality of life. The spine, after all, is a vital stack of bones lined up in precarious proximity to the spinal cord and a buzzing tangle of nerve roots. If these bones fracture or a spinal tumour makes contact with its critical neighbours, the physical fallout could include anything from extreme pain and bowel problems to paralysis and irreversible neural damage.

In her research, Whyne has concerned herself with understanding the mechanics, from a bioengineering point of view, of spinal metastasis. Quantifying tumour burden, the effects of treatments and predicting fracture are the first order of business for this scientist, who oversees the orthopaedic biomechanics laboratory and is an active member of the bone metastatses group at Sunnybrook; helping to develop and improve minimally invasive treatment options, like percutaneous vertebroplasty and photodynamic therapy, is the next. "It's palliative rather than about curing cancer," she qualifies. Indeed, Whyne points out, if medical science wasn't helping cancer patients live longer lives, the imperative to treat these fallout conditions wouldn't be so pressing.

Whyne's lessons on this front have been many. Importantly, she's learned that the likelihood of a burst fracture risk (a fracture of the posterior wall of the vertebral body, whose nearness to the spinal cord and nerve roots makes it the most clinically worrisome) is influenced by tumour size, bone density, the level of the vertebrae involved, the spine's geometry and whether the tumour emerges through the cortical shell. The guidelines she's developed in response are designed to help clinicians assess the probability of a patient suffering this calamity.

This shorthand, says Whyne, means doctors needn't make a computer model of every single patient. Instead her automated methods to analyze patients' CT scans can be used to predict fracture and as a clinical research tool for testing new drugs and radiation therapy protocols. Ultimately, she says, she'd like her work to ease proactively the suffering of people who have suffered enough. "We don't want to look at fracture as our endpoint to determine if a new treatment is worthwhile to pursue," says Whyne. "In fact, we don't want to allow these fractures to occur at all." LP

Whyne's work is supported by the Canadian Breast Cancer Foundation's Ontario chapter, Canadian Breast Cancer Research Initiative, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Ontario Research and Development Challenge Fund.

BREEDING EXPERIMENTS

Leukemia researcher shows scientific method has a life of its own

Starting with what his graduate student Mehran Haeri calls a "simple hypothesis"—that the protein VEGF-A accelerates erythroleukemia within the spleen—Dr. Yaacov Ben-David and his lab inoculated mice bred to overexpress VEGF-A with Friend murine leukemia virus in 2005, hoping to map molecular mechanisms underlying human leukemia. (Erythroleukemia is a rare but aggressive growth of immature red blood cells.) Unexpectedly, the mice lived one-third longer than the control group.

"We were surprised and excited," says Ben-David, a senior scientist in molecular and cellular biology at Sunnybrook Research Institute (SRI). They immediately shifted their research focus, to investigating potential reasons for the delay; upon further experimentation, they found two, thus achieving the goal of their initial experiment with an entirely new hypothesis, and opening new avenues for research into leukemia.

Researchers have known for years that the environment of the spleen encourages leukemia cell growth. Many leukemia patients experience enlarged spleens (Haeri has seen mice spleens 15 times the normal size), and evidence suggests splenectomy, removal of the spleen, can delay disease progression. Indeed, in 2004, Ben-David's lab was the first to identify two factors in the splenic microenvironment that make it conducive to cancer growth. One is the protein MCP-5; the other, VEGF-A. Moreover, several studies have shown that VEGF-A can encourage leukemia and other cancer growth at various stages. Ben-David's results made the cover of the journal *Blood* in 2005, and spurred interest in splenectomy, not only as an established means of relieving extreme discomfort in certain leukemias, but also as therapy.

So there was good reason to disbelieve, when Ben-David submitted his new hypothesis to *Blood* in late 2005, that VEGF-A could cause a significant delay in erythroleukemic growth. It took four rebuttals and a full year before the editors at *Blood* published the work, which finally appeared in October 2006. "It was so difficult," says Ben-David.

Gurpreet Lakhanpal, Dr. Yaacov Ben-David and Mehran Haeri

In 2004, Ben-David's lab was the first to identify two factors in the splenic microenvironment that make it conducive to cancer growth.

"It took us a long time, but it's a good paper."

The paper showed that whether a gene promotes or inhibits cancer is dependent on when it's expressed (as a protein), and its proximity and susceptibility to other genetic elements. While VEGF-A likely encourages growth in some types of cancer in certain contexts, in the enlarged spleens of Ben-David's mice (and in cells cultured in the lab), it increased the number and activity of the immune system's virus- and micro-organism-fighting natural killer (NK) cells, and led to higher numbers of mature red blood cells.

Ben-David's lab is now experimenting with these two factors to map further what role they may play in erythroleukemia. Haeri, whose radioactive chromium-release assay experiments helped characterize the increased NK cell activity, is studying mice bred without NK cells to see if tumours grow faster. The lab is also testing Epo, a synthetic protein similar to VEGF-A. "We've shown Epo can delay leukemogenesis in mice, so it has clinical potential," says Ben-David. "But it can be toxic and produce complications, so we need to find the right dose." Looking toward clinical translation of his results, Ben-David meets regularly with SRI clinician-scientist Dr. David Spaner, who gives next-generation therapies to leukemia patients in clinical trials. (Spaner has had encouraging preliminary success with splenectomy, based in part on Ben-David's research.)

Although experimental hypotheses and clinical approaches to cancer continually evolve, there are two constants required for a cure, says Ben-David. "First, you need therapy that targets the genes causing cancerous transformation. But you also have to handle the microenvironment. These two must work in tandem for the most effective therapy." JO

Ben-David's work was supported by the Canadian Institutes of Health Research and Ontario Cancer Research Network. The Canada Foundation for Innovation and Ontario Innovation Trust provided funding for infrastructure.

AT PLAY IN THE FIELD OF GENOMICS

Immunologists home in on diabetes susceptibility genes

The advent of the mapped human genome in 2000 was not good for the reputation of the rat. Though never a favourite in the popular imagination, the rat had occupied a place of considerable esteem as a preclinical model of disease among medical scientists for generations. But with the preliminary sequencing of the human genome, the rat's repute among researchers took a hit. Within three years, a more complete version of the human genome was enabling scientists to do what was previously impossible — identify multiple genes at play in complex human diseases such as cancer, cardiovascular disease and diabetes. The stature of the once-respected rodent was in retreat.

By 2006, as improving technology allowed biologists to add genetic detail to the sequenced genome, and geneticists began producing genome-wide association studies identifying even the small-effect genes associated with disease in humans, it appeared the study of all preclinical models was becoming rapidly less relevant. Dr. Robert Wallis, a postdoctoral fellow who had come to Sunnybrook Research Institute (SRI) in 2004 to study the etiology of Type 1 diabetes in rats with Dr. Philippe Poussier, was ambivalent. Recalls Wallis, "We were saying to ourselves, 'What are we going to do? Soon we'll have the human genes and mutations contributing to disease. They've found the answer.'"

Not so, it turns out.

Identification of specific human genes and their variegated presence or absence in an individual's genome has proven insufficient for understanding the development of complex diseases. Poussier, a senior scientist in molecular and cellular biology at SRI, explains: "In contrast to, for example, cystic fibrosis, where one abnormal gene simply doesn't make what it should, the genes associated with diabetes and other complex diseases are often not necessarily that abnormal. They are just variations, and it's the combination and number of them that produce a higher risk." Therefore, if gene variations, individually, only increase disease susceptibility a little — they are often merely "flavours," says Poussier, resulting in, say, green or blue eyes, both of which see equally well — then it becomes exceedingly difficult to determine how they contribute to the disease process, especially if their effects are small (and numerous genomic studies have recently demonstrated that those effects are indeed often subtle). So, despite the remarkable scientific achievement that is the sequenced human genome — an advance many scientists compare to the periodic table of elements — the question is now, says Poussier, "What do we do with this new knowledge?"

The answer appears to lie in a return to animal models of disease, as evidenced by renewed scientific interest in those models and, as it relates to Poussier's work, by a recent discovery he and his lab published in *Diabetes* in 2007. Through complex breeding and molecular biology techniques, Poussier and his group identified a novel diabetes susceptibility locus (area of the genome) in rats, and showed that genetic variations in this region result in a striking threefold reduction in disease incidence. "There's absolutely no way we could have done this work in humans," says Wallis.

Through further breeding and experimentation that was in turn based on the recently sequenced rat genome, they determined that the diabetes resistance was coming from chromosome 8, which reduced the number of implicated genes to about 100. From there, through yet more breeding and a reasoned examination of the known functions of the remaining genes, they focused on a small number of "candidate" genes that may be causing the significant resistance they observed initially. Says Poussier, "It has become quite apparent that the only way to understand how small genetic variations contribute to disease has to be done in animals, if good models for the disease in question exist."

Fortunately, an excellent model for Type 1 diabetes does exist in the Bio Breeding (BB) rat, a strain that spontaneously develops the disease, and Poussier and his lab took

Drs. Philippe Poussier and Robert Wallis

The need to find new therapies is pressing. Worldwide there are approximately 246 million people with diabetes, two million of whom are Canadian.

advantage of it for more recent work based on the *Diabetes* paper. By breeding sections of the genome of a non-diabetes-prone rat onto a diabetes-prone rat, they eventually narrowed their list of candidate genes to 30, which they are now testing. Two of those genes, though they have small global effects, look promising as key players in diabetes development. Their possible importance, Poussier suspects, might be related to the stage at which they're active: although an individual may possess "downstream" a large number of the genes that in combination produce disease, resistance at an early point can trump later susceptibility. Poussier likens this resistance to tailoring a suit: a few badly sewn buttons at the end of the process mean little compared to stitching the cloth together.

Of more clinical interest, Poussier and his lab have collaborated with researchers at The Hospital for Sick Children, who in genome-wide association studies showed those two genetic variations to have potential relevance to humans. "The exciting thing," says Wallis, "is that it seems to be a positive resistance coming from the resistant rat, rather than something mutated in the prone rat, and that could be great for potential therapies." If they can show these variations are directly relevant to human diabetes genes, then they already have a model in which they can tweak aspects of the disease process and see if they can affect diabetes outcome.

The need to find new therapies is pressing. Worldwide there are approximately 246 million people with diabetes, two million of whom are Canadian. Roughly 10% of those have Type 1 diabetes, which, as an autoimmune disease, develops when disease-fighting T cells attack insulin-producing cells in the pancreas. Patients require daily insulin injections, are at higher risk for heart, kidney and eye disease, and their life expectancy is shortened by up to 15 years. Perhaps most worrying, incidence of Type 1 diabetes has increased five-fold in high-risk countries over the last 50 years.

Further complicating the need to address this growing problem is the role of environment in the genomics of diabetes. Lab studies have consistently shown that genes contribute to only about 80% of one's diabetes risk, leaving environment responsible for a significant 20%. And in population studies, even countries with low immigration have shown the fivefold increase, which, as they're genetically stable, suggests a major role for environment.

A leading theory on this susceptibility jump is the "hygiene hypothesis," and although it sounds all too human, it too can only be studied usefully in preclinical models. The theory posits that because our environment is much cleaner than in the past, we're exposed to fewer viruses and bacteria; our immune systems, with consequently less to do, turn to innocuous substances (for example, pollen or plastics or, in Type 1 diabetes, our own insulin-producing cells), resulting in potentially lethal immune reactions. Diabetes-prone rodents kept in germ-free facilities almost all get diabetes; the cleaner the environment, the quicker they get sick and the sicker they get. Controlling for this environmental influence in studying disease genomics requires placing some subjects in sterile facilities and comparing them to identical models living in normal environments.

"How can you do this in humans?" asks Poussier. "You can't. So we hope that using animal models, we can see whether this particular region on chromosome 8 that can result in a threefold difference in risk is purely genetic or results from an interaction between genetics and the environment. With the help of our funders, we're doing that work now." JO

Poussier's work is funded by Genome Canada, the Canadian Institutes of Health Research and the Ontario Research Fund-Research Excellence. Wallis is funded by a Canadian Diabetes Association postdoctoral fellowship.

HOT FUSION

Molecular markers for prostate cancer have proven elusive, but change is nigh. A biologist and clinician come together to make it happen

"Quote me on this: geography makes a big difference," says Dr. Robert Nam, an associate scientist in clinical epidemiology at Sunnybrook Research Institute (SRI) and a uro-oncologist at Sunnybrook Health Sciences Centre. "I collaborate with other centres, but it's not as efficient as it is here." Proximity to Sunnybrook's Odette Cancer Centre and pathology lab, says Nam, and tight integration between his surgical oncology practice and SRI biologists have afforded him an unusually dynamic environment for basic-clinical research alliances. Turning to his desktop computer, Nam searches for and finds a file directory, "Seth/Sugar Collaboration." "July 7, 2006," he says. "That's when the directory was created. And you can see from the last two years, we've been hugely productive."

During those two years, Nam has worked with Dr. Arun Seth, a senior scientist in molecular and cellular biology at SRI, and Sunnybrook pathologist Dr. Linda Sugar to co-author three papers on prostate cancer, one of which detailed promising findings on a gene highly predictive of disease recurrence. They also secured a five-year grant to further their study of the gene, and both hired new staff to speed and broaden their work. "It's been a beautiful partnership," says Nam.

Sugar, who originally worked with Seth, brought Seth and Nam together. "Arun needed a prostate cancer researcher, and I needed a molecular biologist. It was to Linda's credit that we met and hit it off," says Nam.

Nam and other uro-oncologists were looking for prognostic molecular tests that would enable them to distinguish patients who need aggressive treatment from those who don't, sparing the latter group common effects of treatment, like erectile dysfunction and incontinence, and enabling individualized therapy for the former. Scientists have made such progress in some breast cancers with the Oncotype DX assay, a multi-gene test that examines tumour tissue to quantify the likelihood of cancer recurrence and assess the potential benefit of chemotherapy. By providing valuable patient-specific information, the Oncotype DX test is leading the way to individualized breast cancer treatment.

"Prostate unfortunately has lagged behind in that regard," says Nam. "There's a clear clinical need for markers, but a lack of science and molecular biology. Enter Arun Seth."

Seth, the director of molecular diagnostics and research in anatomic pathology at Sunnybrook, has studied molecular oncology for more than 20 years. He characterized one of the first oncogenes in mice and the human gene that causes Ewing's sarcoma (a cancer of bone and connective tissue) in children. In the 1980s, while at the U.S. National Cancer Institute, he isolated some of the ETS family of transcription factor genes, which regulate gene expression and are implicated in several cancers. One of the ETS genes, ERG, was identified by scientists in 2005 in some prostate cancers, bound to the prostate-specific gene TMPRSS2 in the form of the "fusion" gene TMPRSS2:ERG. Although Seth's molecular investigations with the ETS family had been largely applicable to breast cancer, he recognized an opportunity to advance TMPRSS2:ERG prostate research.

First, Seth and his lab examined prostate cancer specimens from 165 patients who underwent surgery — many by Nam — for localized prostate cancer between 1998 and 2006. Seth and Nam next compared the frequencies of TMPRSS2:ERG fusion gene status to the prostate cancer variables of grade, stage and prostate-specific-antigen (PSA) level, and looked at rates of disease recurrence in patients with and without the gene. They discovered the gene was expressed within prostate cancer cells in about one-half of the patients. Of the 165 patients, one-quarter suffered disease relapse after an average follow-up of 28 months. Those patients with the fusion protein had a much higher risk of recurrence at five years (58%) than did patients who lacked the fusion protein (8%).

"Our findings suggest that among patients treated with surgery, the expression of the fusion gene is a strong prognostic factor that is independent of grade, stage and PSA level," says Seth. These results, which Seth and Nam are now validating in a larger 1,700-sample study, should allow oncologists to classify prostate cancers as either

fusion-gene-positive or fusion-gene-negative, and tailor treatment accordingly. "That would tell us," says Nam, "that a patient with low-grade cancer but fusion positive will be at high risk of progression, and we need to throw more treatment at him, whereas a gentleman with high-grade cancer but fusion negative—we could say he's cured."

Another hope is that fusion gene status will provide a more objective marker for screening men yet to develop the disease than the PSA test, an unreliable tool that must be followed by a biopsy to confirm diagnosis. This is because the fusion gene is silent in normal and benign tissue and is activated only in cancer cells, thereby resulting in a straightforward positive or negative. Seth's lab is working to develop noninvasive tests that could quickly identify the fusion gene by examining circulating tumour cells that express it. They were successful in preliminary blood testing with 20 patients, and hope to detect the gene in urine samples next.

For Nam, such tests would augment his development of an improved prostate cancer risk assessment tool called a nomogram. A graphical representation of relationships between statistical values, the nomogram in this latest model predicts individual risk for developing the disease—not for recurrence—by including ethnicity, age, family history of the disease, prostate volume and urinary symptoms with the previous nomogram's variables of digital rectal exam and PSA test. The new nomogram, results from which Nam published in the *Journal of Clinical Oncology* in 2007, predicts cancer 74% of the time, an improvement of 12% over the older model. Nam is evaluating the new tool in a 5,000-patient multicentre trial, and it is publicly available online as the Sunnybrook Prostate Cancer Risk Calculator. It's good, says Nam, but not perfect. He will soon add fusion gene status, in addition to other prostate cancer genes he is examining, to the nomogram, and is confident it will account for the 26% of cases in which the current nomogram fails to predict the presence of prostate cancer.

Patients with the fusion protein had a much higher risk of recurrence at five years (58%) than did patients who lacked the fusion protein (8%).

Seth is also looking to the future of patient care, and sees TMPRSS2:ERG not only as a useful biomarker at multiple stages of diagnosis, but as a potential therapeutic target. "With fusion you have an androgen-responsive gene—TMPRSS2—and it's highly specific to prostate because it's only induced by androgen," explains Seth. TMPRSS2 increases by a thousandfold when androgen is present, and when fused to the ERG gene, ERG also increases a thousandfold. "So when you have a thousandfold jump in the ERG transcription factor, it's going to do some strange things. If it hits the wrong targets, it could create cancer," he says. Accordingly, Seth thinks the TMPRSS2:ERG fusion gene could be a biomarker like the Bcr-Abl fusion gene in chronic myelogenous leukemia—which is also a target, for Gleevec—and he's searching for a small molecule to inhibit the gene.

Whatever progress Seth and Nam make, it will likely be together. They meet every other week with Sugar and their lab groups—"Regular meetings keep us focused," says Seth—and invite other pathologists and oncologists to facilitate the exchange of ideas. "We actually like each other, and we like to hang out and think about prostate cancer," says Nam. "He's driven in the molecular field and I'm driven in the clinical field. When you have all of those ingredients, you're bound to succeed." JO

Nam's and Seth's work is supported by the Canadian Institutes of Health Research and Canadian Cancer Society through the National Cancer Institute of Canada. The Canada Foundation for Innovation and Ontario Innovation Trust provided funding for infrastructure.

Drs. Arun Seth and Robert Nam

Cited!

Dr. Juan Carlos Zúñiga-Pflücker

In 2002, Dr. Juan Carlos Zúñiga-Pflücker published a paper in *Immunity* detailing a method for creating T cells — white blood cells that rid the body of viruses, bacteria and tumour cells — in a Petri dish. The method was simple, effective and cheap, and it revolutionized the study of T cell development worldwide. In the short six years since its publication, the paper — "Induction of T cell development from hematopoietic progenitor cells by Delta-like-1 in vitro" — has been cited 300 times in peer-reviewed journals.*

Combining stem cells with Delta-like-1 molecules and supporting stromal cells, Zúñiga-Pflücker's system, developed by his then-graduate student Thomas Schmitt, enabled other biologists to examine the process of T cell development, which had bedeviled them for years, in unparalleled detail. More than 550 labs are now using the cells in new experiments.

"Most highly cited papers are either fundamental discoveries that generate a lot of controversial discussion, or methods papers that are highly applicable to multiple scientific approaches," says Zúñiga-Pflücker. "This finding falls into the latter category, as something people can use. It's efficient and practical and, as time goes by, more accepted as a way to study T cell development."

Six years on, the alternatives to Zúñiga-Pflücker's system are either in vivo study (that is, within a living organism), which is complicated and expensive, or in vitro approaches that require an entire thymus, the organ to which bone marrow stem cells migrate to become mature T cells. Both methods are limited in flexibility, and produce far fewer T cells and rudimentary molecular results.

Although wary of the flip side of producing a crucial methods paper — he has become very associated with his breakthrough and sometimes feels pigeonholed to the role of disseminating it — Zúñiga-Pflücker is delighted by the growing acceptance of his work. "What's surprised me is that people outside the field of T cell development are now able to drop this cell system into their labs and ask questions previously outside their repertoire," he says. JO

* Google Scholar, October 26, 2008.

Dr. Juan Carlos Zúñiga-Pflücker is a senior scientist in the discipline of molecular and cellular biology at Sunnybrook Research Institute and director of its Advanced Regenerative Tissue Engineering Centre. He is also a professor in the department of immunology at the University of Toronto, and holder of the Canada Research Chair in Developmental Immunology.

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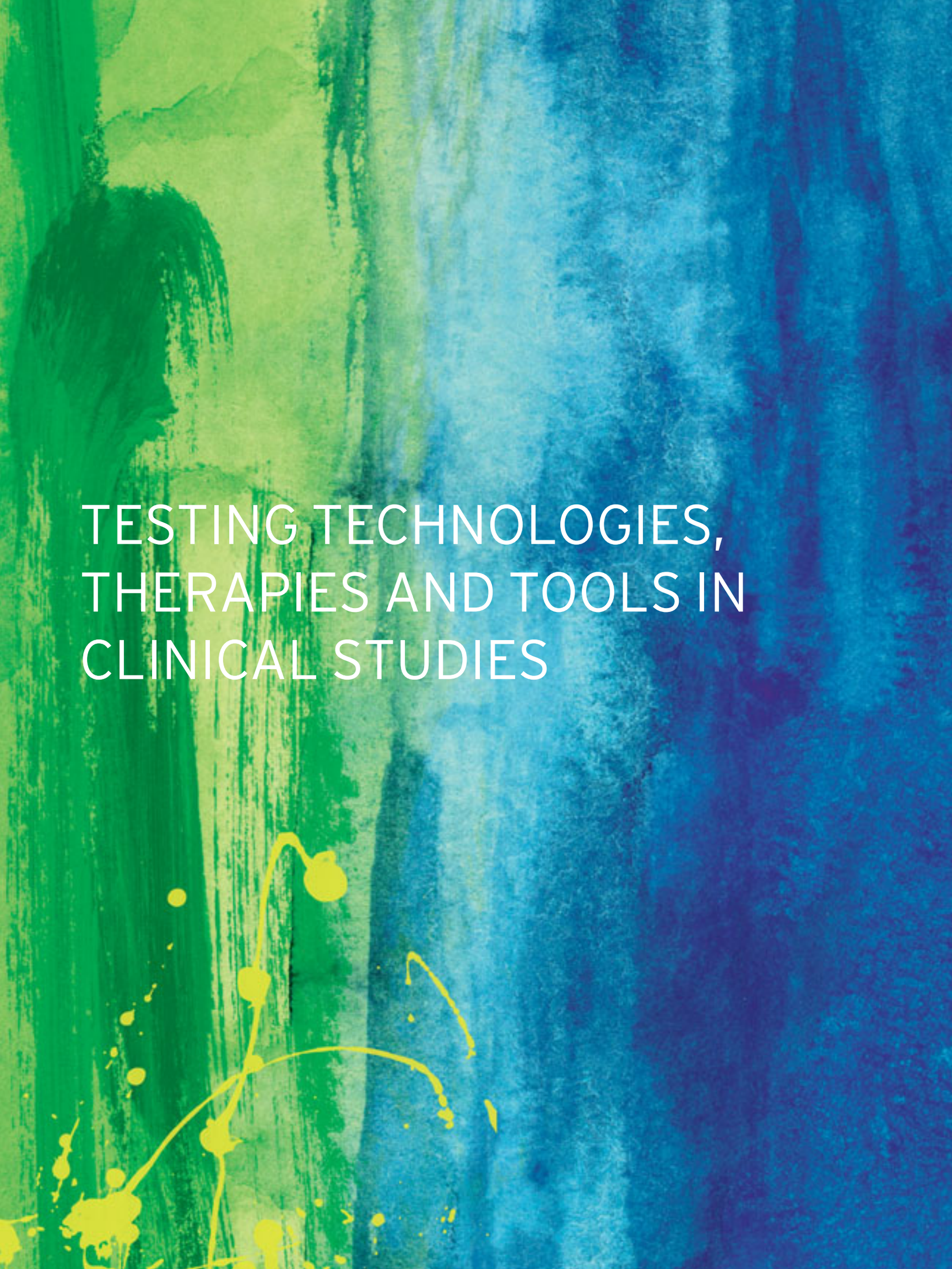

TESTING TECHNOLOGIES, THERAPIES AND TOOLS IN CLINICAL STUDIES

THEIR BEST SHOT

Two Odette scientists target breast cancer treatment from closer range

There is the whiff of revolution in the air. Gone are the days when physicians treated breast cancer with a scattergun. Precision shooting is the order of the day in the rewriting of the treatment protocol that addresses this cancer—the most common of all for women in Canada. Among the sharpshooters find Drs. Jean-Philippe Pignol and Eileen Rakovitch, both scientists in the Odette cancer program at Sunnybrook Research Institute (SRI), whose highly collaborative and convention-upsetting research in radiation oncology is taking precise aim at breast cancer therapy that's been too broadly prescribed. The upheaval, says Pignol, is primarily powered by advancements in imaging techniques that are diagnosing cancer sooner and positioning patients for early-stage treatment that can be more targeted than in the past.

Drs. Eileen Rakovitch and Jean-Philippe Pignol

THESE ARE WELL WOMEN…IF THIS WOMAN IS GOING TO LIVE TO 90, WHY REMOVE HER BREAST?

"These patients know they have cancer earlier, which means that conventional treatments we've had up until now are becoming obsolete," says Pignol. "We're in a phase now of trying to offer more patient-friendly approaches and to de-escalate the aggressiveness of the way we treat these women."

In "A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis," published in the May 2008 issue of the *Journal of Clinical Oncology*, lead author Pignol outlines research that advocates for more exact adjuvant breast radiotherapy to reduce the topical pain a patient sometimes experiences under the beam of an X-ray. Specifically, he addresses the raging red skin inflammation—moist desquamation—that is the result of radiation that's not evenly distributed to the breast. Almost 50% of women undergoing standard treatment for their breast cancer experience moist desquamation.

Typically, says Pignol, radiation therapy is delivered to the breast broadly, missing some areas altogether and causing over-radiated "hot spots" in others. These unpleasant side effects—characterized by angry, weepy skin lesions—are owing to the limitations of conventional radiation techniques to account for the complex three-dimensional shape of the breast. Moist desquamation can present as anything from a thin split in the skin that's painful for a couple of days, to a massive reddening of the breast that can become infected and endure, excruciatingly, for several weeks. The condition is more common in full-breasted women. (The size of the breast is the main factor in determining whether women will suffer breast burns.)

Breast intensity-modulated radiation therapy (IMRT) is a more technologically sophisticated means of delivering radiotherapy to the breast. Its defining characteristic is its promise of a more uniform dose distribution, thanks to radiation therapists "using the radiation machine like a robot, and programming it very precisely at the breast," says Pignol. Convinced it was the better way, Pignol launched a multicentre randomized controlled trial to determine if these new techniques perform better than do the old. They did, says the scientist, who has a PhD in nuclear physics. Dramatically so.

In Pignol's study, 31% of women receiving this targeted therapy suffered moist desquamation—a drop of 35%. "There have been hundreds of studies to address the issue of skin burns during radiation, and not one of them was positive," he says. "People have tried everything: all kinds of cream, hydrocortisone, aloe vera. But nothing worked. This is the first study that proved that an intervention can reduce skin burn." Indeed, Pignol's research now provides level-one evidence in favour of breast IMRT, and the world is responding. Since Pignol's presentation of his work at a September 2006 American Society for Therapeutic Radiology and Oncology conference, where his trial was chosen as a first plenary session (out of the 1,000 submitted abstracts on developments in radiation oncology), the redress has been almost complete. Today, says Pignol, "breast IMRT is being used everywhere. Since the publication of our paper, it's understood that this is what everyone should do."

Such results, he says, are heartening for future study into advancing cancer-treatment technology. "We are now very encouraged to say that, with new technology, we can improve patients' lives."

Patients' lives are in for an upgrade under Rakovitch's watch, too.

Most breast tissue is fat, a spidery web of blood vessels and a network of milk ducts that comes together at the nipple. The duct is lined by a single layer of cells, any one of which can become abnormal and divide, eventually filling the duct with its deviance. When this multiplying maverick is confined within the wall of the duct, this is ductal carcinoma in situ (DCIS), the earliest form of breast cancer.

Over the past 20 years, the incidence of DCIS has risen sharply, and it now represents between 20% and 40% of all breast cancers diagnosed by screening mammography. This reality is a result not of a budding epidemic, but of increasingly sophisticated imaging techniques that are allowing physicians to identify the condition earlier. About 5,000 Canadian women are newly diagnosed with DCIS every year.

The survival rate for DCIS is close to 100% (10-year survival rates are over 95%), but, says Rakovitch, that doesn't mean the standard of treatment is without fault. Indeed, she believes that many of the women with this strain of cancer are potentially being overtreated and having their breasts removed unnecessarily.

The target of Rakovitch's concern specifically is women with multifocal DCIS. Here, the breast is littered with these blooms of abnormal cells, but all of them are restricted to one quadrant of the breast (as opposed to multicentric disease, which features disease in more than one quadrant, and does appear to require a mastectomy to treat). Traditionally, doctors have believed that multifocality was a significant predictor for cancer recurrence, after treatment, and routinely prescribed mastectomies.

That these "upfront mastectomies"—inherently damaging, says Rakovitch, to a person's quality of life, to say nothing of her physical sense of self—have long been the prevailing course of action for women with multifocal DCIS, concerned the researcher. "It was one of these dogmas we were all worried about, but there just weren't good data to convince us to try anything else." As such, this approach

Dr. Jean-Philippe Pignol

went unchallenged for years. Besides, DCIS was usually extensive at time of diagnosis, often involving most of the breast, so alternatives were scarce. With the dawning of the age of screening mammography, however, has come an imperative to revisit this standard.

In "Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy," published in the December 2007 issue of the *Journal of Clinical Oncology*, Rakovitch concluded that, yes, the presence of multifocal DCIS does herald a higher risk of recurrence compared to a woman with single-focus DCIS. But that's primarily if the patient is treated with lumpectomy only. If the treatment combines lumpectomy with radiation therapy, then these women suffer no greater risk of having their cancer return than do women with a single focus of DCIS. "Radiation," says Rakovitch, "not only lowers the risk of DCIS coming back, but, more importantly, lowers the risk of [a woman developing] invasive breast cancer."

Currently, only 50% to 60% of women with multifocal DCIS are receiving the combined treatment of localized surgery and radiation. Meanwhile, about one-third of women with DCIS are still being treated with a mastectomy. That may be too many, says Rakovitch, whose research attracted the distinction of being the featured subject of an editorial in the same issue of the journal in which her paper appeared. "That DCIS is multifocal [does not make it] a definitive indication for mastectomy. Most women with DCIS are candidates for lumpectomy and radiation."

"These are well women," says Rakovitch. "When you're treating something that has a very good prognosis, it's very important that your treatments have the least side effects possible. If this woman is going to live to 90, why remove her breast? As physicians, it's our responsibility to identify the best treatments and offer options. Because let's face it: most women, knowing they could preserve their breast, would."

This work is not Rakovitch's alone, but is the result of a collaborative team effort with other researchers at Sunnybrook, including Drs. Wedad Hanna, an associate scientist in the clinical integrative biology discipline at SRI, and Lawrence Paszat, an SRI scientist and head of the preventive oncology program at Odette Cancer Centre. "It's so wonderful to work together as a team, as we do," she says. Rakovitch contributed to Pignol's IMRT paper, as did Pignol to Rakovitch's DCIS paper.

On the importance of their group effort, Pignol agrees. Because breast cancer is as devastatingly common among Canadian women as it is (one of eight will get the disease in her lifetime, and close to 10% will be seen at Sunnybrook's Odette Cancer Centre), there needs to be a real "team approach" to its treatment, he says. Pignol calls himself and Rakovitch "the nucleus of the team," which several other researchers have joined in recent years. Both clinician-scientists, the pair regularly seeks one another out over the course of a day. "We help each other to apply for funding, we review research papers and provide feedback, and [we help] supervise research and clinical students," says Pignol. "If you have a common project on which each of us gives a little bit of time, at the end of the day, the amount of manpower per project is more. Consequently, the chances of success are higher, and the quality of the work is better." LP

Pignol's and Rakovitch's work was funded by the Canadian Breast Cancer Research Alliance and Canadian Institutes of Health Research. Infrastructure support for the Breast Cancer Research Centre, in which Pignol and Rakovitch are researchers, is from the Canada Foundation for Innovation and Ontario Innovation Trust.

Screen Doors

LEADING RESEARCHER PAIRS WITH SRI'S MARTIN YAFFE TO EXPLORE THE MYSTERIES OF BREAST DENSITY

Drs. Martin Yaffe and Laibao Sun

WHAT IS BREAST DENSITY?

Breast density describes the relative amount of different tissues in the breast as visualized from a mammogram. A dense breast has less fat than it does glandular and connective tissue. Mammograms of breasts with higher density are harder to read and interpret than those of less dense breasts because some tissue appears white on an X-ray, as do tumours. Fatty tissue is less dense and appears clear on the X-ray, allowing better tumour detection.

It's one thing to know you're at risk; it's another to know how large that risk is. In a collaborative effort, Dr. Norman Boyd, a senior scientist at the Ontario Cancer Institute, and Dr. Martin Yaffe, a senior scientist at Sunnybrook Research Institute, sought to quantify the risk women unwittingly face by virtue of biology. The results appeared in a *New England Journal of Medicine (NEJM)* paper lead-authored by Boyd. The researchers were seeking to understand the influence that a woman's breast density has on the likelihood that she'll develop breast cancer, according to method of cancer detection. It's important, says Yaffe, to quantify the role that this cloudy qualifier has on a person's possibility of being diagnosed with this disease, in light of the imaging modality used in the testing. As the paper showed, it turns out that extensive mammographic density is strongly associated with the risk of breast cancer, whether it is detected by, or missed on, screening.

The article—published in the January 2007 issue of the prestigious *NEJM*—revealed that women with very dense breasts have a four to six times higher chance of getting breast cancer than do women with breasts of very low density. As compared with women with density in less than 10% of the mammogram, women with density in 75% or more of the mammogram are at considerably increased risk of developing breast cancer, particularly if they're younger. For those aged under the study's median of 56 years, 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening test were attributable to density in 50% or more of the mammograms. This elevated risk persists for at least eight years after study entry.

The paper broke other ground, too: the news that women who have very dense breasts are, in a sense, at double risk. They not only suffer an increased threat of developing breast cancer, but they're also more likely to have the disease overlooked by radiologists when they get mammograms. In a mammogram—basically, an X-ray of the breast—fat looks like the night sky; fibroglandular tissue appears as streaky white clouds across it. A woman with a dense breast produces a picture of a dramatically overcast day—the more fibroglandular tissue, the denser the breast—and the stark whiteness of the image makes meaningful detection difficult. "If you combine those two factors—the loss of accuracy of mammography and the higher risk—it's a very big effect," says Yaffe, who was recently appointed director of the One Millimetre Cancer Challenge at the Ontario Institute for Cancer Research.

He nonetheless looks to the future of breast cancer research with optimism and is encouraged about the part that medical biophysicists like Boyd and himself will assume in creating it. "Imaging has a really critical role to play," he says, "and it's going to become even greater as we move forward toward developing new targeted molecular imaging techniques for detecting cancer." LP

Yaffe's research on breast density was funded by the Canadian Breast Cancer Research Alliance, the National Cancer Institute of Canada, the Ontario Institute of Cancer Research and the Terry Fox Foundation through the National Cancer Institute of Cancer. Infrastructure funding for the Breast Cancer Research Centre, in which Yaffe is a researcher, is provided by the Canada Foundation for Innovation and Ontario Innovation Trust.

SHOOT THE MESSENGER

An infectious disease specialist seeks to curtail a deadly outbreak by going after its misunderstood source

Dr. Andrew Simor

Sometimes, says Dr. Andrew Simor, a senior scientist at Sunnybrook Research Institute and head of Sunnybrook's department of microbiology and division of infectious diseases, medical science is less about the actual and more about the potential.

In a paper published in *Clinical Infectious Diseases* in 2007, Simor, who directs the research institute's discipline of clinical integrative biology and teaches at the University of Toronto, explored a treatment option for people who are carriers—said to be "colonized"—of methicillin-resistant Staphylococcus aureus (MRSA), a potentially deadly strain of bacteria. It was an effort, he says, apart from the usual energy invested in treating patients already infected with this disease. "It would be nice to find a treatment for the infection," says Simor, whose randomized controlled trial, conducted between 2000 and 2003, was the first to identify a safe and effective therapy for eradicating MRSA colonization in hospitalized patients for at least three months. "But I hope I've also shown why it would be useful to be able to clear the colonized patients, and thereby prevent an infection from happening in the first place."

In the modern definition of a superbug, MRSA emerges as a particularly super one.

The MRSA organism typically resides on skin and mucosal membranes, especially in the nose. Colonized individuals—so-called because they have the staph bacteria but are not ill from it—have a 20% to 30% risk of developing an infection within 18 months of becoming colonized. But it's their exposure to others—whose less resilient natural immunities might render them more susceptible to this infection—that is a greater cause for concern. The mortality rate of MRSA, after all, is between 4% and 10%. And it's thanks in part to encounters with colonized individuals, says Simor, that between 5% and 10% of patients admitted to hospital without an infection, develop one while there. "That's a huge number."

In the modern definition of a superbug, MRSA emerges as a particularly super one. First identified in 1963, the bacterium didn't cause problems in Canada until the late 1990s, when it came to light as the most common antibiotic-resistant organism causing infections in hospitalized patients. The sensitive strain of S. aureus has been around for centuries, but novel community strains of MRSA, which cause disease in nonhospitalized and otherwise healthy people, are the worrying new entity. They appear to be even more virulent, capable of being spread easily and causing severe disease. "This observation makes our study findings even more relevant," says Simor.

In the U.S., a little less than 1% of the general population are MRSA carriers. We don't have any comparable data in Canada, but, says Simor, about eight of every 1,000 patients admitted to hospital in this country are either MRSA carriers or have the staph infection.

Ten years ago, frustrated by the lack of attention being paid the issue of MRSA carriage, Simor and his team began treating patients with a blend of antibiotics and learned, retrospectively, that a combination therapy of antiseptic soap, antibiotic ointment and antibiotic pills seemed to work. The randomized controlled trial he shepherded in response to these findings concluded that, three months in, 74% of MRSA carriers were clear.

The scientist is philosophical about the results. Even this treatment—currently the best available—wasn't effective in the long run with 25% to 30% of patients. Just the same, Simor, who admits to liking things that aren't necessarily straightforward or well understood, is optimistic about this being a first step, and excited to be on the pathway. "I often say to my students, 'When was the last time anyone discovered a new heart or kidney disease?' These organisms are constantly evolving, and that creates new challenges for diagnosis, treatment and prevention. That's what I find so exciting." LP

Simor's work was supported by the Physicians' Services Incorporated Foundation, Ontario.

THE HARMONICS OF COLLABORATION

Imaging physicist and clinical radiologist pair to give liver cancer a new look

When Dr. Stephanie Wilson presents images at radiology seminars and conferences showing that ultrasound can diagnose the nature of a liver mass with equal, and at times better, accuracy than computed tomography (CT) or magnetic resonance imaging (MRI), she often finds her audience surprised and impressed: ultrasound is cheaper, more accessible, faster and produces fewer adverse effects. Those at Wilson's talks surprised by ultrasound's ability to diagnose liver masses—which are extremely common and can produce weeks of worry among patients waiting for CT or MRI—are diminishing in number, however. One reason for this shift in awareness is the appearance of some of those new ultrasound images on the January 2007 cover of *Radiology*, the largest circulation and arguably most prestigious journal in medical imaging. The images are from an article that marks the outcome of a prolific collaboration between Wilson and Dr. Peter Burns, a senior scientist in imaging at Sunnybrook Research Institute (SRI).

Wilson, who served as the first female president of the Canadian Association of Radiologists and is a professor of radiology at the University of Calgary, is an expert on liver disease. Burns is a physicist and the chair of the department of medical biophysics at the University of Toronto. Together with Burns' unique technology, developed and commercialized at SRI, the two have made ultrasound a practice-changing method of diagnosing liver masses in Toronto and, increasingly, internationally.

The story of ultrasound's rise to prominence as a liver imaging technique began more than a decade ago in Burns' lab at SRI, where he and his colleagues developed methods to detect and image microbubbles that would later be used for contrast enhancement in patients undergoing liver ultrasound. Microbubbles are microengineered pockets of gas, smaller than a red blood cell, surrounded and stabilized by a thin layer of protein or lipid—a sort of microscopic soap bubble. They're made from harmless materials found in the body, and only a few drops need be injected into a vein. The bubbles circulate and, when excited with ultrasound waves, ring and produce harmonics, like musical overtones. Burns pioneered an imaging technique called pulse-inversion to capture those harmonics, effectively illuminating blood flow in tissue in real time, and producing an immediate and remarkably detailed picture. The invention was recognized as seminal in the field of ultrasound physics. Says Wilson, "Peter is a brilliant scientist and a very clever investigator."

Translating this science into a method that can be used in clinical practice to image the liver required that Wilson and Burns take several steps. First, the bubbles needed to be approved for clinical use, which was achieved in Canada with the help of their early data in 2002. The European Union and several other countries followed soon thereafter, although the bubbles are still not approved for clinical use in the U.S. by the Food and Drug Administration. (Burns is optimistic that this will change soon.)

Lack of approval in America, which made ultrasound trials using microbubbles less feasible in the U.S., did, however, help Burns and Wilson present a successful case for funding clinical trials in Canada. One of the first trials they set up, at the University Health Network in downtown Toronto where Wilson was then based, was to determine if ultrasound could diagnose liver masses with sufficient accuracy. The study showed it could do, so they next ran a trial in the same Toronto clinic comparing ultrasound to the standard liver imaging techniques of CT and MRI. The trial generated a huge amount of data, and after a long period of analysis, *Radiology* accepted the results with the resounding affirmation of a cover spread, securing ultrasound's place as a viable, and in some instances superior, imaging technique.

A striking finding from this study was that in 25% of patients ultrasound caught one important sign of cancer that CT and MRI did not. "That's a very significant finding," says Burns. He says that this didn't mean CT or MRI led to missed cancer diagnoses; rather, CT and MRI might have been indeterminate, and other signs led radiologists using those methods to suspect cancer. But, as Burns notes, "The problem with an indeterminate test is that it sends patients on to more tests or biopsies, so having a definitive test is much more useful. In these 25% of cases, ultrasound was definitive."

Dr. Peter Burns

"But this test seems successful in that it reduces the number of subsequent investigations and shortens time to diagnosis for patients who are frequently very anxious."

Herein lies one reason — streamlined diagnosis — why ultrasound, when used to image liver masses, has a positive impact, even on a clinical practice that uses CT and MRI. Traditionally, when radiologists discover a liver mass using conventional ultrasound imaging, they report it to the patient's physician, and the physician refers the patient for CT or MRI. The patient then goes home and waits, eventually to return for a scan that is much more expensive than ultrasound and requires time to process the results. The new contrast-ultrasound, on the other hand, is performed in real time when the mass is first detected, bypassing the referral and scan-scheduling process and providing instant results.

Another benefit of ultrasound is fewer adverse effects. The contrast-enhancement agents for CT and MRI can produce negative side effects. In addition, CT imparts a whack of radiation — a concern for all patients, but particularly for women of childbearing age. Wilson notes that research in the U.S. has shown that CT scans may be responsible for up to 2% of cancers in that country.

Following their *Radiology* cover article, Burns and Wilson teamed again and joined other colleagues in a Toronto-based 1,040-person trial to analyze the impact of ultrasound on the care of patients with liver masses. Results showed that in 45% of cases patients' care was changed favourably. "It's always conceivable," says Burns, "that a diagnostic test can make lives more complicated, ring false alarm bells, cause more confusion and testing. But this test seems successful in that it reduces the number of subsequent investigations and shortens time to diagnosis for patients who are frequently very anxious."

Thousands of patients around the world now benefit from contrast-ultrasound liver imaging, especially those in Southeast Asia. Many Asian countries have high rates of hepatitis B and C, which increase the risk for liver cancer dramatically. Toronto, with many people of Southeast Asian origin, also has elevated hepatitis rates. These patients require regular liver scans, part of a strategy to catch cancer early should it develop, and many in Toronto are now routinely scanned with ultrasound at the University Health Network. China, with an enormous population, has made significant use of Burns' invention and continues to expand its implementation.

While contrast ultrasound for liver imaging has become a standard of care in areas of China and Toronto, its recognition and use elsewhere is also increasing. Although it requires a highly skilled operator, a potential hindrance to rapid clinical adoption, Wilson finds growing implementation among her colleagues in Calgary. Moreover, the European Association for the Study of the Liver published guidelines for liver diagnoses that include microbubble ultrasound. The "Barcelona Guidelines," which Burns calls the bible of diagnostic algorithms for the liver, included contrast ultrasound as a definitive method for liver diagnosis. And for his contributions to the field, Burns was awarded the 2008 William Fry Memorial Award of the American Institute for Ultrasound in Medicine, its highest recognition for lifetime achievement in basic science research. But as a physicist, says Burns, "The most valued reward is to see one's work impact patient care. For that reason, and because of the distance it has travelled, we are very happy about this work. Such collaborations between basic scientists and clinicians are the most important we have in medical research." JO

Burns' work is supported by the Canadian Institutes of Health Research, Ontario Institute for Cancer Research, Ontario Research Fund-Research Excellence, and Terry Fox Foundation through the National Cancer Institute of Canada. The Canada Foundation for Innovation and Ontario Innovation Trust provided infrastructure funding.

A GREATER DEPRESSION

Dr. Anthony Levitt finds an acute form of bipolar disorder—in children

Dr. Anthony Levitt

As psychiatrist-in-chief at Sunnybrook Health Sciences Centre, Dr. Anthony Levitt spends a lot of time asking questions of patients. Those patients, in turn, and many health professionals outside Levitt's field often have a question for him: "Don't you get depressed treating people with depression all the time?" It's a question for which Levitt has a ready answer. "I tell them it's quite the opposite. It's exhilarating, because people actually get better," he says during a break between patients in his Sunnybrook office.

Levitt had a case in point the previous week. A woman he'd been treating for six years and who had been in treatment for six years before that came to see him and reported a month of wellness. "Remarkable," he says. "It's not many medical conditions where you can say someone's been ill for 12 years and they've made a recovery."

That recovery, dependent on the combination of a standard treatment with one still experimental, may not have happened without Levitt's approach to depression: maintain a broad perspective and work across the clinical-research spectrum, from genetics and prevention, to treatment resistance and community implementation of new therapies. "Depression has to be addressed at every level," says Levitt, who also wears the hat of scientist at Sunnybrook Research Institute. "It's not simply an infection that needs a drug; it's a multifactorial illness that needs a multifactorial view."

To that end, Levitt has done several studies of depression and other mood disorders, one of which yielded results on bipolar disorder in 2006. Published in *The American Journal of Psychiatry*, the study weighed in on a controversy started a decade ago by researchers in the U.S. who said that the disorder exists in children as young as five years old. Prior to this work, clinicians believed that the disease begins in late adolescence or early adulthood; many doctors and researchers still hold that view. Levitt and his group, however, who treat patients of all ages at Sunnybrook, have observed what they think is bipolar disorder in young children, observations supported by the results of their study. In analyzing 1,411 people with lifetime bipolar disorder, 8% (113) reported onset before age 13 years; another 24% (339) reported onset between age 13 and 18 years.

The study also examined whether the illness as reported by the U.S. group looked like that described by the participants—more severe than average, with longer episodes, and more drug abuse and other psychiatric problems, particularly anxiety. It did. That was significant because, like diabetes and other chronic conditions, bipolar disorder is more resistant to treatment when it begins early. "This gives us more reason to identify kids at risk and then try to 'inoculate' them against ever developing the illness," says Levitt.

Striving for prevention of the disease in this young demographic, Levitt and study coauthor Dr. Benjamin Goldstein, recently a trainee at Sunnybrook and now a staff psychiatrist at the University of Pittsburgh, are tracking children whose relatives have bipolar disorder—measuring their cognition, moods, inflammatory markers in the blood and genetic markers—toward possible intervention with cognitive behavioral therapy or novel treatments.

Levitt is optimistic about those new treatments, which he says are poised to revolutionize mood disorder outcomes. Brain imaging is allowing researchers to pinpoint the geography of depression for the first time, and new biochemical targets, like substance P in the stress system and melatonin, are emerging to complement prior work on serotonin, dopamine and norepinephrine. Most exciting, says Levitt, is the potential therapeutic implications of brain-derived neurotrophic factor, a protein produced in the brain that helps grow and potentially repair damaged or lost brain cells. "These approaches are percolating through to clinical practice," says Levitt. "Our capacity to fight these illnesses and our choice of treatments is about to explode." JQ

Levitt's work is funded by the Canadian Institutes of Health Research, Physicians' Services Incorporated, and private and corporate donors.

Team Effort

ORTHOPAEDIC SURGEON WORKS WITH RESEARCHERS ACROSS THE COUNTRY TO PREDICT RISK FACTORS FOR A DEBILITATING DISEASE STRIKING ONE IN 10 CANADIANS

Drs. Gadi Khan, Paul Marks and Om Sharma. Background: Dr. Chris Robinson

Dr. Paul Marks thinks that when it comes to understanding diseases, two — or in his case, eight — heads are better than one. An orthopaedic surgeon and associate scientist in the Holland musculoskeletal research program at Sunnybrook Research Institute, Marks is a researcher, along with seven others, in the Prospective Study of Patients with Knee Injuries (ProKnee), which seeks to identify risk factors that predict the progression of osteoarthritis after knee injury. For Marks, tackling osteoarthritis — a disease afflicting three million Canadians — requires collaboration: "If we are going to make progress in understanding these complex problems [then] we need a team of people who are like-minded but have their own area of expertise that they can bring to bear on the problem in a more sophisticated way." The multi-institutional ProKnee study, the first of its kind in Canada, does just that, amassing experts in radiology, orthopaedics, statistics, biomechanics and biomedical engineering.

Osteoarthritis, the most common form of arthritis, is caused by the breakdown of cartilage, the dense elastic tissue that covers and protects the ends of the bones. Marks discovered early in his career that the disease was complex, with various factors that were poorly understood. Even patients whose biomechanics were repaired through surgery began to develop the disease. This suggested the presence of biologic factors beneath the cartilage that, according to Marks, "might set the stage for someone developing arthritis."

The varied expertise of the investigators in the ProKnee study addresses the need to use a multifaceted approach in examining the progression of osteoarthritis. They have recruited 121 patients (all of whom came from Marks's practice), between the ages of 18 and 40 years, who have had an anterior cruciate ligament (ACL) injury, a tear in the ligament that is responsible for stabilizing the knee joint. All of the participants had surgery within three months of the injury. They will be monitored for five years to determine whether the knee is healing, or if bone and cartilage are deteriorating. Using mathematical models and diagnostic tests, Marks and his colleagues hope to determine which participants will develop osteoarthritis and why — what he calls "the ACL risk equation." The equation has as its constant ACL injury, and variables such as individual habits and disturbances in the joint, which prevent tissues from fully healing and cause further damage to the knee. They are also targeting new therapeutic strategies, including the use of drugs to stop bone softening and replacing cartilage using cells from other parts of the body.

They are also targeting new therapeutic strategies, including the use of drugs to stop bone softening and replacing cartilage using cells from other parts of the body.

Regardless of whether his patient is an elite athlete (he is also the medical director for the Toronto Raptors — a role he has had since the team's inception), or someone who simply wants to maintain an active lifestyle, Marks strives to treat injuries early to prevent them from becoming more serious. "There is a 'golden interval of time' where we have the opportunity to restore biologic integrity and try to get back to normal physiology. That's why our focus is at the beginning — right after the injuries have occurred," he says.

Although time is of the essence for the treatment of injuries, Marks and his colleagues will have to wait and see if they can come up with the risk equation. The ProKnee team will follow patients for five years, but Marks suspects that because major problems likely won't surface until much later, it could be 10 or 15 years before the answers are uncovered.

Only time will tell. AK

Marks's research is funded by the Canadian Institutes of Health Research and Canadian Arthritis Network.

Managing Multiples

Twin births are surging, but they're high-risk. An eight-year, $8 million trial will determine if Caesarean section is the best method of delivery

In July 2000, the Society of Obstetricians and Gynaecologists of Canada published a consensus statement on the management of twin pregnancies. Based on a literature review spanning more than two years by dozens of experts from across Canada and the world, the statement reflected broad agreement on the many complexities of twin pregnancies, and answered several questions. One question the panel couldn't answer, however, was the best way to deliver twins — vaginal birth or planned Caesarean section.

Twin and other multiple pregnancies — triplets, quadruplets and quintuplets — have much higher rates of premature birth and growth abnormalities than do singletons. But even in optimal circumstances, when the babies have reached full term without problems and the first twin is presenting head down, twins still have a threefold higher chance of dying. The expert panel, chaired by Dr. Yosef Barrett, an associate scientist at Sunnybrook Research Institute and director of the perinatal and gynaecology research program at Sunnybrook Health Sciences Centre, did agree that existing literature on the best method of delivering twins was inconclusive, despite preliminary evidence suggesting that Caesarean section may be better (especially for the second twin), and a drift toward it in obstetrical practice. They recommended further research on the subject, and it was from this Canadian seed that the global Twin Birth Study (TBS) was born.

Funded by an $8.6 million grant from the Canadian Institutes of Health Research and led by Barrett, the TBS is an eight-year, international, multicentre, randomized controlled trial (RCT) coordinated by Sunnybrook Research Institute's Centre for Mother, Infant and Child Research. Its mission is clear: "We'll find the answer to this very basic but very important question of what's the best way to deliver twins," says Barrett in an interview between patients at the bustling Sunnybrook multiple births clinic. Although RCTs take a long time — this one in particular because the statistical differences between delivery options are likely to be small and therefore require a high sample size — in the end, says Barrett, they're the only route to a definitive answer. "The RCT is the gold standard for evaluating clinical therapies. There's no other good way of doing it."

Finding that answer has become more important over the last 30 years because the rate of multiples has exploded. In Canada, from 1974 to 1990, twin births rose 35% (per 100,000 births). This change is similar to data from other developed countries, including the U.S., where the rate of twin births grew 70% from 1980 to 2005, climbing an average of 3% a year between 1990 and 2004. In Canada, there are now more than 4,000 sets of twins born each year. The incidence of other multiples has risen even more so; although rates have fallen slightly since the late 1990s, triplets increased almost 300%, and quadruplets over 400%, from 1974 to 1990. Multiples are, says Barrett, a "modern epidemic."

Two factors have contributed to the dramatic rise in multiples: more women choosing to have babies at an older age and new fertility treatments. Women in their thirties are more likely than younger women to have multiples spontaneously, and fertility treatments including assistive reproductive technologies (particularly in vitro fertilization), intrauterine insemination and ovulation stimulants have become common. Scientists estimate that fertility treatments account for about 16% of multiple births in Canada.

To manage this demand, Barrett, in addition to leading the study, helped found Canada's first multiple births clinic in 1999 at what was then known as Sunnybrook & Women's College (now Sunnybrook Health Sciences Centre). As a pregnancy clinic dedicated to seeing women with multiples, it was and still is unique because, according to Barrett, it's unusually multidisciplinary, involving doctors, ministers, midwives, dieticians and other support staff. Clinic staff created Canada's first electronic patient record, such that patients' data are entered directly into a computer—all the rooms are wired with computers, so staff can stream the data straight into a database server. The patient is also given a record, confidential between her and her doctor, which she carries. (It was the first medical clinic in Canada where patients could carry their own records.) The clinic has garnered Sunnybrook an outstanding reputation for multiple births care.

Dr. Yosef Barrett and Jessica Ganas, with her twins Peter (left) and Carys

Two factors have contributed to the dramatic rise in multiples: more women choosing to have babies at an older age and new fertility treatments.

Although this new influx of women and their babies has helped make Sunnybrook the largest Canadian centre for the TBS (to date the clinic has enrolled 60 women), difficulty in finding participants has made reaching the study's recruitment goal of 2,800 a significant challenge. "As anyone who's done a randomized trial will tell you, the biggest challenge is recruitment, recruitment, recruitment," says Barrett. He has seen many patients with preconceived ideas about trials; some worry they won't receive the best care. Dalah Mason, a senior research coordinator for the TBS, seconds that experience. She also feels that preconceived ideas from patients' families or friends can sometimes hinder recruitment. "Occasionally women are interested, then go home and talk about it and later decide they're no longer interested," says Mason. She adds that although the TBS doesn't involve a new or untested treatment, many women don't like the idea of giving up the choice of how they deliver — another obstacle for this trial.

A further recruitment challenge lies in doctor equipoise, which Barrett calls "a fancy term for, 'I don't know what to do.' A patient comes to you because you're the doctor, and says, 'What's the best way to deliver my baby?' and you say, 'I don't know.' Well, it can be difficult to admit that, but it's the truth — right now, the literature is in that position of equipoise." Recruitment for the TBS was supposed to have reached 2,800 by June 2008, but enrollment is only halfway there.

Recruitment aside, two other challenges exist for the TBS: data collection and funding. Says Barrett, "We have to make sure the data are clean and accurate, which means hours of meticulous work with the data forms we get back from the centres." While a challenge for any study, it's particularly daunting in this one, which has 87 centres in 22 countries, and requires two years of follow-up with each patient. Says Mason, "Follow-up is time-consuming, because people move away and need to be located, or they may lose interest. Then, we may lose them."

As another challenge, centres in Canada may be more hesitant to take on the work of a large trial like the TBS owing to Canada's funding structure. Although the Canadian Institutes of Health Research has provided significant funding for the study, all that money goes to running the grant, and none goes to investigators (unlike in the U.S. and some other countries). So, says Barrett, "it's up to individual universities, departments and practice plans to somehow pay people to do research, and that's a challenge."

This and other difficulties notwithstanding, Barrett is excited about the TBS and what it will reveal. An earlier RCT carried out by the Maternal, Infant and Reproductive Health Research Unit at Sunnybrook and Women's College Health Sciences Centre addressed a similar question — the best way to deliver breech babies — and the answer was Caesarean section. "Almost overnight, or at least within a year," says Barrett, "the practice internationally swung. It was one of the very few results of a study that globally, rapidly, changed the whole practice of obstetrics. And I have no doubt this trial will do the same thing." JO

The Twin Birth Study is funded by the Canadian Institutes of Health Research.

THINK AGAIN

A pair of researchers approaches Alzheimer's disease with new perspective

Research on Alzheimer's disease (AD) has historically cut a swath up the middle of the condition. Although patterns of decline are well documented across all phases of AD (a test categorizes AD patients according to disease progression: mild, moderate or severe), few studies have sought to characterize the cognitive and functional abilities of patients in its later stages. This oversight has been deliberate, says Dr. Sandra Black, a senior scientist and director of the neurosciences research program at Sunnybrook Research Institute (SRI). "No one has wanted to touch this [severe-stage] population." That's because, just as drugs delivered too early in AD's progression might fail to inspire a response, drugs delivered too late might miss the window of opportunity, she says. Thus, almost every man-made innovation designed to mitigate the devastation of this neurological nightmare has focused on its mild-to-moderate stage.

Until recently.

Acetylcholine is a neurotransmitter that plays an important role in how the brain functions. It affects certain cerebral tasks, including attentional focus, intentional thinking, memory and maintaining vigilance. In the 1970s, researchers identified that this system was a target of AD, gradually destroyed as the disease progresses, for reasons no one entirely understands. This realization, says Black, "led to the idea that a strategy to restore its function might help to combat the symptoms of AD."

Scientists conducted the first clinical trials with a drug that inhibits the breakdown of acetylcholine in the 1980s. The thinking, says Black, was that inhibiting its breakdown at synapses would help the neurotransmitter to last longer, to activate cholinergic receptors, thereby giving "a bigger bang for the buck." The drug—tacrine was first on the scene, marketed under the trade name Cognex—helped, but with caveats. Patients had to take it four times a day. And tacrine appeared to be toxic to the liver. Some also experienced nausea and diarrhea.

In the late 1990s, the second generation of these drugs appeared, donepezil being the first. Typically, the trials exploring this new generation of drugs, called cholinesterase inhibitors, focused on the middle band of severity. There, they showed a modest benefit. Says Black, "You could stabilize the symptoms for a period. But a big unanswered question was: Would these drugs make any difference in severe-stage disease?"

She was keen to find out.

Black headed up an international multicentre pharmaceutical trial, which led to a 2007 *Neurology* paper, "Donepezil preserves cognition and global function in patients with severe Alzheimer's disease." The research team found that donepezil has "beneficial effects, slowing decline in cognitive and overall functioning in severe-stage AD." This study, conducted in patients still living at home, demonstrated that this drug could also be helpful in late-stage disease.

Still, response to such promise has been halting. While donepezil's use for this late-stage purpose was approved, the formularies in most provinces do not cover the cost of the cholinergic drugs or another new drug for moderate to severe disease, called memantine, which is about $5 a day. "For people who can afford it, it's a no-brainer, but it's a cost that many families can't afford," says Black.

On another front, Black and her team have been actively investigating interactions between AD and cerebrovascular disease, especially small-vessel brain disease, which increases with aging and is becoming prevalent in developed societies.

Historically, researchers have approached the two conditions independently, failing to exploit the potential of modern computerized analysis and to acknowledge new data showing the most common cause of dementia is a combination of the two diseases. "There's a lot of 'silent' brain vascular disease that's visible on brain scans but ignored because it's so common," Black says. "But Alzheimer's and cerebrovascular disease, including stroke, can no longer be regarded as two separate disorders, because there's a lot of interaction between them."

Drs. Sandra Black and Fuqiang Gao

"Silent strokes" may occur up to 10 times more often than symptomatic strokes.

In a paper published in *Stroke* in March 2008, Black and lead author Dr. Richard Swartz — an MD-PhD student, supervised by Black during the research — analyzed both disorders and explored their combined impact on neurological deterioration.

Swartz, now a final-year resident in neurology at the University of Toronto, says that any other approach is folly. The two diseases are common afflictions of the aged. Dementia affects one in three people aged over 85, and AD and strokes accelerate as we age. Because they can affect thinking, memory and cognition, understanding how stroke disease and degenerative pathologies interact has become an important and urgent goal, says Swartz. To appreciate how brain changes contribute to cognitive impairment, he says, scientists need to move away from diagnostic groupings and look at different measures of atrophy, vascular disease and cognition, and work to understand how they all relate.

What's more, population studies have revealed that lots of folk are walking around with vascular changes in their brains, but no symptoms. These "silent strokes," says Swartz, may occur up to 10 times more often than symptomatic strokes (those everyone notices because they cause sensory loss or weakness). "Silent stroke disease is very common in the elderly, and may subtly affect functions like abstract thinking, planning and motivation, even though they don't wipe out the ability to, say, move your arm."

In their research, the team sought to understand how brain shrinkage interacts with some of these silent strokes and incidental white matter findings (as we age, many of us develop structural abnormalities on the brain — white matter hyperintensities — that show up as white spots on imaging). "We wanted to tease out which of the changes we see on imaging are most important to mental functioning, and to evaluate the correlation of these different types of pathology with different mental tasks," says Swartz.

Using measures of global severity that rated functional impairment and cognition, along with cognitive tests that analyzed participants' short-term memory and language, working memory and mental flexibility, the researchers found that measures of atrophy were the strongest correlates of all cognitive domains. Measures of small-vessel disease (white matter changes and small strokes in the brain's deep grey matter) were correlated with memory, language and mental flexibility. "Furthermore," says Swartz, "our data show that the more of one type of change you have, the more of the other you have. Studies that try to tease out which is the most relevant are highly flawed."

They showed that small-vessel disease affects the ability of anterior brain regions to plan, shift attention and multitask. In contrast, they found that large-vessel strokes contribute to memory, language and working memory, but not to mental flexibility.

It's not all brand new, Swartz admits, of their research. "But it's the first time it's all been tied together." Armed with specifics on which brain measures matter most for understanding breakdown of particular areas of cognitive function, doctors can gain new insight into why a patient's abilities are disappearing in a certain way. "And the results," says Swartz, "argue that treatments aimed at preventing vascular disease should help to prevent some of the [breakdown] of cognition."

The most critical finding of the research, says Black, is that, "to understand the relationship between brain tissue volumes and cognitive abilities, you need to look at all the brain tissue compartments, including the white matter lesions. You can't just ignore the lesions, as many people do in studies of Alzheimer's, or ignore the rest of the brain if you focus on white matter disease. If you do, you'll miss the fuller explanation of what's going on." LP

Black's and Swartz's research was funded by the Canadian Institutes of Health Research. The donepezil study was funded by Eisai-Pfizer. In addition, Black receives funding from the Heart and Stroke Foundation; she is co-director of the Heart and Stroke Foundation Centre for Stroke Recovery.

Cited!

Dr. Robert Kerbel

Writing a paper for *Nature Reviews Cancer* was, Dr. Robert Kerbel recalls, excruciating. The journal's standards are impeccable — peer review is rigorous, editors' demands extraordinary. "They kept asking us to do more. We were shocked at how difficult it was," says Kerbel. At one point, his coauthor Dr. Judah Folkman told one of the editors in exasperation that she should put her name on the paper instead of his. "But," says Kerbel, "it made the paper better. That's one reason it's highly cited."

Highly cited it is — 757 times.* Published in 2002, "Clinical translation of angiogenesis inhibitors" assessed the preclinical success and translational challenges of a class of drugs that allay cancerous growth by targeting tumour-feeding blood vessels.

Controversy around angiogenesis inhibitors generated immediate interest in the paper. Folkman had published results in *Nature* a few years earlier showing that an antiangiogenic drug discovered in his lab, endostatin, led to major regression of tumours in mice. It created a media frenzy, culminating in a May 3, 1998, *New York Times* front-page spread, which quoted Dr. James Watson saying Folkman would "cure cancer in two years." The drug was rushed to phase 1 clinical trials and — it bombed. "There was a huge backlash — against Folkman, to some extent, and the field of angiogenesis," says Kerbel.

That atmosphere, and a pragmatic temperament, encouraged in Kerbel a balanced approach to the paper. "It was defensive: instead of saying angiogenesis drugs work, we said they should work in people, but so far they haven't; here are possible reasons why." While that caution likely contributed to the paper's credibility, Genentech's announcement in 2003 of the first-ever positive trial of an antiangiogenic drug (Avastin) vindicated its optimism — and the 12 years Kerbel had spent researching angiogenesis inhibitors. "You can't imagine the euphoria, excitement and relief I felt at that announcement," says Kerbel. "I said to my lab, 'Life is going to change for all of us, mostly for the better.' And that's exactly what's happened." JO

* Google Scholar, October 26, 2008.

Dr. Robert Kerbel is a senior scientist in molecular and cellular biology at Sunnybrook Research Institute (SRI) and a professor in the departments of medical biophysics, and laboratory medicine and pathobiology at the University of Toronto. He holds the Canada Research Chair in Tumour Biology, Angiogenesis and Antiangiogenic Therapy, and is a co-director of the Toronto Angiogenesis Research Centre at SRI.

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TRANSLATING KNOWLEDGE, INFLUENCING POLICY AND CHANGING PRACTICE

RANDOM BY METHOD

Dr. Thérèse Stukel takes a cue from econometrics for a new approach to epidemiology

Early in 2008, editorial staff at *The Lancet*, one of the oldest and most prestigious general medical journals in the world, asked its international advisory board to nominate the research papers that made the greatest contribution to clinical research in 2007. To preempt the inevitable criticism of this "paper-of-the-year" exercise, a feature of the journal since 2003, the editors took care to note in a jocular preamble to the list of 12 finalists that the ambitiousness of the process "invites incredulity," given the extraordinary breadth and complexity of research published each year. On the other hand, they pointed out, in lieu of workable judging criteria the process is "an opportunity to celebrate research and researchers, enriched by the passion of colleagues about the papers that excited them most." Considerable if informal grounds, in other words, for some serious global boasting should one's publication be nominated for the award.

Dr. Thérèse Stukel

THE 16% REDUCTION SHE SAW INSTEAD, WHICH SQUARELY MATCHED RCT RESULTS FOR THE SAME PROCEDURE, WAS EVIDENCE THAT HER APPROACH AND INSTRUMENT WERE VALID.

News of precisely that honour traversed the grapevine to Dr. Thérèse Stukel a few weeks later, for her *The Journal of the American Medical Association (JAMA)* paper, "Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods." Stukel, a senior scientist in clinical epidemiology at Sunnybrook Research Institute (SRI), as well as at the Institute for Clinical Evaluative Sciences, was shocked. "It was a huge honour and a big surprise," she said the following month in her office at SRI. An honour, because *The Lancet* is a high-impact journal; a surprise, because it's unusual for any medical research journal to place a statistical methods paper alongside valued medical advances. "It was a good day for biostatisticians everywhere," she said with a smile.

It has been a decent 18 months for biostatisticians since Stukel published her article. At the time this magazine went to press, the paper had been cited 34 times in peer-reviewed journal articles. Some of those citations were in methodology and epidemiology journals, but several were in general medical research publications, suggesting that the paper is having an impact where Stukel says it's most needed — among a broad audience of clinical researchers whose specialty is not statistical methods, and who rely on methodologists to ensure the validity of their observational studies.

Stukel and her team showed that conventional statistical analyses of cardiac catheterization (an invasive test that measures blood flow and heart function, results of which often lead to surgery) indicate the procedure reduces mortality by 50%. Randomized controlled trials (RCTs) — considered a much more reliable method of testing efficacy than observational studies — show a decrease of just 8% to 21%. Using an econometric technique new to epidemiology, instrumental variable analysis, Stukel came up with a decrease in mortality that strikingly matched RCT results — 16%. "We caught the perfect example," said Stukel. "Nobody believes that an invasive diagnostic test reduces mortality by 50%, so almost nobody could dispute those findings. The only response could be, 'Do we have to pay attention to this?' and 'What's going on?'"

What's going on is that many observational studies have a problem called treatment selection bias, and it's not an easy problem to fix. Treatment selection bias is the inadvertent tendency to attribute to a particular treatment the improved outcomes in a group that received that treatment, when compared to a group that didn't get it, even though the underlying reason for those improvements is better preexisting health in the group that fared better. Numerous factors can affect interpretations of baseline health, including age, education, income and other medical problems. Many studies have shown that, in some instances, physicians will perform more aggressive treatment — especially surgery — on healthier patients who are at lower risk for complications from surgery or for dying, than on patients who are at higher risk, even though the latter group may benefit more from the treatment. Reasons for this phenomenon include physicians' perceived potential for causing more harm in high-risk patients, and devotion of time and resources to patients' other problems in place of the treatment in question. As a result, those who get a certain therapy don't always have the same risk profile or prognosis for improvement and survival as those who don't get it, and this discrepancy can skew the results of a study that compares treatment efficacy in the two groups.

Randomized controlled trials are one solution to this problem. In an RCT, randomization determines which patients are selected for treatment and which aren't, so the two groups should theoretically have similar baseline characteristics and health, eliminating selection bias. This approach works well (although not without its own recruitment challenges — patients must be free of certain comorbid conditions to be eligible, resulting in underrepresentation of these), and RCTs are considered the best means of assessing therapies and procedures. The trouble is, they're expensive to run, time-consuming, potentially unethical and for some treatments, impossible. A pill is easily given as a placebo, but surgeons, for example, can't perform sham operations, and a trial to test for linkage between cancer and smoking would clearly have ethical problems. For these reasons, most studies are observational, not RCTs.

Researchers use several strategies to deal with selection bias in observational studies. They ensure good study design, which can minimize opportunities for bias, and use statistical models to adjust for baseline differences between patient groups, to make outcome comparisons in those groups more valid. One common approach, standard regression analysis, incorporates all available covariates (patient risk factors) into the model to control for patient differences. This works, provided those risk factors are the only ones at play. If there are unmeasured factors, however, for example, diet, environmental toxicity or genetics, then regression can't control for them.

Epidemiologists therefore use another set of techniques called propensity score methods. Propensity score methods classify patients into deciles of risk to determine their probability of getting treatment, then look at outcomes among patients within the resulting strata to ensure similar risk and health baselines in treated and untreated patients. The problem with this approach, as Stukel explained, is "it's subject to the same caveats as regression models — if you don't control for a certain risk factor because you can't see it, you can't measure it in the propensity score."

Propensity-based matching is a third method that restricts the analysis to a group of patients who are much closer in baseline risk and then only looks at them. But this technique has the same problem as propensity score, and as Stukel expected, it produced a similarly misleading (50%) decrease in mortality when assessing the effect of cardiac catheterization.

Stukel's instrumental variable analysis, in contrast, produced a significantly more realistic measure of catheterization's benefit, and for what appears to be a compelling reason: it mimicked the randomization of an RCT. In an earlier *JAMA* paper in 2005, Stukel showed that although regional rates of catheterization vary dramatically

Dr. Thérèse Stukel

(from 29% to 93%, depending on availability of cath labs and services, among other factors), patients themselves were largely the same across regions in their baseline risk and other potentially confounding influences. Confident that patients were similar, and then comparing outcomes in regions with high rates to those with low rates, Stukel used geography as an instrument of randomization and control: if catheterization does reduce mortality significantly, she reasoned, one would expect to see a much greater reduction in areas where it's performed regularly. The 16% reduction she saw instead, which squarely matched RCT results for the same procedure, was evidence that her approach and instrument were valid.

Dr. Muhammed Mamdani, director of the Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute at St. Michael's Hospital in Toronto, read Stukel's paper and found it compelling. Mamdani has extensive training in pharmacology, epidemiology and economics, and was the director of outcomes research at Pfizer Global Pharmaceuticals in Manhattan before moving to Toronto. "I think this method of approaching observational studies in a different way, using instrumental variable analysis, is fantastic, because it tends to get at this issue of selection bias better than the traditional designs we're used to seeing," he said by telephone this September.

Mamdani is comfortable with instrumental variable analysis in part because he's seen it used extensively in econometrics, where it originated some 30 or 40 years ago. Although medical researchers have only turned to the technique in the last 10 to 15 years, Mamdani says its use is growing as technology enables more sophisticated statistical modeling and journals demand that studies pay more rigorous attention to selection bias. "I'd now believe a good instrumental analysis over a decent cohort study done in the traditional way," he said.

There are drawbacks to instrumental variable analysis, and a critical one that Mamdani, Stukel and other epidemiologists note is that it's rare to find a good instrument. Stukel admits this was her biggest challenge, and that her team considered several instruments before settling on regional catheterization rate, in part because it produced the best clinical interpretation.

Another problem is the difficulty of testing an instrument to be sure it's really functioning as it appears to be. Dr. Donald Redelmeier, Canada Research Chair in Medical Decision Sciences, and senior scientist and director of clinical epidemiology at SRI, was intrigued by Stukel's study, but not unreservedly. "An instrumental variable analysis has a big assumption about independence which is impossible to test," said Redelmeier in his office at SRI this past summer. "Sometimes it may give you an answer that corresponds with things you already know, but that may be due to offsetting errors. It may be the analysis has two errors built into it that just by a fluke cancel out, so it ends up pointing in the right direction." Regional catheterization rates, Redelmeier noted, may appear unrelated to the baseline health of study patients, but perhaps a community with a large amount of smoking, diabetes or high blood pressure will eventually bear a greater disease burden, leading to more cardiologists, more cath suites and more catheterizations, thereby confounding the apparent randomization of an instrumental variable analysis. Still, said Redelmeier, "Any methodological tool can cause problems if misapplied," and whether instrumental variable analyses will garner further attention as an epidemiological technique is "certainly a frontier question."

That this question has already found traction among clinical researchers is a testament to the credibility of Stukel's work. And while Stukel's assessment of her paper's impact is cautious—"One robin doesn't make a spring," she said—several calls from clinical researchers asking if instrumental variable analysis might work for them have boosted her optimism. Some of those inquiries didn't evolve into studies, but several are moving forward, including two at the University Health Network on blood transfusion and colonoscopy screening. Mamdani is also seeing more instrumental variable analyses, and expects that trend to continue over the next few years. As for Stukel and her paper, Mamdani said, "She's brilliant. It's one of the better methods papers that's been written in a very long time." JO

Stukel's work was supported by the Canadian Institutes of Health Research, the U.S. National Institute on Aging and the Robert Wood Johnson Foundation.

THE UNDERBELLY
of Overachievement

An SRI researcher works to explain an alarming surge in diabetes diagnosis—and to stem its flow

Like so many of her peers, Dr. Jan Hux, a scientist in clinical epidemiology at Sunnybrook Research Institute and at the Institute for Clinical Evaluative Sciences (ICES), where she is chief operating officer, toils in the usual isolation of the medical research universe. But she keeps a companion beside her, in spirit. This friend is a marginalized woman, a person at risk for disease, a potential victim of the malady Hux studies. She is a single mother, without money for running shoes, without access to child care, without education, without reach of healthy food, without hope. She is the one who inspires knee-jerk responses in the general psyche that produce no meaningful results and that arrest this imagined casualty forever as the embodiment of a statistic, hurtling toward the destiny of diabetes. That is, unless Hux's research can intervene and erase the perception of this person as the weak-willed prey to her own inability to increase her odds in the lottery of good health.

In her population-based study on diabetes prevalence, incidence and mortality in Ontario, published in *The Lancet* in 2007, Hux determined that the World Health Organization's (WHO's) prediction for the rise of the global rate of diabetes was a dramatic underestimation in this part of the world.

Drawing deeply from the rich database of the Ontario Health Insurance Plan records held at ICES, Hux followed up on research she launched 10 years ago tracking the progression of diabetes in this province, and was alarmed to learn that the incidence of the disease among Ontario residents had increased by 27% between 2000 and 2005, a far cry from WHO's prediction of a 39% worldwide spike between 2000 and 2030. "We'd almost achieved the 30-year projection in five years," she says.

Hux compares the phenomenon to the relative congestion of a swimming pool. The pool can become more crowded either because more bathers are coming into it, or because fewer are leaving it (by dying). "We find the main thing driving that increase is not so much newly diagnosed patients, but the fact that people are living longer with the disease. We're a victim of our own success."

Bearing that unique bit of contradiction in hand then, Hux approached the Ontario Ministry of Health and Long-Term Care and insisted that it pay it some mind. She and her colleagues are making the data more accessible, she says, by dividing them according to gender, age and affluence, such that ministry minds can get a more detailed picture of the at-risk groups within the population. They are pointing fingers, too, at the regional disparities within the province that her research revealed, with northern Ontario surfacing as the spot with the highest at-risk residents. Of the top five places in Ontario, the one that wasn't in the north was Toronto—a function, Hux believes, of immigration from at-risk ethnicities, such as South Asians.

But it's the massive swing of statistics to the younger end of the generational spectrum that caught Hux the most unprepared. "Diabetes used to be a disease of older age," she says. Between 2000 and 2005, the prevalence of diabetes diagnosis in people aged under 50 years increased by 94% (versus 63% in their 50-years-and-older counterparts). "Kids are sitting in front of their iPods instead of going outside and playing," she says. "They don't walk to school, they have access to gadgets that require almost no caloric investment to keep them busy, and there may be a tendency to use foods that are less focused on healthy fresh fruit and vegetables."

The economics of a community has tales to tell, too, when it comes to predicting diabetes incidence. "If you live [in a rough neighbourhood] and your literacy is so low you can't read a recipe, and you don't have access to the Internet to get lifestyle tips, and you're obese, and you are a single parent with three young kids, and it's not safe to walk in your neighbourhood, and at the only

Between 2000 and 2005, the prevalence of diabetes diagnosis in people aged under 50 years increased by 94% . . . "Kids are sitting in front of their iPods instead of going outside and playing," she says. "They don't walk to school, they have access to gadgets that require almost no caloric investment to keep them busy, and there may be a tendency to use foods that are less focused on healthy fresh fruit and vegetables."

grocery stores in walking distance the vegetables are brown and the cheesies are cheap and plentiful, I would contend that it's not really your fault, and blaming you for your weight is really placing on the individual a problem that's much more societal. I get angry with people when they think that way. That's a real challenge for us."

So, too, is negotiating the faulty ground upon which WHO's numbers were based from the start, believes Hux. The looming likelihood of an obesity epidemic was largely overlooked, she says. "They made an assumption that obesity rates would be constant." It was a critical oversight, because, says Hux, if the world responded in the way she feared it would do, and ascribed to WHO data a gold-standard reputation, then public health planners would never be able to move forward responsibly. "It's really important to get a bead on these numbers," she says. "With lots of programs crying out for dollars, it's easy to ignore it if you don't have information. Having this information means this now becomes an inescapable fact, this public-health crisis on our doorsteps. Lifestyle is a really important component of diabetes prevention, but lifestyle programs are really expensive to mount. We can't prove cause-and-effect, but [we] can certainly show an association. Good planning and good access to services appear to mitigate that risk."

As for the fallout Hux imagines her research will inspire, she admits to being called a Pollyanna. But she points to the speed with which the charge into the diabetes pool has taken place as evidence that change is likely. After all, she says, if you get sick quickly, goes the old clinical medicine adage, then there is a chance you'll recover well. "The fact that this has come on over the last decade suggests this isn't a genetic issue. It isn't because our genes have mutated and we now have this inescapable genetic doom of destiny. There are things that can be done to turn things around. It's a basic management principle that you can't manage what you can't measure." LP

Hux's research is funded by the Institute for Clinical Evaluative Sciences, core funding of which is provided by the Ministry of Health and Long-Term Care.

Dr. Jan Hux

DO THE RIGHT THING

Sunnybrook trauma chief works to rewrite the reality of an emergency room where the lurking presence of a deadly infection is acknowledged—but not always addressed

Dr. Gordon Rubenfeld (left)

Spotting a gap in medical science, Dr. Gordon Rubenfeld hurled himself into it.

It started in the index, this leap of faith, of Crossing the Quality Chasm, the go-to publication the U.S.-based Institute of Medicine produces to try to assess quality of medical care in the U.S. In this index, the authors explore the disconnect between the kind of care that the evidence says physicians should be giving to their patients and the care they do give. But the index didn't include even a reference to the part of the hospital where, Rubenfeld thinks, care needs to be most assiduously taken given the lurking killer that resides there: the emergency room. And that oversight blew Rubenfeld, a senior scientist at Sunnybrook Research Institute, away.

Early sepsis is difficult to recognize. The body's response to severe infection, sepsis can present as anything from wooziness to full-on shock. Why one victim suffers a septic response to bacteria while another sails through unscathed is not well understood, says Rubenfeld, who is also chief of the trauma, emergency and critical care program at Sunnybrook. But it needs to be. Sepsis (often assigned the shorthand moniker of "blood poisoning") can lead to septic shock, multiple organ dysfunction syndrome and death.

> We don't have any trouble recognizing who's been hit by a car, who's had a stroke, who's had a heart attack. That's not the case for sepsis.

The "golden hour of trauma" is an ironically poetic term for the 60 minutes the medical system has determined critical for getting trauma victims set up with the care that may save them. But to the quartet of acknowledged time-sensitive conditions (along with trauma, there's stroke, cardiac arrest and myocardial infarction), Rubenfeld wants to add a fifth: sepsis. "We don't have any trouble recognizing who's been hit by a car, who's had a stroke, who's had a heart attack," he says. "That's not the case for sepsis."

Worse, says Rubenfeld, is that "there's evidence to suggest that sepsis treatments work—but that they're not being provided." The reasons for this aren't clear. Certainly there are complicating factors for this condition, including its requirement to be handed off from emergency medical services personnel to hospital-based doctors, that it demands a "high degree of suspicion" (that is, that a physician has to be versed enough in the condition to suspect it strongly) and that it involves a battery of resuscitative treatments.

Rubenfeld and his colleague Dr. David Carlbom (an intensive care and emergency physician) found in their study "Barriers to implementing protocol-based sepsis resuscitation in the emergency department," published in *Critical Care Medicine* in 2007, that placing a central venous catheter into the patient and monitoring it faithfully, was a principal hurdle to successful implementation of sepsis treatment. The study also confirmed something Rubenfeld had found in other studies evaluating barriers to changing practice: clinicians on the same team don't always see the same problems or solutions. The doctors interviewed said there was no problem in placing the central venous catheters; but the nurses, some from the same emergency departments, said no way, that they didn't have the staff to do it. This disparity alarmed Rubenfeld. "If we're going to save lives with sepsis," he says, "we're going to have to make significant investments in training and public relations, and make emergency departments as sensitive to sepsis as to trauma."

At the end of the day, says Rubenfeld, the sepsis business is but "one small piece of information that fits into a larger push to export best practices." Improving the quality of care in a hospital, he points out, is tricky business, and it's folly to imagine unrealistic goals. "All we can do in medicine is get as close as possible to delivering perfect care." LP

Rubenfeld's work is supported by the Canadian Institutes of Health Research and the National Institutes of Health (U.S.).

Trial and Error

THIS SRI EPIDEMIOLOGIST BEMOANS THE LIMITATIONS OF THE WAY NEW TREATMENTS ARE TESTED

Dr. Rob Fowler is worried. His brain so distractedly churns over the way modern medicine ushers in its new developments that the preoccupation with this perceived ill is affecting his sleep. Randomized controlled trials (RCTs), he laments, are woefully inadequate assessments of the efficacy of a new procedure or drug. Their cautiously exclusive design coupled with their reflexively inclusive uptake, he says, produce a reality that's as ineffective as it is scary. "I worry," the Sunnybrook Research Institute (SRI) associate scientist says, again and again, from his fourth-floor office. "I worry."

Randomized controlled trials are generally accepted as the most unbiased measures of efficacy for new interventions, drugs or devices. Informally, RCTs have been the de facto approach for appraising how well an upstart therapy for a "condition of interest" performs against the status quo, as represented by the placebo, for decades. But, as Fowler showed in a paper published in 2007 in *The Journal of the American Medical Association*, the very restrictive RCTs aren't always the best way to advance medical science.

In their aim to investigate those people with the greatest chance of benefiting and the smallest chance of suffering ill effects from an intervention, RCTs generally pass over a chunk of the populace (often, says Fowler, with poor justification) that includes children, women, the elderly and those with common medical conditions. This reality, says Fowler, combined with the fact that the results published in major medical journals don't always explicitly report exclusion criteria, produces a scenario that may impair the effective application of RCT results to the entire clinical population of interest, a concept called "generalizability."

"You whittle down the potential population to a very small subset of patients who are predominantly male," he says. "You end up with a very homogeneous [group] and, typically, not people many doctors are treating." What's more, he says, doctors generally respond to the positive results of a study with increased prescription of the drug in question to a wide-ranging audience — including those left out of the research. These trials, says Fowler, are designed to be accurate with regard to internal validity, or the extent to which systematic error — or bias — is minimized in RCTs. "But the external validity [or the extent to which the results are a legitimate foundation for transfer to other clinical circumstances] is questionable."

Dr. Merrick Zwarenstein, senior scientist and director of the discipline of combined health services sciences at SRI, as well as chair of Sunnybrook's Centre for Health Services Sciences, shares Fowler's concerns. "The vast majority of the more than quarter-million [RCTs] were done in a fashion designed to maximize the chances of getting a positive result on the investigative drug or device," he says. "The answers given by these selective trials are often misleading for real-world decision-making."

"I worry," Fowler says, "that, as much as we consider ourselves a sophisticated medical community in 2008, 50 years from now people will look back and see terrible shortcomings in the work we do." Still, he has hope. He suggests that reporting the results of clinical trials more transparently, with data about their participants featured in a table as opposed to small print, would help. So, too, would the endorsement by the CONSORT group, an international collection of medical journal editors dedicated to improving the methods and reporting of RCTs, of a set of guidelines that insists upon the adherence to more comprehensive trial practices before RCT results can be published. Either way, Fowler says, raising awareness about this deficiency in the way the medical world approaches its trials, "is the most important thing." LP

Fowler's work was supported by the Ministry of Health and Long-Term Care's Career Scientist program and Sunnybrook Research Institute.

Dr. Rob Fowler

STAYING ALIVE

Two Schulich Heart Centre doctors work to keep the beat for cardiac patients

DR. JACK TU INVALIDATES A DEAL-BREAKER FOR HEART SURGERY DEVICE WITH EVIDENCE THAT IMBUES IT WITH RENEWED CREDIBILITY

The car was late and Dr. Jack Tu was starting to panic. Tu, a senior scientist at Sunnybrook Research Institute, was bound for Bloomberg TV, a business network whose Toronto office was awaiting the stock-shaking news this science-minded guest promised to deliver. But with the car lost and the clock ticking, Tu found he was reduced to a race into the financial district as a passenger in a Sunnybrook media relations officer's car. Just under the wire he arrived, with time only to get outfitted with an earpiece and installed in a studio before setting about turning the lucrative and closely watched world of cardiac surgical devices on its head.

The news that Tu, who's also a practising internist at Sunnybrook and holder of the Canada Research Chair in Health Services Research, shared with the world that 2007 September day was that drug-eluting stents — once the darlings of the cardiac surgery set but dismissed when their safety was thrown into doubt — were darlings once more.

Before stents revolutionized this arm of medicine 20 years ago, 30% to 40% of angioplasty patients' arteries reclogged within one year of the procedure. With no interventional fix available, the patient had to undergo emergency bypass graft surgery. "It was the biggest problem with angioplasties," says Tu. "Scar tissue would form and chest pain would return."

A stent is a metal tube that's inserted into the coronary artery after balloon angioplasty (the technique of widening a narrowed or totally obstructed blood vessel; tightly folded balloons are passed into the narrowed locations and inflated) to stop the once-blocked artery from closing again. In France in 1986, the first stent was put into a human coronary artery. Eight years later, the Food and Drug Administration (FDA) approved stents for use. In response, the rate of postsurgery blockage there dropped to 20%.

The first stent was bare metal. Its fine wire mesh allows blood to pass through but prevents scar tissue from forming and jamming the artery. Drug-eluting stents were introduced to Ontario hospital rooms in 2003. An improvement on their predecessors, they were a departure from the purely mechanical approach to postsurgery therapy, and capitalized on pharmacologic advances. Drug-eluting stents are coated with drugs that leach into the patient's bloodstream over the three months following a surgical procedure.

In the U.S., physicians embraced the improved stents, and had increased by 2004 their use to about 90% of all stent procedures. Encouraged by their promise but concerned about their price (about $3,000, compared with $600 for bare-metal stents), the Ontario Ministry of Health and Long-Term Care nominated a 60-40 split for stent coverage, favouring the bare-metal variety, in September 2003. Cardiologists were to use the more expensive version for their high-risk patients: those with diabetes, longer-duration blockages of the arteries or smaller vessels. This determination of eligibility made for some "difficult conversations with patients," says Tu, but doctors here nevertheless joined the world in their enthusiasm for this innovation, and the international market for them exploded.

Then came the crash.

At a European Society of Cardiology meeting in September 2006, a group of Swiss scientists presented a paper that claimed drug-eluting stents increased patients' risk of postoperative heart attacks from blood clots forming around the sticky metal in the artery. With some six million drug-eluting stents implanted in patients at the time, this revelation incited a kind of panic. In December 2006, the FDA convened a hearing to which they invited international experts. A group of Swedish scientists presented data there that showed a 30% higher risk of dying with these new models than with the bare-metal variety. The mood among cardiologists, Tu says, remained "scared."

Dr. Gerald Cohen and Dr. Jack Tu

In Ontario, the government makes it a condition of funding that data be collected on every patient outfitted with either type of stent. These data, housed in the Cardiac Care Network of Ontario, could provide the means for a real-world evaluation of the effectiveness of drug-eluting stents, Tu realized. Using a tool he developed called the propensity score-matching technique, Tu paired bare-metal-stent with drug-eluting-stent patients according to identifying characteristics, including age, sex, cardiac history and other medical conditions. These statistical methods, he says, were superior to those used in the Swedish study.

But more than comprehensive and sophisticated, Tu's study was groundbreaking. For drug-eluting-stent patients who were given blood thinners for one year after surgery, the risk of postop heart attacks was the same as for patients with bare-metal stents. What's more, Tu found that the mortality rate was lower for drug-coated-stent patients.

The response was immediate. The media jumped on it, and in the markets, where stents are a $6-billion-a-year business, the freefall among drug-eluting stent manufacturers' stocks halted and started the climb back. Other scientists have published studies confirming Tu's research since, and neither of the cart-tipping original studies' findings has been duplicated. In the U.S., a resurgence in drug-eluting stents' usage now puts this segment of the market at almost 70%. "They've come back into vogue as a result of our work," says Tu, whose study was named one of the American Heart Association's top 10 research advances in the field of cardiology in 2007. "It's exciting to be doing science that affects practice."

HEART ATTACK PATIENTS LIVE LONGER IN REGIONS WHERE MEDICINE IS A FIRST RESORT OVER SURGERY —BUT CARE ISN'T DELIVERED AS DISCRIMINATELY AS IT MIGHT BE

The question of how successfully a person will rise from his misfortune, it turns out, has much to do with where he was when he fell.

Drs. Dennis Ko and Jack Tu explored this premise in a widely cited 2007 *Circulation* paper that compares quality of care and outcomes of heart attack patients in the U.S. and Ontario. At the end of this, the most comprehensive study ever conducted on the subject, they concluded that it's better to be stricken in Ontario or the northeastern U.S. than anywhere else.

Taking advantage of the clinical data available to them through the Canadian Enhanced Feedback for Effective Cardiac Treatment project (one of the largest initiatives in the world looking at quality of cardiac care), and the Department of Health and Human Services in the U.S., the researchers looked at the medical experience of a person felled by an acute myocardial infarction (AMI), including occurrence of surgery and prescription of drugs. With their American counterparts, Ko and Tu collected data over two years, culling stats from almost every hospital in Ontario. Their objectives were clear: to determine, first, whether one country uses more procedures than the other; and, second, to consider its effect on the outcomes.

That there are higher rates of procedure use in the U.S. was no surprise to the scientists. Recent research had suggested that American practitioners are fonder of invasive procedures—like angiograms, angioplasties and bypass surgeries—for treating AMI patients than are Canadian physicians. But in Ontario and the northeastern U.S., it's

AFTER ALL, SAYS KO, HE AND HIS COLLEAGUES HAVE PROVEN THAT THE IMPACT OF MEDICATION ON MORTALITY IS PROBABLY GREATER THAN THE IMPACT OF SURGERY.

Drs. Jack Tu and Dennis Ko

a different story. There, clinicians were revealed to engage in relatively low use of invasive procedures and high use of evidence-based medication, like beta blockers, cholesterol drugs and aspirin.

The outcome of these treatments was the punctuation to Ko and Tu's research: patients treated for AMI in Ontario and the northeastern U.S. fared much better than those treated in the rest of the U.S. Elsewhere in the U.S. doctors are doing more invasive surgery and, say the scientists, more patients are dying.

The connection between higher rates of invasive surgery and death from AMI is as important as it is tricky to explain. Ko — a scientist at Sunnybrook Research Institute and interventional cardiologist at Sunnybrook's Schulich Heart Centre, and Tu — a senior scientist at the research institute, practising internist and holder of the Canada Research Chair in Health Services Research — speculate on possible reasons, including better access to medication and outpatient care in Canada, healthier lifestyles among the older citizens of Canada, and increased exposure to the risk of death that comes with every surgery. What's more, says Ko, centres that do a lot of procedures tend to underemphasize medication use.

The clinical revelations to be extracted from this research are revolutionary. After all, says Ko, he and his colleagues have proven that the impact of medication on mortality is probably greater than the impact of surgery. "It's an argument against doing lots of procedures," he says. "It gets to questions of efficiency. Invasive therapies like angiograms are very expensive. Medication is cheap and easy."

Curious about the details of such revolution, Ko followed up with "Regional variation in cardiac catheterization appropriateness and baseline risk after acute myocardial infarction," published in 2008 in the *Journal of the American College of Cardiology*. Here, he sought to understand the specifics of the regional variation his earlier research identified. "If you're using it a lot, are you using it appropriately and on the patients who would benefit the most?"

The answer surprised him. Patients at higher risk for problems, and those with more appropriate indications for surgery (positive enzymes in their blood or limited life expectancy, for example) are the ones who might benefit the most from an invasive strategy after having an AMI. But they aren't the focus of clinical attention on this front. When Ko looked at geographic regions where highly invasive procedures are the norm, he found that physicians don't discriminate among their patients when determining candidates for surgery. Procedure selection, he says, "is not based on whether a patient will benefit; it's likely based on availability. Physicians aren't performing the procedures according to the needs of the patient."

From a policy angle, says Ko, this news is big. "We need to examine physician practice to ensure that procedures are performed appropriately." In the U.S., spurred by money-focused health maintenance organizations, a movement has begun to create guidelines on appropriateness (first for diagnostic procedures like echocardiograms and stress testing; up next is cardiac revascularization). "I hope Canada will follow suit," Ko says, because despite Canada's lower utilization of invasive procedures, "the field is changing rapidly, and as the volume of procedures goes up, the potential for inappropriateness also increases. It's simple. Appropriateness criteria are linked to benefits. If the medical community is performing more appropriate procedures, outcome is better." LP

Ko's and Tu's research is funded by the Canadian Institutes of Health Research in Canada, and the Department of Health and Human Services in the U.S. Tu holds the Canada Research Chair in Health Services Research. Ko is supported by a Heart and Stroke Foundation of Ontario Clinician Scientist Award.

GOOD ALTERNATIVE FOR BAD SURGERY

ACE inhibitors, an established defence against hypertension and heart disease, get a new role

Abdominal aortic aneurysm is a common and dangerous condition without a clinically proven nonsurgical therapy. Defined as an expansion greater than 150% of the normal diameter of the abdominal aorta—the artery that carries blood away from the heart, supplying the lower part of the body—the disorder is less common in women but afflicts from 4% to 8% of men aged over 50 years. One-third of those men and women, if left untreated, will suffer aortic rupture, and most of them will die.

The pressing need for a treatment is clear, especially in Canada and other countries with a rapidly aging population, and in 2006 Dr. Donald Redelmeier and colleagues addressed that want with an observational study showing that angiotensin-converting enzyme (ACE) inhibitors might be a solution for some patients. Published in *The Lancet*, the study looked at more than 15,000 patients over a 10-year period and found that those receiving ACE inhibitor therapy had an 18% lower risk of rupture than patients not on the medication. "Though not a panacea, ACE inhibitors could be offered to patients who are not fit for surgery, for example, or who just don't want to go through a major operation," says Redelmeier, director of clinical epidemiology at Sunnybrook Research Institute and holder of the Canada Research Chair in Medical Decision Sciences.

Surgical repair, previously the only validated alternative for patients choosing a preemptive approach to potential rupture, is a "distinctly unpleasant form of surgery," says Redelmeier, "often complicated by devastating outcomes—strokes, heart attacks or prolonged recovery." That ACE inhibitor therapy is now an option for eligible patients (those with an aneurysm of a given size and without competing medical conditions, among other criteria) was echoed in a commentary by two experts on diseases of the circulation that accompanied Redelmeier's article in *The Lancet*: "On the basis of insight from animal models and results from this study, we also favour ACE inhibitor treatment."

What surprised Redelmeier was less the efficacy of ACE inhibitors and more that the nature of their effect in animal studies seemed to extend to humans. Preclinical studies had suggested that the protection against rupture was coming from a blockage of angiotensin II, a naturally occurring substance in the body that alters connective tissues, as opposed to lower blood pressure, the latter suspected by some researchers as a cause of the reduced risk. Redelmeier's study was consistent with these findings, showing the benefit conferred in aortic aneurysm was exclusive to ACE inhibitors and not found with other blood-pressure-lowering agents such as beta blockers or diuretics.

While this insight may spur further molecular investigation into the enigmatic mechanisms involved in ACE inhibitor efficacy, the results of Redelmeier's study should renew interest in ongoing randomized controlled trials testing patients with aortic aneurysm. "I hope our science helps in terms of recruiting into those trials," says Redelmeier. "It certainly raises awareness for potential future studies and provides valuable data on sample size calculations and how such a study could be designed." Perhaps most encouraging for researchers and patients, those studies could be done any time because ACE inhibitors are generic, readily available and affordable. JO

Redelmeier's work is supported by the Canada Research Chairs Program, Canadian Institutes of Health Research, National Institutes of Health (U.S.) and Sunnybrook Health Sciences Centre.

Dr. Donald Redelmeier

Cited!

Dr. Bill Geerts

It's one of the most cited papers in medicine, and its lead author, Dr. Bill Geerts, calls the changes to clinical practice that it has inspired a gratifying reward for a 22-year career. "I'm not solving world hunger or curing cancer," he says, "but presumably fewer people are dying because of me." That's thanks to his leadership in producing the seventh "Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines," the 2004 version of which was cited more than 2,200 times.*

Every three years since 1986, international experts have produced a set of guidelines for the management of venous thromboembolism (VTE), a potentially life-threatening disorder that includes deep vein thrombosis (abnormal clotting of the blood in deep veins, most commonly in the leg) and pulmonary embolism (when a deep vein thrombosis travels into the lungs). The experts appraise the recent literature on the subject ("I'd bet my house there's not a single important paper we haven't covered," says Geerts) and make recommendations for practice. A Grade 1A recommendation is the highest level, with the number indicating the reviewers' strength of conviction about the reference, and the letter indicating the quality of evidence supporting it.

Geerts has led the guidelines on the prevention of VTE for the past 10 years, including the eighth edition, which was published in June 2008. "This is the most important contribution I've made in my career," he says, of his efforts to prevent blood clots in hospital patients. Sweeping an arm across 24 filing cabinet drawers that contain "virtually every paper on the prevention of VTE ever written," he admits to the trait that's made him the preferred author for the last four iterations of the guidelines: "I'm super-obsessive," he says. LP

* Google Scholar, October 26, 2008.

Dr. Bill Geerts is a senior scientist in the discipline of clinical epidemiology at Sunnybrook Research Institute and director of the thromboembolism program at Sunnybrook Health Sciences Centre. He is also a professor of medicine at the University of Toronto.

COMMERCIALIZING RESEARCH AND BRINGING BREAKTHROUGHS TO PATIENTS

THINK CLINICALLY, ACT COMMERCIALLY

Two SRI physicists develop and market a novel treatment for prostate cancer

In spring 2007, Raphael Ronen was looking into the commercial potential of several medical science technologies that had emerged from research at the University of Toronto (U of T). A number of the projects looked promising, but one—magnetic resonance image (MRI)-guided ultrasound therapy for prostate cancer—left him particularly excited and puzzled. "It seemed too good to be true," recalled Ronen in an airy conference room at the MaRS Centre, the glass, steel and brick hub of Toronto's medical science-meets-biotech Discovery District. "I felt there had to be something wrong with it, because it was such a good technology. I was really blown away." Ronen, a life sciences commercialization manager at The Innovation Group, which handles technology transfer for U of T and some of its affiliated research institutes, including Sunnybrook Research Institute (SRI), examined the new concept closely. Looking for flaws, assessing its patents and patent space (competing patents for similar technology, of which there were few), he concluded the technology was sound.

Dr. Michael Bronskill, Raphael Ronen and Dr. Rajiv Chopra

The only explanation he could see for why such a well-developed system wasn't already commercialized was that its inventors—SRI imaging physicists Drs. Michael Bronskill and Rajiv Chopra—hadn't been exposed to the investment community. "Where other people might have been promoting their technology, looking for partnerships," Ronen explained, "Mike and Rajiv were just working away below the surface. They're very, very low key." That was good news for Ronen. "It's probably the biggest undiscovered gem I've found," he says.

Magnetic resonance imaging-guided transurethral ultrasound may prove even better news for men with localized prostate cancer. The technology, which Bronskill and Chopra developed over 12 years at SRI, enables precise, MRI-guided focusing of heat-generating ultrasound to coagulate targeted cells while leaving surrounding healthy tissue intact. Bronskill and Chopra are working to translate the technology for clinical use via Profound Medical Inc.—a startup company formed in 2008—to offer patients a therapy with fewer side effects than those associated with existing clinical options, particularly prostatectomy (surgical removal of the prostate), and external-beam radiation therapy. Those treatments often result in side effects that significantly disrupt life after treatment for many men.

Statistics vary depending on the nature and degree of treatment, but most men who undergo prostatectomy will have erectile dysfunction, and about one in three will suffer urinary or bowel incontinence, diarrhea or rectal bleeding. Drug therapy, physiotherapy and other rehabilitation techniques can relieve these side effects, but with limited success. A large *Journal of the National Cancer Institute* study published in 2004 found that 79% of men treated with prostatectomy and 63% given radiation had some form of impotence five years after treatment; 15% of the prostatectomy patients were incontinent, as were 4% who received radiation.

Adding urgency to this quality-of-life issue is a surge in the number of men diagnosed with prostate cancer, owing in part to more screening and better detection techniques. Diagnoses, based primarily on biopsies, jumped fourfold from 1983 to 1992, according to a 1995 study in *The Journal of the American Medical Association* that looked at rates before and after widespread implementation of the prostate-specific antigen test (a standard screening tool, as is digital rectal exam). The study found a dramatic rise in diagnoses among younger men, especially those in their 50s. Prostate cancer is now the most common cancer in Canadian men, an estimated 24,700 of whom will be diagnosed with it in 2008.

The growing cohort diagnosed with the disease at a relatively young age has complicated physicians' treatment decisions. "When it was a disease of someone 75 or 80 years old—not that it was acceptable—it was less of a dilemma to deal with," says Chopra, in his office at SRI. "Whereas with someone in their 50s or 60s, the prospect of wearing absorbent pads or having bowel problems for the rest of their life—that can't be ignored." Consequently, patients and clinicians are facing a predicament: most men diagnosed with prostate cancer will not die from it, because usually it's slow-growing and remains localized in the gland; yet, roughly 90% choose some form of aggressive treatment, risking distressing side effects. There is swelling clinical interest in "watchful waiting," which foregoes invasive treatment while the disease remains low-risk, but this shift hasn't greatly affected the number of men who choose more aggressive treatment.

Chopra, a young scientist with a brisk but gentle manner, has studied ultrasound and its potential for cancer therapy since he was a graduate student in Bronskill's lab in the mid-1990s. He acknowledges the rationale for treating prostate cancer aggressively, given the dire consequences of metastases, but he says there is growing interest in treating only parts of the gland—an approach that the precision of the transurethral ultrasound applicator may bring to fruition. The applicator is inserted into the urethra through the penis and into the prostate gland. Its end contains a column of transducers, powered electronically to emit high-intensity ultrasound. "By adjusting the number and size of transducers, rotating the device, and modulating the power and frequency of each transducer," says Chopra, "we control for length and depth to create a 3-D pattern of energy and heating. That's where the precision comes in."

The treatment is performed inside an MR imager, a technical advance that Chopra says took years of experimentation, given that ultrasound and MRI are disparate technologies that typically interfere with each other. During treatment, magnetic resonance imaging provides noninvasive 3-D temperature images of the prostate every five seconds. A separate computer system automatically analyzes and processes those temperature images, and incorporates them into algorithms that in turn control and adjust the device, under supervision by the treatment team. The system creates what Chopra calls a feedback loop—sophisticated, elegant and precise. Additionally, MRI profiles the treated gland right after treatment using contrast agents to detail coagulated tissues and halted blood flow, providing immediate treatment validation.

Compared with transrectal ultrasound, a similar first-generation technology approved by Health Canada and offered at some clinics in Toronto, this new treatment has several advantages. It's faster (about 30 minutes versus three hours for transrectal ultrasound) and provides real-time visualization of the heating generated in the prostate gland and surrounding tissue. The scientists foresee the treatment requiring only a spinal block, which would make it a day procedure. Also, the older technology is delivered somewhat blindly. Using pretreatment ultrasound images, the transrectal technology coagulates tissue about the size of a grain of rice, waits for several seconds, moves, and then targets another area of similar size, hundreds of times. The device is unable to adjust for swelling and gland movement during the procedure, so treatment tends to cover a larger area, running greater risk of damage to healthy tissue. Chopra and Bronskill have

Dr. Rajiv Chopra, Raphael Ronen and Dr. Michael Bronskill

Prostate cancer is now the most common cancer in Canadian men, an estimated 24,700 of whom will be diagnosed with it in 2008.

shown in preclinical models that their technology accurately targets tissue to within one millimetre, which should mean fewer side effects. Moreover, it costs less than transrectal ultrasound.

Picking up a prototype applicator from a bench in his lab at SRI, Bronskill moves toward an adjustable MRI-compatible brass and plastic mount. "We can't at this point claim side effects are lower because we have no clinical data yet," he says. "One of our goals with Profound during the next year is to get this therapy to a clinical trial. Envisage—whoops!" Water streams out the probe's end onto the floor near an empty seat. "Aaron will want to know why there's a puddle by his chair," says Bronskill, as members of his lab look on. "It'll be dry by the time he shows up," he chuckles.

Bronskill is affable, especially with his lab group, as at ease discussing the breezy hotspots that fuel his windsurfing passion as the technology of ultrasound, and that quality serves him well as an academic physicist. Matthew Asselin, a research assistant responsible for software and hardware integration who has worked for Bronskill for two years, says he is easy to approach and doesn't run his lab as a hierarchy. "He affords us a good amount of experimentation, probably more than we'd get in the private sector," says Asselin, who adds that at first he found the hands-off approach too loose, but now believes it produces results, especially when shaped by Bronskill's guidance at weekly lab meetings.

Bronskill studied math and physics before doing a PhD in the department of medical biophysics at U of T in the early 1970s. Now a professor in that department with cross-appointments in medical imaging and physics, he wasn't always keen on commercialization. "Fifteen years ago, I probably couldn't have seen myself involved in a venture like this," says Bronskill of Profound. "What I've learned in the interim—and you might argue I've been a slow learner," he laughs, "is that there's really only one road for taking a new medical device or technology through to clinical application, and that is through commercialization."

The target when he and Chopra began their project 12 years ago, with basic-science funding from the Terry Fox Foundation, was not the medical device market or prostate cancer specifically. That early-stage high-risk funding enabled them to explore the feasibility of this concept as a general therapeutic tool. Then, as the technology matured, it became clear that commercialization was the only way to get their innovation to patients. A $500,000 commercialization grant from the Ontario Institute for Cancer Research (OICR) that triggered immediate venture capital interest in the formation of Profound drove the point home. "Basic scientists tend to regard commercialization as a bad word," says Bronskill, "but the harsh realities are that no hospital will take the financial risks of implementing a clinical trial with a new technology, whereas a startup company will."

Back at MaRS, Ronen, who was instrumental in securing the OICR grant, says that Bronskill and Chopra "get" commercialization. They had already pushed the physics of their technology beyond early prototypes when Ronen first saw their work, incorporating miniaturization and human factors to make the whole therapeutic system function effectively. "That's rare in an academic setting," he says. "Many scientists lose interest before that point, because it's not about publishing key papers." Bronskill and Chopra are still focused on publishing, but see it and commercialization as two halves of the same whole. "Research is about testing new ideas and hypotheses, demonstrating if they work," says Chopra. "But we can't get to patients without commercialization, so I'm happy about Profound. It's enabling us to see the fruits of our research."

The Canadian Institutes of Health Research, Ontario Institute for Cancer Research, Ontario Research Fund-Research Excellence, Ontario Research and Development Challenge Fund and the Terry Fox Foundation through the National Cancer Institute of Canada funded this work. The Canada Foundation for Innovation and Ontario Innovation Trust provided infrastructure support.

STAUNCHING THE FLOW

Scientist looks to commercialize a wound-healing compound that mimics regenerative blood growth

"We're trying to find money," says Dr. Dan Dumont, aiming straight for the point in an explanation of where he sits with his efforts to bring to market a line of synthetic compounds that make blood vessels grow artificially and promote the healing of wounds. To increase his chances of same, this director of the discipline of molecular and cellular biology at Sunnybrook Research Institute (SRI) and holder of the Canada Research Chair in Angiogenic and Lymphangiogenic Signalling, has launched his own commercial spinoff company, Biellette Therapeutics. He's done so, he says, in the hopes that it will "open new doors for funding from government agencies." The lead compound at Biellette is called Vasculotide, and it's being heralded as revolutionary in its demonstrated ability to heal wounds in genetically diabetic mice.

"Vasculotide provides a way to produce a substance that has the activity of the natural growth factor," says Dumont, "but we can make it completely synthetically. From that perspective, it's cheap to make, and you can alter it to make it more of a clinically relevant drug."

The first indication Dumont is targeting for this clinical relevance is chronic wound care in diabetes, partly "because it's such a growing issue" and partly because Dumont believes U.S. Food and Drug Administration approval is easier secured with a topical rather than an injectible drug. Dumont and his colleagues have shown that the application of this peptide mimetic to wounds causes blood vessels to grow and the wounds to heal more efficiently than they otherwise would do. Indeed, says Dumont, foot ulcers — infamously difficult-to-treat complications of diabetes — could heal completely with this innovation, and patients could benefit from greater mobility and quality of life.

Among the adverse effects of diabetes, complications with the blood vessels rank prominently. Fluctuating blood sugar levels compromise a person's vasculature, and infected injuries become chronic wounds that struggle to heal. "Diabetics have unhealthy blood vessels," says Dumont, "and that leads to all kinds of problems. One of them is that, if you get a wound and it gets infected, and if you don't get adequate blood flow to it, you can't get rid of the thing. And that sets up a whole cascade of events [that turn it into] a chronic wound. The idea is that you clean the wound, add Vasculotide to it and cover it to keep it moist. The Vasculotide promotes the growth of new blood vessels that aid in closing the wound and fighting infection there."

The second indication Biellette (French for a small connecting rod) is pursuing — and, says Dumont, "this may be the one that drives the development of the drug" — is acute lung injury or acute respiratory distress syndrome (ALI/ARDS), conditions that suffer from a lack of therapeutic options. For ALI, the product would be delivered as an injectible or an aerosol in nebutizers. "We believe Vasculotide will improve the ability of patients to recover from ALI/ARDS, which is fatal in almost 50% of those diagnosed with these conditions," the scientist says.

Another indication on which Dumont wants to test his innovation is diabetic retinopathy. People with diabetes frequently have issues with blindness, one of the underlying causes of which is the rupture of blood vessels in the retina. "This growth factor has been shown to prevent that." The kidneys also host an abundance of blood vessels, making them yet another weak spot for diabetics — and potential targets for Vasculotide.

Fed by a $150,000 investment from a proof of principle grant from the Canadian Institutes of Health Research, along with $115,000 from BioDiscovery Toronto and a $10,000 studentship from the Advanced Regenerative Tissue Engineering Centre

Drs. Dan Dumont and Jennifer Alami

This wide-ranging patent is critical for Dumont, who faces considerable competition with his innovation. Several companies produce "wound-care drugs" that are already in clinical trials. "It's a very crowded field," Dumont admits. But his is the only one that's able to grow blood vessels and bring supporting cells, like muscle cells, along for the ride.

at SRI, of which Dumont is a lead investigator, Biellette is still hat-in-hand. And Dumont's wish list for filling it is particular: "You want to use undiluted funding, mostly from a government agency or foundation. They're just giving it to you for the benefit of mankind, and aren't asking for payback or continued revenue stream."

"It's still in the very early stages of development," says Jennifer Fraser, director of commercialization, life sciences, for The Innovations Group at the University of Toronto, which handles technology transfer for the university and some of its affiliated research institutes, including SRI. She has been working with Dumont for the last couple of years on securing a broad patent claim so that, as the product moves forward, its 20 years of industry exclusivity will be protected.

This wide-ranging patent is critical for Dumont, who faces considerable competition with his innovation. Several companies produce "wound-care drugs" that are already in clinical trials. "It's a very crowded field," Dumont admits. But his is the only one that's able to grow blood vessels and bring supporting cells, like muscle cells, along for the ride. "For a blood vessel to grow and be functioning, it needs to induce supporting muscle cells to grow around it," he says. "Without them, the vasculature will be leaky and fall apart. To the best of my knowledge, ours is the only factor that can induce blood vessel growth and recruit those support cells."

The audience for his peptide mimetic is "huge," says Dumont, and growing by 250,000 a year. "The market is predicted to be about $6 billion annually, worldwide."

Just the same, says Fraser, the new corporate entity needs to sit tight for a bit, yet. "[Getting] this thing on the streets is still a good 10 years out," she says. What's more, she predicts that the researchers are still $2 million or $3 million away from being able to nudge the product into investigational new drug status, which would enable them to put it into clinical trials, and a full $80 million from getting it to market.

"I think a lot of this issue is just trying to generate that interest in investors," says Dumont. "They're always asking for the next step. They want to know: Have you tried it on a patient yet? But there's promise there, and I think they know it." LP

Dumont's work is funded by BioDiscovery Toronto, the Canada Research Chairs Program, Canadian Institutes of Health Research, and Ontario Research and Development Challenge Fund. Infrastructure support comes from the Canada Foundation for Innovation and Ontario Innovation Trust.

Cited!

Dr. Jorge Filmus

"Basic scientists," says Dr. Jorge Filmus, in defense of a profession that has served him well, "sometimes come across discoveries that revolutionize medicine." So it has been with Filmus, whose 2003 *Gastroenterology* paper, "Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma," has won him much notice. The paper, which identifies a new marker for the early diagnosis of one of cancer's most deadly strains, has attracted more than 158 citations in peer-reviewed journals in the five years since its publication.*

Filmus, whose research centres on the presence of a protein called glypican-3 that's bound to the cell membrane in the blood-streams of many patients with early-stage liver cancer, thinks the attention the piece has attracted is in recognition of the gravity of the disease his discovery helps to diagnose.

The average life expectancy for someone with advanced hepatocellular carcinoma — the most prevalent form of liver cancer, the third most frequent cause of cancer-related death and the fifth most deadly cancer in the world — is six months.

More often than not, liver cancer develops out of chronic hepatitis. In the Far East, some 30 million people suffer not only from this condition, but also from a dearth of tests that might uncover an incipient cancer sooner. By the time most liver cancer patients are experiencing symptoms, the cancer is too far-gone to make it go away. "The trick," says Filmus, "is to get it early, while surgical treat-ment could be effective."

Introduced slowly to the clinical landscape, the glypican-3 test — licensed by Sunnybrook Research Institute to BioMosaics, an American biotechnology firm — is still imperfect, and the subject of regular revisions to its sensitivity and robustness. The improvements are critical, says Filmus, who estimates that 300 million people worldwide suffer from chronic hepatitis. "That's big," he says. "This is a tool that can save a lot of lives." LP

* Google Scholar, October 26, 2008.

Dr. Jorge Filmus is a senior scientist in the discipline of molecular and cellular biology at Sunnybrook Research Institute and an associate professor in the department of medical biophysics at the University of Toronto. He is also a career scientist with Cancer Care Ontario.

Current funding comes from the Canadian Breast Cancer Foundation, Canadian Institutes of Health Research and the Ontario Institute of Cancer Research.

BUILDING CAPACITY AND FORGING PARTNERSHIPS

BALANCING ACT

Teaching the next generation of clinician-scientists to straddle bench and bedside

Training to become a clinician-scientist is difficult, expensive and time-consuming. But for Drs. Amanda Caissie and Michael Rauh, two Sunnybrook Research Institute (SRI) trainees who each have their MD and PhD degrees, practising medicine and being a researcher was not an either-or proposition. Caissie and Rauh were warned about the difficulty of this two-pronged profession but were determined to pursue both passions.

Caissie is in the second year of a five-year residency in radiation oncology at the University of Toronto. Her supervisor is Dr. Greg Czarnota, a clinician-scientist at SRI, who spends four days of the week doing research on ultrasound imaging, and one day treating women with breast cancer at Sunnybrook's Odette Cancer Centre. As a co-supervisor, Caissie has chosen Dr. Shun Wong, another SRI clinician-scientist with gastroenterology as a clinical focus, and radiation central nervous system effects as an area of research expertise.

Finding the right supervisors was extremely important to Caissie, and the deciding factor in doing her research at Sunnybrook. In addition to weekly face-to-face meetings where she can discuss clinical issues or bounce research ideas off Czarnota and Wong, Caissie values the informal mentoring she receives by observing them at work: "Even if I didn't do experiments, I'd still learn a lot from them because I learn how they write grants, how they write papers, how to manage time, and balance between the clinic and the research," she says. Indeed, not allowing work to consume him has proven tricky for Czarnota. "What's challenging is striking a balance between work and life, which can easily become nonexistent," he says half-jokingly. "It really is two full-time jobs."

Caissie took her PhD from McGill University, defending her dissertation while completing her medical degree at Queen's University. Besides hard work, training to become a clinician-scientist requires a staggering investment of time and money. Caissie calculates that by the time she finishes her postdoctoral fellowship (which she will do after her residency) the process will have taken 18 years.

Debt is another major issue for these students, whose loans can reach hundreds of thousands of dollars. Moreover, Caissie must deal with the uncertainty of where she will work and eventually settle down, which in turn affects family planning. Dr. Richard Wells, director of the Odette cancer research program at Sunnybrook and an oncologist specializing in hematology, took out loans to pay for child care and groceries as he and his wife completed their postdoctoral fellowships. "Organizing a family around such long training is a challenge. There's no doubt about it. But it can be done. We did it—probably the worst way—and we still got through," recalls Wells.

For trainees, hearing honest feedback regarding the process from other clinician-scientists is a valuable aspect of mentoring. "Sometimes it's about talking to the people who will be frank and tell you, 'This is not going to be easy. These are the obstacles you're going to face, and this is what you can do to get through.' Finding someone who will understand your limits and push you is a big thing," says Caissie. She is fortunate. When Czarnota was completing his training only a decade ago, there were few people in his field who had chosen the same path: "When I went through there was just

Dr. Amanda Caissie

Drs. Richard Wells and Michael Rauh

one [clinician-scientist] in the whole department of radiation oncology in Toronto, whereas now here at Sunnybrook there are eight, and probably another 10 downtown, so there's more opportunity for young people to have guidance."

In spite of the sacrifices and second-guessing—"People told me I was crazy to go to med school," recalls Caissie—there is little she would do differently. In hindsight, she says she might have kept up with her research during medical school, but questions whether this would have been possible given the demands of her studies. Her goal is to have her own biology lab, devoting 80% of her time to research and 20% to treating patients (as her mentors do), but she acknowledges that this neat division of labour doesn't always correspond with the reality of caring for very sick people: "It's never just 20%. You can't just leave a patient if something comes up."

It is this movement from bench to bedside that for Czarnota defines the work of a clinician-scientist: "I think of it as integrative research—integrating aspects of the basic science world with aspects of the medical world, and coming up with a unique way of operating and thinking. You know what the pertinent questions are from the clinical side, and you know what's available and where to focus on the laboratory side and you're integrating the two."

Maintaining this dual focus on the lab and the clinic was something Rauh, now a second-year resident in hematology training under Wells, learned to do while completing the MD/PhD program at the University of British Columbia. His supervisor at the Terry Fox Laboratory in B.C., though supportive of Rauh's goals, had seen student attrition from the program and advised him about the difficulty of trying to do both degrees. Aware of the potential for burnout, as well as the pressure of competing with others focused solely on research or medical school, Rauh developed a strategy for getting through the program: keep up with his research, rather than put it on hold and strive for perfect test scores. "The [main] challenge is feeling that you don't belong to one thing completely. The other challenge is trying to maintain research while doing medical studies, or trying to study for exams while doing experiments. It involves compromise, organization and balance," he says.

With his residency concluding in 2011, Rauh's training will have taken 19 years. Although he could have taken a position sooner, Rauh does not regret pursuing both designations. On the contrary, he views the experience as "holistic," and values the opportunity to be a "bridge between the research community and pure clinicians." Wells agrees, and describes how clinician-scientists are uniquely positioned to ease this communication: "There has to be some transition where basic science knowledge is translated into clinical knowledge, and that's hard because clinicians and basic scientists don't speak in the same terms, don't understand things in the same way. I think it's part of our responsibility to bridge that chasm."

Rauh, who also views mentoring as a critical aspect of his training, is grateful to be working with Wells, who shares with him his expertise and resources. Under Wells' supervision, Rauh sees patients at Sunnybrook with blood production disorders, specializing in myelodysplastic syndrome, a precancerous condition in which the formation of blood cells in the bone marrow is impaired. Wells is trying to arrange for Rauh to do rotations with renowned experts in myelodysplastic syndrome—educational opportunities for which Rauh is very appreciative.

It will be years before his training is complete, but Rauh is optimistic about the contributions to health care that he and others who choose to pursue this lengthy path may make: "There are so many opportunities for people to apply an exciting career in medicine as a clinician-scientist and within their lifetime see the true impact of their work—to see things translated into improved care for patients." AK

THE GOOD FIGHT

Colin and Barbara Watson applaud scientific investigation at SRI with a donation earmarked for research

While living in Vancouver as a young man, Colin Watson's father, Harry Homer Watson, enlisted with the Princess Patricia's Canadian Light Infantry. He served from 1939 to 1945, first in the United Kingdom, next in the invasion of Italy in 1943, and then in the subsequent actions in France, Holland and Germany, post D-Day. The senior Watson died in 1960, partially, his son suspects, from war-related ailments.

But for all that his father gave, Colin Watson is determined to give even more.

Today, this Toronto philanthropist keeps his dad close through donations — both in time and in money — to Sunnybrook Health Sciences Centre. Indeed, it was largely because of its strong tradition as a veterans' hospital that Sunnybrook captured the attention and beneficence of Colin and his wife Barbara a dozen years ago when they were seeking a home for their charitable efforts.

The Watsons' relationship with Sunnybrook began in 1996, when Sunnybrook Foundation invited Colin, then CEO of Spar Aerospace, to become a director. He accepted and invested several years in the post. Also around that time, the couple began to invest in the hospital materially, passing generous contributions across the philanthropic divide.

All told, the Watsons have bestowed some $250,000 of their own money to Sunnybrook's cause over the last decade. "There's so much that needs to be done," says Barbara. "Some of the patient care areas definitely need to be renovated. They're old and out of date. The quality of the environment needs to match the quality of care."

The Watsons' most recent donation — $130,000 — was their most sizeable. It was unique, too, for being the first one the couple allocated to a particular destination at the hospital.

"We asked that it go to [the] research department," says Barbara, who was thrilled to participate in a recent tour of the hospital's research arm, Sunnybrook Research Institute. "I think research generally is very important. I have a daughter who is diabetic. I think what they're doing with stem cell research at Sunnybrook Research Institute is very important and that it, down the line, will help people with diabetes, along with a whole lot of other things, as well."

The promise that lives in this area of the hospital, says Colin, is "staggering." Now retired, he peeks in on it from his seat on the finance committee of Sunnybrook Foundation's Governing Council, a position he's held for the last four years.

But it's the hospital's military legacy that persists as a theme in the Watsons' accounts of their Sunnybrook experience. "It's probably one of the more mundane aspects of the hospital," says Colin, who has lovingly catalogued his father's wartime artifacts for his grandchildren's eventual safekeeping. "But my father spent five years with the military overseas and suffered badly for it. I like to think that his colleagues are well looked after at Sunnybrook." LP

Barbara and Colin Watson

"There's so much that needs to be done," says Barbara. "Some of the patient care areas definitely need to be renovated. They're old and out of date. The quality of the environment needs to match the quality of care."

DR. JONATHAN RAST

IT TOOK HUNDREDS OF SCIENTISTS AND 10 YEARS TO SEQUENCE THE GENOME OF THE PURPLE SEA URCHIN. DR. JONATHAN RAST ON WHY IT WAS WORTH THE EFFORT

Q&A

Dr. Jonathan Rast

A sense of big time lurks behind Dr. Jonathan Rast's easy and laconic semi-drawl. Listening to Rast, the desire to grasp the temporal nature of his research—evolutionary years counted in hundreds of millions, human ancestry shared with creatures extinct or remarkably unlike ourselves—could drive even an earnest intellect to capitulatory indulgence in the mere visual splendour of his chosen experimental subject, the purple sea urchin. But that would be to miss out, at an especially exciting time in the evolution of science.

In 2006, 240 researchers from over 70 institutions announced they had sequenced the sea urchin genome; they published their initial findings in a special edition of the journal *Science*. Rast coordinated the immune-gene-sequencing part of the 10-year, $15-million project, and was lead author on a special-issue *Science* paper. A scientist in molecular and cellular biology at SRI, Rast outlines what the project has meant for his and other researchers' work.

Why is the sea urchin of interest to biologists?

The sea urchin's evolutionary relationship to us makes it uniquely useful for understanding our own genome. We both emerged from a common ancestor more than 550 million years ago, and although they're invertebrates [and we're vertebrates], they're close to us evolutionarily. Also, it's easier to observe gene networks in the relatively simple sea urchin embryo and larva, which have far fewer cells than do most other models or humans.

What does the sequenced sea urchin genome do for you?

It provides a parts list, to some extent, of what's in the genome, and it gives us better sensitivity to find homologues—genes that correspond to those in vertebrates like us. Ten or 15 years ago, when I looked for immune gene homologues in sea urchins, I came up against a wall. I know people who quit science because it was so frustrating. Now, it's all there in the genome, so it has really changed the whole playing field.

What can the sea urchin tell us about immunity?

Because it's relatively simple, the sea urchin larva is a good model for looking at how an immune system is set up in the context of the whole organism—systems biology. We can look at not only the genes that go on and off, but also at how they interact with the rest of the organism to allow immune function to take place.

What does the future hold?

Well, one thing that should really open up research on immunity, for us and other researchers, is high-throughput sequencing. Say we interfere with the function of an immune gene, trying to see what changes in an embryo. We can look at things we think might change, but we really want to find things we never guessed would be targeted by this gene. Until recently we used microarrays for this work; they're great, but limited in sensitivity. Now, we can just sequence everything that's turned on. Instead of muddy data from arrays, we can get digital-type data on number of transcripts per gene. And for the sea urchin it's great, because we don't have to know what's a gene and what's not. We can just reference it back to the genome. So I think there's going to be a revolution over the next five years in how we put together an understanding of gene networks. JO

Rast's work was funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Ontario Ministry of Research and Innovation. Infrastructure support was provided by the Canada Foundation for Innovation and Ontario Innovation Trust.

The sea urchin genome was sequenced at the Baylor College of Medicine Human Genome Sequencing Center; the project was funded by the National Human Genome Research Institute (National Institutes of Health).

CAPITAL PROJECTS

AT SUNNYBROOK RESEARCH INSTITUTE

IMAGING RESEARCH CENTRE FOR CARDIAC INTERVENTION

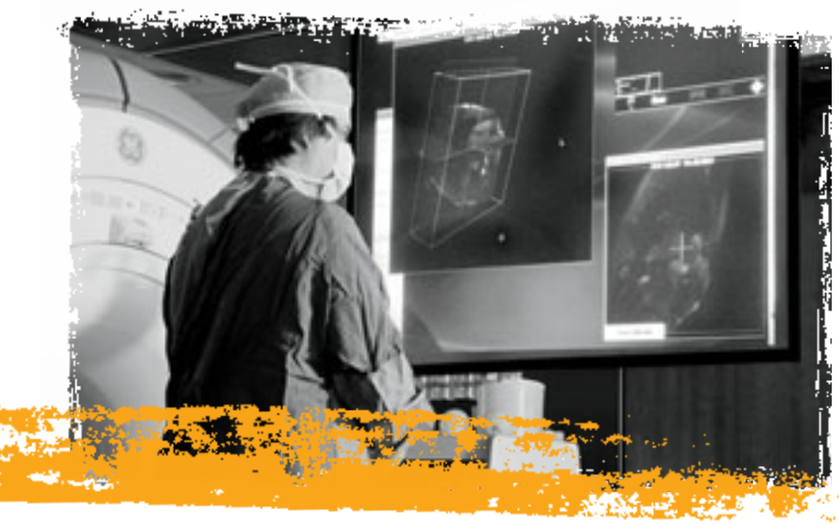
Launched in 2006, the Imaging Research Centre for Cardiac Intervention (IRCCI) is the first of its kind in Canada. This state-of-the-art facility located on Sunnybrook Health Sciences Centre's M wing integrates basic imaging science with clinical interventional applications to improve the assessment of cardiac disease and discover the best methods for cardiac treatment planning, therapy guidance and outcome evaluation. It combines the latest in cardiac imaging technology — including X-ray, magnetic resonance imaging (MRI), ultrasound and optical coherence tomography — to address the full spectrum of cardiovascular disease, from diagnosis, to guidance, to measurement of effectiveness. There are only a few sites in the world where it is possible to use MRI and X-ray imaging during the same interventional procedure, desirable medically because the two types of imaging give important and complementary information. Sunnybrook Research Institute (SRI) is now one of these sites. In collaboration with GE Healthcare, the imaging systems in the IRCCI have been brought together into an integrated configuration, incorporating a unique remote-controlled patient transport system compatible with X-ray and MRI.

The IRCCI also brings together the brightest minds in cardiac research, under the directorship of Dr. Alexander Dick. Research teams are working in three main areas: revascularization (improving blood supply by opening closed vessels minimally invasively), regenerative medicine (stem cell work), and resynchronization therapies or "rewiring" for irregular heartbeats (arrhythmias).

Funded by the Canada Foundation for Innovation and Ontario Innovation Trust, as well as industry sponsorship and generous investment from members of the community, including the Schulich Heart Program's benefactor Dr. Seymour Schulich, the IRCCI is the cardiac imaging research centre for University of Toronto teaching hospitals including Sunnybrook Health Sciences Centre, University Health Network and St. Michael's Hospital. This $15.7-million centre is poised to lead the way in interventional cardiology for all of Canada, and beyond.

CENTRE FOR HEALTH SERVICES SCIENCES

Launched in 2007, the Centre for Health Services Sciences (CHSS) is a joint initiative of Sunnybrook Health Sciences Centre and Sunnybrook Research Institute (SRI) that brings together and builds upon scientific, clinical and managerial expertise at the hospital and SRI, with a special focus on safety, services and quality problems. Through CHSS, researchers, clinicians and managers work together within a coordinated framework to understand barriers to providing evidence-based care, and to develop and test new methods to help translate evidence into practice more effectively. The overarching goal is to overcome these barriers, identify and leverage catalysts for change, and support the diffusion of best practices



Dr. Alexander Dick

Dr. Merrick Zwarenstein

throughout Sunnybrook. The centre has four platforms—the clinical studies resource centre, hospital epidemiology, knowledge translation and patient safety improvement research—led by experts in their fields.

Dr. Merrick Zwarenstein, director of the discipline of combined health services sciences at SRI, is the founding chair of CHSS. He notes that a hospital is a complex place, with many forces at work, which can make it difficult to improve safety and quality in the health care system. The establishment of CHSS aims to change that. Says Zwarenstein, "The Centre for Health Services Sciences is about leading this initiative with science, about engaging all of the stakeholders in ways that are different from before, about being honest about what we did wrong in the past." A current and exciting project underway is a campaign to intensify the hospital's efforts to reduce surgical site infections.

CENTRE FOR RESEARCH IN IMAGE-GUIDED THERAPEUTICS

The newest capital project at Sunnybrook Research Institute (SRI) is the Centre for Research in Image-Guided Therapeutics. This facility will add more than 100,000 square feet of research space to Sunnybrook, primarily on two new floors atop the main (M) wing. The centre, which has a total project cost of $160 million, will have four institute-wide platform-based facilities, which will maximize interaction among scientists. Dr. Kullervo Hynynen, director of the discipline of imaging at SRI, leads the centre, which amasses a team of 55 scientists and clinician-scientists spanning every discipline and four research programs (cancer, cardiac, musculoskeletal and neurosciences) at SRI.

"With this award, we can build a centre that will be the only one of its kind in the country and perhaps in the world," says Hynynen. "It will help us do the innovative research in medical imaging, with an emphasis on developing new therapeutics, for which Sunnybrook is known globally. It will also be very attractive to collaborators, industry partners and young trainees."

Researchers at the centre will develop and test state-of-the-art medical imaging technologies, therapeutics and standards of practice, and translate them into the clinic. It will transform medical imaging by enhancing diagnosis and therapy for some of the most urgent problems in health care.

The new facility is a result of the success of an institute-wide team of Sunnybrook researchers, in the highly competitive Canada Foundation for Innovation (CFI) Research Hospital Fund, a program created to address the need for investment in research hospital infrastructure. To this end, the CFI will fund 40% of the project cost, and has committed an additional $17.2 million to SRI toward the running of the centre, bringing its total investment to $74.6 million. The remaining $86 million was secured from other funding agencies, industry partners, SRI and Sunnybrook Foundation.

PARTNERSHIPS

Drs. Laura Curiel and Samuel Pichardo

MOLECULAR MEDICINE RESEARCH CENTRE

The Molecular Medicine Research Centre (MMRC) is an Ontario-wide partnership among Thunder Bay Regional Research Institute (TBRRI), Sunnybrook Health Sciences Centre, Lakehead University and Philips Medical Systems. Dedicated to producing results that will enhance our understanding of health and disease at the cellular and molecular level, the MMRC brings together researchers in biology, physics and engineering, who are developing new molecular imaging-based diagnostic technologies for disease prevention, early detection and image-guided treatment. Dr. John Rowlands, a senior scientist in imaging at Sunnybrook Research Institute (SRI) and head of medical physics research at Sunnybrook's Odette Cancer Centre, is the TBRRI's founding scientific director.

On July 7, 2007, the Federal Economic Development Initiative for Northern Ontario (FedNor) announced it was investing $14.7 million in the institute. Other funding partners—the city of Thunder Bay, the province and Philips Medical Systems—together have invested $38.7 million over the five-year first phase of the project, for a total investment of $53.4 million.

About 50,000 square feet of new lab space will be christened in Thunder Bay by the end of phase one; at Sunnybrook, the partnership will take shape as the Translational Research Centre, co-led by Rowlands and Dr. Kullervo Hynynen, director of imaging at SRI and Canada Research Chair in Imaging Systems and Image-Guided Therapy. The cornerstone of the $7-million centre will be the development of MRI-guided focused ultrasound facilitated by the acquisition of a 3-tesla magnetic resonance imaging scanner. This developing technology has already provided new modalities of noninvasive treatment of cancers and precancerous tissues.

"In creating this partnership," says Dr. Michael Julius, vice-president of research at Sunnybrook, "we saw the potential not only to further our research agenda in cancer, and in heart and circulation, but also to create resource and knowledge-sharing with a private industry partner. Philips' research and development is very well aligned with our research goals, and provides access to an incredible pool of research talent, resources, technology and funding support from a global health care technology leader."

Partnering with industry not only enables leading-edge research that lays the groundwork for improved patient care, it also creates economic benefits. Recruitment of new scientists at all partner sites will generate jobs for postdoctoral fellows, graduate students, technicians and administrators. Fully staffed and well-equipped labs in turn secure operating funding and bring more infrastructure support, opening new avenues for further collaborations. "Canada will achieve global competitiveness through multisector partnerships like the MMRC, where support of excellence in discovery research can align with, and capitalize on, industry investment," says Julius. "This is a transformative initiative, and we're proud to be part of it."

Dr. Sandra Black, Industry Minister Tony Clement and Finance Minister Jim Flaherty

HEART AND STROKE FOUNDATION CENTRE FOR STROKE RECOVERY

Founded in 2002, the Heart and Stroke Foundation Centre for Stroke Recovery is a partnership among Sunnybrook Health Sciences Centre and Baycrest Centre for Geriatric Care in Toronto, and the University of Ottawa. The virtual centre is designed to capitalize on complementary expertise and facilities at the three sites, to develop new ways to repair the brain after stroke through basic and clinical research on stroke recovery and rehabilitation.

In January 2008, Federal Minister of Finance Jim Flaherty and Minister of Industry Tony Clement (Minister of Health at the time) announced $15 million—the largest investment ever in stroke recovery and rehabilitation in Canada—to support the centre. Dr. Sandra Black, the centre's Sunnybrook site director and director of the neurosciences research program at Sunnybrook Research Institute, says, "We have been very successful in treating people with acute stroke, but as a result, we now have a record number—360,000 Canadians—of stroke survivors. We're confident that with the right help and determination, people can achieve their personal best in recovery, and we're inventing better ways for them to achieve that goal."

At Sunnybrook, clinical researchers are designing and testing pharmaceutical and physical interventions toward recovery of ambulation and upper arm and hand function. They are also examining patterns of brain activity using functional magnetic resonance imaging (MRI) and perfusion imaging as well as structural MRI to quantify brain tissue loss related to focal stroke and more diffuse small vessel disease, which can impede the recovery process, especially in the presence of concomitant Alzheimer's disease.

The prospective longitudinal Sunnybrook dementia study, which has a 13-year history, has become an invaluable resource and archive of standardized, comprehensive clinical-behavioural data and brain images in over 1,000 patients. With this resource, researchers have developed computational volumetric analysis software, and contributed many original observations on relationships between large and small vessel cerebrovascular injury and Alzheimer's disease.

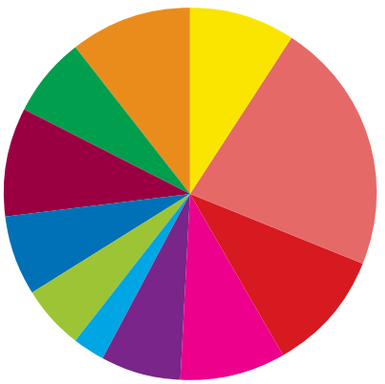
Scientists in the Rotman Research Institute and Kunin-Lunenfeld Applied Research Unit at Baycrest are designing cognitive-behavioural therapies, and acquiring and analyzing brain imaging networks through functional MRI, magnetoencephalography and evoked potentials. They aim to provide a more dynamic understanding of brain recovery and the data required to evaluate treatment options. At the University of Ottawa and Ottawa Health Research Institute, scientists are working to advance understanding of the molecular and cellular mechanisms involved in brain repair.

The centre has 21 core scientists, who have obtained more than $20 million in stroke-related peer-reviewed funding. Additionally, 35 associate members and 10 affiliate trainees are working collaboratively to speed the development of new treatments to optimize stroke recovery. These teams will move promising treatments from the lab to proof-of-concept clinical trials over the next decade.

QUICK STATISTICS

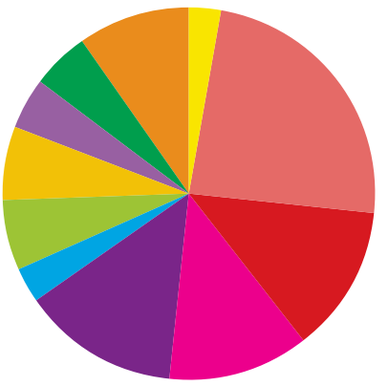
Major sources of external funding

Sunnybrook Research Institute is grateful to the many sponsors who, with each dollar they give, help support research here.



$64.2 MILLION (2006—2007)

- Canada Foundation for Innovation 9%
- Canadian Institutes of Health Research 22%
- Donations and Trust Income 11%
- Foundations 9%
- Industry 7%
- Ministry of Health and Long-Term Care 3%
- National Cancer Institute of Canada 6%
- Ontario Innovation Trust 7%
- Ontario Research and Development Challenge Fund 9%
- Other Funding Sources 7%
- Other Government Sources 10%

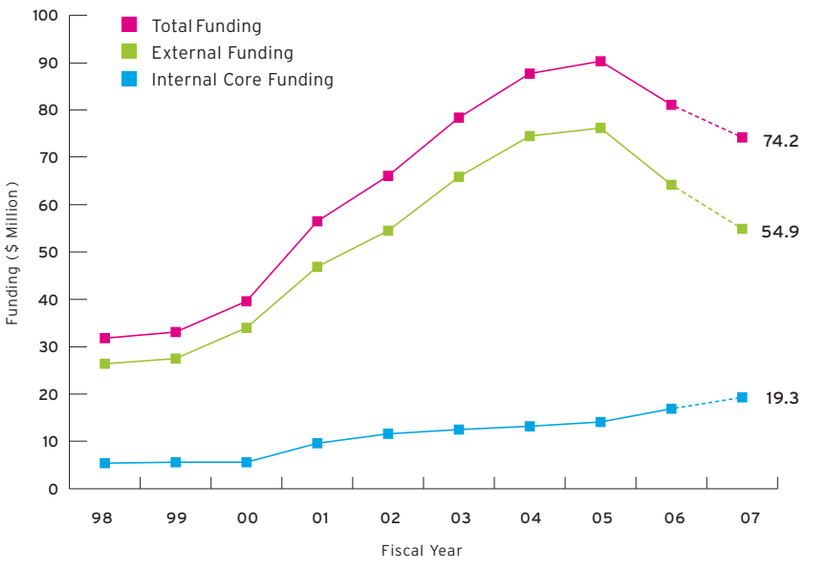


$54.9 MILLION (2007—2008)

- Canada Foundation for Innovation 3%
- Canadian Institutes of Health Research 25%
- Donations and Trust Income 13%
- Foundations 12%
- Industry 14%
- Ministry of Health and Long-Term Care 3%
- National Cancer Institute of Canada 6%
- Ontario Institute for Cancer Research 6%
- Ontario Research Fund 4%
- Other Funding Sources 5%
- Other Government Sources 9%

History of Research

Expenditures at Sunnybrook Research Institute



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RESEARCH STAFF

Senior scientists and scientists	100
Associate scientists	94
Research associates, engineers and physicists	74
Laboratory technicians and research assistants	190
Research fellows and graduate students	326
Total	784

YOU CAN SAVE A LIFE.

You can help Sunnybrook Research Institute invent the future of health care and create the next set of medical breakthroughs that will transform patient care and save lives. Your support will lead to discoveries that mean earlier and more accurate diagnoses, less invasive therapy and better treatment for the most pressing problems in health care.

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