Toronto's Discovery District

- Key Researchers -

Innovation – Technology - Business

Aled Edwards and Cheryl Arrowsmith: International Partnership, Innovative Ideas, Lofty Goals

Aled Edwards and Cheryl Arrowsmith are leaders in an international initiative that may transform the world of medical science.

Called the Structural Genomics Consortium (SGC), the $100 million, three-year project brings together researchers from U of T and the University of Oxford, with Edwards acting as chief executive officer and Arrowsmith as the Canadian team's scientific director, to determine the structure of over 350 protein structures that play a significant role in human disease.

The SGC's work is made possible by funding from UK-based Wellcome Trust, GlaxoSmithKline, Genome Canada, the Ontario Research and Development Challenge Fund, the Canada Foundation for Innovation, the Ontario Innovation Trust and the Canadian Institutes of Health Research. Results will be placed in a public database, giving scientists around the world access to this groundbreaking information and speeding up the development of new treatments for disease.

Ross Ethier: Investigating the Riddle of Glaucoma

Glaucoma is the second most common cause of blindness in Canada. The disease, which gradually steals sight without warning and often without symptoms, affects an estimated 65 to 70 million people worldwide.

The mechanisms of glaucoma damage are poorly understood, making this common disease difficult to treat. But Ross Ethier is working toward a solution by marrying engineering and medicine.

World-renowned in the field of biofluid mechanics, Ethier - a professor in Mechanical and Industrial Engineering who is also cross-appointed to the Institute of Biomaterials and Biomedical Engineering and the Faculty of Medicine's ophthalmology department – is collaborating with clinical ophthalmologists, glaucoma specialists, optometrists and biologists to understand how pressure in the eye is controlled, how and why it becomes elevated and how it damages optic nerve cells.

His latest project is a mechanical shunt to assist in controlling pressure, which he recently patented with colleagues. "There are other devices," he says, "but they don't work very well, so doctors tend to use them only as a last resort." Ethier's new device fills a tall order: "It had to be small enough to fit on the surface of the eye, be bio-compatible, have no moving parts, last 30 years, be cheap and not require any external power source." His shunt, only two millimetres thick, is intended to bypass the eye's plugged drainage system and ensure a constant flow of fluid. "I'm excited about its potential. But the proof will be in how well it performs in trials over the next few years."

Amira Klip: An Inside Look at Insulin

Type II diabetes is a growing health problem among children and adolescents. It affects an estimated two million Canadians and one out of fifteen people in the Western world. The main problem for those with the disease is resistance to insulin, a hormone that allows muscles to use dietary sugars (glucose) to produce energy for activity. In those with type II diabetes, insulin-sensitive tissues lose the ability to respond properly to insulin, ushering in a host of complications including circulatory defects, blindness and cardiovascular disease, which carries an increased risk of death.

Dr. Amira Klip of Biochemistry and the Hospital for Sick Children, who is also a Canada Research Chair, is breaking new ground in diabetes research in two specific areas. In one, she is unravelling the fine details of insulin signalling with insulin-sensitive tissues; in the other, she is characterizing the final step of insulin action in muscle.

Her work focuses on the molecular mechanisms whereby insulin increases the number and function of glucose “entry ports”—also known as glucose transporters (GLUTs)—on muscle cells, in order to increase glucose uptake. A 2000 Fellow of the Royal Society of Canada, Dr. Klip used cell biology and biochemical methods to identify these entry ports for glucose, both for muscle cells and across the blood-brain barrier. She found that insulin causes a type of glucose transporter known as GLUT4 to move from inside the cell to the muscle plasma membrane, in order to bring glucose into the cell.

Dr. Klip is further clarifying the mobilization and activation of GLUT4, with an emphasis on defining which of the many steps involved may be defective (and potentially reversible) in type II diabetes. By clarifying the molecular details of these phenomena, Dr. Klip’s research is generating new approaches to combating insulin resistance and diabetes.

Kelly MacDonald: An Unlikely Weapon in the Battle Against HIV/AIDS

Are our bodies equipped with a secret weapon to fight AIDS? Quite possibly, says Kelly MacDonald.

Director of the HIV Research Program in U of T's Faculty of Medicine and the Ontario HIV Treatment Network (OHTN) Chair in HIV Research, MacDonald has been studying the virus for over 10 years and has spent the last seven developing a novel vaccine target that originates in our own cells.

The story began over a decade ago. When AIDS was spreading across Africa, MacDonald travelled to Kenya to help conduct an epidemiological study on sex trade workers in order to understand risk factors for transmission.

The team discovered that, while most sex trade workers were at a very high risk of infection, some of them seemed to be immune to the disease. When further epidemiological studies yielded no clues, MacDonald and her team turned to basic science.

"What we discovered was that certain types of a genetic marker known as human leukocyte antigen (HLA) were associated with reduced risk of infection," says MacDonald.

Found in virtually all human cells, HLAs essentially "show" the immune system where a virus is so that the body can fight it. This process works well for many viruses, but because HIV mutates so quickly the body can't recognize it long enough to kill it.

So MacDonald's team began studying the HLAs found in the group that seemed to be immune to the virus. Meanwhile, studies conducted by other researchers yielded important information: when HIV is transmitted, it carries some of the HLA from the last person it was in.

Applying this information, MacDonald and her collaborators showed that sex workers with a less common type of HLA have a lower risk of acquiring HIV, suggesting that the immune system may be able to neutralize the virus by recognizing and attacking the foreign HLA rather than the highly mutable viral proteins.

Armed with this knowledge, MacDonald and her colleagues did the unthinkable: they began to create a vaccine based on HLA instead of on the virus itself. "This was basically heresy because everyone thinks about making a vaccine from whatever the pathogen is," admits MacDonald. "But in the case of a virus that 'steals' HLA, this was a better idea."

MacDonald says that the benefit of this vaccine, which is currently being tested in monkeys, is that HLA itself does not mutate, so it is much easier for our bodies to recognize and fight off foreign HLA - which floats along with the HIV virus - than it is to recognize and kill the rapidly-mutating virus.

If successful, what will this new vaccine mean for the battle against AIDS?

"Realistically, I think we'll discover that our vaccine provides partial protection, which is great," says MacDonald, "but it may not be the 'whole enchilada.' The lesson we have learned thus far is that HIV is a wily virus and it will likely take many types of immune response to contain it."

JoAnne McLaurin: Back on Track

When you're part of a leading research team, what do you do when a much-vaunted discovery fails in human trials?

If you're JoAnne McLaurin, a principal investigator in U of T's Centre for Research in Neurodegenerative Diseases (CRND), you keep going, looking for innovative new ways to reach the same goal.

The CRND is a jewel in the Faculty of Medicine's glittering research crown. Led by world-renowned researcher Peter St George-Hyslop, the 10-year-old centre has been responsible for a number of significant advances, including the discovery of five genes associated with Alzheimer's Disease.

McLaurin and her colleagues are searching for a way to prevent or stop the progression of Alzheimer's Disease. Despite the remarkable achievements of the past decade, hopes seemed to dim earlier in 2000, when the first human trial of a vaccine had to be cancelled.

The story began in 1999, when Elan Pharmaceuticals published a report suggesting that it was possible to immunize mice susceptible to Alzheimer's Disease. The immunization produced antibodies that prevented plaques – deposits of a protein called amyloid beta peptide – from forming in their brains. The over-production of amyloid beta peptide is associated with cognitive impairment in the disease.

CRND principal investigators David Westaway and Peter St George-Hyslop developed an Alzheimer's mouse and designed an experiment to test whether immunization could improve cognitive function. The experimental animals were placed in a pool of water divided into four quadrants, with visual clues marking each quadrant. In one quadrant a platform was built just below the level of the water. As soon as a mouse succeeded in reaching the platform, it was lifted out. Researchers recorded the swim pattern of each mouse with a digital camera, then evaluated the results.

With training, a healthy mouse could find the platform with little difficulty. A mouse affected by Alzheimer's had difficulty finding the platform both before and after training. The exciting discovery was that immunized Alzheimer's mice had a swim pattern very similar to healthy mice.

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With this promising data in hand, McLaurin and her lab went to work analyzing how the antibodies produced by immunization worked. She was able to show that they prevent fibers from forming, and dissolved them after they had already formed. She also found that amyloid beta protein, when added to a cell culture of neurons, kills the neurons. When the antibodies are added, they prevent cell death.

Human trials began early in 2002 with 365 patients, but were stopped when 15 developed inflammatory reactions.

McLaurin and her team were not discouraged. Using mathematical algorithms and further experimentation, they discovered that it might be possible to circumvent the inflammatory response by refining the vaccine. Another idea is to develop a “molecular mimic” – a molecule that acts in the same way as the antibody without producing a generalized immune response. Both suggestions were published in a landmark article in *Nature Medicine*.

How long before she and her colleagues find something to prevent the march of Alzheimer ’s Disease? McLaurin says the horizon is five to 10 years. Meanwhile, she gets up every morning excited about her work and the advances it will bring. “I like what I do,” she says. “I’ve always said I wouldn’t do it anymore when it stopped being fun.”

Freda Miller: Building and Repairing the Nervous System

During embryonic development, the nervous system is faced with an enormous task – to progress from a thin sheet of cells to a complex circuit network. What results is a veritable motherboard capable of processing sensory information and generating motor outputs. When the nervous system is damaged, through spinal injury or diseases such as Parkinson’s, there are frequently no treatments available.

Dr. Freda Miller of the Faculty of Medicine and the Hospital for Sick Children Research Institute, is also a Canada Research Chair who looks at the factors that effect developing and injured neurons in the hope that her findings may be used to treat debilitating conditions of the nervous system. Her recent work indicates that environmental cues, such as growth factors, influence the creation and survival of neurons. Moreover, a neuron’s environment may actually “select” appropriate neurons and connectors, and in so doing, build functional circuitry.

Dr. Miller is also trying to develop an adult stem cell that can be used to treat damaged nervous systems. When the potential of neural stem cells became apparent four years ago, what became equally apparent was the ethical controversy surrounding embryonic and human neural stem cell research. Dr. Miller's laboratory discovered SKin-Derived Precursors (SKPs), a type of stem cell located in accessible adult tissue. Through her research program, Dr. Miller plans to determine whether rodent and human SKPs can be used for treatments in nervous system disorders.

Michael Sefton: U of T's Bioengineering Buzz

Welcome to Michael Sefton's multi- and interdisciplinary bio-world. Sefton is regularly acknowledged as one of the top minds in the brave new world of tissue engineering - his research into the complex challenge of growing a human heart in a laboratory is internationally renowned and last year he was named a University Professor, the highest honour U of T bestows on its faculty. But Sefton has also made his mark as team captain of the Institute of Biomaterials and Biomedical Engineering (IBBME), a bioengineering group that ranks among the best on the planet.

IBBME was formed officially in 1999, as the result of a merger between the Institute of Biomedical Engineering, the Centre for Biomaterials and the tissue engineering group in the Department of Chemical Engineering and Applied Chemistry. But its roots actually go back to the early 1960s, when the Institute of Biomedical Electronics was created to tackle a new branch of engineering that would combine the engineering used in more traditional areas with research into the puzzles of human health.

"What was unique about the creation of this group back in 1962 was that it was born as a 50-50 partnership between engineering and medicine," says Sefton. "From the beginning, the idea was to bring engineers and medical researchers into the same room to approach health research in a new way." Shift forward 40 years and Sefton's team is pursuing biomedical possibilities once thought impossible. "Even in the early 1980s, the ideas of repairing spinal cords using polymers or creating an artificial liver were considered off-the-wall. Now, we see these areas as having very real challenges, but possible enough that they are worth considering."

In fact, Sefton looks at a biblical passage as the IBBME's unofficial strategic goal: *The lame shall walk and the blind shall see*.

"That really embodies the possibilities we are investigating in biomedical research. And I think our people are literally putting this strategic goal into action."

Sefton is eagerly looking forward to the opening of the Centre for Cellular and Biomolecular Research (CCBR) on the St. George campus in 2005. "The CCBR will really give us a boost in terms of excellent research space for our people. And the plan with CCBR has always been to create a research facility without walls, so that our interdisciplinary nature can blossom even further."

The CCBR will also be a key factor in helping Sefton in what he believes is his key role at the IBBME - building one of the world's top bioengineering communities by recruiting great people.

"To be a leading research enterprise, you need spectacular people. This is how the IBBME has come so far. We are deliberate and competitive in hiring brilliant young people. In the past few years, we have hired among the best young minds in North America in leading-edge areas. We have to keep doing this. It's essential for medicine and biomedical engineering, but more importantly, it is essential for humanity."

Molly Shoichet: Regenerating Transplant Technology

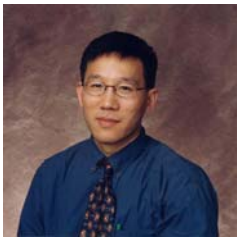
Medical miracles have been made possible through the transplantation of human tissue. Yet this powerful technique remains hampered in many ways. Vital organs such as hearts and kidneys remain in short supply. In addition, the body often rejects these life-saving replacements. And transplants are all but impossible to cope with damage in critical sites such as the brain or spinal cord. But the news isn't all negative.

In fact, there's fresh new hope. Molly Shoichet of the Faculty of Chemical Engineering and Applied Chemistry and the Institute for Biomaterials and Biomedical Engineering is addressing these shortcomings in an innovative way. The Canada Research Chair's work has already introduced a novel technique for growing nerve cells in the laboratory. She has made it possible to consider how these cells could be implanted, not simply as replacements, but as a way to allow the body to regenerate nerve fibres to replace injured ones. Her work is a vital step toward another medical miracle—restoring feeling and movement to individuals suffering from paralysis.

Shoichet continues to expand the frontier of tissue engineering well beyond the bounds of simple transplantation. She is studying the properties of new materials that provide the framework for tissue regeneration within the body. Such materials must be specifically designed and synthesized for that purpose. They require a unique three-dimensional structure and chemical character that will promote the release of agents that can stimulate cellular interaction and promote regeneration.

These techniques represent just one aspect of this promising field. Shoichet and her colleagues foresee the prospect that Canada will continue to emerge as a world leader in tissue engineering. Besides resolving the current shortage of donor organs, this capability will establish entirely new approaches to dealing with medical conditions that are currently very difficult to treat.

Christopher Yip: Taking a closer look



Many chemists with an interest in creating new materials would like to do so molecule by molecule. In this way, they can ensure that the resulting products meet their requirements for a specific medical or industrial application. Until recently, though, these researchers were operating in the dark.

Even though the advent of ever-more powerful imaging technology has enabled us to witness some of the most minute features of the biological world, large parts of that world remain invisible to us. Most approaches yield only static images, while some require preparatory steps that physically damage or alter the sample of material being examined.

These limitations do not sit well with Christopher Yip. The assistant professor of Chemical Engineering and Applied Chemistry and the Institute for Biomaterials and Biomedical Engineering who is also a Canada Research Chair insists that our ability to understand and manipulate how molecules, such as proteins, interact will depend on how well we can see what we're doing. As a result, he has dedicated his efforts to enhancing existing methods in order to provide a better view of the actions taking place at this level.

Among Yip's earliest accomplishments in this field was the first demonstration that a powerful class of microscope could be adapted to watch protein crystals as they grow at the molecular level. And now he is building on this work. Yip intends to integrate the leading imaging systems now in use, combining their various features to assemble a much more comprehensive means of studying molecular structures, processes, and events.

Yip's goal is nothing less than the introduction of technology that provides three-dimensional images of such events as they occur. He expects the result to offer an entirely new perspective on the critical interactions that take place between molecules, proteins and cells. Being able to see those interactions could make their purpose much clearer. And such insights will be essential to designing new materials from scratch, allowing us to now create them at the molecular scale.

Peter Zandstra: Surveying Cells of Unlimited Possibility

Organ transplant candidates around the world wait impatiently for donor organs to become available. This awkward situation could improve dramatically if we could simply grow new organs for these patients.

Does this all sound like pure science fiction? Not at all. Peter Zandstra of the Institute of Biomaterials and Biomedical Engineering, who is also a Canada Research Chair, has demonstrated the astonishing ability of unspecialized cells (stem cells) to take on new functions as they multiply. Through the same biochemical process that turns each of us from a single cell into a newborn child, doctors could grow a new heart to replace a patient's damaged one.

By the time a baby is born, that ability has yielded the kaleidoscope of different types of cells making up the human body, most of which are highly specialized and utterly distinct from one another. After birth, this dramatic flurry of diversification greatly subsides. Although cells with a significant developmental capacity live on in adults, under most circumstances, the body cannot harness this developmental potential.

However, researchers like Zandstra are making it possible to employ this developmental capability of stem cells as a new way to address some challenging medical conditions. Such work focuses on blood stem cells, which are capable of producing all blood cell types and embryonic stem cells, which retain the potential to grow into any other type of cell found in the body. Cultivated in a laboratory, these cells could be used to grow a suitable replacement for various body tissues, such as the heart.

This kind of cell cultivation, however, has proven difficult. Zandstra has contributed to our knowledge of how it could be accomplished. He has effectively described the role of substances that govern the growth and reproduction of stem cells. A broader understanding of these substances lays the foundation for techniques that could guide the cells to develop in specific ways, producing specific types of tissue desired for medical use.

Zandstra investigates the best means of obtaining and growing stem cells. He explores the agents responsible for initiating and controlling the process of cell development. Ultimately, he foresees the development of technology necessary to construct clinical bioreactors, which will be capable of growing a wide range of different tissues from small populations of stem cells.

Dr. S. Lee Adamson
Senior Investigator

Dr. Adamson´s laboratory uses the mouse as a model to explore the developmental mechanisms responsible for abnormal waveforms in the umbilical and uterine arteries, and the impact of abnormal flows on fetal growth and development. Maternal and fetal cardiovascular function are montitored using high frequency ultrasonic imaging and Doppler blood velocities. Utero- and feto-placental structures are being assessed using histological and vascular casting techniques.

Dr. Irene Andrulis
Senior Investigator

Dr. Andrulis´s research program investigates the molecular alterations in cancer and how these genetic events contribute to the development of human cancers. Her team is investigating changes associated with the acquisition of drug resistance and the abnormal expression of proto-oncogenes in primary tumors. Her work involves the study of the prognostic value of neu oncogene amplification in patients with node-negative breast cancer, a group which would benefit from better prognostic indicators.

Dr. Alan Bernstein
Senior Investigator

Dr. Bernstein´s laboratory is interested in understanding the molecular events that underlie vascular development and normal blood cell development. Various genetic approaches are utilzied to identify the genes involved in these processes, and apply the knowledge to understanding disease conditions such as leukemia and cardiovascular disease.

Dr. Laurent Briollais
Investigator

Dr. Briollais´s team focuses on developing parametric and non-parametric methods for mapping and analyzing gene-environment interactions. A biostatistitian with an ongoing interest in the genetic epidemiology of complex diseases, Dr. Briollais is developing statistical methods for studying the role of genetic and enviornomental factors on diseases such as cancer.

Dr. Shelley B. Bull
Senior Investigator

Dr. Bull´s research focuses on the development and application of new statistical methodologies to study disease etiology and prognosis. She has developed and evaluated new approaches for statistical inference for nominal outcomes in clinical and population epidemiology using the logistic regression model.

Dr. Robert Casper
Senior Investigator

The Casper lab undertakes a number of major areas of research aimed at improving clinical practice and patient care. One is the investigation of the role of mitochondrial mutation in oocyte aging. The lab also focuses on the invitro expansion of human umbilical cord blood stem cells and their use for tissue therapeutics. The third area of research is the use of aromatase inhibitors for induction of ovulation and for improving implantation in assisted reproductive technology.

Dr. Sabine Cordes
Investigator

Dr. Cordes´s laboratory is using molecular techniques and analysis of pre-existing and newly generated mouse mutations to understand early neural development, especially that of the vertebrate hindbrain segmentation and serotonergic neuron. To investigate neurotonal specification, Dr. Cordes's lab is using chemical mutagenesis and a series of streamlined assays to generate and identify novel mouse mutations which affect serotonergic neuron specification, differentiation, and neurotransmission.

Dr. Joseph G. Culotti
Investigator

Dr. Culotti´s laboratory is using the simple nematode Caenorhabditis elegans to identify and characterize the function of gene products that are responsible for neurogenesis and for guiding the migration of growing axons. Other projects in the laboratory involve identifying mutations in homologues of genes known to affect axon guidance in vertebrates.

Dr. James W. Dennis
Senior Investigator

Dr. Dennis´s laboratory is studying receptor glycosylation regulating signaling in systems affecting cancer and autoimmunity, focusing on the role of N- and O- linked glycan chains on cell surface receptors including T cell receptor and integrins. Using genetic analysis and synthetic screens with gly-2 null worms, the lab hopes to identify glycoprotein substrates, signaling pathways and cell lineages requiring gly-2. Analogous glycoproteins and signaling pathways in mammals are likely to regulate related physiological processes, such as cell growth and movement.

Dr. Daniel Durocher
Investigator

The major goal of Dr. Durocher´s lab is to understand how normal cells become cancerous cells. Since genome instability is a hallmark of the cancer phenotype, his lab is studying cell cycle checkpoints, the gate keepers of the genome. Dr. Durocher investigates the role of the protein module FHA domain in controlling the specificity of DNA damage signalling. Recently, an exciting initiative of a chemical genetics program to investigate the use of small molecules in biological discovery has been undertaken.

Dr. Steven Gallinger
Senior Investigator

Dr. Gallinger´s laboratory is studying both inherited and acquired molecular aspects of colorectal cancer and pancreatic cancer. His team is using a number of different approaches including small and large-scale population-based studies, gene identification studies, and investigation of tumours in mouse models. Dr. Gallinger is currently undertaking identification and characterization of the early molecular events during the development of pancreatic cancer.

Dr. Pamela J. Goodwin
Senior Investigator

Dr. Goodwin has focused her research activities in the area of breast cancer. She has a longstanding interest in the role of obesity and nutrition-related factors in breast cancer development and recurrence. Dr. Goodwin has recently turned her attention to research into the management of women who carry mutations in breast cancer predisposition genes and to the potential role of mutations in these genes in determining survival from breast cancer in women who develop the disease.

Dr. Marc D.Grynpas
Senior Investigator

Dr. Grynpas has focused his research program on developing new insights into the factors that contribute to bone loss, which lead to osteoporosis. This interest has led him to investigate the mechanisms of bone remodeling and the impact of different regimens on the mechanical properties of bone. He is also interested in the effects of bisphosphonates on bone, role of environmental fluoride in the risk of fractures and cigarette smoking as a risk for osteoporosis.

Dr. Christopher W. Hogue
Investigator

Dr. Hogue´s team is using computers to describe how proteins - especially the ones important for disease - interact with each other. A new database called BIND (Biomolecular Interaction Network Database) catalogues how proteins, DNA, RNA, and other biomolecules interact with each other. The assembly of a unique "supercomputer" at MSH allows the Hogue lab to generate and predict the 3-dimensional structure of proteins.

Dr. Julia Knight
Investigator

Dr. Knight´s team investigates the genetic and non-genetic causes of cancer, particularly breast cancer, in human populations. Her focus is on using epidemiological approaches to understand gene-environment interactions in complex systems. Current specific factors of interest include vitamin D, alcohol, and artificial light.

Dr. Alexander (Sandy) Logan
Investigator

Dr. Logan´s research examines the hypothesis that polymorphisms in genes considered to be important in blood pressure regulation may be involved in the pathogenesis of salt-sensitive hypertension. He is using epidemiological and genetic approaches to test the hypothesis that the magnitude of the response of the kidney to insulin is determined by genetic variants of the thiazide receptor gene.

Dr. Stephen J. Lye
Senior Investigator

The focus of our laboratory is to understand the mechanisms responsible for the onset of labour. We are investigating whether the change in the myometrium from a dormant state to the contractile state that occurs during labour is caused by the activation of genes. The lab has shown that both mechanical signals (due to stretching of the myometrium) and endocrine signals are required to activate a cassette of genes called "contractile-associated proteins" (e.g. Cx-43 and oxytocin receptor) and initiate labour.

Dr. John R. McLaughlin
Senior Investigator and Head

Our research team aims to determine the relative contribution of environmental and genetic factors in the development of human cancers. Research includes investigation of ovarian cancer, for which the genetic contribution dominates (family history, BRCA1/BRCA2 mutation) but there is also a well established environmental component (decreased risk among oral contraceptive users). The genetic epidemiology of lung cancer is also being investigated, a disease with a major environmental component (smoking) and a smaller genetic componen

Dr. Robin McLeod
Senior Investigator

Dr. McLeod´s research interests support her clinical activity in Inflammatory Bowel Disease (IBD) and colorectal diseases and is designed to impact directly on patient care. Her team undertakes clinical trials of a number of different surgical procedures for a variety of conditions, to determine the best surgical procedures to use. Quality of life following surgery is another area of Dr. McLeod´s research program.

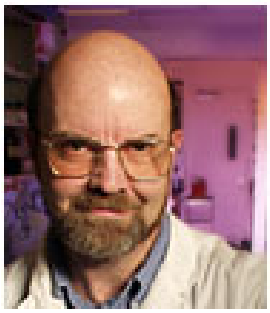
Dr. Andras Nagy
Senior Investigator

The Nagy laboratory is interested in using mouse genetics to study mammalian development and to apply this knowledge to human disease. Dr. Nagy is also developing new, powerful tools for genetic approaches and phenotype analysis for these ongoing studies. Another main activity of the Nagy lab is connected to mammalian genomic imprinting.

Dr. Anthony J. Pawson
Senior Investigator and Director of Research

Our laboratory is interested in the mechanisms by which cells convert an external signal into an intracellular response. In analysing the signalling properties of normal and oncogenic protein-tyrosine kinases we have identified a protein module, the SH2 domain, which is a common feature of many cytoplasmic signalling proteins, and acts through its ability to recognise specific phosphotyrosine-containing peptide motifs. SH2 domains therefore function to physically couple activated cell surface receptors, that regulate cell growth, differentiation and movement, to cytoplasmic biochemical pathways. SH2 domains serve as the prototype for a large family of protein modules that act in concert to control many aspects of cellular behaviour.

Dr. John Roder
Senior Investigator



Dr. Roder is exploring the link between long-term potentiation (LTP), learning and memory using engineered mice that lack the mGluR5, glutamate receptor. His lab is focusing on the steps of the complex cascade of events that lead to LTP. Specifically, the Roder lab is examining the means by which NMDA, AMPA and metabotropic glutamate receptors, and their downstream signalling cascades, act to regulate synaptic strength.

Dr. Janet Rossant
Senior Investigator

Our laboratory is interested in the mechanisms by which the early mammalian embryo develops different cell lineages and establishes a basic body pattern. Using a combination of embryological and molecular tools, we are studying the formation and function of the trophoblast, the establishment of embryonic patterning at the onset of gastrulation and the early development of the vascular system. This research utilises genetic and experimental strategies in mice to dissect processes of normal development and disease. A major initiative is developing new mouse models of human disease, using genome-wide mutagenesis.

Dr. Frank Sicheri
Investigator

Dr. Sicheri´s lab is interested in the structure and function of protein kinase signaling molecules. His laboratory employs x-ray crystallography to determine the detailed structure of individual protein domains and their assembly into higher-order complexes. Structures that the Sicheri lab is working on are the catalytic domain of the Eph receptor tyrosine kinase, the SCF E3 ubiquitin ligase, the RNA dependent protein kinase PKR, the polo family kinase Sak and the proto-oncogene Akt.

Dr. Katherine Siminovitch
Senior Investigator

Dr. Siminovitch´s research program is directed at identifying the genetic and cellular mechanisms modulating expression of the immune response and development of immunologic diseases. The lab has focused on defining the molecular events underlying expression of the Wiskott-Aldrich syndrome (WAS) immunodeficiency disease and the murine motheaten syndrome of systemic autoimmunity, both of which are caused by dysfunction of signaling effectors that regulate lymphocyte activation. The group is also interested in the genetics of chronic inflammatory diseases and is specifically concentrating on the characterization of genes involved in inflammatory bowel disease and arthritis.

Dr. Michael Tyers
Senior Investigator

The Tyers laboratory uses biochemical and genetic approaches to understand how the cell division cycle works and how it is regulated by extracellular signals. Current efforts to understand the signals that regulate cell division are focused on a conserved mitogen activator protein kinase (MAPK) pathway, and on pathways that co-ordinate cell growth with division. Future work will include generation of genome-wide and proteome-wide data sets to fully understand the pathways that control cell division in yeast and mammalian systems.

Dr. Jeffrey Wrana
Senior Investigator

Dr. Wrana´s lab is primarily interested in defining the signal transduction pathways for a superfamily of proteins known as TGF-beta. Dr. Wrana´s lab has defined some of the key steps in this pathway and determined that Smad2 is mutated in some colorectal cancers. Recently, the lab identified SARA (for Smad Anchor for Receptor Activation). The biological function of SARA is currently being elucidated using a knockout mouse of SA

Dr. Mei Zhen
Investigator

Dr. Zhen´s laboratory investigates how neurons establish synaptic connectivitites during development. The focus is on dissecting the molecular compoents of syd-2 and sad-1 signaling pathways using C. elegans as a model system. The lab has developed a number of fluorescent GFP/YFP/CFP markers which allows direct visualization of different synaptic structures in live C. elegans.

Dr. Bernard Zinman
Senior Investigator

Dr. Zinman´s research interests include both type 1 and type 2 diabetes. His research team focuses on three areas: the long-term complications of diabetes, approaches to insulin therapy, and diabetes in Aboriginal communites. Since 1992, Dr. Zinman and his collaborators have been examining the prevalence of diabetes and its associated risk factors in Sandy Lake, an isolated native community located in the Sioux Lookout Zone of northwestern Ontario.

Dr. Arthur Slutsky

Research involves the development of better techniques and technologies to ventilate critically ill patients to avoid lung injury

Dr. Duncan Stewart

Research involves gene therapy and stem cell transplantation to repair heart muscles and restore heart function.

Dr. David Jenkins,

Research involves studying the relationship between diet and chronic disease and results will be used to create new diet guidelines

Dr. Prabhat Jha,

Fundamental research to generate, synthesize, and disseminate real-world evidence about the spread of HIV1 and tobacco related diseases, and to develop more effective intervention tools to control these major causes of premature death. Expected results include improved health and decreased mortality among the world's 1.3 billion poor

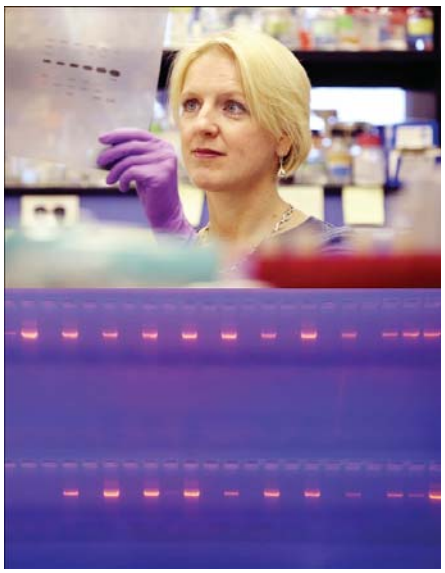
Dr. Wendy Levinson

Research involves studying the patterns in various aspects of physician-patient communication, combining descriptive studies with active training and testing programs in order to improve standards of patient care. The goal is to improve patient satisfaction with their medical care, improve treatment of chronic disease due to better communication and fewer incidences of malpractice litigation.

Dr. Susan Quaggin

Research involves studying the mechanisms of kidney disease at the cellular level with the goal of developing new research and diagnostic tools

RACHEL TYNDALE: A new approach to help people quit smoking



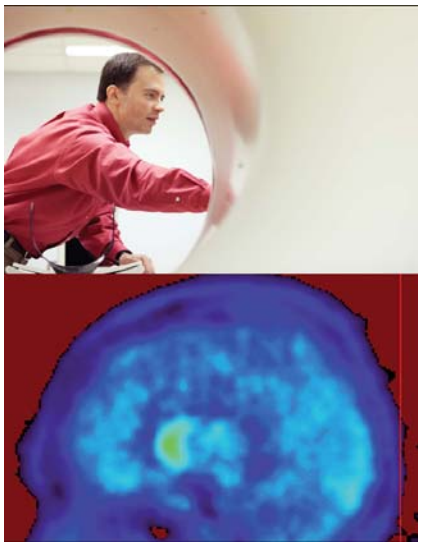
Although we all know the dangers of tobacco smoking, our efforts to help people quit have been only partly successful. Dr. Rachel Tyndale, Head of the Pharmacogenetics Research Section at CAMH, is tackling the serious public health issue of smoking by trying to better understand why some people smoke more than others, and why some find it easier to quit. One answer may lie in our genes. We know that variations in genes can account for why some people respond to drugs differently than others. Understanding the role such variations play in why and how we become addicted to smoking can give us a new approach to individualized medicine. Dr. Tyndale's goal is to use genetic information to personalize treatment for people who want to quit smoking. At CAMH, her work has already evolved from very basic studies in the test tube to clinical drug trials, based on her scientific findings, in people who are dependent on nicotine (the substance in tobacco responsible for dependence). Dr. Tyndale's laboratory investigations initially focused on the genetic differences among people who smoke, in the enzyme that breaks down nicotine.

"The really exciting part of my research is the possibility of using genetic information, for the first time, to individualize treatment to help smokers quit this highly addictive drug."

— Dr. Rachel Tyndale

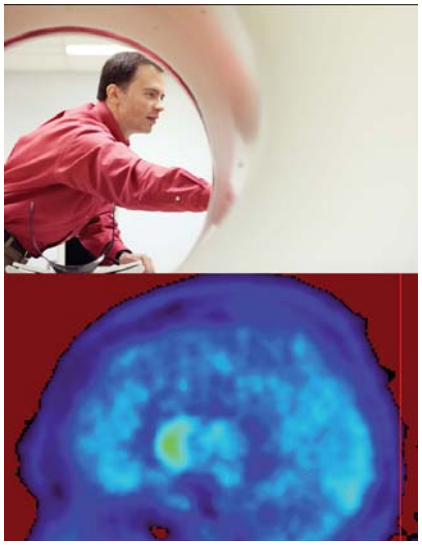
She discovered that some people have a genetic variation in this enzyme that causes them to break down, or metabolize, nicotine slowly. These people are less likely to smoke, smoke less each day if they do smoke and have greater success in quitting smoking. A different variant of the same gene has the opposite effect in other people: their bodies break down nicotine faster. These people are more likely to smoke heavily, have greater problems quitting and have more smokingrelated health problems, such as lung cancer. Dr. Tyndale's hope is that, in future, when people seek help for nicotine dependence, clinicians will be able to look first at the person's genetic makeup to see whether that person will metabolize nicotine quickly or slowly and then tailor treatment accordingly. In clinical trials, Dr. Tyndale found that people who metabolize nicotine slowly are able to quit smoking more efficiently, and that their efforts to quit are enhanced by smoking cessation drugs. Preliminary data from other clinical studies suggest that drugs that can block the metabolism of nicotine can reduce daily smoking. These studies show great promise, and her group is preparing for larger-scale clinical trials.

JEFF MEYER: Brain imaging to help develop new antidepressant medications



Eighty per cent of serotonin transporter sites are blocked by the lowest therapeutic dose of the five most common antidepressants.

To make progress in our understanding of depression and antidepressant treatment, we need to better understand the balance and functions of chemicals in the brain, such as serotonin, that play a role in mood disorders. Dr. Jeff Meyer, Head of Neurochemical Imaging in Mood Disorders at the *PET* Centre, is working to understand depression using positron emission tomography (PET). PET is a "brain scan" procedure that allows us to measure proteins and chemicals in the brain. Dr. Meyer is using a new PET technique developed in Toronto to measure serotonin transporters. Serotonin transporters, located on the ends of nerves, are sites that remove serotonin from active areas to inactive areas. In short, they control serotonin levels in active areas of the brain. Key questions about these sites needed to be answered: Are there more or fewer serotonin transporter sites during depression? How much do antidepressants affect these sites to change serotonin levels? "In the past, most treatments for depression were found with a lot of luck," says Dr. Meyer. "To advance in the future, we need to better understand the details of the illness and treatments." Two recent studies illustrate the way Dr. Meyer's work will help generate future treatments and allow for more effective prescribing today. The first question Dr. Meyer asked was whether the amount of serotonin transporter is changed in the brain of people who are depressed. In the December 2004 issue of the *Archives of General Psychiatry*, Dr. Meyer and colleagues reported on his study of serotonin transporters in the brain of people living with depression. In this study, they found that when serotonin transporters are elevated by about 25 per cent in people with depression, they develop symptoms of severe pessimism. This project helps us better understand the complexity of how brain chemicals and the serotonin transporter are involved and altered in depression. In the second study, Dr. Meyer used this PET approach to measure the percentage of brain serotonin transporter sites that are typically blocked by antidepressant medications. This measurement, it was hoped, would help us see how frequently prescribed medications affect the serotonin transporter.



In the May 2004 issue of the *American Journal of Psychiatry*, he reported that 80 per cent of serotonin transporter sites are blocked by the lowest therapeutic dose of the five most common antidepressants. The long-term benefit will be to improve our understanding of how these antidepressants work. For example, one can see by these two studies that antidepressants that target the serotonin transporter do more than just balance serotonin—treatment lowers the measure by at least 80 per cent, and the measure is raised in depression at most by 25 per cent. The short-term benefit of this information is that clinicians can better tailor the dose of antidepressant drugs to meet individual needs. Choosing the right dose for some could mean lessened side effects; for others, it could mean getting a better response. Another short-term benefit is that Dr. Meyer's results are now the industry standard for developing new antidepressant treatments.