

Discovery science and clinical synergy

Maximising impact nationally and internationally...

The Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital (Toronto) is a landmark in the Canadian biomedical research landscape. Home to 50 core investigators and 60 clinical researchers, the institute is small, but mighty. While seen as a top tier leader in discovery research in its own right, the institute also effectively synergises with the clinical programmes of the hospital, creating value for patients, researchers and the community.

The Lunenfeld-Tanenbaum (formerly the Samuel Lunenfeld Research Institute) has a short but storied past. In 1985, its Founding Director, Dr Lou Siminovitch, a Canadian research pioneer and master architect of the modern Toronto research landscape, fused the disciplines of genetics and molecular biology in the institute. A decade later, the institute was already ranked within the top 10 research institutes worldwide, with peers such as the Salk Institute and the Whitehead Institute, based on citation analysis in the field of genetics and molecular biology (Science-Watch, papers published 1994-1998).

More recently, the institute has strategically expanded its focus. Scientists such as Andras Nagy, Janet Rossant and John Roder steered the institute in the late 1990s as a powerhouse for embryonic stem cell science and mouse transgenesis – areas that continue as strengths today.

In the early 21st Century, cancer biologists, including Jeff Wrana, Frank Sicheri and Jim Dennis, introduced high-throughput methods and robotics infrastructure as key

to systems biology, while recruitment of investigators such as Anne-Claude Gingras, Dan Durocher, Laurence Pelletier and Fritz Roth has maintained the institute at the cutting edge of large-scale data analysis, visualisation and imaging.

Today the institute's lauded productivity continues, with researchers publishing 600+ research articles in peer reviewed journals each year. Its \$100m budget positions it in 10th place in size among research hospitals in Canada, but its research intensity, as measured in \$ per investigator, ranks it easily in first place (www.researchinfosource.com).

Lunenfeld-Tanenbaum researchers have been internationally recognised for their research impact; lauded researchers include Tony Pawson, pioneer in understanding modular protein interactions, winner of, among others, the Gairdner Foundation International Award, the Kyoto Prize and the Wolf Prize in Medicine, and one of seven worldwide 'Citation Laureates' (Medicine) named by Thomson Reuters in 2012. The institute is also home to four 'Highly Cited Researchers': Jeff Wrana (molecular biology), Tony Pawson (dual awardee: biology and molecular biology), and Eleftherios Diamandis and Edward Keystone (both clinical medicine).

The institute's leadership and extensive collaboration in biomedical research is shown in the large range of multi-institutional clinical trials it has led, with participation in 70 large clinical trials and research consortia, and collaborations with nearly 1,000 institutions in 60 countries.

For example, Irene Andrusis heads the Ontario Familial Breast Cancer Registry, part of the international Breast Cancer Family Registry, and recently helped launch the Canadian-American LEGACY Girls Study tracking how lifestyle, environment and biology affect development. Neonatologist Shoo Lee established the Canadian Neonatal Network (27 hospitals and 16 universities) and the International Neonatal Collaboration, and is involved in collaborations with 200 hospitals internationally. Mark Silverberg has been involved in leading several international efforts in inflammatory bowel disease, including the International IBD Genetics Consortium, the NIDDK IBD Genetics Consortium and the CCFR Microbiome Initiative.

Research at the Lunenfeld-Tanenbaum falls under the following broad disease or discipline-based umbrellas:

Cancer research

Representing the largest disease areas in terms of funding, the cancer programme is broadly defined and embraces a range of approaches from molecular and structural biology-based discovery programmes and high-throughput systems biology through clinical trials to population-based studies. Of particular note are the breast cancer and sarcoma programmes.

Systems biology

The myriad of processes that cells and tissues employ to communicate and function act in coordinated and consequential patterns that can only be discerned by analysis that accounts for multiplicity and complexity. The systems biology group is



Lunenfeld-Tanenbaum's Bernard Zinman (left) played a key role in the 25 year international Diabetes Control and Complications Study. Daniel Drucker has developed two new drug treatments for Type 2 diabetes and has recently obtained FDA approval of a new drug to treat a bowel condition associated with colon cancer and IBD

developing and employing state-of-the-art mass spectrophotometric, imaging and robotic technologies to capture datasets that reflect the layers of controls and outputs of biological systems – and developing the computing technologies to make sense of the data.

Diabetes research

The Lunenfeld-Tanenbaum's potent diabetes team boasts remarkable expertise in tackling the challenges of this devastating, costly and pervasive chronic illness. Bernard Zinman, Daniel Drucker, Bruce Perkins and Ravi Retnakaran, working with the Leadership Sinai Diabetes Centre, have been at the forefront of new therapeutic interventions and glucose control studies for Type 1, Type 2 and gestational diabetes.

Neuroscience

The sheer complexity of the human brain presents an immense scientific challenge and researchers have therefore relied upon model organisms in order to simplify analysis and determine fundamental principles. The nematode worm and genetically engineered mouse models are employed to better understand neurological disorders such as depression, schizophrenia and dementia.

Genomic medicine

As the cost of whole-genome DNA sequencing plummets (achieving increases in efficiency that dwarf advances in microprocessor technologies) to sub-\$1,000, the future is clear: genomic information will be fully accessible to healthcare and will become an important baseline tool for patient care. Moreover, while the technology is essentially in place, efficient methodologies for sifting through and understanding the reams of

data (2x3 billion nucleotides per individual, much of which has low information content) is still in its infancy. Lunenfeld-Tanenbaum's Kathy Siminovitch is leading a provincially funded pilot programme in personalised medicine that combines genomic information with clinical data to enhance clinical decision-making.

Stem cells and regenerative medicine

By developing techniques such as tetraploid aggregation and isolation of mouse embryonic stem cell lines that are used around the world, Lunenfeld-Tanenbaum scientists were pioneers in embryonic stem cell science and mouse transgenesis, and, more recently, induced pluripotent stem cell technology that allows adult tissues (such as skin cells or blood cells) to be reprogrammed to an 'embryonic state', which in turn allows their reprogramming into essentially any other cell type. Other Lunenfeld-Tanenbaum researchers apply regenerative medicine techniques to produce cartilage, bone, small blood vessels and beta-islet cells with potential for tissue replacement.

Women's and infants' health

Mount Sinai Hospital is home to Canada's largest clinical programme in obstetrics and gynaecology with ~7,000 births per annum and the institute has a complementary and equally high performing research programme in this discipline, along with its close ties to physiology and developmental biology. Researchers study pre-eclampsia, intrauterine growth restriction, preterm birth, gestational diabetes and placental insufficiency, as well as elements of reproductive health, including *in vitro* fertilisation, stem cell differentiation and ovarian health. A key building block is the newly

launched Ontario Birth Study, a longitudinal study conceived by Stephen Lye and Alan Bocking that will follow thousands of babies *in utero* and throughout childhood.

Prosserman Centre for Health Research

The results of studies of populations with different propensities to various diseases have firmly established the field of genetic epidemiology at the Lunenfeld-Tanenbaum as a key methodology for identification of behavioural and genetic factors associated with health, including vitamin D and breast cancer risk and identification of causal associations between disease and gene variants.

From its founding to the present day, the Lunenfeld-Tanenbaum's strengths have arisen from the conjunction of a world-leading discovery research platform twinned with centres of clinical excellence. Multiple institute and hospital-led studies – the Personal Genomics project, the Ontario Birth Study – as well as leadership and participation in international consortia, attest to this. Going forward, the institute's goal is to continue to align and enhance these programmes, maximising its impact nationally and internationally.

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