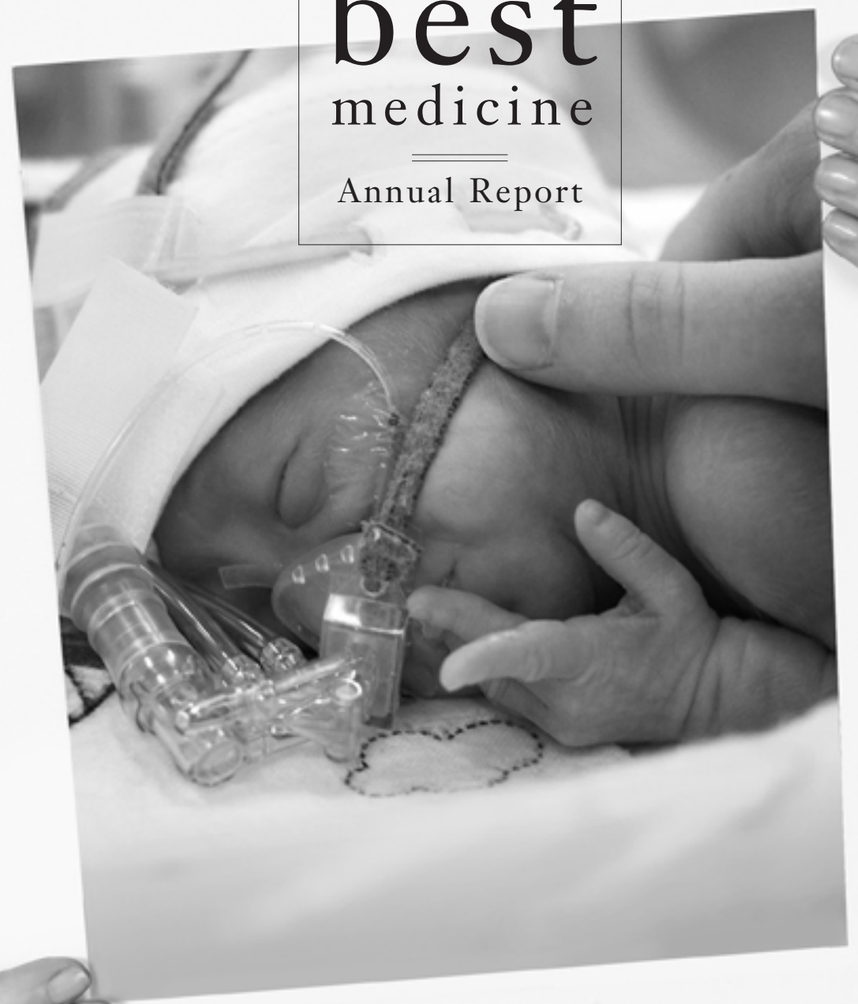
Samuel Lunenfeld Research Institute

2004-05

Research is the best medicine

Annual Report



MOUNT SINAI HOSPITAL

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Welcome to the annual report of world-renowned Samuel Lunenfeld Research Institute (SLRI) at Mount Sinai Hospital, which, in 2005, celebrated 20 years of conducting leading-edge research – the building blocks of new treatments and therapies that will ultimately improve outcomes and quality of life for our patients.

Our anniversary celebration, *Decades of Discovery*, was a reflection on the remarkable growth of the SLRI, and a springboard for our exciting future. At this dynamic time in medical history, when the mapping of the human genome has enabled better understanding of the causes of common and chronic diseases, research is the foundation of innovative medicine, leading to new treatments and ensuring a higher level of patient care. Our continuing quest is to find the underlying genetic answers to society's most pressing health problems.

Over the years, the SLRI has grown in both size and reputation, and is now considered one of the top ten biomedical research centres in the world. From its founding in 1985 under the Directorship of Dr. Lou Siminovitch, to successor Dr. Alan Bernstein, and under the exceptional recent leadership of Dr. Tony Pawson, the SLRI focuses the efforts of some of the world's brightest minds toward improving people's lives. At the end of 2005, Dr. Pawson completed an outstanding five-year term as Director and we thank him for his leadership. We are also delighted that Tony will remain with the SLRI, continuing his pioneering research on how cells communicate with

one other. We are pleased to welcome a new Director of Research, Dr. James Woodgett, a world-class scientist most recently with the Ontario Cancer Institute at Princess Margaret Hospital. Jim says that he is "honoured to follow such a remarkable immediate predecessor as Tony Pawson; I hope to live up to his standards and to inspire all of the Institute's scientists – and to be inspired by them."

With over 700 staff, more than 125,000 square feet of lab space, and a $64-million budget (2004-05), the SLRI is committed to discovering and delivering the best research, which, in turn leads to the best patient care. It's a complex, challenging, yet extremely rewarding task, as we work tirelessly to expedite the journey from "bench to bedside."

Our award-winning researchers are taking steps every day toward a better understanding of chronic illnesses such as cancer, gastrointestinal disease, heart disease, arthritis, and diabetes, as well as making important strides in other areas such as women's and infants' health.

Please enjoy this publication, which illuminates just some of the wonderful scientists and the work of the various centres comprising the Samuel Lunenfeld Research Institute. The SLRI has a proud history, and an ambitious goal ahead, aimed at improving people's lives now – and in the future.

Sincerely,

Lawrence Bloomberg
Chair of the Board of Directors

Lawrence Tanenbaum
Co-Chair of the Research Committee

Joseph Mapa
President and CEO

Thomas Kierans
Co-Chair of the Research Committee

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Message from the SLRI Leadership

Canadians tend to be modest by nature, and it is sometimes hard to appreciate that one of the very best biomedical research institutes in the world, the Samuel Lunenfeld Research Institute, is located right here in Mount Sinai Hospital.

The scientists in the SLRI range from those making profound new discoveries about the functions of cells and their organization into tissues, to those who directly apply such new discoveries to treat individual patients, or to prevent disease in the community at large. Fundamental science can reveal the way a gene, a protein, or a drug functions in the body, uncover previously unimagined ways in which our cells work, and identify effective new targets for therapy. Without these intellectual advances, medicine itself cannot progress. Importantly, through the intimate association of the SLRI and Mount Sinai Hospital, and the intermingling of basic scientists, clinical scientists, epidemiologists, and physicians, we have a unique opportunity to learn how to better combat human disease. Any disease, no matter how complex and devastating it may appear, has as its root cause one or a few underlying aberrations that we can discover and treat.

One of the great virtues of the Institute is that it is rather small, encouraging collaboration. Our ability to secure peer-reviewed research funds has continued to escalate at an astonishing rate. As a few examples, we received $15M from the Canada Foundation for Innovation for new equipment and towards an expansion of the Institute in the area of Systems Biology, Andras Nagy has been highly funded for his exciting work on human stem cells, James Dennis heads a Canadian Institutes of Health Research (CIHR) funded team project that will investigate the genetic differences among patients who are sensitive or resistant to the SARS virus, and Genome Canada will support a $12M project on protein interactions, in collaboration with the University of Western Ontario. In the last CIHR grants competition we received $6.9M, almost exactly the same as very much larger research enterprises in Toronto.

Indeed, younger scientists are the lifeblood of any research institute. We are very excited about the recruitment of two outstanding investigators, both of whom bring new scientific expertise and vigour. Helen McNeil comes from Cancer Research UK in London, and is an expert in the genetics of cellular organization. Anne-Claude Gingras trained at McGill University and at the Institute for Systems Biology in Seattle, and is an authority in the field of proteomics (the comprehensive analysis of proteins), and in the cellular pathways that control cell growth, with important implications for cancer and diabetes.

Importantly, the successes of the SLRI have depended on the support and commitment of the Hospital and Research Boards, and their approval to renew the Institute through an expansion on the Lebovic site is a remarkable visionary development.

It has been an exciting time to lead the Institute. Please venture through the following pages and learn how our scientists' research enables medicine at home and around the world.

Professor Anthony J. Pawson, FRS
Director of Research
Samuel Lunenfeld Research Institute

Dr. Stephen J. Lye, Ph. D.
Associate Director
Samuel Lunenfeld Research Institute

“Finding out how the mouse avoids a disease can give us insights into how to prevent it in humans”

Dr. Sabine Cordes

To state the obvious, mice are not men. Yet, from a genetic point of view, they are remarkably similar. Researchers at the Centre for Modeling Human Disease are using the mouse to model and understand a wide range of human diseases.

“We share more than 90 percent of our genes with the mouse,” explains Dr. Janet Rossant, Co-ordinator of the Centre. “Knowing what a gene does in the mouse, and what happens if that gene is altered or mutated, can give us insight into the effect the same genetic alteration would have in humans.”

Whether a mouse has osteoporosis, heart problems, or some other disease, researchers at the Centre can often find the gene involved. Then, they can explore whether the same gene is involved in the human disease. Or, if a gene is important in a human disease, they can make a mouse that lacks that gene and explore what happens to its health. Then, using special equipment, scientists can monitor the mouses’s blood pressure and blood chemistry or even perform MRI and ultra-sound scans on it.

While human diseases don’t always have the same symptoms as their mouse equivalents, they are often very similar. “In cases where they differ, the mouse has usually developed some genetic ‘coping mechanism’ to make up for a particular defect,” explains scientist Dr. Sabine Cordes. “Finding out how the mouse avoids the disease can give us insights into how to prevent it in humans.”

Researchers at the Centre have already developed mouse models for kidney disease, epilepsy, and a human syndrome that causes developmental anomalies. Research groups across Toronto use the Centre’s mice to model a range of human diseases, including bone, blood, and cardiovascular disorders. “This will open up exciting new possibilities for studying the genetics of human diseases,” says Dr. Rossant.

Quick facts about the Centre for Modeling Human Disease

Number of staff: 60

Funding sources:

- Canadian Institutes of Health Research (CIHR)
- Canada Foundation for Innovation(CFI)
- Genome Canada
- Industrial partners

Investigators with primary appointments:

- Dr. Janet Rossant (Co-ordinator)
- Dr. Lee Adamson
- Dr. Alan Bernstein
- Dr. Sabine Cordes
- Dr. George Fantus
- Dr. Marc Grynpas
- Dr. Colin McKerlie
- Dr. Andras Nagy
- Dr. Susan Quaggin
- Dr. John Roder
- Dr. William Stanford

Scientists at the Auxiliary Centre for Women's and Infants' Health are studying the earliest stages of human life. Their research into reproductive biology, pregnancy, and the transition to the newborn period is paving the way for medical advances on several key fronts.

"A good deal of our research focuses on the placenta, the structure that nourishes the fetus during development," explains Dr. Lee Adamson, Centre Co-ordinator. "The placenta regulates maternal changes during pregnancy and provides the nutrition and environment that allow the embryo to develop. It is vital to pregnancy, and so it's a subject of considerable attention here."

Scientists at the Centre are also studying pre-eclampsia and intra-uterine growth restriction, two major disorders that can occur during pregnancy. Both can be life-threatening and neither can currently be treated effectively.

Premature delivery is another research focus. "We don't really know how to stop labour when it starts too early," says Dr. Adamson. "In about 50 per cent of cases, pre-term labour stops spontaneously. One of our labs is developing a blood test to differentiate women who really will deliver prematurely from those who won't."

Some of the Centre's research into early development has implications for adults. "We're learning that people who do not have an optimum early environment are more likely to have diabetes, heart disease, osteoporosis, and other problems as adults," says Dr. Adamson.

In addition to serving as a research hub, the Centre hosts a tissue bank containing samples of placenta, blood, and other tissues. This is an invaluable resource for scientists needing access to large numbers of tissue samples for genetic research.

Promoting interaction between clinicians and basic researchers is a major objective at the Centre. The goal is to ensure that new knowledge gained from research is quickly translated into medical practice.

Quick facts about the Auxiliary Centre for Women's and Infants' Health

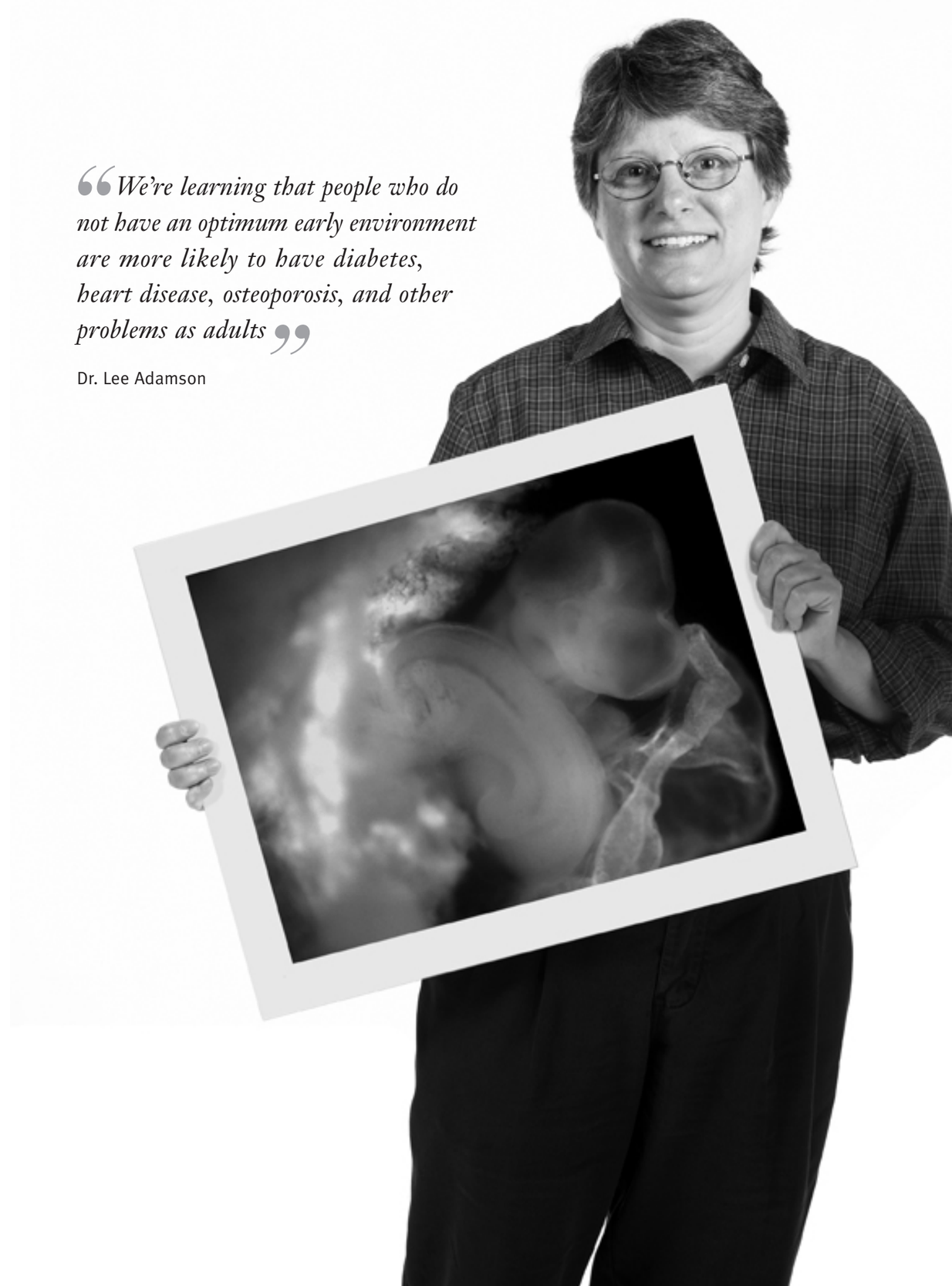
Number of staff: 106

Funding sources:

- Canadian Institutes of Health Research (CIHR)
- Heart and Stroke Foundation of Canada
- March of Dimes
- Mount Sinai Hospital Auxiliary
- National Insitutes of Health (NIH)

Investigators with primary appointments:

- Dr. Lee Adamson (Co-ordinator)
- Dr. Theodore Brown
- Dr. Isabella Caniggia
- Dr. Robert Casper
- Dr. Stephen Lye
- Dr. Susan Quaggin
- Dr. Janet Rossant



"We're learning that people who do not have an optimum early environment are more likely to have diabetes, heart disease, osteoporosis, and other problems as adults"

Dr. Lee Adamson

"We hope to one day be able to offer a real cure for the many people suffering from conditions that are now considered incurable"

Dr. Andras Nagy

Stem cells haven't made up their minds what to be when they grow up. They have a great ability to develop into many kinds of cells, and to replace cells damaged by accident or disease. Harnessing the potential of these versatile cells to improve human health is the research focus of the Centre for Stem Cells and Tissue Engineering.

Many diseases damage vital tissues. Heart attacks often kill cardiac muscle, while arthritis eats away joint cartilage. Autoimmune reactions can lead to the destruction of vitally important cell types, as is the case in diabetes and multiple sclerosis. Accidents can lead to damage of spinal cord cells. All these and many more conditions cannot be cured with medication and techniques available to us today. Our hope for the future lies in using stem cell based therapies for these devastating conditions. Instead of giving drugs to treat symptoms, stem cell therapy aims at actually repairing damage caused by disease or trauma to organs and tissues. "We hope to one day be able to offer a real cure for the many people suffering from conditions that are now considered incurable," says Dr. Andras Nagy, Co-ordinator of the Centre.

In many cases, replacing cells alone is not enough to give a cure. The joint, for example, is very complex in terms of its cells, shape, and structure. Scientists are working hard on finding ways to help stem cells properly form these intricate structures. Using a technique called tissue engineering, scientists at the Centre are trying to regenerate these complex tissues. "These techniques may help us to one day rebuild whole organs," explains Dr. Nagy.

Stem cells hold great promises for many people around the globe now desperately waiting for us to give them a cure. It is our obligation to humankind to make our best effort to bring these new hopes to reality as soon as possible.

The Centre leadership is well aware that this can only be done if all researchers work hard together. "We support this goal by making our stem cells available to laboratories in Canada and around the world," says Dr. Nagy.

Quick facts about the Centre for Stem Cells and Tissue Engineering

Number of staff: 100

Funding sources:

- Canadian Institutes of Health Research (CIHR)
- The Stem Cell Network
- Specific disease-related societies

Investigators with primary appointments:

- Dr. Andras Nagy (Co-ordinator)
- Dr. Alan Bernstein
- Dr. Robert Casper
- Dr. Sabine Cordes
- Dr. Marc Grynpas
- Dr. Rita Kandel
- Dr. Susan Quaggin
- Dr. Janet Rossant

"Once we know what genes are involved, we will be able to look for drugs that target disease-related proteins we have identified"

Dr. Mei Zhen

Mental illness and learning disabilities are major health concerns in Canada. At the Centre for Neurodevelopment and Cognitive Function, researchers are learning more about disorders of the human brain by studying the nervous systems of organisms ranging from worms to mice.

"We're trying to understand which molecules are required for the nervous system to function and how they affect the whole range of brain functions, from learning to mood disorders," explains Dr. Mei Zhen, Co-ordinator of the Centre. "For example, researchers here are working with mice with specific cognitive defects. These produce mental illnesses very similar to those found in humans."

Research teams have produced mouse models for schizophrenia, depression, and anxiety that have already made significant contributions to understanding how the brain functions. In the near future, our scientists will continue to identify and study genes directly related to human mental health.

"We are working to understand what happens at the molecular level to people with mental illnesses – the functions of genes associated with mental illness, what proteins they produce, and how they cause mental disorders," explains Dr. Zhen. "Unless we really understand the specific genes that result in mental defects, there's no way to design really effective treatments. Now that we know what genes are involved, we are testing for drugs that target disease-related proteins we have identified. This may lead us to develop drugs for mental illnesses that will be tailored to individual patient needs."

Quick facts about the Centre for Neurodevelopment and Cognitive Function

Number of staff: 88

Funding sources:

- Canadian Institutes of Health Research (CIHR)
- Canada Foundation for Innovation (CFI)
- National Institutes of Health (NIH)
- National Sciences and Engineering Research Council (NSERC)
- Private foundations

Investigators with primary appointments:

- Dr. Mei Zhen (Co-ordinator)
- Dr. Sabine Cordes
- Dr. Joseph Culotti
- Dr. Tony Pawson
- Dr. John Roder

The Human Genome Project has unlocked a treasure trove of new information about human genetics. Researchers at the Centre for Genomic Medicine are working to translate this knowledge into innovative strategies to prevent, diagnose and cure disease.

"Genomics involves large scale of genes and their functions," explains Dr. Katherine Siminovitch, Co-ordinator of the Centre. "We're now entering an era of genomic medicine, medical care based upon genetic knowledge. At the Centre, our goal is to find genes that cause disease and to quickly apply that information to improving patient care."

Areas of research include rheumatoid arthritis, inflammatory bowel disease (IBD), and the inflammatory processes associated with various other diseases. A research team at the Centre recently identified one of the genes responsible for IBD – a discovery that will ultimately help doctors diagnose, classify, and treat IBD patients.

Teams at the Centre are also studying the genetics of many other common diseases and disorders, including breast and colon cancer, infertility, diabetes, and host responses to infectious pathogens such as SARS and HIV.

"We don't yet know the causes of many common diseases," says Dr. Siminovitch. "As a result, our treatments are not always effective, and may have significant side effects. Moreover, we are unable to prevent most diseases. This situation can only be changed by aquiring understanding of the root causes of such illnesses."

Because the focus of genomic medicine is on translating research findings into clinical practice, the Centre fosters close collaborations between basic scientists and clinical researchers. "Physicians from Mount Sinai Hospital are key players on our research teams," says Dr. Siminovitch. "They help Mount Sinai provide the best medical care to patients by building on our work and translating discoveries made at the Centre into clinical practice."

Quick facts about the Centre for Genomic Medicine

Number of staff: 86

Funding sources:

Canadian Institutes of Health Research (CIHR)

Canadian Genetic Disease Network

Crohn's and Colitis Foundation of Canada

Canadian Arthritis Network

Genome Canada

Private corporations

Investigators with primary appointments:

Dr. Katherine Siminovitch (Co-ordinator)

Dr. George Fantus

Dr. Steven Gallinger

Dr. Pamela Goodwin

Dr. Alexandra Logan

Dr. Susan Quaggin

Dr. Bernard Zinman

"Our clinical research teams allow Mount Sinai to provide the best medical care to patients translating discoveries made at the Centre into clinical practice"

Dr. Katherine Siminovitch

Cancer is one of the leading causes of death in Canada – and the number of cases is rising. To design truly effective prevention strategies and treatments, scientists must first try to understand the genetic basis of cancer. That is exactly what researchers at the Fred A. Litwin Centre for Cancer Genetics are doing.

"Our teams study cancer genetics at the molecular level as well as conducting animal and human studies," says Dr. Steven Gallinger, Co-Director of the Centre. "We study common cancers like breast and colorectal cancer, as well as less common ones, including pancreatic cancer, sarcoma, and endometrial cancer."

Scientists already understand a great deal about the genetic basis of common cancers. By studying genes that cause rare cancers, they are learning even more about the common forms.

Researchers at the Centre recently analyzed the frequency in the population of a gene linked to inherited colorectal cancer. Although the gene is relatively rare, its presence has important implications for carriers.

To learn more about the genes involved in cancer, researchers across the world often turn to the Centre's Biospecimens Repository. This tissue bank contains samples from thousands of cancer patients and healthy individuals taken over more than a decade.

"The Repository is a fantastic resource," says Dr. Gallinger. "New, high-throughput technologies allow us to analyze huge numbers of genes in tissue samples, looking for common patterns in people who had cancer, and those who didn't. We can look at millions of variations in a genetic sequence in weeks. Until recently, the same task would have taken years."

The Centre also serves a vital training function. Graduate students, postdoctoral fellows, and clinical fellows – the next generation of researchers – are important members of its research teams. "Developing and attracting new talent is important to the future of this Centre," says Dr. Gallinger.

"Because of the multi-disciplinary nature of the Centre, our trainees are exposed to basic laboratory science, epidemiology, biostatistics, and clinical research," says Dr. Irene Andrulis, Co-Director of the Centre.

Quick facts about the Fred A. Litwin Centre for Cancer Genetics

Number of staff: 75

Funding sources:

Canadian Breast Cancer Foundation

Canadian Breast Cancer Research Association (CBCRA)

Canadian Institutes of Health Research (CIHR)

Canada Foundation for Innovation (CFI)

National Cancer Institute of Canada (NCIC)

National Institutes of Health (NIH)

Ontario Cancer Research Network

Mr. Fred A. Litwin

Terry Fox Foundation

Investigators with primary appointments:

Dr. Irene Andrulis (Co-Director)

Dr. Steven Gallinger (Co-Director)

Dr. Bharati Bapat

Dr. Hilmi Ozcelik

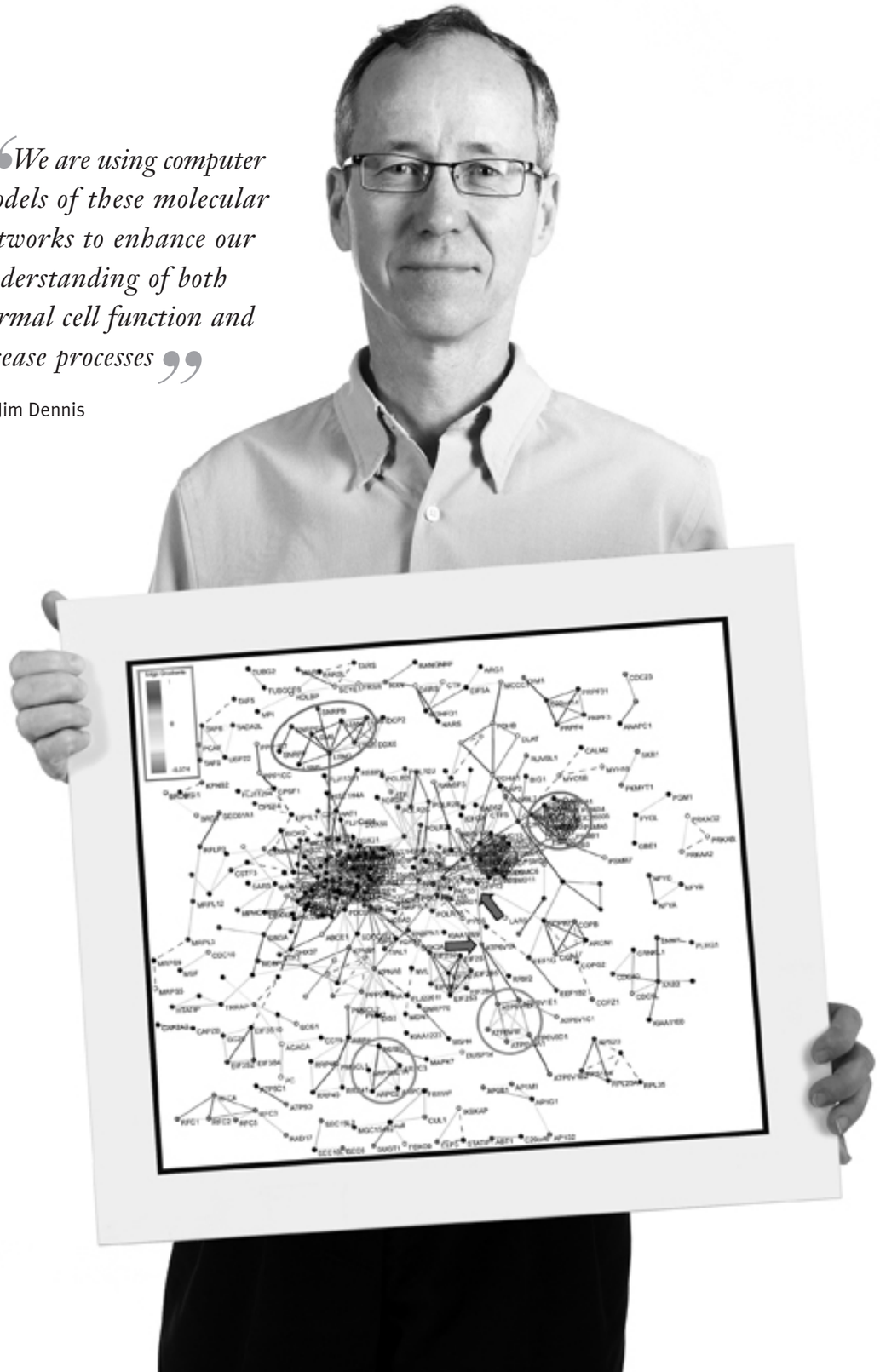
Dr. Jay Wunder

"Developing and attracting new research talent is important to the future of this Centre"

Dr. Irene Andrulis and Dr. Steven Gallinger

"We are using computer models of these molecular networks to enhance our understanding of both normal cell function and disease processes"

Dr. Jim Dennis



Complex electrical devices are controlled by networks of electronic circuits. In the same way, cellular sub-components, cells, and larger, multi-cell structures are controlled by networks of interacting proteins, working in harmony to maintain life. Studying and understanding these interactions is the primary focus of the Centre for Systems Biology.

"We're working to identify the molecular circuitry controlling cell growth and other functions critical to the development of cancer and other major diseases," explains Dr. Jim Dennis, Co-ordinator of the Centre. "Our goal is to first understand the disease process, taking into account the entire molecular environment of the cell. Then, we hope to target critical network nodes that control the disease process."

Inputs to these incredibly complex biological networks include nutrients and environmental factors. Network outputs are the behaviour of cells and, ultimately, the individual's vulnerability to disease.

"We are using computational models of these molecular networks to enhance our understanding of both normal cell function and disease processes," explains Dr. Dennis. "In the future, we hope these models will help doctors predict the likely course of diseases and choose the best therapies for people, given their genetic makeup and disease status."

Because computation and mathematical modelling are key to the Centre's work, researchers are integrating traditionally separate disciplines such as biology, genetics, and mathematics. Some teams are also building chemical libraries, to isolate compounds with specific cellular activities that can be used to treat diseases such as cancer.

One research team recently mapped the interactions in signalling pathways critical to cancer cell growth. This will allow scientists to develop drugs that slow or stop cancer development by targeting the cancer's circuitry.

Quick facts about the Centre for Systems Biology

Number of staff: 167

Funding sources:

Canadian Institutes of Health Research (CIHR)

Genome Canada

Canada Foundation for Innovation (CFI)

National Cancer Institute of Canada (NCIC)

Private foundations

Investigators with primary appointments:

Dr. Jim Dennis (Co-ordinator)

Dr. Dan Durocher

Dr. Gerry Gish

Dr. Tony Pawson

Dr. Frank Sicheri

Dr. Mike Tyers

Dr. Jeff Wrana

“Our work is, by its very nature, collaborative. We build bridges between the many disciplines needed to translate scientific discoveries into improved human health”

Dr. John McLaughlin

Epidemiology is the study of how disease is distributed and controlled in large populations. At the Prosserman Centre for Health Research, leading epidemiologists and biostatisticians study both individuals and large populations. Their goal is to understand the role of genetic and environmental factors in diseases and their treatment.

“We can’t learn how to prevent serious illness just by looking at individuals,” explains Dr. John McLaughlin, Co-ordinator of the Centre. “Often, we can detect patterns of disease earlier using population studies. Our research helps healthcare officials plan services and strategies for everyone.”

In addition to doing research, scientists at the Centre are working to improve research methods. Biostatisticians have developed new methodologies – carefully crafted procedures and processes – to study complex diseases. Using these new methodologies, scientists have made great progress in understanding a variety of illnesses.

“For example, one team has identified genetic factors that allow some women with breast cancer to respond better to therapy,” says Dr. McLaughlin. “Another team is studying genetic factors that put some people at higher risk of high blood pressure and kidney stones.

“Our work has already led to some real improvements in health. For example, one team has learned a great deal about the susceptibility of First Nations people to diabetes, and is now applying that knowledge to treat the disease and prevent complications within the community.”

As scientific knowledge continues to accumulate, health research is becoming more and more complex. Recognizing this, the Centre is building its capacity to undertake large-scale research projects in collaboration with other facilities. “Our work is, by its very nature, collaborative,” says Dr. McLaughlin. “We don’t do everything ourselves. Instead, we build bridges between the many disciplines needed to translate scientific discoveries into improved human health.”

Quick facts about the Prosserman Centre for Health Research

Number of staff: 62

Funding sources:

Canada Foundation for Innovation (CFI)

Canadian Institutes of Health Research (CIHR)

National Cancer Institute of Canada (NCIC)

Investigators with primary appointments:

Dr. John McLaughlin (Co-ordinator)

Dr. Laurent Briollais

Dr. Shelley Bull

Dr. Mary Jane Esplen

Dr. Pamela Goodwin

Dr. Julia Knight

Dr. Alexander Logan

Dr. Robin McLeod

Dr. Bernard Zinman

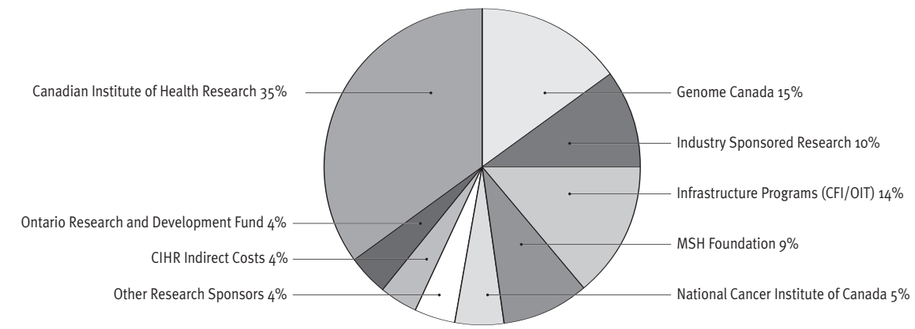
Quick Statistics 2004-05

Number of Personnel	
Number of Institute PIs	45
Number of Clinical Researchers	76
Number of trainees *(Research Fellows, graduate students, undergraduate students)*	294
Number of other research staff *(Technician, administrative staff, clinical staff)*	304
Total number of Personnel	719

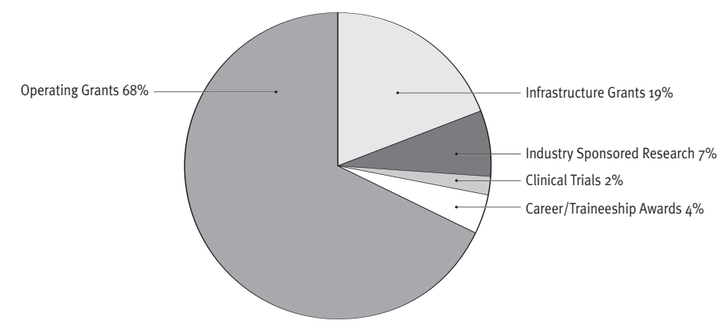
Number of Projects	
Number of funded Research Projects	576
Number of active clinical protocols	95
Number of salary awards	118
Total number of Projects	789

Selected Financial Information	
Total infrastructure grants	$11.8 million
Total research budget 2004-05	$64.2 million

Total Research Funding ($64.2 million)



Total Research Funding Awarded by Grant Type ($64.2 million)



The Samuel Lunenfeld Research Institute is truly a scientific and educational jewel. It has been an outstanding breeding ground for research leadership and the site of wonderful breakthroughs in bioscience since its inception. Today, the Lunenfeld remains a source of great pride for both the Mount Sinai Hospital and the University of Toronto academic family in general.

Dr. David Naylor
President, University of Toronto

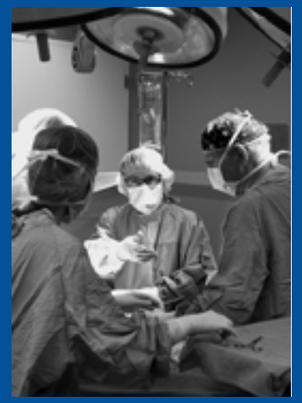
The research at the Samuel Lunenfeld Research Institute continues to go from strength to strength. John McLaughlin's elegant population-based studies on colon cancer in Ontario and Newfoundland, the research of Stephen Lye and his team's work on pre-eclampsia and pre-term labour, and Mike Tyers' beautiful work discerning the function of all the genes in a single organism are examples of the excellence and relevance that have characterized SLRI research from the very beginning.

Dr. Alan Bernstein
President, Canadian Institutes of Health Research

The University of Toronto values immensely its close working relationship with colleagues at affiliated institutions such as the Samuel Lunenfeld Research Institute. The scientific leadership provided by SLRI investigators, the quality of the training environment, and the collaborative interactions they foster across the city, are exemplary in enhancing the investigator profile of the University of Toronto and its hospital affiliates.

Dr. John Challis
Vice President, Research, University of Toronto

Mount Sinai Hospital's Samuel Lunenfeld Research Institute is committed to excellence in health research, the training of young investigators, and a culture of research-based medicine both within the Hospital and the Institute.



Dr. Zane Cohen, centre, Surgeon-in-Chief and world-renowned gastro-intestinal specialist, performs surgery at Mount Sinai Hospital, where leading-edge research comes together with excellence in patient care. For example, researchers from Mount Sinai's Samuel Lunenfeld Research Institute have discovered that the mutation of a specific gene in some patients with colon cancer indicates a risk of acquiring the disease.

MOUNT SINAI HOSPITAL

600 University Avenue
Toronto, Ontario, Canada M5G 1X5
Tel: 416.586.5065 Fax: 416.586.8555
www.mtsinai.on.ca