inventing the future of health care...

piece by piece

sunnybrook & women's research institute | 2002–2004

SUNNYBROOK & WOMEN'S
Sunnybrook and Women's College Health Sciences Centre

Solving the puzzles of how our body and mind work, in sickness and in health, inspires scientists at Sunnybrook & Women's Research Institute. Some researchers are probing the basic mechanisms of the gene, the molecule, the cell and the organism to find and assemble the first critical pieces of the puzzle.

Others are working to connect these findings and translate them to clinical problems through new treatments and technologies to begin to fill out pictures of improved health care. Yet others are transferring the results of this knowledge in ways that transform health care practice and policy to fit in the final pieces of the puzzles and reveal pictures of optimal health. Finally, private donors, government agencies, foundations and industry partners are investing in research to enable scientists to tackle new puzzles and train a new generation of puzzle-solvers. Piece by piece, Sunnybrook & Women's Research Institute is inventing the future of health care.

message from senior leadership, sunnybrook & women's

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

Every day, Sunnybrook & Women's strives to be extraordinary. Sunnybrook & Women's Research Institute is no exception. Home to hundreds of world-class scientists who conducted more than $80 million in research last year alone, SWRI is unearthing some of the most dramatic discoveries in health care.

Proximity to the clinical activity and excellence in patient care at Sunnybrook & Women's is a distinguishing feature of SWRI. Learning from our patients is key to SWRI's success, and the organization takes pride in this strong collaboration.

Over the last year, SWRI researchers have explored methods of minimally invasive heart surgery, used leading-edge imaging techniques to improve diagnosis and treatment of cancer, and uncovered important gender differences in Alzheimer's disease. Our researchers are working to improve the quality of life for our patients and are achieving breakthroughs that are changing the face of health care.

As leaders, our researchers have been the recipients of numerous honours and awards, including Canada Research Chairs and National Cancer Institute of Canada awards.

The six programs of SWRI are areas of clinically focused research activity. Each scientist belongs to a discipline and to a program: Toronto Sunnybrook Regional Cancer Centre (Cancer Research Program), Schulich Heart Centre (Heart & Circulation Research Program), Orthopaedic & Arthritic Institute (Musculoskeletal Research Program), Neurosciences, Perinatal & Gynaecology and Trauma. This synergy ensures that SWRI and Sunnybrook & Women's truly are transforming health care.

We would like to personally acknowledge and thank each researcher, as well as our funding partners and collaborators, for their tremendous efforts and successes.

VIRGINIA MCLAUGHLIN
CHAIR OF THE BOARD OF DIRECTORS
SUNNYBROOK & WOMEN'S

LEO STEVEN
PRESIDENT AND CEO
SUNNYBROOK & WOMEN'S

message from the vice-president of research, sunnybrook & women's

Left to right: Leo Steven, Michael Julius and Virginia McLaughlin

At Sunnybrook & Women's Research Institute, we focus on the continuum of research: all the steps – from basic discovery to knowledge translation – that lead to innovation and, ultimately, improved health for everyone in our local, Canadian and global communities.

We know that no plan for research can chart the course of science definitively. Many brilliant discoveries emerged accidentally or by chance. This does not mean, however, that the process of scientific discovery is haphazard, only that it has the capacity to embrace and work with uncertainty. It means, too, that any plan for research must be dynamic and responsive, while simultaneously poised in a state of readiness to address new questions as old ones are resolved. Grasping the potential for innovation inherent in this dynamic and sometimes chance-driven path requires talented people and an environment that supports a free exchange of ideas.

With the help of our funding partners and collaborators, SWRI is creating and nurturing that environment, bringing together scientists and clinicians who have diverse skills and backgrounds but a common commitment to excellence in their fields. Central to our effort is how we integrate research with clinical care. As the stories in this report show, clinical problems and the experiences of caregivers inspire our scientists to throw themselves into finding solutions so that Sunnybrook & Women's can do better by its patients – now and in the future.

In its short 15-year history, SWRI has fostered an unusually close level of collaboration among PhD-trained scientists, clinician scientists and other caregivers. We have many outstanding achievements, including external research funding of $65.9 million in 2003–2004, a figure that has increased more than $38 million in just five years. However, the real day-to-day integration of research and clinical care remains our most extraordinary accomplishment and provides an unparalleled setting to train the next generation of scientists and caregivers.

Solving the puzzles of human disease requires the work of a dedicated team of scientists, clinicians, students, fellows, and administrative and research staff. It also requires, and receives, support from Sunnybrook & Women's senior leadership team and the Board of Directors. This team, led by Leo Steven, CEO and President, and Virginia McLaughlin, Chair of the Board, is committed to ensuring that our research does and will continue to improve health care.

The stories in this report highlight some of the extraordinary work conducted at SWRI from 2002 to 2004 toward creating pictures of optimal health. Each solution we find, while it improves treatment and quality of life for our patients, also raises new questions at different points along the continuum of research. We are prepared to tackle these emerging questions, to make the most of chance and to invent the future of health care.

MICHAEL JULIUS
VICE-PRESIDENT, RESEARCH
SUNNYBROOK & WOMEN'S

PROFESSOR, DEPARTMENTS OF IMMUNOLOGY,
MEDICAL BIOPHYSICS
FACULTY OF MEDICINE, UNIVERSITY OF TORONTO

focusing on excellence: our six priorities

Sunnybrook & Women's Research Institute encompasses six research programs that align with Sunnybrook & Women's (S&W) clinical service priorities: *cancer* (Toronto Sunnybrook Regional Cancer Centre); *heart and circulation* (Schulich Heart Centre); *musculoskeletal* (Orthopaedic & Arthritic Institute); *neurosciences; perinatal and gynaecology;* and *trauma*. A focus on aging and women's health runs throughout these programs.

cancer

For more than 25 years, the Toronto Sunnybrook Regional Cancer Centre has been one of Canada's most comprehensive cancer prevention, research, teaching and treatment centres, caring for more than 12,000 new cases of cancer per year. Researchers are transforming cancer care through the study of the genetics, biochemistry and biology of cancer; experimental treatments; and social factors and quality of life.

heart and circulation

Named to honour Seymour Schulich, the Schulich Heart Centre is a national leader and one of the largest cardiac care centres in Ontario. It handles more than 6,500 surgical, catheterization, angioplasty and pacemaker cases annually. Scientists are creating and testing less invasive and more effective ways to diagnose and treat coronary disease, which limits blood supply to the heart; valvular diseases; high blood pressure; congestive heart failure; and irregular heart rhythms. Population studies are looking at risk and the access to, and benefits of, various treatments.

musculoskeletal

The Orthopaedic & Arthritic Institute is one of the best-known Canadian centres for clinical and surgical expertise, education and research in musculoskeletal care. Scientists and clinicians across S&W's three campuses are building on innovations in surgery and research to improve outcomes for patients with musculoskeletal disease.

neurosciences

Researchers in neurosciences strive to understand and treat disorders of the central nervous system by integrating the mind and brain and by destigmatizing mental and neurological diseases. They aim to improve care and quality of life in stroke, neurodegenerative disorders like Alzheimer's disease, mood disorders such as depression, traumatic brain injury and brain tumours.

perinatal and gynaecology

S&W continues its role as a world leader in perinatal and gynaecology teaching, research and care. The research program covers a spectrum of issues on infertility and pregnancy, birth and infancy, and the reproductive health of women. Particularly emphasized is clinical epidemiology, a discipline that explores the causes, consequences and treatment of disease.

trauma

S&W is home to Canada's first and largest trauma unit. Annually, the program sees more than 1,200 patients who require immediate and often life-saving care. To advance the study of trauma, scientists integrate findings from basic and clinical research to further molecular and physiological knowledge and then test these findings in practice.

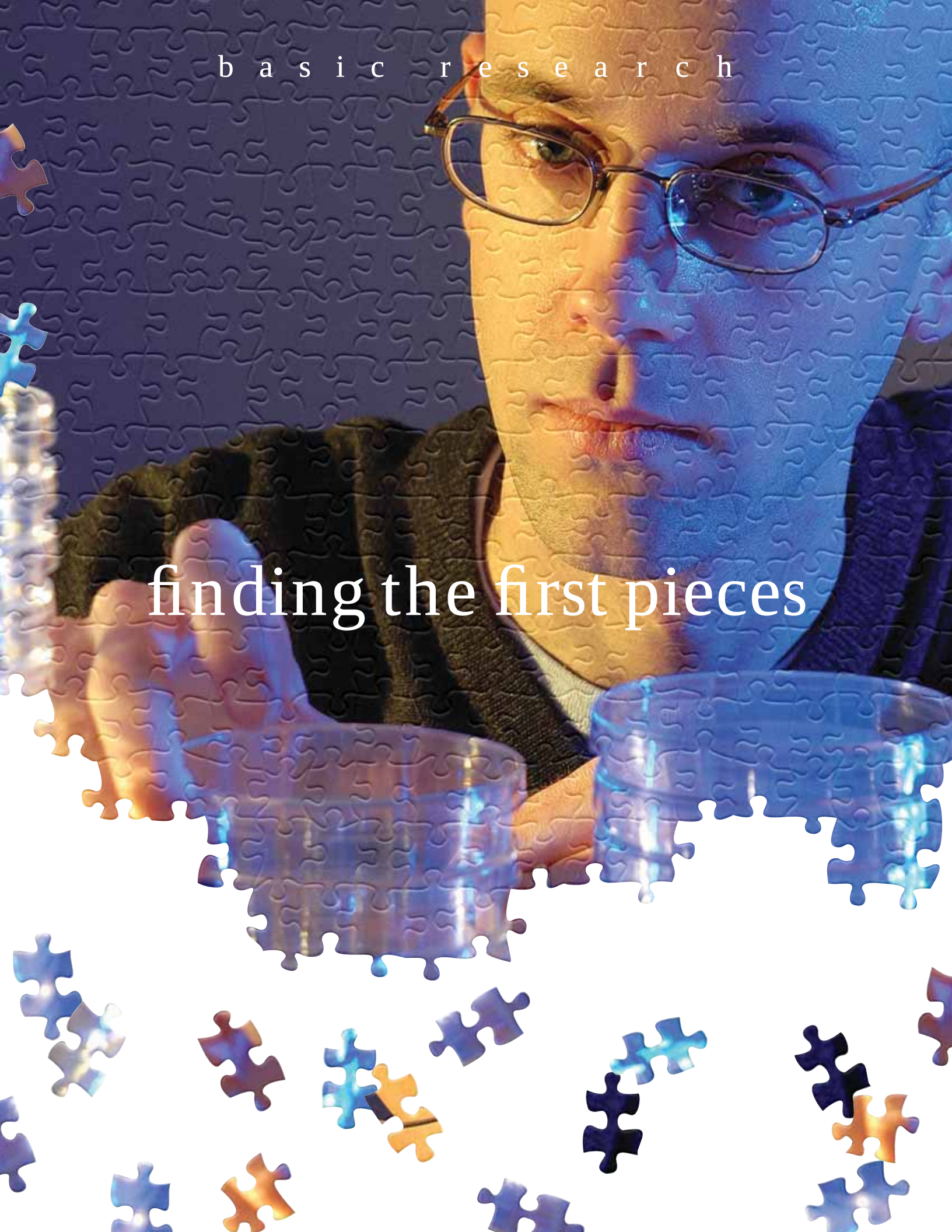
cutting across the six priorities: aging and women's health

An extraordinary legacy informs research, teaching and care at Sunnybrook & Women's and inspires our focus on aging and women's health.

S&W has a distinguished history of excellence in the acute and long-term care of the elderly. The Sunnybrook campus originally was a war veterans' hospital. Founded in 1948, it served as a symbol of a nation's gratitude to its veterans. Today, S&W has the largest care facility for veterans in Canada. Aging and veterans' care remain a strategic priority for S&W.

Women's health is a proud part of our past and an integral part of our future. S&W is the only hospital in Ontario with a legislated mandate in women's health. Our dedication to providing up-to-date information to help women make informed health decisions is outlined in our mandate, mission and history, and is integrated into our clinical services priorities and research programs. The Centre for Research in Women's Health (see page 27) is an international leader in this area.

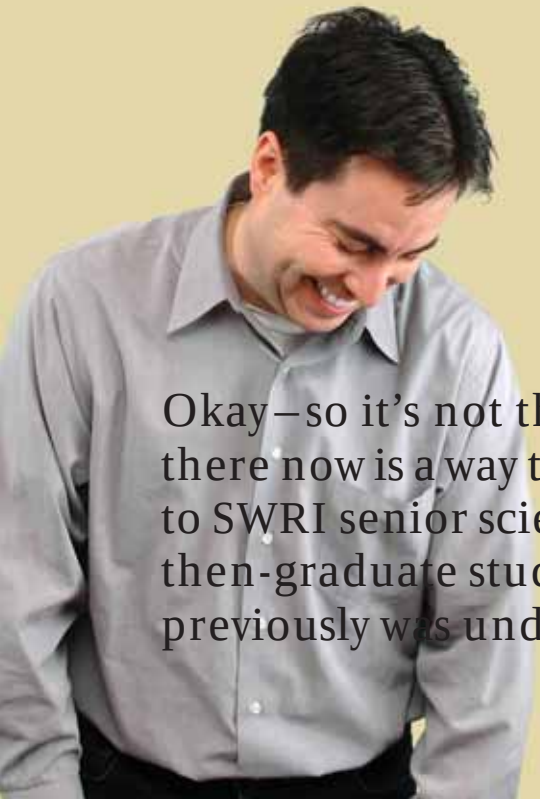
Photo: Thomas Schmitt, with senior scientist Juan Carlos Zúñiga-Pflücker, discovered how to generate T cells in a Petri dish. This finding points toward future clinical therapies for people with HIV and cancer.



finding the first pieces

Take a Petri dish.
Put stem cells in it. Add
some delta-like
molecules and stromal
cells. Mix well.
Let stand for a while.

Congratulations. You have just made Tcells.



Okay—so it's not this simple—not even almost; but, remarkably, there now is a way to create T cells from stem cells this way, thanks to SWRI senior scientist Dr. Juan Carlos Zúñiga-Pflücker and his then-graduate student, Thomas Schmitt. In 2002, they did what previously was undoable.

‘Oh, it’s complicated; you need a whole structure,’ says Zúñiga-Pflücker.

Zúñiga-Pflücker laughs as he recalls the process. “It’s almost like an equation. You have these three variables, and if you put them together, it’s a combination that gives you a T cell as opposed to something else. And that is likely to be useful one day.”

Indeed, the breakthrough has huge implications – if scientists can create immune-essential T cells at will, then doctors can treat immune-wrecking diseases, like AIDS and cancer.

We need T cells. Without them, our immune systems would collapse. In the body, stem cells with the potential to be various kinds of cells travel from the bone marrow to the thymus. There, some become T cells. Unlike B cells and other immune cells, which grow in bone marrow, T cells develop only in the thymus. This posed a challenge for scientists.

“Puzzling us for years was what is it about the thymus that is unique and special, that isn’t in the bone marrow, which allows T cells to grow there as opposed to elsewhere?” says Zúñiga-Pflücker.

This was a driving question, because the molecule that controlled signalling was unknown. Also, researchers had grown T cells only in thymus-like structures. They thought three-dimensionality was critical. “That was the dogma – people thought that T cell development was unique because it required a complex structure to take place in,” he says.

So he and Schmitt started their experiments. In culture (i.e., a Petri dish), they combined stem cells from the bone marrow, delta-like molecules from the thymus and bone-marrow-supporting stromal cells. This combination, and importantly the delta-like molecule, turned out to be the solution.

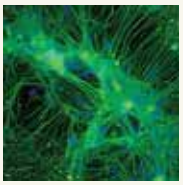
“We never actually assumed this would support T cell development from beginning to end, because we belonged to that group that thought, ‘Oh, it’s complicated; you need a whole structure,’” says Zúñiga-Pflücker. They were delightfully surprised.

“The nice result was that the T cell not only began to look like a T cell, it basically ended up being a mature, functional – as if it was in the thymus – type of T cell.”

This allows scientists to study T cell development in a straightforward system, so they can advance the work toward clinical translation, still years away. Today, Zúñiga-Pflücker’s lab is tackling challenges like creating stem cells from different sources and making a “plastic thymus.”

Science – the process of – is like a story on a loop: it has a beginning, middle and end, and then another beginning. Zúñiga-Pflücker’s start came as an undergraduate student, when he fell in love with the idea of T cell development. Since then, it’s been a series of middles and ends and new beginnings. Lucky for the field of T cell development. Very lucky. SR

The Canadian Institutes of Health Research and the National Cancer Institute of Canada funded Zúñiga-Pflücker's research in this area.



The lab of **Daniel Dumont** works on receptor tyrosine kinase, Tek/Tie2, a protein that is essential for angiogenesis, the growth of blood vessels. This protein must interact with other proteins inside the cell to accomplish its task. Dumont identified the unique and specific site on the Tie2 receptor that mediates binding between these critical proteins. This discovery underscores the importance of this receptor in angiogenesis. Furthermore, these findings may prove useful in the design of new targeted drugs that affect how this protein mediates angiogenesis.

Research by **Michael Julius** and colleagues provided the first, definitive molecular basis for the spatial and temporal coordination of the kinases Lck and Fyn in T cell activation by showing that their roles are interdependent and not redundant. They showed that lipid rafts, cholesterol-rich micro-domains, work to separate the kinases in T cells before activation. A subsequent study underscored the important role lipid rafts play in coordinating the interaction of these kinases.

Martin McGavin and colleagues found that the staphylococcal cysteine protease of Staphylococcus aureus shows a novel maturation mechanism and mimics the specificity of plasma serine proteases. S. aureus is a leading cause of nosocomial bacteremia and is the overall leading cause of nosocomial infections of all kinds. It has the ability to colonize and infect almost every tissue and organ system of the body.

Philippe Poussier and colleagues showed that a T cell population of unknown function in the intestines of healthy people plays a central role in protecting against the development of ulcerative colitis. They provided evidence for extra-thymic origin of intestinal TCR gamma/delta + T cells in normal rats and for an impairment of this differentiation pathway in spontaneously diabetic BB rats. In an unrelated study, they developed a novel model of experimentally induced diabetes and mapped the genetic loci that control disease susceptibility in this model. They characterized the role of SOCS1 in regulating the function of T lymphocytes that are toxic to cells.

Michael Ratcliffe and colleagues designed a system that allowed them to identify the roles of the components of the B cell receptor complex in regulating B cell development. The B cell receptor complex is essential for the development of B cells, which are involved in antibody-related immunity. They presented the first direct evidence that the cytoplasmic domain of Ig alpha is sufficient to drive the early stages of B cell development with the same efficiency as the entire cell receptor complex.

Conventional chemotherapy is not effective against certain forms of cancer. Immunotherapy, treatment that improves the immune system's ability to kill cancer cells, may hold more promise. Cancer vaccines are a type of immunotherapy that help T cells, the building blocks of the immune system, attack the cancer; however, vaccines generally aren't effective on their own. **David Spaner** and colleagues found that giving high doses of Interferon (a natural immune-strengthening substance) led to a clearance of metastatic melanoma in some patients after vaccination. These findings suggest a strategy to improve the efficacy of cancer vaccines.

Other research by **David Spaner** and colleagues found the mechanisms that normally regulate strongly activated T cells in animals with competent immune systems are lost after adoptive transfer into immunodeficient hosts. They suggested that this loss plays a role in the development of Graft-versus-host disease (GVHD). GVHD is the main complication of stem cell transplantation. It prevents the potentially curative treatment from being offered to more patients.

Burton Yang and colleagues found the first evidence that G3, a type of protein found outside cells, promotes the growth of brain tumours and plays a role in angiogenesis, the formation of blood vessels that feed tumours. They also found that G3 binds to two molecules that, when combined, enhance angiogenesis. Taken together, these findings suggest that G3 fragments might be a target for anticancer and antiangiogenic therapies.

Photo: Dr. Claire Holloway prepares to do image-guided surgery in the experimental operating room. At this developmental stage, she is using ultrasound to see what the edges of tumours look like.

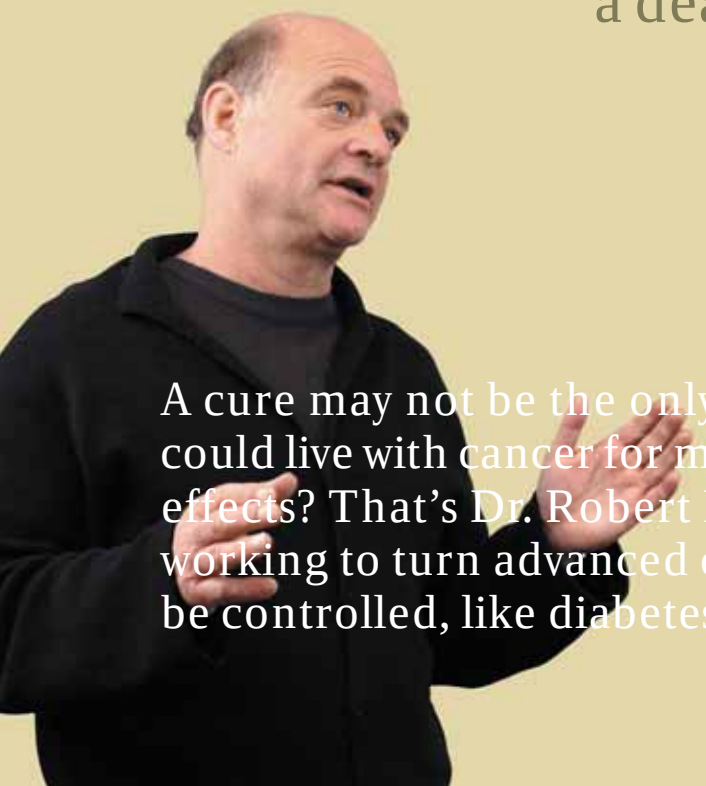
H I G H L I G H T S

t r a n s l a t i o n a l r e s e a r c h

connecting the pieces

You've been given three wishes to make the world a better place: an end to hunger, global peace and a cure for cancer. Sound good?

It's a beautiful dream. But one of your wishes might be different if cancer didn't hold the threat of a death sentence.



A cure may not be the only path to a happy ending. What if you could live with cancer for many years by taking drugs with few side effects? That's Dr. Robert Kerbel's dream. He and his team are working to turn advanced cancer into a chronic disease that can be controlled, like diabetes.

"There are two Holy Grails in treating cancer: to find a therapy that will not be made quickly obsolete by drug resistance and to find drugs that are almost completely safe to take," Kerbel explains.

Kerbel is passionate about the need to improve quality of life for cancer sufferers. "You just have to walk into a cancer clinic and to see that traditional chemotherapy has very unpleasant side effects. Currently, many patients almost fear the therapy as much as the disease. We have to do a lot better," he says.

Why is a cure so elusive? Well, the same genetic instability that causes cancer cells to grow so wildly also makes them mutate quickly to outwit the latest and greatest cancer drugs, causing drug resistance.

"There are two Holy Grails in treating cancer: to find a therapy that will not be made quickly obsolete by drug resistance and to find drugs that are almost completely safe to take," Kerbel explains.

Tumours grow in part by stimulating the development of new blood vessels, a process called angiogenesis. Kerbel is a pioneer in discovering the mechanisms underlying antiangiogenic treatments, which compromise blood supply to tumours. Because the cells that line blood vessels, called endothelial cells, do not mutate like cancer cells, they may not develop drug resistance so readily. Therefore, it is theoretically possible to have an antiangiogenic drug control cancer for many years.

Kerbel's particular specialty is the combination of antiangiogenic drugs with low-dose "metronomic" chemotherapy, the frequent administration of small amounts of traditional chemotherapeutic drugs over an extended period. Antiangiogenic drugs alone are not effective enough, but ongoing clinical trials suggest that the combination strategy shows promise.

Kerbel recently discovered a "marker," a substance that measures the effectiveness of an antiangiogenic drug through simple means, such as a blood test. His research showed that levels of certain types of cells found in the bloodstream that appear to contribute to new blood vessel formation parallel blood vessel growth and can thereby reveal the impact that an antiangiogenic therapy is having on tumours. In other words, if the numbers of these cells go up, the treatment is not stopping angiogenesis; if they go down, it is working.

These markers are vital, Kerbel says, because "you could determine early on whether a drug has a better chance of working before starting long and expensive clinical trials." Kerbel's new marker should help cancer doctors quickly determine the optimal dosage of an antiangiogenic drug, currently a matter of trial and error, to get it into the clinic where it can help patients.

Maybe controlling cancer isn't as thrilling a dream as curing it. But it may actually work. SM

The National Cancer Institute of Canada/Canadian Cancer Society, the Canadian Institutes of Health Research and the National Institutes of Health (U.S.) funded Kerbel's research. The Canada Foundation for Innovation and the Ontario Innovation Trust provided infrastructure support. He holds a Canada Research Chair in Molecular Biology and Applied Genomics.

Ten million. In 2041, just 36 years

from now, that's how many Canadians will be aged 65 and over. With this aging explosion will come a surge in the number of people living with Alzheimer's disease (AD) and other dementias, and the cognitive aftershocks of stroke.

Related economic costs are as-yet incalculable. The human impact is easier to imagine, because it'll be much as it is now – but hugely magnified – as individuals and families struggle to cope with the frustration and upheaval that come with stroke and AD.

Powerful motivation, that. The kind that pushes neurosciences researchers Drs. Sandra Black and Simon Graham to test relentlessly the edge of possibility in their work.

Black doesn't have a lot of "free" time for interviews. Between caring for patients, running studies and writing up results for publication, finding a block of time to chat is a Herculean task. But Black, a clinician-scientist at S&W since 1985, manages to find time even for that.

There is much to talk about. Over the last two years, she has published many papers in her areas of expertise: stroke, AD and other dementias, like vascular dementia. Much of her work focuses on the interaction between AD and stroke, including the small, silent strokes, so-called because people aren't aware of having them. Cerebrovascular disease, the death of blood cells in the brain, can lead to a stroke, silent or otherwise, and is linked to vascular dementia.

"We've developed a sophisticated way to look at not just the strokes that are clinically obvious, but the silent strokes and the hardening of the arteries which look to be critical in the expression of dementia in older people," says Black. "You can die with Alzheimer's pathology and not be demented. You can die from strokes and not be demented, but if you have both, you're much more likely to be demented. They keep very bad company."

Her group has been working to understand the overlap between AD and stroke for 10 years. They've developed ways to analyze the brain using structural imaging to account for the probability of both diseases. "We don't have a direct way of knowing that a person has Alzheimer's, but there are patterns of shrinkage that suggest it, and if you can also look at the amount of 'silent' cerebrovascular disease, you get a much better reading of what's actually going on in the person and what their cognitive function is likely to be," she explains.

Understanding how these conditions interact is also important to developing targeted treatments. Black was the lead author reporting the results of a multinational clinical trial to test the effects of the drug donepezil on the cognitive functioning of more than 600 people with vascular dementia arising from cerebrovascular disease. Researchers knew donepezil, which acts on the cholinergic system, was effective for people with AD, but they didn't know if it would work for people with vascular dementia. The study, published in *Stroke* in 2003, showed that it was indeed therapeutic for these people.

More and longer-term study is needed, says Black, but the evidence is growing that the cholinergic system, involved in AD, also figures in vascular dementia. In addition to the treatment implications, results like these have immediate applications, she notes. "All of those healthy lifestyle and diet decisions, and taking medications if needed to keep your blood pressure and cholesterol under control, aren't just protecting you from heart disease and stroke; they're also protecting you from Alzheimer's."

In other research, she and Graham, an imaging scientist, are doing studies with functional magnetic resonance imaging, or fMRI, to track brain activity during a behaviour like navigation. They've been using fMRI to study which regions of the brain are involved in problems with finding one's way around, which can be an early sign of

"We're making some good strides, but there's lots more to undertake," says Graham. "A lot of people out there are living with the consequences of these types of injuries and not at their full potential."

AD. Sunnybrook & Women's Research Institute has a 3T-magnet for experiments, made possible by a grant from the Canada Foundation for Innovation. This magnet is double the strength of a hospital-grade MRI machine, and getting it ready for research use is no easy feat. "There's a bit of an art to it," says Graham. "And there's a lot of engineering," he adds, laughing.

The aim is to go beyond the standard paper-and-pencil maze tests used to measure navigation. "That's not a good representation of how people navigate in the real world. We're looking for a better, more real-world assessment," says Graham, who is also a medical physicist.

Enter the pairing of fMRI with virtual reality, or "pretend" environments. This is where the brain activity of people is measured as they do tasks in simulated environments while lying in an MRI machine wearing magnet-compatible gear, like gloves and goggles.

Graham and Black looked at how people first learn and then remember how to get around the virtual "Sunnybrook City." Participants learned a path while in the magnet and then were tested on their ability to retrace that path 20 minutes later – all virtually, of course. Because both tasks took place in the magnet, the brain activity of each was visible. "That's important," says Graham, "because if you have impaired memory, you want to know if it's a failure to store the information or to retrieve it." The findings suggest that many parts of the brain are implicated.

They're also using neuroimaging to study where the silent strokes are happening, how the location of a stroke affects cognition, and how the brain reorganizes after a stroke so that targeted treatments can be developed. Collaboration is essential to their success, they agree. Both belong to the Heart and Stroke Foundation of Ontario's Centre for Stroke Recovery, a partnership between S&W, the Baycrest Centre for Geriatric Care and the Ottawa Health Research Institute.

"We're making some good strides, but there's lots more to undertake," says Graham. "A lot of people out there are living with the consequences of these types of injuries and not at their full potential."

Although rehabilitation strategies and treatments to halt the downward cognitive spiral of stroke, AD and other dementias are still being developed, the notable progress of neuroimaging in the last decade offers hope for an aging population. With each new insight, researchers like Black and Graham move closer to the brink of a breakthrough, which, after all, is just a series of incremental achievements.

Achievements, Black emphasizes, that wouldn't be possible without her patients, who remain her priority. "My focus is to try to take good care of my patients and to learn from them and help them learn from me. They're the experts in their experience of the disease, and I'm an expert in what's known about the disease. It's very much a partnership." SR

The Alzheimer's Association (U.S.), the Alzheimer Society of Canada, the Canadian Institutes of Health Research, Eisai Inc. and Pfizer Inc. funded Black's research. The Ontario Research Development Challenge Fund, Heart and Stroke Foundation of Ontario and the Canada Foundation for Innovation funded Graham's work.

Spotlight on Breast Cancer Research

aiming for a biological bull's-eye

"The dream is to develop some small molecule that will shrink breast tumours…to treat women so that they never get metastases," says Seth.

Picture a dartboard. Pick up an imaginary dart and toss it at the dartboard. Where does it land? If you're like most people and me, you probably hit the board, but well outside the bull's-eye, an apt metaphor for where treatment is in breast cancer. That is, treatments like chemotherapy and drugs are having a real impact, saving lives even, but they are far from being targeted and effective for women at all stages of breast cancer. And the largely one-size-fits-all dosing means many women deal with painful side effects *and* the disease.

Dr. Arun Seth is a molecular biologist at SWRI. Through his work in genomics, the study of genes and their function, he is trying to solve these problems. "Once we know what's happening in the cell, which genes are involved in cancer, then we can develop therapies that are more targeted and mechanism-based," says Seth, who also heads SWRI's Centre for Genomics.

The work is painstaking. Because it happens at the level of molecules, even the most encouraging results are a ways off from helping patients. Nonetheless, the work is foundational. Without it, the dream of targeted therapies remains just that.

Seth is examining the molecules inside tumour cells at each stage of breast cancer to identify patterns, including which are markers (and thus "point to" cancer) and which contribute to cancer. Already, he has made a mouse model that produces more of a gene found in breast cancer. His lab is characterizing the model to see if it can find tumours earlier, or if tumours are more frequent or aggressive. They've also made a mouse model that lacks a cancer-suppressing gene; they expect that cancer will develop faster in these mice than in normal mice.

Simultaneously, they're looking at human tumours to see if these genes are there, too. The science behind this is complex, but the aims are simple: detecting breast cancer early, predicting if it will spread after surgery, and tailoring therapies to women based on the stage of cancer for the best results with the least bad effects. "The dream is to develop some small molecule that will shrink breast tumours … to treat women so that they never get metastases," says Seth.

Especially neat is how tumours are analyzed. Seth brought technology to SWRI that allows 300 tumours, instead of one, to be examined on each slide. This is a huge leap into efficiency. "And we have this state-of-the-art microscope that captures these images on its own, and we can look at them later on. We don't even have to be there," adds Seth.

Then there's the bank – tumour, not money – unlike any other. Seth enjoys access to 6,000 frozen tumours at SWRI and 1800 paraffin tumour blocks with known outcomes and follow-up. "We have huge resources here." This includes collaborations with top pathologists, like Drs. Wedad Hanna and Harriette Kahn, and researchers, like Drs. Steven Narod and Kathy Pritchard.

"I can't see myself doing anything else," he says of his round-the-clock hours. "I'm just delighted that I and my colleagues have the potential to 'hit the mark' of targeting more effective therapy for women with breast cancer." SR

The Canada Foundation for Innovation, Canadian Breast Cancer Research Alliance, and Canadian Institutes of Health Research funded this research.

Spotlight on Breast Cancer Research

let's get digital

Early detection means early diagnosis and, for some women, a chance to live a life that might otherwise be snatched away.

In 2003, invisible tumours became visible. Senior scientist Dr. Martin Yaffe, working with Dr. Roberta Jong, director of breast imaging, published the first results showing that contrast-enhanced digital mammography could "see" breast cancer tumours that regular film mammography sometimes misses. And we're not talking about the vague outline of "something" in the tissue – we're talking about high-contrast, high-resolution images. Digital mammography can illuminate a lesion the size of a wild blueberry.

It was a pivotal finding in breast cancer research. The contrast agent, or dye, that is used marks where new blood vessels are growing, and thus may allow specialists to detect cancer earlier. Early detection means early diagnosis and, for some women, a chance to live a life that might otherwise be snatched away. This finding is especially relevant for women with dense breasts, who are often young, because the thickness of their breast tissue can hide tumours from film mammography, essentially rendering them invisible.

A true lab-to-bedside success story, digital mammography is now used all over the world. Meanwhile, Yaffe and his team continue to develop and refine digital techniques.

He's been doing imaging research at SWRI for 15 years, and his drive is obvious. Of his main goal, he says, "We're trying to move forward the whole area of breast cancer detection. It's very exciting. Because of better detection and treatment, we're seeing the mortality from breast cancer going down. That's the main focus – we've got an important problem that affects people's lives, and not just the people who get it, but their families and those around them."

Yet, he also radiates matter-of-factness – for all his achievements, and the resultant recognition, he says quietly, "This is what our lab does – we develop technology and techniques to refine and optimize imaging detection." Simply stated, but that's a lot of puzzle pieces to assemble.

Digital tomosynthesis is one technology with promise. Yaffe and his lab – he firmly points out that results come from working with top-tier engineers, graduate students, and others – have been collaborating with General Electric since late 2003. In digital tomosynthesis, multiple X-rays of the breast are taken from various angles. These are then sent to a computer that constructs three-dimensional images that can be scrutinized. This deals with the problem of overlapping tissue in regular mammography that causes some shadows to be mistaken for lesions.

They're also testing if the procedure is more comfortable for women, because it might be possible to use less pressure. If screening is more comfortable, then women are more likely to get it done – another good way to raise detection rates.

Although digital mammography is being used in clinics, this is not yet the case with the other techniques, like tomosynthesis, that Yaffe is refining. Most are translational research in progress. That is, they're not yet widely available, but they likely will be in less than a decade. It's a process. "We try to take our conclusions and move them forward in a logical way," says Yaffe.

Piece by piece, one might say. SR

The Canada Foundation for Innovation, the Canadian Breast Cancer Research Alliance, the Canadian Institutes of Health Research, the Ontario Research and Development Challenge Fund, The Terry Fox Foundation and the National Cancer Institute (U.S.) funded Yaffe's research.

Spotlight on Breast Cancer Research

screening for breast cancer: an exposé

"It was incredibly exciting to find for the first time tiny cancers that clearly were invisible with mammography," Warner says.

Mammography and clinical breast exams: useful tumour-detecting techniques that have saved, and will continue to save, the lives of countless women globally? Or suboptimal techniques that have failed countless women globally?

This isn't a test. There's no need to pick the right answer, because they're both right – as with many questions in life, it depends on the context.

Clinical breast exams (CBEs) are cost-effective and non-invasive. Experts generally agree that having a doctor probe for lumps during a check-up is a good idea. While more costly and invasive, a mammogram (a breast X-ray) is recommended for most women older than 40. It can detect abnormal growth earlier than a CBE can, which in turn can boost the survival rate in women aged 50 to 69 by up to 35%. In this context, then, these are useful screening methods.

For young women with a family history of breast cancer, however, these techniques aren't optimal. By the time a lesion is detected in a woman who carries a gene for breast cancer (BRCA1 or BRCA2), the likelihood is high that the disease will have advanced. This is partly because young women have denser breast tissue, and their tumours are trickier to detect with the usual methods. These women have a lifetime risk of up to 85%, compared with 11% for most women; therefore, even a finding of no finding isn't reassuring. Furthermore, most of these women will get cancer during the most active years of their lives. At this stage, the options are limited and grim.

"They're left with the alternative of prophylactic mastectomies, which is a difficult and horrific choice to have to make," says Dr. Don Plewes, a physicist and the director of imaging research at SWRI. A prophylactic mastectomy is the removal of both breasts.

It's an option that has left many oncologists, including S&W's Dr. Ellen Warner, perennially frustrated. And it led her to ask an important question: "Is there something we can do better than just watching these women with mammography, knowing that we are going to miss more than half the cancers, which was everyone's clinical experience?"

Turns out there is. Researchers led by Warner and including Plewes recently finished analyzing five years' of data on women with the BRCA1 and BRCA2 genes. Hailed as a landmark result – it was the largest such single-centre study – they found magnetic resonance imaging (MRI) detected lesions with much higher sensitivity then mammography and CBE. (Sensitivity is the ability of a test to detect a disease when it is truly there.)

The results were published in *The Journal of the American Medical Association* in September 2004. Across the five years, MRI detected breast cancer tumours with 77% sensitivity, compared with 36% for mammography, 33% for ultrasound and 9% for CBE. When MRI was combined with the other techniques, sensitivity surged to 95%. Even the false positive rate (when a tumour is identified as being there, but is not), which often is high with MRI, dipped over time.

Warner thinks back. "It was incredibly exciting to find for the first time tiny cancers that clearly were invisible with mammography," she says.

Plewes recalls that the team was "thrilled." An extra dollop of gratification, flavoured by mild surprise, came from seeing that other large studies had similar findings, he adds. They know they're on the right track. Naturally, there are still questions – this is the infinity loop of science. The biggest one is, does early detection with MRI save lives?

"My gut feeling is yes, but we have to prove it," says Warner, smiling. And this is just what she says she and the "amazing imaging researchers" at SWRI are working to do. SR

cutting to the core of the issue

"Modern-day research cannot be done by investigators in isolation," she asserts.

Plewes is also part of a group studying the use of imaging in surgery. "I've always been impressed when I see breast MR images," he says. "I see these beautiful images that give such exquisite detail of the tumour that it seems a shame we use (MRI) only for diagnosis and detection. Is there not some way we can use it to facilitate therapies with real impact?"

Quite possibly. Currently, surgeons must rely on where a radiologist has preoperatively placed a blob of dye or a fine wire to know where a tumour is and where to cut. "That doesn't really give us a clear picture in three dimensions as to exactly where the edge of the tumour is," says Dr. Claire Holloway, a surgical oncologist at Sunnybrook & Women's since 1993.

The idea instead is to use imaging modalities – MR and ultrasound, for example – to plan and guide the surgery in real-time. "We would like to be able to mark the edges of the tumour in a way that makes it easier to see with ultrasound. It's not always easy to see where the tumour starts and ends. Some aren't even visible on ultrasound," says Holloway, the study's principal investigator. Plewes is developing markers that can pinpoint these edges, rather than only one spot in the middle.

To what benefit? "This would make the surgical procedures more precise, more accurate in terms of knowing where we should be confidently defining that surgical margin, and hopefully reduce the required re-excisions," Plewes says. It also can be used to verify that everything was removed, without the usual time- and labour-intensive trips to an X-ray lab, Holloway notes.

"If we can do this right then and there as we're taking the tumour out, we can say, 'OK we've got it … we're sure that we've got it;' this minimizes the need for a second operation and makes for more efficient use of scarce resources."

She's been doing image-guided surgery in S&W's experimental operating room for one year – about 100 operations. At this developmental stage, she's using ultrasound to see what the tumours' edges look like. The use of markers with ultrasound will be tested next.

The surgical oncology department is an active one. Over the last two years, she's been involved in several multicentre clinical trials, including the pivotal trial known as NSABP B-32 that is testing the effectiveness of sentinel lymph node biopsy, another procedure where technology has been incorporated into surgery to minimize the short- and long-term effects of breast cancer treatment.

Holloway says it's been an exciting few years for breast cancer research at SWRI, the more so because of the team approach. "Modern-day research cannot be done by investigators in isolation," she asserts. "It's clear to me that we make our best contributions by developing collaborations with people with different expertise. That's what's so great about this group." SR

The breast MRI study is funded by the Canadian Breast Cancer Research Alliance and The Terry Fox Foundation. The image-guided surgery research is funded by the Canada Foundation for Innovation, the Ontario Research and Development Challenge Fund and The Terry Fox Foundation.

trial and success

Findings like these, clear and certain, are the crystalline moments of clinical trials. With each new finding, the volume of knowledge on what works best for which women expands.

Head of clinical trials at the Toronto Sunnybrook Regional Cancer Centre and a senior scientist at SWRI, Dr. Kathy Pritchard seems to draw from a bottomless well of energy. She dashes with her signature speed from one appointment to the next, interspersing patient care with research-related, teaching and administrative activities. No doubt this comes in handy for her leadership role in conducting studies that transform how breast cancer is treated.

Take the practice-changing letrozole trial. It enrolled over 5,000 postmenopausal women with breast cancer worldwide, one-third in Canada. Pritchard, as co-chair of the breast cancer site group of the National Cancer Institute of Canada, co-led the trial. Letrozole is a type of aromatase inhibitor, a class of drugs that has few bad side effects. The pill is given as an adjuvant therapy, that is, after the main therapy, like surgery or tamoxifen, to help stop the cancer from returning. It works by limiting the postmenopausal production of estrogen that tumours need to grow. In this study, Pritchard and colleagues wanted to see if letrozole improved disease-free survival in women who had taken tamoxifen for five years.

They got what they asked for and more. The trial was halted well before the planned end date, so startling were the results. Pritchard recalls the thrill of that extended "eureka" of realization. "It was very exciting, because halfway through the trial we did an interim analysis and found that in the letrozole group, patients had done much, much better," she says.

The drug reduced the risk of recurrence by over 40%. It decreased local recurrences and the spread of cancer to other parts of the body. After a quick conference call, the group decided to stop the trial and reveal the outcome. *The New England Journal of Medicine* published the results in October 2003. Patients in the placebo group were quickly offered letrozole. In early 2005, Health Canada approved letrozole for the treatment of breast cancer in postmenopausal women who have had the standard treatment of tamoxifen for five years.

Findings like these, clear and certain, are the crystalline moments of clinical trials. With each new finding, the volume of knowledge on what works best for which women expands.

Research has shown, for example, that different therapies work best for certain groups of women. Herceptin works only for women who overexpress the HER2 / neu protein. Adding chemotherapy boosts this effect. Letrozole works well for postmenopausal women. There are many and varied combinations. Accordingly, the research effort in this field has moved toward investigating individualized treatments.

Sunnybrook & Women's is well placed with its expert staff at TSRCC and SWRI to advance this movement. In addition to conducting ongoing clinical trials, Pritchard has teamed with a multidisciplinary group, including Drs. Arun Seth, Steven Narod, Larry Paszat and Wedad Hanna, to explore the use of genomic profiling. They're analyzing frozen tumour and normal tissue samples and matching them against information in databases on treatment outcomes. The aim is to find more accurate prognostic and predictive factors for breast cancer that can then be tested in clinical trials.

"It's all about tailoring treatment to patients to ensure that individuals are getting the best treatment for their diseases," says Pritchard. "In this way, we can offer the most hope." SR

This research was supported by the Canadian Breast Cancer Research Alliance, the Canadian Institutes of Health Research, the National Cancer Institute of Canada and Sunnybrook & Women's Foundation.

research without borders

His reach extends beyond provincial borders. He has compiled the world's largest database on women with the BRCA mutations.

Doing research that saves lives is his life. Dr. Steven Narod, a clinical scientist at Sunnybrook & Women's Research Institute's partner organization the Centre for Research in Women's Health, leads massive studies, nationally and internationally, on how to prevent and treat breast cancer in women at high genetic risk for the disease.

Narod was part of the team that identified the genes involved in breast cancer, BRCA1 and BRCA2. Recognized as a leader in the field – he holds a Tier 1 Canada Research Chair in Breast Cancer – he publishes papers that are cited widely and have maximum impact.

In 2002, he published findings that were trumpeted in media reports: *Pill alert for cancer risk women*, was one British headline. More precisely, Narod and colleagues found there was a slightly higher risk for some women with the BRCA mutations. "What we showed in fact was that there was a small increased risk that seemed to be restricted to women who took it before age 25 for longer than five years," he says.

The study arose because the researchers wanted to ensure the commonly taken pill did not raise the risk of breast cancer. Also, Narod had already shown that women could lower their risk of ovarian cancer, which BRCA gene carriers are at higher risk for, by 60% by taking the pill. "So there was potential for enormous benefit, but people were reluctant to take it, because they thought there would be a risk of breast cancer." With these rationales, Narod started the study, aiming to show the pill was safe.

In the end, the results weren't unqualified, but they were still highly reassuring for most women, media spin aside. "We published enormously strong findings on that, and they keep getting stronger year after year," says Narod. "I thought by showing it was safe, we'd be able to save lives, which is what I think we did." He recommends women take the pill for three years after age 25. "You should get a 60% reduction in the risk of ovarian cancer without any increased risk of breast cancer."

Whether women follow the advice is another matter, and a challenge and source of fascination for Narod. "One of the problems psychologically is that if something is shown to increase the risk at all, people tend to shy away from it. They don't do a risk-benefit analysis." He cites the example of tamoxifen, which researchers believe slashes the risk by half of breast cancer in gene carriers, but which carries a small risk of endometrial cancer. Knowing this, what do women tend to do? Not take the tamoxifen.

As a public health doctor, he takes seriously the implications of faulty risk perception. He wants his research to have as big an effect on as many people as possible, perhaps even to influence policy, as it did in 2000 when Ontario introduced genetic testing for ovarian cancer patients based on one of his papers that said 12% of ovarian cancer patients have a BRCA1 mutation.

His reach extends beyond provincial borders. He has compiled the world's largest database on women with the BRCA mutations. He is studying between- and within-country variations in prevention and treatment practices for breast cancer across 13 countries. The work demands 100%. As he notes matter-of-factly, it's no hobby. "I love the science. This is what I do for a living." SR

The Canadian Breast Cancer Research Alliance and the Canadian Breast Cancer Foundation (Ontario chapter) funded this research.

Neil Cashman and researchers at Caprion Pharmaceuticals Inc. found a way to make the immune system specifically recognize infectious prions, proteins that cause brain-wasting diseases. These diseases include bovine spongiform encephalopathy (BSE), or mad cow disease, and human variant Creutzfeldt-Jakob disease. This critical discovery paves the way to the development of new diagnostic tools and therapeutics for prion diseases.

Anthony Feinstein and colleagues examined the relationship between major depression and brain abnormalities in people with multiple sclerosis, a disease of the central nervous system. They found two independent predictors of depression, one related to lesion volume, the other to cerebrospinal fluid volume, which together accounted for 42% of the depression variance score. Based on these findings, they concluded that although structural brain abnormalities appear to be related to depression in MS, psychosocial influences should also be considered.

Jorge Filmus and colleagues discovered a biochemical marker that differentiates hepatocellular carcinoma (HCC), the most common type of liver cancer, from non-cancerous liver diseases. HCC has a high death rate if it is not caught early. Finding a molecular marker could improve early detection and be used to screen people at risk of HCC, like those with hepatitis B or C. Filmus has parlayed this discovery into a new diagnostic tool to screen those at high risk.

A proof-of-principle study by **Stuart Foster** and colleagues showed the feasibility of using high-frequency Doppler (HFD) ultrasound to monitor the effects of therapies that act on the blood flow of tumours. HFD was effective in imaging small tumours in mice in three dimensions at high resolution. These finding suggest HFD could be used to track, over time, the effectiveness of antiangiogenic therapies, which aim to halt the growth of blood vessels that feed tumours.

Alan Moody and colleagues in the United Kingdom found that magnetic resonance direct thrombus imaging (MRDTI) accurately detects complicated carotid plaque in patients with cerebral ischemia, or reduced blood flow to the brain. This type of "high-risk" plaque is associated with a risk of blocked blood vessels, which, if blocked long enough, could lead to a stroke. These findings suggest that MRDTI, which is non-invasive, and simple and quick to do, has high applicability as a technique for research and clinical investigations of atherosclerotic disease.

Research by **Robert Nam** and **Steven Narod** showed that the combination of a polymorphism of the KLK2 gene and hK2 serum levels was highly predictive for prostate cancer, the most common cancer diagnosis for men. This combination also enhanced the predictive value of known risk factors, including age and prostate-specific antigen level. These findings could help to identify subgroups of men who are either at high or low risk of prostate cancer.

Shun Wong and colleagues did the first study to show that the death of endothelial cells initiates acute disruption to the blood-brain barrier in the central nervous system after X-ray therapy. They also identified a pathway that mediates the disruption of the blood-brain barrier. These findings have implications for developing new neuroprotective strategies and targeted ways to improve drug delivery in the treatment of brain tumours.

Research by **Graham Wright** and colleagues showed that changes in microcirculation oxygen levels during the dilation of blood vessels can be used to measure the heart's blood flow reserve without directly measuring blood flow. They found that these changes were sufficiently sensitive to differentiate normal from abnormal muscle tissue of the heart. Non-invasive tests that have this differentiation capacity could be used to help predict the clinical benefit of surgical or other procedures for patients with coronary artery disease.

H I G H L I G H T S

mighty bubbles

"People don't understand bubbles," says Burns, holding the vial in his hand. "They think that if you inject bubbles, you must be intending harm." This is far from the truth.

There's a lot to catch the eye in the office of Dr. Peter Burns, a senior scientist at SWRI. There's the mass of books heaped on shelves, their spines spiked with colour. There's the sixth-floor view of sky and green pines in the distance against it. There's a vial of what looks like white powder, which wouldn't be at all interesting if it didn't hold the stuff that enables Burns and others to see blood vessels too tiny to be seen otherwise: microbubbles.

"People don't understand bubbles," says Burns, holding the vial in his hand. "They think that if you inject bubbles, you must be intending harm." This is far from the truth. Not only are the microscopic bubbles of encapsulated gas harmless, they're also useful, because they give information about the smallest of our blood vessels. For example, during a heart attack, they show where blood flow is poor. In cancer, they can show where angiogenesis, the birth of tumour-feeding vessels, is happening.

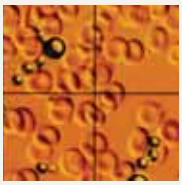
Less than a droplet of microbubbles is injected into a vein. Viewed with an ultrasound technique developed at SWRI, the bubbles look bright as they swim through the bloodstream. The tissue looks dark. This is because of the bubbles' acoustic properties. "We excite the bubbles to ring like a bell. Just as a resonant source of sound stands out, so these bubbles stand out in their acoustic surroundings," explains Burns.

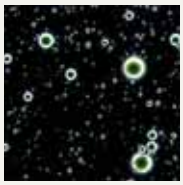
Many clinical research centres are already using microbubble techniques to diagnose heart disease. And recent studies in liver cancer, a disease where early detection might mean recovery rather than death, have affirmed the method works. It can be used to guide new minimally invasive therapies and to verify that a tumour has been completely removed, all without the patient leaving the table. Furthermore, it's less expensive than other imaging methods.

An angiogenesis-tracking method Burns is refining adds more information. It helps doctors to identify benign and cancerous tumours in real time. Burns explains it using the example of watching cars travel from above. Individual cars cease to be recognizable; instead, you see arcs of brightness that illuminate their path. Because blood vessels sprout chaotically from a tumour, unlike in normal tissue, their travel appears random as viewed on a screen with this tracking method.

Looking ahead, it has other potential clinical uses, like testing the effects of antiangiogenic therapies and as a simple test in emergency rooms to see if chest pain is related to blood flow in the heart. This research is still in the translational stage. But, as Burns notes, shaking the vial slightly, this is the natural course of medical research. "You must remember that the advance of even obstetrical scans, which we now take for granted, took decades." SR

This work is supported by The Terry Fox Foundation and the Canadian Institutes of Health Research.





by accident

Remembering the excitement that hypertonic saline provoked in Brazil and seeing the clinical need first-hand, Rizoli threw himself into the subject.

An accident started the ball rolling. In the 1970s, doctors in Brazil mistakenly injected a small amount of highly concentrated saline solution into a patient in shock and found it stabilized blood pressure.

It was great news. For a while, many believed this concentrated solution, called hypertonic saline, was the ideal resuscitation fluid for trauma patients. But further study revealed that stabilization of blood pressure had no effect on survival. Oops. The clinical use of hypertonic saline was abandoned.

But a recent 27-person clinical trial led by Dr. Sandro Rizoli, director of trauma research at SWRI, hints that hypertonic saline may be an effective treatment after all.

In the mid-1990s, when Rizoli was beginning his doctoral studies in Toronto, research was starting to suggest that hypertonic saline could regulate the immune system in non-human models, a result that may improve long-term survival of trauma victims.

Recent advances to the care offered to patients immediately after an accident means that many more survive initial hemorrhage. Now, Rizoli explains, "If you are involved in a car accident, chances are you will not die from the initial trauma itself, but from multiple organ failure weeks later in the intensive care unit. Hemorrhage is not the direct cause of death but it often results in organ failure."

After major trauma, particularly when the body goes into shock, the immune system mounts a huge inflammatory response. Ironically, the very means that the body uses to protect itself backfires and causes organs to shut down. Therefore, if you can regulate the inflammatory response of the immune system, you may increase long-term survival.

Remembering the excitement that hypertonic saline provoked in Brazil and seeing the clinical need first-hand, Rizoli threw himself into the subject.

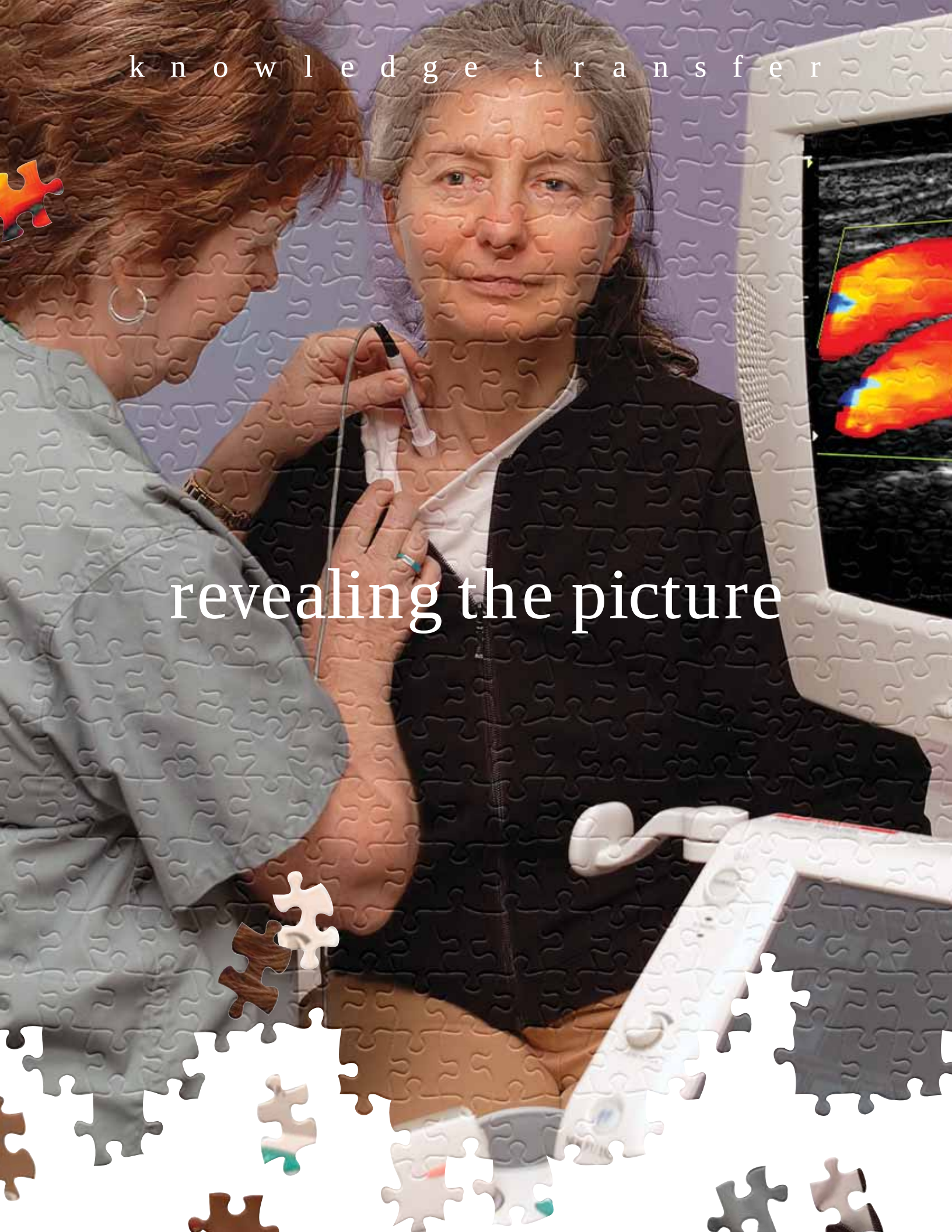
Interest in hypertonic saline is exploding. Building on Rizoli's small study funded by Defense Research and Development Canada, another 100-person trial led by scientists at St. Michael's Hospital and Sunnybrook & Women's, including Rizoli, is looking for definitive answers as to whether hypertonic saline can prevent organ failure in trauma patients. A larger National Institutes of Health trial involving 10 centres across North America is planned to start soon after.

Rizoli's fascination with hypertonic saline stems not only from the impact it could have clinically but also how it exemplifies the winding path that discovery takes. The accidental eureka in Brazil in the 1970s led to laboratory work on model systems in the 1990s, which is now provoking this new spate of clinical trials.

"It started as a clinical problem, then became basic science, and we are now moving back to the bedside, this time with a different premise: modulating inflammation and preventing patients from developing multiple organ failure," he marvels.

This often complicated interplay between laboratory science and clinical care is what drives Rizoli to juggle a busy schedule as both a trauma surgeon and researcher. "I think there are two motivators to do basic science: an interest in understanding things, and the hope that one day you are going to apply it to patients," he says. "And hypertonic saline is a beautiful combination of both." SM

Photo: Charge technologist Dianne Brodie does a carotid ultrasound exam to image the carotid arteries, the vessels in the neck that deliver blood to the brain. This test can detect narrowed or blocked arteries.



revealing the picture

Instant gratification?

It's not exactly common in research, and most will agree instant is a relative term. When much of the most clinically critical science–such as preventing and curing disease–takes lifetimes to do, studies that can be done in a few years and affect patient care soon after are Superman fast.

Dr. Jack Tu, an internist at S&W and a senior scientist at the Institute for Clinical Evaluative Sciences, or ICES*, cross-appointed to SWRI, has done several such studies recently.

The challenge now, says Tu, is to develop guidelines on consent and educate people about how registry research benefits society.

In one, he looked at heart failure. It's the most common reason why Canadians go to hospitals, but until this study in 2003, doctors couldn't tell which patients were most likely to die after heart failure. Tu and graduate student Doug Lee, the lead author, found that older age, lower blood pressure and comorbid illnesses, among other factors, were critical. Then they worked to get these findings to those best placed to use them.

What emerged was a Net-based, clinician-friendly predictive risk model and scoring system. "Doctors from all over the world can logon to our Web site and figure out immediately what their patients' risk of dying is in the next 30 days and the next year," says Tu. "They punch in their patients' characteristics, and the computer spits out what their likelihood of dying is."

Within days of the article's appearance in *The Journal of the American Medical Association*, they had received hits from seemingly everywhere."We're probably at over 10,000 hits now," says Tu. No wonder. It's free, takes five minutes and helps doctors to save lives.

He also gets far-flung e-mail for another study, although given the topic, not all are positive. Tu examined the practicality of getting informed consent from everyone entering a clinical – in this case stroke – registry. A registry compiles data on every occurrence, treatment and outcome of a condition. It captures no names. These data allow scientists to do observational studies that track diseases over time. To be valid, the results must be from everyone with the condition.

Tu's conclusion? "Although it's desirable to try to get consent from everybody, it's often not practical." There were too many people, and some left hospital or died before consenting. Others couldn't consent, for example, because they didn't understand the language. This left a biased sample. *The New England Journal of Medicine* published the results in April 2004.

Reaction was swift. Researchers were supportive. Privacy advocates, less so. The challenge now, says Tu, is to develop guidelines on consent and educate people about how registry research benefits society. "We can determine how often cancer occurs in Canada due to the cancer registry, but if (Cancer Care Ontario) had to get informed consent from everyone, the registry would probably collapse overnight. It would be a real disservice to the health of Canadians."

Although measuring the study's impact is tricky, Tu speculates it has informed the thinking of researchers, ethics boards and perhaps even Ontario's privacy commissioner, with whom he spoke. "There's been a worldwide push for researchers doing observational studies to get informed consent. I think it reversed the momentum toward that, because people are realizing it's not going to be practical," he says.

Research with the power to reverse momentum? Beat that, Superman. SR

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*ICES is an independent, non-profit organization funded by the Ministry of Health and Long-Term Care. It uses population-based health information to produce unbiased knowledge on health care issues. It is located on the Sunnybrook campus, and many scientists in clinical epidemiology at SWRI work at ICES. Of his work at both, Tu says, "It's a synergistic and symbiotic relationship. I've benefited greatly from having both the research grants through Sunnybrook and the funding through the Ministry."

The Canada Foundation for Innovation, Canadian Institutes of Health Research, and Heart and Stroke Foundation funded these studies. Tu holds a Tier 2 Canada Research Chair in Health Services Research.

a labour of love

"We knew it would be a major undertaking," she says. "Many people thought it would be an impossible task."

Labour and delivery is hard work for mothers and doctors alike. But when Dr. Mary Hannah stepped out of the delivery room in 1989, the work didn't end there. Her 26-country randomized controlled trial comparing planned vaginal delivery versus planned caesarean sections for breech babies gave "labour" a whole new meaning.

Driven by her fierce desire as an obstetrician to make birth as safe as possible, Hannah, who is also an SWRI senior scientist and director of the Maternal Infant and Reproductive Health Research Unit at the Centre for Research in Women's Health, decided to test which delivery method was best for breech babies and their mothers. Since breech births occur in only 3% to 4% of pregnancies, a trial large enough to get definitive results needed significant international participation.

"We knew it would be a major undertaking," she says. "Many people thought it would be an impossible task."

The "impossible task" produced results so important that two prestigious journals, *The Lancet* and *The New England Journal of Medicine*, vied to publish them, with *The Lancet* fast-tracking publication a mere four weeks after submission date.

But a long, long gestation period lasting 11 years led up to the initial publication in October 2000. First, extensive preparatory work convinced Hannah that the undertaking was possible. And so began years of networking and cajoling.

A grant to fund the study was not awarded until 1996, due to the constrained budget of the Medical Research Council (now the Canadian Institutes of Health Research) in the 1990s.

Impeccable study design was key to good results. But as important was motivating the caregivers across the globe who submitted data and followed-up with families.

Hannah found herself on the road weekly, visiting existing sites, recruiting new sites and generally trying to keep up the level of enthusiasm. "The travel can take away from your family life," she sighs.

Motivated collaborators were critical, as the shoestring budget meant the work relied heavily on volunteer labour. And Hannah is proud that the participation rate was exceptionally high, even with years of follow-up.

Hannah's study found that the risk of death or serious complications for infants was significantly lower for the planned caesarean group versus the planned vaginal delivery group (1.6% versus 5.0%). For many of her collaborators, who were comfortable with vaginal breech deliveries, "The fact that caesarean section came out on top was a disappointment," she says. "It was a surprise that C-sections are now so safe." Follow-up studies published in 2002 and 2004 revealed a lower risk of urinary incontinence at three months postpartum for mothers in the planned caesarean group but no significant difference in outcomes two years after the birth for children or mothers for the different delivery methods.

"The impact on clinical practice was huge and immediate," Hannah says, citing international papers and new clinical practice guidelines for the United States. Her research has also spawned other major trials investigating delivery methods. As no large randomized trial comparing safety of delivery method had ever been conducted, the results had implications for more than just breech births.

After such a laborious journey, how does it feel to achieve such influential results? "It's satisfying work," she says. "This field attracts people who want to make a difference." SM

RAPID RESEARCH RESPONSE

The ease and speed with which severe acute respiratory syndrome (SARS) spread from Southeast Asia throughout the world in March 2003 created an urgent need to understand its clinical symptoms and epidemiology – especially in Toronto, one of the earliest and hardest-hit areas outside of Asia. A research group involving S&W's Dr. Andrew Simor and researchers at Mount Sinai Hospital and the University of Toronto responded to this need with an expedited online publication describing the clinical features of SARS in Canada in *The New England Journal of Medicine* in March 2003, just weeks after Canada's first SARS case.

Simor, director of clinical integrative biology research and head of S&W's department of microbiology, says, "This article was among the first in medical literature worldwide on SARS, and really the first to provide a detailed clinical description of the disease."

It also provided an epidemiological map of the close contact and resulting transmission of disease among Canada's first 10 SARS patients while identifying potential risk factors and outlining treatment efficacy. The study helped lay the groundwork for more research on SARS and led to the development of treatment and containment methods that kept it from becoming a full-blown epidemic. "I think this study speaks to the rapidity with which the community mobilized to respond to this emergency," says Simor.

In an era of frequent international travel, Simor believes that a new and similarly dangerous respiratory outbreak is likely to occur again, and that SARS was "an important example of why we need to be aware and prepared" for this eventuality. Preparation requires the capacity to conduct high-impact epidemiological research swiftly.

centre for research in women's health

Drs. Mary Hannah and Gillian Hawker, profiled on pages 26 and 28, respectively, are just two of the outstanding researchers associated with the Centre for Research in Women's Health (CRWH) and Sunnybrook & Women's Research Institute.

Established in 1996 as a partnership between the University of Toronto and Sunnybrook & Women's, CRWH works to bring together researchers who are dedicated to understanding the conditions that have the greatest effect on women and disseminating that knowledge around the globe to improve women's lives.

"Multidisciplinary collaboration is vital to creating health research that gives us comprehensive information about women's health," says CRWH director Heather Maclean. "We bring together health care professionals with basic and social scientists from across the University of Toronto and with members of community organizations, because all of them have unique perspectives on women's needs."

To help diverse groups work together, CRWH has made knowledge exchange an increasingly important focus. CRWH investigators strive to present their findings in ways that are useful to clinicians, policy makers and community members and to integrate the people who will use research knowledge into the process of creating it. CRWH partners with community agencies and helps S&W clinicians like those at the Women's Cardiovascular Health Centre gather data to evaluate their work. CRWH hosts workshops and seminars and publishes a range of resources, like Globalization and Health: The Gender Dimension, to influence how policy is made and care is delivered.

Active in mentorship and teaching, CRWH is shaping the future of women's health. Graduate student awards, the summer student program and events like the annual graduate student research day all contribute to fostering critical skills in tomorrow's researchers.

Gillian Einstein, associate director, University of Toronto Partnerships, says it is essential to offer students a perspective that integrates disciplines as diverse as physiology, immunology, public health and feminist studies. "We need to provide a comprehensive intellectual grounding in the many fields that can contribute to women's health. We want researchers who can build on what we know about the reproductive body and move forward with new investigations about why women are more likely to carry the burden of autoimmune disease, or how the interaction of mood and the reproductive cycle affects women's mental health."

By integrating scientific and humanistic perspectives, CRWH ensures that women's health is examined from cell to society to create better, more relevant research to improve women's lives.

For a closer look at CRWH, visit http://www.crwh.org.

this time, it's personal

The underlying message? "We don't have universal access to health care – we have a long way to go," says Hawker.

Dr. Gillian Hawker loves a challenge. Having decided to conduct research into joint replacement, the gutsy scientist and her team began by surveying an incredible 48,000 people: every individual over 55 years of age in Oxford County, which has one of the highest rates of joint replacement in Ontario, and in East York, which has one of the lowest. A cohort of 2400 identified as suffering from joint pain were followed-up. The gargantuan task took three years.

Hawker, SWRI senior scientist and director of the Osteoporosis Research Program at the Centre for Research in Women's Health, focused on what factors, including need and willingness to undergo joint replacement, cause rates of the procedure to vary across the province, and if socioeconomic status or sex affects access to the operation.

Her findings led to a publication and an editorial in *The New England Journal of Medicine* in 2000, with related publications in other prestigious journals over the next four years. The research provided sobering food for thought on how we manage and can improve the health care system.

Hawker found a large discrepancy between the number of women and people with lower socioeconomic status who needed the surgery and those offered it. Hawker's methods, which involve getting information from an entire population, regardless if the individuals have interacted with the health care system, point out the limitations of common sense in determining policy.

"The numbers of joint replacement procedures we perform in women is much higher than in men," she says, "so we think that we are doing a good job. In fact, three times the number of women with horrible arthritis wanted the surgery and had never been offered it. So, administrative data like the number of operations performed doesn't give any clear understanding of what is actually happening." The underlying message? "We don't have universal access to health care – we have a long way to go," says Hawker.

She also found Oxford County's rate of joint replacement was higher partly because its prevalence of severe arthritis was greater – unsurprising for a farming community – and also because area residents were more willing to consider the surgery. "Prior to this study," Hawker says, "the government thought we should bring the low rates up to the average and eventually bring the high rates down. Our study showed that area variation is a normal phenomenon that responds to patients' needs and demands."

The drive to improve the health care system is a huge motivator for Hawker. But "by far the best thing," she says, is the personal connection she and her team of "the best interviewers in the whole wide world" have made with the people in East York and Oxford County with joint pain who volunteer the information needed to conduct her research. It's a bond that makes her a passionate advocate for people with osteoarthritis.

"These people write just to tell us how critical we have been in their lives, how much they appreciate being part of the study, how much they gained. They're just incredible people – incredible," she says. "You can't do anything without the people behind this, and they are phenomenal." SM

The Canadian Institutes of Health Research and The Arthritis Society of Canada fund Dr. Hawker's research.

a sound venture

This creation sped up the process of scientific discovery. "Many more mice could be examined, many more drugs could be tested and more disease models could be researched," says Foster.

Genetically altered mouse models of human disease are critical to understanding how diseases work and to creating and testing treatments for humans. But once you tinker with a mouse's genetic makeup, how do you know what effect the altered gene has had in that mouse? How can you tell if an experimental treatment is working?

As genomic research was erupting in the late 1990's, scientists were grappling with these problems, looking for efficient, non-invasive ways to track the progress of their experiments.

That's where Dr. Stuart Foster and his lab came in. Funding from the National Cancer Institute of Canada and the Canadian Institutes of Health Research allowed them to create a new ultrasound tool incorporating high-frequency transducers that made tiny physiological details – such as the blood flow feeding a mouse tumour – visible.

This creation sped up the process of scientific discovery. "Many more mice could be examined, many more drugs could be tested and more disease models could be researched," says Foster.

The demand for this new technology was so great that Foster, with support from the Ontario Research and Development Challenge Fund (ORDCF), formed VisualSonics Inc., a start-up that has grown to 58 employees over the last five years. "The genome creates the questions," Tom Little, president and CEO of VisualSonics, Inc., says. "The animal models give us the answers. The things we're seeing continue to amaze me."

VisualSonics has since redeveloped the original prototype and sold 150 new systems to organizations like the National Institutes of Health, Harvard University and Stanford University, as well as most major pharmaceutical companies.

Creating this humane, non-invasive technology was "the tricky part," says Foster. But forming and funding a new company was not as easy as setting up a lemonade stand in your front yard. Commercialization through the investment of government and the private sector is an important way to expedite the development of new technology beyond that which academic funding can support. The process, Foster says with a raised eyebrow, was "very educational."

"Scanning mice as a commercial venture – that doesn't mean a lot to most venture capital people," says Foster. He notes that funding from ORDCF, in which industrial dollars are matched by the Ontario government and support from an institutional partner (SWRI was a willing participant in this case), was crucial.

Little agrees. "The ORDCF program allows us to invest in basic research that we otherwise could not afford to do." VisualSonics continues to grow and expects about $20 million in equipment sales in 2005. Any proceeds to SWRI, which is of course a non-profit organization, are rolled immediately back into research. Foster and his lab – which includes some 22 people Foster is quick to credit – are continuing to improve ultrasound techniques. And it is this – the drive to get helpful technology to the people who need it – that motivates him.

They are applying their ultrasound technology in studies using mouse models aimed at identifying and optimizing the selection of drug therapies in conditions like glaucoma, melanoma, and breast and prostate cancer. The next step is to use the technology in clinical trials. As Foster notes, it can take a long time for a drug to go from basic discovery to being approved for human use – up to 20 years for some. Thanks in part to Foster and his lab, the next generation of cancer therapy and ocular medications is likely to be in people's medicine cabinets much sooner.

Photo: Scientist Dean Rowe-Magnus and research technician Mira Cucuri discuss lab results. Rowe-Magnus's group is studying the evolution of bacterial pathogens by lateral gene transfer.

David Alter and colleagues revealed a risk-treatment paradox for lipid-lowering statins in high-risk patients. Analyzing data on almost 400,000 elderly people in health care administrative databases, they found that the prescribing of statins fell as baseline cardiovascular risk and probability of death rose. Because the benefits of statin therapy depend on baseline risk, the full benefits of this therapy might not be seen until it is expanded to include patients at highest risk.

With colleagues at the Institute for Clinical Evaluative Studies (ICES), **David Alter** found that people with higher levels of income or education were more likely to receive specialized services or be followed-up by a cardiologist after having a heart attack, compared with people with lower levels of income or education. They were also more likely to be dissatisfied with access to specialized care and to prefer out-of-pocket fees for wider access to more treatments.

Anthony Feinstein and colleagues found that journalists reporting on war have more psychiatric disorders than do other journalists. The research was the first to explore the psychological well-being of war correspondents. Collaborating with CNN, BBC and other major news groups, they found that war journalists have higher rates of post-traumatic stress disorder, depression and alcohol drinking but are not more likely to get treatment.

As part of the Toronto SARS Critical Care Group, **Robert Fowler** studied the outcomes of people with SARS-related critical illness who were in intensive care during the outbreak. They found that critical illness was common among these patients. Those who died were more likely to be older or have diabetes already. One-half of those who died had needed mechanical ventilation. The outbreak greatly strained regional critical care resources.

Janet Hux and colleagues at ICES tracked changes in drug prescriptions among elderly people in Ontario in the weeks after the September 11, 2001 attacks in the U.S. They looked at claims for antidepressants, sedatives and antibiotics, the last as an indicator for anxiety about anthrax. The trends for antidepressants and sedatives were similar to those in 1999 and 2000 for the same period, but there was a slight increase in the dispensing of the antibiotic ciprofloxacin after October 4, 2001, when the first anthrax infection was reported in the U.S.

In a population-based study, **David Juurlink** and colleagues found that elderly patients who were admitted for drug toxicity were likely to have been prescribed a drug known to cause drug-drug interactions in the week before they were admitted. They concluded that many of these interactions were avoidable. These findings have implications for preventing deaths in this vulnerable population and reducing the costs of hospitalization due to drug toxicity.

Trauma researcher **Jacques Lee** and colleagues found a way to define the minimum clinically important difference for the visual analogue scale (VAS) of pain severity, a common pain-rating tool. Patients rate their pain on the VAS from 0 mm, no pain, to 100 mm, the worst pain possible. In a sample of emergency department patients, Lee found that, on average, a reduction of 30 mm in the VAS represents a clinically important difference in pain severity that corresponds to patients' perception of adequate pain control after taking pain-relieving drugs.

In an Ontario-based database study, **Donald Redelmeier** and colleagues found that enforcing traffic laws reduces the rate of fatal motor vehicle crashes. In another study on traffic, Redelmeier found that there was a 41% jump in driving fatalities on Super Bowl Sunday, higher than that even for New Year's Eve. The number of fatalities was lowest in states with a winning team. Both of these findings have important implications for policy-making.

With colleagues in the United States, **Donald Redelmeier** found that hospitalized patients in Canada and the States that were isolated for infection control reasons had more preventable adverse events, were more likely to complain about their care and didn't have as much of their care documented, compared with control patients. These findings highlight the need to ensure the system is designed to ensure the safety of all patients in hospitals.

Andrew Simor and colleagues in the Ontario Group A Streptococcal Study did the first modern population-based study of the clinical and epidemiological features of group A streptococcus (GAS) pneumonia. They found that it is a common form of invasive GAS disease that can affect all ages, and that time to death was rapid, faster than for GAS necrotizing fasciitis, despite therapy. Although rare, its frequency has risen and is similar to that for necrotizing fasciitis. These findings have implications for instituting new therapies early in the disease.

Ken Shulman and colleagues documented a shift in prescribing drugs to treat bipolar disorder in elderly people. From 1993 to 2001, they found that there were fewer "new users" of lithium, and more of valproic acid. By 1997, the number of new users of valproic acid had surpassed those of lithium, which continued to fall. They noted that this shift happened despite a lack of evidence showing that valproic acid works better or is safer.

H I G H L I G H T S

funding new puzzles and new puzzle-solvers

Two donors, two medical challenges, one reason for donating to research at Sunnybrook & Women's:

because they believe in the power of research to heal and in the scientists that are making it happen. "Without research, I don't think we'd get anywhere," says Gabi Weisfeld. "It's the only way we can go ahead," agrees Barbara Hollander.

Weisfeld took part in a clinical trial on shoulder replacement surgery led by Dr. Richard Holtby, an orthopaedic surgeon at the Orthopaedic & Arthritic Institute campus of Sunnybrook & Women's. In this trial, patients undergoing shoulder replacement received either a cement injection or no cement injection.

Left to right: Mrs. Gabi Weisfeld and Mrs. Barbara Hollander.

"Sunnybrook & Women's is a treasure," Hollander says. "It's world-renowned, certainly in all of the reading that I've done..."

Although the 74-year-old doesn't know which group she was in, she feels much better. "I was suffering too much pain from arthritis. I had no shoulder left. Now, I don't have pain in the middle of the night that wakes me up." She can't wait to play tennis again.

Weisfeld's generosity wasn't tied to any specific outcome. Results haven't even been published. Rather, it's linked to a belief in the transforming power of research, especially as directed by people like Holtby, who did a "magnificent job." And that, matched by a giving nature, led her to donate. "This can help me and others lead a more productive and comfortable life. And it's thanks to research."

Hollander has similar views. As a former researcher in psychology, she believes that medical research is essential to advance knowledge and help people live longer and happier lives.

She participated in a clinical trial comparing a new type of radiation therapy called intensity modulated radiation therapy, or IMRT, to standard radiation therapy. Radiation therapy is given after a lump is removed to help stop cancer from returning. IMRT delivers thin beams of high-dose radiation precisely to a tumour, thereby sparing healthy tissue and lowering the rate of painful effects of radiation.

Drs. Jean-Philippe Pignol and Veronica Benk led the study at the Toronto Sunnybrook Regional Cancer Centre, where each day for five weeks Hollander received one of the therapies. In a clinical trial, it's important that participants don't know which group they're in, in case this affects the results, so Hollander, like Weisfeld, doesn't know which treatment she received. "I had the gut feeling that I might have had the trial therapy, because I didn't have any redness," she confides. "It's not new skin, but it feels like new skin." The doctors have told the energetic 70-year-old that the prognosis is very good.

Ever research-minded, she read extensively on breast cancer research. She found ample evidence of the hospital's leadership in the area.

"Sunnybrook & Women's is a treasure," she says. "It's world-renowned, certainly in all of the reading that I've done. They're making a world-class organization, and they have the top people – have you read Dr. Pignol's resume? I mean, how many degrees can you get?" she says laughing. This, coupled with a "very impressive" experience in the trial, compelled Hollander to donate.

"I felt like it was the thing to do. I feel that if you can, you should," she says.

And, as Weisfeld notes, every dollar counts. "You don't have to be a billionaire, believe me," she says. "You just have to be cognizant of what's out there and what's needed." SR

a primer on education at swri

Education and research are linked inextricably at SWRI. Scientists teach at the University of Toronto, with which the research institute is fully affiliated, and they act as mentors to the graduate students who work in their research groups and labs at SWRI.

"Education is very important," says Dr. Juan-Carlos Zúñiga-Pflücker, coordinator of the specialist program in immunology at the University of Toronto and senior scientist at SWRI. "Grad students are given the opportunity to try out and develop new things from the ground up, which is important. They also take ownership of their work as they go along."

SWRI is not only training the established scientists of tomorrow, but guiding the young scientists of today. Together, researchers and students work on projects that often succeed in being published in high-impact journals. As the stories in this report have shown, students have had a hand in achieving some of the most thrilling findings.

Many were first authors on the studies. For example, Tom Schmitt helped Zúñiga-Pflücker figure out how to make T cells in a Petri dish. Doug Lee helped Jack Tu develop a risk model to predict death after heart failure. Each of these findings was a major contributor to medical research.

In addition to new graduate students, each year SWRI welcomes new post-doctoral fellows and research trainees, like engineers and physicists, into its labs. They get the chance to refine their skills as they apply their expertise to research problems, and SWRI gets the benefit of that expertise. The relationships are symbiotic: space and mentorship from the researchers and keen minds and fresh perspectives from the students, fellows and trainees.

industry partner: sanofi pasteur

Research breakthroughs require ingenuity, patience, a dedicated team and sustained funding support. Private-sector contributions often provide that support, to the benefit of the company and the research enterprise. Sunnybrook & Women's Research Institute has many industrial partners who are investing in the expertise of the research and researchers here. Their common aim is to generate discoveries that will fuel the capacity of their companies to innovate.

One partner is sanofi pasteur, the vaccines business of sanofi-aventis Group. Sanofi pasteur is Canada's largest vaccine company. It sponsors research at SWRI through its Cancer Vaccine Network, which Industry Canada's Technology Partnerships Program also supports.

The work aims to harness the body's built-in ability to destroy unwanted cells and thereby control or eliminate tumours. This requires an in-depth understanding of the immune system, a specialty of scientists at the research institute.

Senior scientist Dr. David Spaner receives funding from the Cancer Vaccine Network. The company supplies the vaccines that he tests in clinical trials. His aim is to find ways to increase the effectiveness of the vaccines. Sanofi pasteur then uses this knowledge as the basis for developing new and improved vaccines. "We couldn't do these trials without them," says Spaner. "They provide the vaccines and we provide them with an understanding of how those vaccines are working."

The $600,000 that sanofi pasteur gives to SWRI annually for cancer vaccine research is vital, but the gains are greater still. Having the world headquarters of sanofi pasteur's Cancer Vaccine Program at the research institute enables close interaction among the scientists and staff. And, as Spaner notes, students benefit too. "Exposure to sanofi pasteur scientists creates a more robust research environment, and this is of clear benefit to the students."

Below we spotlight some especially notable achievements of scientists at Sunnybrook & Women's Research Institute from 2002 to 2004.

canada research chairs program

Steven Narod and **Donald Redelmeier** were awarded Tier 1 Chairs in Breast Cancer and Medical Decision Sciences, respectively. They join previous Tier 1 recipients, **Mark Henkelman,** who holds the Chair for Imaging Technologies in Human Disease and Preclinical Models; and **Robert Kerbel,** who holds the Chair for Molecular Biology and Applied Genomics. **Jack Tu** has a Tier 2 Chair in Health Systems and Knowledge Transfer.

canada foundation for innovation: new opportunities funds

These were awarded to four new scientists: **Michele Anderson, James Booth** and **Jonathan Rast,** in molecular and cellular biology; and **Dean Rowe-Magnus,** in clinical integrative biology.

national cancer institute of canada prizes

Daniel Dumont received the William E. Rawls Prize, bestowed annually on an investigator whose work has led to the advance of cancer control. Dumont discovered new proteins critical to angiogenesis and a way to turn their activity on and off in mice. **Robert Kerbel** received the Robert L. Noble Prize, given annually for outstanding achievement in cancer research. He has made pioneering discoveries in tumour angiogenesis, antiangiogenic therapy and drug resistance.

ontario research development challenge fund (ordcf)

In 2002, the ORDCF funded the **Advanced Regenerative Tissue Engineering Centre,** a $12.6 million initiative in collaboration with the University of Toronto. **John Semple** and **Kim Woodhouse** lead the project, which aims to solve issues in burn, trauma and cancer treatment. ApoPharma (Apotex), Elastin, Rimon Therapeutics and Matregen are partners.

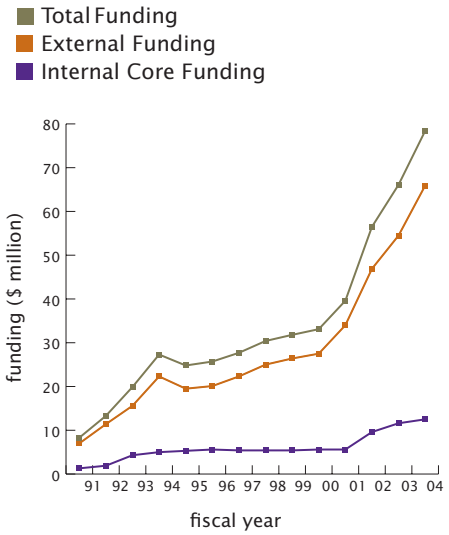
The ORDCF also funded the **Ontario Consortium for Small Animal Imaging** in 2002. This is a $39.5 million project to which more than a dozen industry partners contribute. Led by **Stuart Foster,** it aims to develop and refine micro-imaging technologies to establish Ontario as the main supplier of these for the genomics and drug development industries. Other partners are the Hospital for Sick Children, McMaster University and Robarts Research Institute.

other awards

- The Governor General of Canada awarded **Stuart Foster,** a senior scientist in imaging, a Queen's Golden Jubilee Medal.
- The Canadian Institutes of Health Research gave **Robert Jankov,** a scientist in molecular and cellular biology, a Career Development Award.
- The Canadian Society of Internal Medicine awarded **Andreas Laupacis,** a senior scientist in clinical epidemiology and president and CEO of the Institute for Clinical Evaluative Sciences (ICES), a Senior Investigator Award.
- The Society for Academic Emergency Medicine gave **Michael Schull,** a physician at S&W and a scientist in clinical epidemiology at SWRI, a Young Investigator Award.
- The Royal Society of Canada elected associate imaging scientist **Donald Stuss** to fellowship.
- The U.S. Commonwealth Fund and the Canadian Health Services Research Foundation selected **Jack Tu,** a scientist in clinical epidemiology cross-appointed to ICES and a general internist at S&W, as a Canadian Harkness Associate in Health Care Policy.

quick statistics

history of research expenditures at sunnybrook & women's research institute

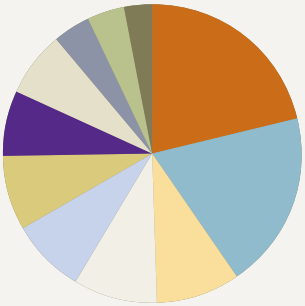


research staff

Senior scientists and scientists	79
Associate scientists	98
Research associates, engineers and physicists	68
Laboratory technicians and research assistants	149
Research fellows and graduate students	147
Total	541

major sources of external funding

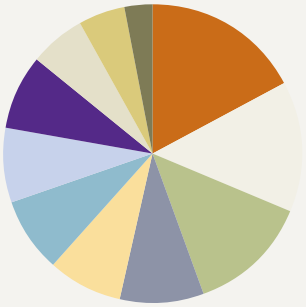
$54.5 million (02–03)



2002-2003

- Canada Foundation for Innovation 4%
- Ontario Innovation Trust 4%
- Donations 19%
- Foundations 7%
- Other Government Sources 7%
- Industry 9%
- Other Research Funding 3%
- Ontario Research and Development Challenge Fund 8%
- National Cancer Institute of Canada 8%
- Ministry of Health and Long-Term Care 9%
- Canadian Institutes of Health Research 21%

$65.9 million (03–04)



2003-2004

- Canada Foundation for Innovation 9%
- Ontario Innovation Trust 13%
- Donations 8%
- Foundations 8%
- Other Government Sources 6%
- Industry 14%
- Other Research Funding 3%
- Ontario Research and Development Challenge Fund 8%
- National Cancer Institute of Canada 5%
- Ministry of Health and Long-Term Care 8%
- Canadian Institutes of Health Research 17%

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Sunnybrook & Women's Foundation is proud to support the world-class work of Sunnybrook & Women's Research Institute. Your support will help to ensure life-changing medical research breakthroughs, like those profiled in the stories you have just read, happen every day at Sunnybrook & Women's.

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inventing the future of health care...piece by piece
Sunnybrook & Women's Research Institute, 2002–2004

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