Manitoba Institute of Cell Biology
The Lyonel G. Israels Laboratories
Annual Report 2009
The Manitoba Institute of Cell Biology (MICB)

gratefully acknowledges

the following organizations

for their on-going support and commitment

without which the achievements
documented in this report would not have been possible:

CancerCare Manitoba Foundation
CancerCare Manitoba
The University of Manitoba

And most especially to those who unselfishly contributed

their dollars to cancer research.
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Changes in administrative leadership, new recruits and multiple research prizes for MICB trainees are among the highlights of this year’s annual report from the Manitoba Institute of Cell Biology. Importantly, our senior investigators have continued their success in obtaining funding from various agencies to support their research and so were our trainees in obtaining pre- and post-doctoral career awards.

Dr James Davie stepped down as Director of MICB and Provincial Director of Research at the end of 2008 to take up the Executive Directorship of the new Manitoba Health Research Council. We wish him well in this new and challenging endeavor. He has graciously remained as acting Associate Director of MICB to support Dr Leigh Murphy who has taken on the Acting Directorship of MICB as well as Dr Spencer Gibson has been appointed Interim Provincial Director, Research CancerCare Manitoba.

We were thrilled to welcome Dr Afshin Raouf as a Senior Investigator at MICB. His major research interest is to understand the molecular mechanisms that are involved in the regulation of normal human mammary stem cells and how these may be altered to produce breast tumours.

We are equally thrilled to welcome Dr Kirk McManus as a Senior Investigator at MICB. His major research interest is the molecular mechanisms of chromosome instability and its contribution to the development and progression of cancer particularly colon cancer.

Our Senior Scientists have been again successful in having their research funded from both local and national agencies. Notable among our successes were MICB scientists receiving a CFI Leading Edge Fund award, CIHR operating grants as well as several awards from the Canadian Breast Cancer Foundation and the Prostate Cancer Foundation of Canada.

Once again our graduate students and post-doctoral fellow trainees have done extremely well in receiving prestigious awards from NCIC, CIHR and NSERC. As well MICB trainees have almost cornered the market on research prizes awarded locally. Of note Teralee Burton a PhD student with Dr Spencer Gibson won the coveted E.L.Dewry award at the University of Manitoba research day. The success of our trainees locally, nationally and internationally speaks highly of their quality and the superior mentorship they receive.
MICB has an established reputation not only in training high quality graduate students and postdoctoral fellows but also in introducing and mentoring gifted high school students to science and research. Once again some of these students have had outstanding success in local and national science competitions this year.

This year MICB’s senior investigators have published 43 research articles and acquired $5.89 million in external grant support. Our success was made possible by the strong support from CancerCare Manitoba, the CancerCare Manitoba Foundation Inc, the University of Manitoba and the Province of Manitoba.
The Manitoba Institute of Cell Biology (MICB) was founded in 1969 by CancerCare Manitoba (formerly the Manitoba Cancer Treatment and Research Foundation) and the University of Manitoba. The Institute is associated with the Faculty of Medicine and the Health Sciences Centre and is located on the 5th, 6th and 7th floors of the CancerCare Manitoba (CCMB) building at 675 McDermot Avenue in Winnipeg, Manitoba, Canada.

It is dedicated to basic and translational research in biology and its relation to health, with a primary emphasis on cancer and related diseases. Scientists study such challenging problems as the molecular origins of cancer, the role of signal transduction pathways in regulating cell proliferation, cell death, gene expression and platelet function, development of markers of risk of developing invasive breast cancer, neuronal growth and differentiation during development, programmed cell death and the biochemical action of cancer chemotherapeutics.

Although not a degree-granting institution, the Institute plays a major role in training scientists, whether graduate or postgraduate students, medical trainees and investigators who come from around the world to work with our staff. Degrees are granted through the Faculty of Medicine, Departments of Human Anatomy and Cell Science, Biochemistry and Medical Genetics, Immunology, Pharmacology and Therapeutics, Physiology and Medical Microbiology. Information on training programs can be obtained from our office and the Dean of Graduate Studies.

The Institute’s web page address is:
http://www.umanitoba.ca/institutes/manitoba_institute_cell_biology/index.html
The Manitoba Institute of Cell Biology receives a core-operating budget from CCMF and CCMB. Prior to being approved by CCMB Board the budget proposal is first presented and approved by the MICB Board of Management. Currently the Institute’s operating budget is $1.57 M. The funding covers salary support, the general operation of the facility, visiting lectureships, equipment, maintenance and repair costs.

In the 2008-2009 fiscal year, the Institute received $2,589,598 from the following Institutions:

University of Manitoba (Administered by other Departments):
  Salaries for Senior Staff                                  $  776,991
University of Manitoba (Administered by MICB):
  Salaries for Senior Staff                                  $  213,013
CancerCare Manitoba
  Salaries for Senior Staff                                  $  59,549
CancerCare Manitoba Foundation
  Operating & Equipment/CFI Grants, Studentships & PDF Awards $1,472,574
Health Sciences Center
  Salaries for Senior Staff                                  $   67,471

Senior staff operate their research programs by applying for external grants. For the year ending June 30, 2009 this funding totalled $5,894,758. Sources of funding included:

Operating and Equipment Grants                                  $ 5,696,193
Industry Grants and Contracts                                    $  20,213
Personnel Awards
  Career Awards for Senior Staff                                 $   61,618
  PDF and Student Awards                                         $ 111,125
Donations                                                        $   822
Sponsor Donations                                                 $  4,787
The MICB Advisory Board meets 2-3 times per year and oversees the general operation of the Institute. CancerCare Manitoba and the University of Manitoba appoint representatives on the Board, and jointly appoint members at large.

Members during the 2008-2009 year include:

Dr. Janice Dodd (Chair) Professor and Head
Department of Physiology
University of Manitoba

Mr. David Carrick Aikins MacAulay & Thorvaldson

Dr. Leigh Murphy Acting Director, Manitoba Institute of Cell Biology

Dr. Lesley Degner Professor, University of Manitoba
CHSRF/CIHR Chair in Nursing Care
Helen Glass Centre for Nursing

Dr. H. S. Dhaliwal President & CEO
CancerCare Manitoba

Dr. Garry Krepart Chair, Gyne Oncologic Cancer Disease Site Group
CancerCare Manitoba

Dr. Dean Sandham Dean of Medicine
University of Manitoba

Dr. Ian Smith Institute of Biodiagnostics
National Research Council of Canada

Dr. K. Dakshinamurti Division of Stroke and Vascular Disease
St. Boniface Hospital Research Centre
MEMBERS WHO HAVE SERVED ON VARIOUS SCIENTIFIC REVIEW AND ADVISORY PANELS

Members during 2008-2009:

Dr. Leigh Murphy  
Program Chair - Fellowship Review Panel MHRC  
Member, Executive Committee MICB  
Member, Manitoba Breast Tumor Bank Scientific Review Panel  
Scientific Reviewer, CIHR-Endocrinology Panel  
Scientific Reviewer, DOD-BCRP-Concept Grants-Endocrinology panel  
Member of the College of Reviewers for the Canada Research Chairs  
Scientific Reviewer, Alberta Cancer Board-Breast Cancer Research Program  
Member of review panel for Winnipeg Rh Award nominees  
Scientific Reviewer, Postdoctoral Fellowships-Susan Komen Foundation

Dr. Jim Davie  
Scientific Reviewer, Grant Review Committee Biochemistry and Molecular Biology Panel, CIHR  
Member of NCIC Program Project Site Visit Team  
Member, CFI College of Reviewers, New Opportunities Fund  
Member, College of Reviewers for CRC Program  
Member, MHRC Research Advisory Committee  
Member, NorCOMM Scientific Advisory Board  
Member, Institute of Cardiovascular Sciences Awards Committee  
Member, Scientific and Medical Advisory Committee, Prostate Cancer Research Foundation of Canada  
Member, Molecular and Cellular Oncology P01 Special Emphasis Panel, US National Cancer Institute  
Member, US Congressionally Directed Medical Research Programs review panel for the pre-doctoral traineeship award in breast cancer

Dr. David Eisenstat  
Scientific Reviewer, Leukemia and Lymphoma Society of Canada  
Member, Scientific Advisory Committee, National Brain Tumor Society, US  
Scientific Reviewer, Brain Tumor Society (USA), Low Grade Gliomas  
Scientific Reviewer, NCIC, Clinical Research Fellowship panel  
Member, Brain Tumor Funders Collaborative  
Scientific Reviewer, Brain Tumor Funders Collaborative  
Scientific Reviewer, Ontario Institute of Cancer Research (OICR) clinical & translational operating grants committee
Dr. Spencer Gibson  Scientific Reviewer, NCIC Personnel Awards Committee  
Scientific Reviewer, Leukemia and Lymphoma Society of Canada Operating Grants Panel  
Member, Scientific Advisory Board, Lymphoma Foundation of Canada  
Scientific Reviewer, NIH, BMCT Study Section  
Member of the NCIC-CTG, Correlative Science Hematology Committee  
Scientific Reviewer, CIHR, New Investigator awards panel  
Member of the NCIC Health Research Ethics Board

Dr. Geoff Hicks  Manitoba Health Research Council, Research Advisory Committee  
Canadian Institutes of Health Research, Reviewer for G, CPT, MCC and GMX Panels  
Member, CIHR Institute of Genetics Advisory Panel  
Scientific Advisory Board Member, Genomic Quebec, Gene Regulators is Disease  
Scientific Advisory Board Member, Genomic BC, Pathogenomics of Innate Immunity  
Scientific Reviewer, BC Transgenics Centre

Dr. Sara Israels  Chair, Simon and Sara Israels Thesis Awards Committee  
Member, CCMF Project Grants and Awards Committee  
Royal College of Physicians and Surgeons Specialty Committee (Nucleus) in Pediatric Hematology/Oncology  
Royal College of Physicians and Surgeons Pediatric Hematology/Oncology Examination Committee

Dr. James Johnston  Scientific Reviewer, Alberta Cancer Board

Dr. Michael Mowat  Scientific Reviewer, NCIC Panel J

Dr. Etienne Leygue  Member, Operating Grant Competition of the National Cancer Institute of Canada (NCIC), Panel D  
Member, DOD-BCRP-USAMRMC Pre and Post Doctoral Awards Panel
Basic Researchers
Dr. Leigh Murphy  Acting Director and Margaret A. Sellers Chair and Professor (Biochemistry and Medical Genetics)
Dr. James Davie  Professor (Biochemistry and Medical Genetics) and Acting Associate Director of MICB
Dr. Spencer Gibson  Interim Provincial Director of Research of CCMB
Dr. Geoff Hicks  Associate Professor (Biochemistry and Medical Genetics)
Dr. Sabine Mai  Professor (Physiology)
Dr. Kirk McManus  Assistant Professor (Biochemistry and Medical Genetics)
Dr. Michael Mowat  Professor (Biochemistry and Medical Genetics)
Dr. Etienne Leygue  Professor (Biochemistry and Medical Genetics)
Dr. Afshin Raouf  Assistant Professor (Immunology)
Dr. Robert Shiu  Professor (Physiology)

Clinicians
Dr. David Eisenstat  Associate Professor (Pediatrics and Child Health) and Director of Brain Tumor Disease Site Group
Dr. Don Houston  Associate Professor (Internal Medicine) and Clinician (Medical Oncology and Haematology, CCMB)
Dr. Sara Israels  Professor (Pediatrics and Child Health) and Head (Section of Paediatrics) Haematology/Oncology/BMT)
Dr. James Johnston  Professor (Internal Medicine), Associate Director (Clinical ) MICB and Clinician (Medical Oncology and Haematology, (CCMB)
Dr. Peter Watson  Professor (Pathology and Laboratory Medicine)
University of British Columbia  Director, Tumor Tissue Repository, BC Cancer Agency

Affiliated Members
Dr. James Lau  Assistant Professor (Internal Medicine)
Dr. Janice Richman-Eisenstat  Assistant Professor (Internal Medicine, Pharmacology and Therapeutics)
Dr. Frixos Paraskevas (Manitoba Institute of Cell Biology)
Dr. Asher Begleiter  Professor (Internal Medicine, Pharmacology and Therapeutics)
Dr. Lorne Brandes  Professor (Internal Medicine, and Pharmacology and Therapeutics) and Clinician (Medical Oncology and Haematology, CCMB)
Dr. Leigh Murphy was appointed as Acting Director for the Manitoba Institute of Cell Biology for the period January 1 to December 31, 2009.

Leigh is responsible for providing leadership in all research and administrative activities within the Manitoba Institute of Cell Biology. In addition, Leigh is responsible for continuing the implementation of the Manitoba Institute of Cell Biology Strategic Plan.

We wish her success in her new role as Acting Director for the Manitoba Institute of Cell Biology

CONGRATULATIONS DR. MURPHY
DR. SPENCER GIBSON IS THE NEW INTERIM PROVINCIAL DIRECTOR, RESEARCH CANCERCARE MANITOBA

Dr. Spencer Gibson was appointed as Interim Provincial Director, Research, for CancerCare Manitoba for the period April 1 to December 31, 2009. Spencer will be responsible for providing leadership for all cancer related basic, epidemiological behavioral, applied, translational, and clinical research activities undertaken by CancerCare Manitoba. This will include administration of all research business within CCMB.

Dr. Gibson will represent Manitoba at various local, provincial, national and international committees, boards, and meetings related to cancer research. He will provide leadership in identifying and funding opportunities for researchers from local, provincial, national and international organizations supporting cancer research. He is also responsible for oversight of the Clinical Investigation Office (CIO), and the Oncology Library and the organization of the CancerCare Manitoba Foundation (CCMF) Grant Competition. Finally, he will coordinate the translational research program to increase intra-disciplinary cancer research in Manitoba.

We wish him success in his new role as interim Provincial Director, Research, CCMB.

CONGRATULATIONS DR. GIBSON
An Appreciation Reception in honor of Dr. Davie was held on December 19, 2009 for his vision, innovation and leadership as Director of MICB and to congratulate him on his upcoming position as Executive Director of the Manitoba Health Research Council.
Dr. Afshin Raouf joined the Manitoba Institute of Cell Biology as a Senior Scientist on March 1st, 2009.

 Accumulating evidence suggests that human breast tumours are a heterogeneous population of cells, maintained by a rare subset of cells in the tumour that have stem cell properties suggesting that while the current therapeutic approaches may eradicate the vast majority of cells in a tumour they might not eliminate the more relevant and rare stem cells which slowly but eventually can regenerate new tumours. This concept also reinforces the hypothesis that normal stem and progenitor cells are important cellular targets in the initiation and recurrence of human breast cancer. Indeed, mutations arising in stem cells could represent an efficient process for hijacking the regulated proliferation and differentiation of primitive normal mammary cells. These possibilities have recently focused much interest in investigating the molecular mechanisms that are active in normal mammary stem cells and how these may be altered to produce tumours.

 In pursuit of this goal, I have set up a research program that has 3 major objectives:
 1. Identify primitive cell programs that regulate the normal function of the mammary stem and progenitor cells.
 2. Establish how the inappropriate execution of these programs causes the normal stem cells and progenitors to acquire a cancer stem cell phenotype.
 3. Determine whether this understanding can be leveraged to develop therapies against breast cancer stem cell populations.
Dr. Kirk McManus joined the Manitoba Institute of Cell Biology as a Senior Scientist on June 1st, 2009.

Genome instability is widely associated with a variety of tumor types including colon, breast, ovarian and various lymphoma. Mutations that cause chromosome instability (CIN) are now widely recognized as predisposing factors that contribute to the etiology of tumorigenesis. One of my main goals is to identify and characterize genes that regulate chromosome stability in humans to generate a candidate list of genes that may be somatically mutated in CIN tumors. I have previously utilized this approach to identify several key genes that are somatically mutated in colorectal carcinomas exhibiting CIN. Interestingly, many of these genes encode proteins that regulate sister chromatid cohesion and knock-down or knock-out of the genes underlies CIN. Because sister chromatid cohesion appears to be a central theme in colon cancer, I hypothesize that this pathway may also be aberrantly affected in other tumor types exhibiting CIN such as Hodgkin or non-Hodgkin lymphoma. As a result I am currently undertaking a series of studies to investigate sister-chromatid cohesion in various lymphoma cell lines.

Another major focus of my lab is to identify synthetic lethal (SL) interaction partners for the CIN genes identified above. Conceptually, the somatic CIN mutations present in cancer cells represent a genetic distinction from the normal surrounding tissues, that may permit the selective targeting and killing of cancer cells. Accordingly, a major goal of my work is to identify SL genetic interaction networks for those CIN genes identified above. Utilizing cross-species candidate gene approaches I have begun to uncover candidate SL interaction partners and networks that I am beginning to investigate through RNAi-mediated approaches coupled with high content digital imaging microscopy. Once these interactions are confirmed and validated, chemical libraries will be screened to identify small molecule inhibitors of the novel candidate therapeutic targets.
Congratulations to Dr. Jim Davie who’s published research has been cited 220 times.
Title: Histone H4-K16 acetylation controls chromatin structure and protein interactions
Author(s): Shogren-Knaak, M; Ishii, H; Sun, JM, James Davie et al. Source: SCIENCE Volume: 311 Issue: 5762 Pages: 844-847 Published: FEB 10 2006.

Dr. Davie’s research has also been featured on the cover of the following publications:
Dr. Geoffrey Hicks, Canadians for Health Research/Researcher of the Month
Deciphering the Double Helix, Winnipeg Researcher Building a Rosetta Stone for the Human Genome

The entire human genome was mapped by the end of 2003. Technology and resources promoted by this project have already impacted biomedical research and promise to change the way medicine is practiced. For example, detailed genome maps have aided researchers seeking genes associated with dozens of genetic conditions.

Geoffrey Hicks, PhD, Director of the Mammalian Functional Genomics Centre (MFGC) is linking genes to their specific functions to help unravel their role in day-to-day activities and in disease. Dr. Hicks is a University of Manitoba professor who is working on analyzing the genetic factors which play a role in leukemia. His technique of disrupting the genes in mouse embryonic stem cells and observing the results was key in understanding how different suspected genes affected the progression of the disease.

Having demonstrated the strengths of using this targeted animal model for gene-based disease research, Dr. Hicks and the MFGC are now involved in generating a mouse cell library that will contain mutations in every gene in the mouse genome. This project has been specifically identified as the next most important step following the Human Genome Project. It will advance the understanding of how the sequence of letters (our DNA) translates into gene function, providing a living blueprint of instruction and design. This library will be freely available to all biomedical researchers, and will significantly impact biomedical disease-focused research programs and biotech companies in Canada.

Dr Hicks received his PhD in Physiology at the University of Manitoba and was a National Cancer Institute of Canada postdoctoral fellow at the Massachusetts Institute of Technology and the Vanderbilt School of Medicine. He is a Canada Research Chair in Functional Genomics and is the Director of the Mammalian Functional Genomics Centre, a centre in the Manitoba Institute of Cell Biology (a joint institute between CancerCare Manitoba and the University of Manitoba) and the Genetics Modeling Centre in the University of Manitoba. He is currently leader of the North American Conditional Mouse Mutagenesis Project (NorCOMM), the Canadian component of The International Knockout Mouse Project, with Janet Rossant Chief of Research, at University of Toronto’s Hospital for Sick Children. NorCOMM is supported by Genome Prairie with funding of $13.5 million from Genome Canada and other partners.
Dr. Sabine Mai received a CFI Leading Edge Fund (LEF) award for a “Three-dimensional nanoBioMedical Imaging Node (3D-nBMIN)”. Principle users on this application are: Dr. Jim Davie (MICB), Dr. Andrew Halayko (Physiology), Dr. Thomas Klonisch (Human Anatomy and Cell Science), Dr. Jan Friedman (U of B), Dr. William Foulkes (McGill), and Dr. Regen Drouin (U of Sherbrooke). The total eligible costs of this CFI project are $3,065,159.

The proposed infrastructure will enable novel high-resolution multicolour imaging. This will be possible due to innovative 3D structured illumination microscopy, termed “3D-SIM”. 3D-SIM enables high-resolution multi-fluorescent detection and analysis of cellular structures at sub-physical resolution (sub-Abbe) limits, i.e. beyond the physical limits defined by the physicist Ernst Abbe (1840-1905). The current resolving power is reached at 200 nm, which is also called the “Abbe limit”. Recent discoveries, however, now allow for imaging beyond this limit: 3D-SIM permits ‘sub-Abbe’ resolution based on structured illumination and thus provides high spatial resolution in the cellular context. The inventors of this technology, Schermelleh et al. (Science, 2008), have successfully analyzed the nuclear lamina, nuclear pores and nuclear pore complexes. The thickness of the nuclear lamina is in the range of 20-50 nm. 3D-SIM allowed them to visualize this lamin network at an upper limit of $98 \pm 12$ nm laterally and $229 \pm 22$ nm axially. Confocal images showed more than 2 fold higher values. Nuclear pore complexes resolved by 3D-SIM showed an average of $5.6 \pm 3.3$ foci per um$^2$, whereas only $2.8 \pm 1.1$ foci per um$^2$ were detected by confocal analysis. Electron microscopy detects $12 \pm 1.8$ foci per um$^2$. Thus, 3D-SIM reaches a resolution between wide field microscopy and electron microscopy, having the advantage of multicolor fluorescence capabilities.

This instrument is currently only available as a beta version but will be commercially available by the end of 2009. We are excited about these new opportunities for basic and clinical research and envision important new insights into the biology of normal and tumour cells.
Open one of the massive refrigerators in Room 6058 of the CancerCare building on McDermot Avenue and 30 seconds later an alarm will go off -- just a precaution to protect its precious contents. Inside the giant sub -70C fridges are rows of boxes speckled with ice crystals. Peer inside the boxes and you'll find frozen breast tumours.

Dr. Jim Davie holds a slide containing a cancer sample at CancerCare Manitoba

All the tumours have come from more than 5,000 Manitobans -- mostly women -- who donated their cancerous tissue to science. The collection is a pivotal component of the Manitoba Breast Cancer Research Centre, says Dr. Jim Davie, who runs the facility. "I can say without any doubt that it is one of the best tissue banks in Canada, if not one of the best tissue banks in the world," he says. "These freezers are backed up like you wouldn't believe. It's a very valuable resource." So valuable that the fridges are flanked with liquid nitrogen in case the power goes down. If the temperature in the fridges falls below or rises above normal, an alarm goes off and an alarm company calls someone in charge of the bank -- whether it's day or night.

It's all part of the Manitoba Breast Cancer Research Centre. The facility opened in 2004 within the Manitoba Institute of Cell Biology, of which Davie is director. Hidden away on the fifth and sixth floors of the CancerCare building, the Manitoba Breast Cancer Research Centre takes up about 6,000 square feet and employs approximately 50 researchers.

Davie says his scientists could not do their research without the breast tumour bank. Along with helping them pinpoint new biomarkers, or signals that help diagnose breast cancer, the tumours also help scientists determine what types of breast cancer are likely to respond to certain treatments and whether that cancer is likely to spread.
Although the bank existed before the Manitoba Breast Cancer Research Centre opened its doors, it was not as useful, considering it was spread out all over the Health Sciences Centre. Today, the thousands of breast tumours are housed in four fridges in one room. Most have come from live patients; fewer come from autopsies. One tumour can be divided and used in several research studies.

Since the bank began, Davie says he and his colleagues have given over 130,000 breast tumour sections supporting more than 90 research studies. Most were given to scientists in Manitoba and across Canada, while 25 per cent were given to international scientists from places including China and Germany, says Davie. "Most other banks, they just serve their in-house research groups; they don't serve the larger community. That's what makes ours really special," says Davie, noting that samples are given away essentially for free. Tumour banks exist throughout Canada. The Manitoba Breast Tumour Bank is part of the Canadian Tumour Repository Network (CTRNet), a not-for-profit network funded by the Canadian Institutes of Health Research (CIHR). Davie says word of mouth and reputation have made the Manitoba Breast Tumour Bank respected around the world. Though it's not the biggest, he says that it's one of the best-managed. "It's the way that you have the tumours organized and classified".

Michelle Parisien, project co-ordinator for the Manitoba Breast Tumour Bank, provides a tour of a room where tumours are stored in paraffin in mini "cassette" boxes. These samples are used in different applications than frozen material. Parisien says the samples coming into the bank are shrinking, noting that in the past, tumours could be as big as 10 centimetres. "Now they're one centimetre," she says. "With all the screening and mammograms, they are getting smaller and smaller, which is great for the patient, but not so great for us."

Dr. Georgios Skliris, a research associate at the Manitoba Breast Cancer Research Centre, says he couldn't do his work without the breast tumour bank. Sitting at his work station, which is covered with scattered papers and beakers, the scientist admits that his work is tedious. It often takes years before a result is validated and considered to be groundbreaking. "What keeps you going is maybe one day there will be a breakthrough and you will be responsible for it, along with other people, because this cannot be done by one person."

The Manitoba Breast Cancer Research Centre is funded by several sources, including the Canadian Foundation of Innovation and the CancerCare Manitoba Foundation.
Dr. Gordon Keller, Director of the McEwen Centre for Regenerative Medicine University Health Network, Toronto, Canada and Research Chair in Stem Cell Biology, University of Toronto was the speaker for the **DR. ARNOLD GREENBERG LECTURESHIP**.
The Second International Conference on Functional Annotation of the Mammalian Genome was held on April 24-27, 2009 at the Rimrock Resort Hotel located within the national park grounds in Banff, Alberta, Canada.
Dr. Sabine Mai was the organizer of the 10th Anniversary of the Genomic Centre Imaging Symposium which was held on June 5, 2009 at CancerCare Manitoba.

10th Anniversary of the Genomic Centre. We celebrated the 10th anniversary of the Genomic Centre with an Imaging Symposium that covered the previous, current and future aspects of molecular imaging and gave an overview of current research in the area. Guest speakers included Dr. Jeremy Squire (Queens University), Frank Somogy (Zeiss), Dr. Bart Vermolen (Twente, The Netherlands), Dr. Verayuth Praphanphoj (Bangkok, Thailand), Dr. Piranit Nik Kantaputra (Chiang Mai, Thailand), Dr. Hans Knecht (U of Sherbrooke, QC), Dr. Jim Davie (MICB), Dr. Sabine Mai (MICB), as well as current trainees (Dr. Md Gollam Sabbir, Sumit Sandhu, Landon Wark, Macoura Gadji). The event was supported by Carl Zeiss Canada and MICB/CCMF.
From left to right: Frank Somogy, Hart Vermeulen, Piranit Nik Kantaputra, Sabine Mai, Jeremy Squire, Verayuth Praphanphoj

"Transcription factor and chromatin eraser distribution throughout mitosis"
The MICB Annual Retreat was held at the Lakeview Resort in Gimli, Manitoba on September 26-28, 2008.

Pediatric Oncology, Development and Cancer was the theme for the 2008 retreat. Dr. Meredith Irwin, Staff Oncologist from the Hospital for Sick Kids in Toronto and Dr. Rod Bremner, Senior Scientist, Division of Genetics & Development, Toronto Western Research Institute were our out of town keynote speakers. Drs. Sara Israels, David Eisenstat, Jeff Wigle and Hao Ding as well as students and postdoctoral fellows from the various MICB labs were among our local speakers for the event.
A celebration was held in honor of Marilyn Meakin on October 29, 2008 on the occasion of her retirement. Marilyn was the Administrative Assistant to the Provincial Director of Research CancerCare Manitoba.
The 11th annual CancerCare Manitoba Research Day for trainees in clinical and basic medical sciences was held April 24, 2009. Organized by the Medical Staff Association at CancerCare Manitoba, the event is designed to promote oncology and hematology research among trainees. The following MICB trainees received awards:

**Beatriz Perez-Cadahia**, a PDF with Dr. Jim Davie, won 1st prize in the Basic Science Oral Presentation category for her presentation entitled: “Role of 14-3-3 in transcriptional activation in response to Ras-MAPK signaling pathway”.

**Elizabeth McLachlan**, a PDF with Dr. Leigh Murphy, won 2nd prize in the Basic Science Oral Presentation category for her presentation entitled: “Estrogen Receptor beta-1 (ERβ1) regulates expression of the inflammatory genes serpin-A1 and serpin-A3 in breast cancer cells”. Please note that Dr. Ketan Badiani a Research Associate in Dr. Murphy’s laboratory, actually gave the presentation as Dr. McLachlan was celebration the birth of her son that morning.

**Teralee Burton**, a PhD student with Dr. Spencer Gibson, won 1st prize in the Basic Science Poster Presentation category for her presentation entitled: “The Pro-Cell Death Bcl-2 family member BNIP3 promotes Tumor Cell Survival in Glioblastoma Multiforme (GBM)”.

**Yueqin Zhou**, a MSc. student with Dr. Geoff Hicks, won 2nd prize in the Basic Science Poster Presentation category for her presentation entitled: “Identification of RNA Targets of TLS During B Cell Development”.

**Meghan Azad**, a PhD student with Dr. Spencer Gibson, won 3rd prize in the Basic Science Poster Presentation category for her presentation entitled: “Characterizing Hypoxia-Induced Autophagy: The Role of BNIP3 and ROS in Solid Tumors”.

**Golam Sabbir**, a PDF with Dr. Mike Mowat, won 4th prize in the Basic Science Oral Presentation category for his presentation entitled: “The Role of DLC-1 tumor suppressor gene in transformation and metastasis using transgenic mouse models”.
Francisco Mendoza, a Ph.D student in Dr. Spencer Gibson’s lab was this year’s recipient of the Simon and Sarah Israels Graduate Thesis Prize. Francisco has now successfully defended his Ph.D. and is currently a medical student at the University of Manitoba.

Teralee Burton, a Ph.D. Student in Dr. Spencer Gibson’s lab was the recipient of this year’s Portigal award. Teralee also received the Manitoba Health Research Poster Competition MMSF award and the Apotex Fermentation Inc. Faculty of Medicine Major Award in Molecular Biology.

Golam Sabbir, a Postdoctoral Fellow in Dr. Mike Mowat’s lab was the recipient of this year’s Hester award. Golam also received the Dean of Medicine MMSF award.

Mario Fonseca, a MSc Student in Dr. David Eisenstat’s lab received the Manitoba Health Research Poster Competition Dean of Medicine award.

Meghan Azad, a Ph.D. Student in Dr. Spencer Gibson’s lab won Second Prize in the Life Sciences Association of Manitoba “Venture Zone” pitch competition. Meghan also received the Human Genetics Endowment Fund Graduate Student Award and the US Department of Defence Breast Cancer Research Program - Doctoral Award.

Merrill Isenor, a MSc Student is Dr. Sabine Mai’s lab was the recipient of the Hugh J. Anderson Graduate Award in Chemistry and the Ernst and Ingrid Bock Graduate Award.

Evan Booy, a Ph.D. Student in Dr. Spencer Gibson’s lab received the Manitoba Health Research Poster Competition MMSF award and the CIHR Poster competition honorable mention.

Yi Yan, a MSc Student in Dr. Leygue’s lab received an Honorable Mention in the (Manitoba & CIHR Research Poster Competition) 2009 Canadian Student's Research Forum.
RESEARCH HIGHLIGHTS

University of Manitoba Research Days
E.L. Drewry award presented to Teralee Burton

University of Manitoba Research Days
Canadian National Medical Student Research Symposium
Basic/Translational Research (MD/PhD category)
Honorable Mention – Trung Le
University of Manitoba Research Days
Health Sciences Foundation Award for Excellence in a PhD Thesis research presented to Sherif Louis

University of Manitoba Research Days
Health Sciences Graduate Student Association award presented to Yueqin Zhou
Juliet Dae  a volunteer researcher with Dr. Leigh Murphy won best overall in the biological category for a high school senior at the Provincial science fair for her project entitled: 'Inhibition of Cell Growth and Proliferation by the Polyamine Analogue DENSPM in HER2/neu-Overexpressing Estrogen Receptor-Positive Breast Cancer’.

The grade twelve St. Mary's Academy student said, in a nutshell, she was looking at novel cancer treatments and is excited about doing more research in health care and cancer. "Eventually it may become a therapy for cancer treatment.”

Juliet’s other achievements include:

- Manitoba Schools’ Science Symposium Gold Medal and Best Overall Health and Biological Sciences Project
- Excellence in Women’s Health Research Project Award
- Manitoba Delegate to the Canada-Wide Science Fair
- Sanofi-Aventis BioTalent Challenge 2nd Place Overall
- Canada-Wide Science Fair - Bronze Medal
The Institute offers seminars on a weekly basis, which are open to all. In the past year, guest lecturers included:

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</table>
| July 2, 2008       | CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue  | 11:00 – 12:00PM | Dr. Donald White  
Postdoctoral Fellow  
Cancer Research UK Centre for Cell and Molecular Biology Institute of Cancer Research London, United Kingdom | “Adhesion complex signalling in the mouse” |
| July 10, 2008      | CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue  | 11:00 – 12:00PM | Dr. Stuart Berger  
Associate Professor  
Senior Scientist  
Department of Immunology  
University of Toronto | “Activation Enhanced Cell Death” |
| October 23, 2008   | CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue  | 11:00 – 12:00PM | Dr. Brad Nelson  
Director and Senior Scientist Of  
The Deeley Research Centre  
B.C. Cancer Agency  
Adjunct Associate Professor  
University of Victoria | “Toward Predictive and Personalized Immunotherapy of Cancer” |
| October 29, 2008   | CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue  | 1:00 – 2:00PM  | Dr. Loydie A. Jerome- Majewska  
Assistant Professor  
Department of Pediatrics and Human Genetics  
McGill University, Montreal, QC | “En route to the Placenta: Traffic stalls between the ER and Golgi” |
| November 6, 2008   | CCMB AHG Lecture Theatre ON2134-675 McDermot Ave.  | 11:00 – 12:00PM | Dr. Kerry Campbell  
Director, Cell Culture Facility  
Institute of Cancer Research  
Adjunct Associate Professor  
Department of Microbiology and Immunology Philadelphia, PA. | “Signals regulating natural killer cell development and function” |
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<td>March 19, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermont Ave. 11:00-12:00 P.M.</td>
<td>Dr. Versha Banerji Post Doctoral Fellow Dana Farber Cancer Institute Broad Institute of Genomics of Harvard and MIT</td>
<td>“The Changing Paradigm of Drug Discovery: Gene Expression-based High-throughput Screening in Acute Myeloid Leukemia”</td>
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<td>April 2, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue 1:00-2:00 P.M.</td>
<td>Dr. Pam Del Maestro Brain Tumor Foundation of Canada, Canadian Cancer Action Network, North American Brain Tumor Coalition</td>
<td>“Advocacy and the Patient Voice”</td>
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<td>April 2, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue 3:00-4:00 P.M.</td>
<td>Dr. Roland Del Maestro William Feindel Chair in Neuro-Oncology Director, Brain Tumour Research Centre Professor, Division of Neurosurgery and Oncology Montreal Neurological Institute and Hospital McGill University</td>
<td>“Integrating Molecular Information into the Treatment of Gliomas”</td>
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<td>April 9, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Ave. 11:00-12:00 P.M.</td>
<td>Dr. Mark Nachtigal Assistant Professor Dalhousie University Department s of Pharmacology and Medicine Canadian Cancer Society Research Scientist</td>
<td>“Investigating whether Altered Pro-Protein Convertase Activity may Contribute to Ovarian Cancer Formation”</td>
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<td>April 20, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue 10:30-11:30 A.M</td>
<td>Dr. Howard Cedar Professor of Molecular Biology, Hebrew University of Jerusalem, Department of Cellular Biochemistry and Human Genetics, Hadassah Medical School, Ein Kerem, Jerusalem</td>
<td>“Genome wide association studies in colorectal cancer”</td>
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### MICB SEMINARS

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<td>April 23, 2009</td>
<td>CCMB AHG Lecture Theatre</td>
<td>3:00-4:00 P.M.</td>
<td>Dr. Andrew Li-jen Kung</td>
<td>&quot;Incorporation of Imaging Endpoints in Cancer Drug Discovery&quot;</td>
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<td>Director of Preclinical Imaging Assistant Professor of Pediatrics, Dana-Farber Cancer Institute, Boston, Massachusetts</td>
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<td>May 12, 2009</td>
<td>CCMB AHG Lecture Theatre</td>
<td>10:00-11:00 A.M.</td>
<td>Dr. Francis J Giles</td>
<td>&quot;Molecular insights: Therapeutic progress and challenges&quot;</td>
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<td>Director, Institute for Drug Development</td>
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<td>Deputy Director, Cancer Therapy &amp; Research Centre at the University of Texas Health Science Centre San Antonio</td>
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<td>May 25, 2009</td>
<td>CCMB AHG Lecture Theatre</td>
<td>2:00-3:00 P.M.</td>
<td>Dr. Robert Bristow</td>
<td>&quot;Tumor Hypoxia and Genetic Instability: An Achilles Heel for Cancer Therapies&quot;</td>
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<td>Director, Core I – STTARR and LEGEND Labs, Canadian Cancer Society Research Scientist</td>
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<td>May 28, 2009</td>
<td>CCMB AHG Lecture Theatre</td>
<td>11:00-12:00 P.M.</td>
<td>Dr. P. Jeremy Wang</td>
<td>&quot;Concerted Regulation of Mitosis and Meiosis in the Germline&quot;</td>
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<td>Assistant Professor of Developmental Biology Department of Animal Biology University of Pennsylvania Philadelphia, Pennsylvania</td>
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<td>May 28, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue 2:00-3:00 P.M.</td>
<td>Dr. Eftekhar Eftekharpour Associate Neuroscientist, Spine Program Division of Genetics and Development Toronto Western Research Institute</td>
<td>“Stem Cell Therapy for Central Nervous System Disorders: Victories of the Past, Challenges of the Future”</td>
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<td>June 4, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue 11:00-12:00 P.M.</td>
<td>Simon &amp; Sara Israels Graduate Thesis Prize Francisco Mendoza Ph.D. Medical Student Faculty of Medicine, University of Manitoba</td>
<td>“A Balancing Act Between Life and Death ” MEKK1 and the Apoptotic Pathway</td>
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<td>June 23, 2009</td>
<td>CCMB AHG Lecture Theatre ON2134 675 McDermot Avenue 12:00-1:00 P.M.</td>
<td>Dr. Arnold Greenberg Lectureship Dr. Gordon Keller Director, McEwan Centre for Regenerative Medicine, University Health Network, Toronto Canada Research Chair in Stem Cell Biology, University of Toronto</td>
<td>“Generating functional tissues from human pluripotent stem cells”</td>
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17. Klionsky, DJ; Abeliovich, H; Agostinis, P, Gibson, S. B. et al. 2008 Guidelines for the use and interpretation of assays for monitoring autophagy in higher eukaryotes. **Autophagy** 4:151-75


# DISTRIBUTION OF IMPACT FACTORS AND CITED PUBLICATIONS

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Distribution of Impact Factors in journals of MICB’s published work
2006 - 2008

- Impact Factor <5: 1%
- Impact Factor 5-10: 55%
- Impact Factor >10: 44%

Distribution of Citations of MICB’s published work
2006 - 2008

- Citations <5: 6%
- Citations 5-30: 52%
- Citations >30: 42%
# TOTAL NUMBER OF GRANT AWARDS

## 2008-2009

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**TOTAL GRANTS** 168 6 85 7 266
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<td>Dr. Arnold Greenberg</td>
<td>• The Nip3 Family of Proteins – Necrosis</td>
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<td>Dr. Janice Richman-Eisenstat</td>
<td>• Modulation of Mesenchymal Cells Via IgA-Receptors</td>
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<td>Dr. Sabine Mai</td>
<td>• Telomeric Disk</td>
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<td>Dr. Sabine Mai</td>
<td>• Methods of Detecting and Monitoring Cancer Using 3D Analysis of Centromeres</td>
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<td>• Methods of Diagnosis or Detection Using 3D Analysis</td>
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<td>• Method &amp; System for the 3D Analysis of Chromosomes</td>
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<td>Dr. David Eisenstat</td>
<td>• Mutation in the Pro-Apoptotic Protein BNIP3 as a Biomarker for Solid Tumors</td>
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<td>Dr. Geoff Hicks</td>
<td>• A Novel SMART shRNA System for Disease Diagnosis and Therapy</td>
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<td>Dr. Etienne Leygue</td>
<td>• SBEM Promoter</td>
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<td>Dr. Marek Los</td>
<td>• Anticancer, Antimicrobial And Immuno-Suppressive Properties Of Brevinin-Like Peptides</td>
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<td>• Anticancer Peptides Derived From A Viral Protein Apoptin (VP3)</td>
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<td>Dr. Marek Los</td>
<td>• A Novel Role For BAX In The Bystander Effect</td>
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Since estrogen is a major driver of human breast cancer, and the action of estrogen changes during breast tumorigenesis and breast cancer progression, the overall aim of my research program is to elucidate the mechanisms by which estrogen action changes during the development of breast cancer and how breast cancers develop resistance to endocrine therapies and progress from hormone dependence to independence. To do this my group is identifying the molecular players involved in the estrogen receptor signaling pathways in human breast tissues, how they are altered during tumorigenesis, and breast cancer progression to hormone independence. I am specifically determining the types and putative function of estrogen receptor isoforms, i.e. estrogen receptor alpha and beta and phosphorylated forms of estrogen receptor alpha, that are expressed in human breast tissues in vivo, using tissues obtained from the Manitoba Breast Tumor Bank/Clinical Database. Isoforms that are altered in vivo are tested in laboratory models for the functional consequences of that alteration. Estrogen signalling may have a role in some lung cancers so in collaboration with Drs Sri Navaratnam and Gefei Qing, we are developing human lung cancer tissue microarrays to explore the molecular players involved in the estrogen signaling pathways in lung tissue. In collaboration with Dr Peter Watson and the Manitoba Tumorbank, we are also investigating tissue collection issues that may affect detection of various gene products in banked tissues.

Publications Since 2006
5. George P. Skliris, Florent Hubé, Ionela Gheorghiu, Mark M. Mutawe, Carla Penner, Peter H. Watson, Leigh C. Murphy, Etienne Leygue, Yvonne Myal. (2008) Expression of small breast epithelial mucin (SBEM) protein in tissue microarrays (TMAs) of primary invasive breast cancers. **Histopathology** 52:355-69


**Chapters and Invited reviews**


Invited Seminars and Presentations at Symposia/Meetings


3. November 6, 2008- Estrogen Receptor Profiling in Human Breast Cancer: towards the better prediction of endocrine therapy response. Dept of Biochemistry and Molecular Biology, Dalhousie University, Halifax, Nova Scotia


**Special Awards and Distinctions**
Member of the Canada Foundation for Innovation, 2007 to present

**Administrative Service - MICB**
**Director (Acting ) January 2009 to present**
**Associate Director, April 1, 2006 to Dec 2008**
Member, Executive Committee MICB - 2000 to present
Member, Space Committee - 2000 to present
Member, Manitoba Breast Tumor Bank Scientific Review Panel – 2003 to present

**Department**
**Department of Biochemistry and Medical Genetics**
Academic Standards – member
Graduate Students Acceptance Committee - Chair 2000 to 2008
Member, Medicine Teaching Committee - 2000 to present
Member, Candidacy examination committee - 2000 to present

**Faculty and University Level**
Member, Search Committee Head of Pharmacology, Faculty of Medicine
Member, selection committee for the Head of Human Genetics, Faculty of Medicine.
Member of the Accreditation Committee Considering the Faculty, U of Manitoba.
Biochemistry Representative on the Reproductive Systems Committee for Medical Student Curriculum Reform, U of Manitoba.
Chair for PhD Oral Defense of Sandra Koesters, Dept of Medical Microbiology, University of Manitoba, February, 2007
Chair for PhD Oral Defense of Harjot Chohan, Dept of Physiology, University of Manitoba. July, 2007
Member of review panel for Winnipeg Rh Award nominees 2005-08

**Professional Service**
Scientific Reviewer, DOD-BCRP-Concept Grants- Endocrinology panel, February, 2008
Scientific Reviewer, CIHR- Endocrinology Panel. November 2008
Chair- Fellowship Review Panel MHRC. 2008, 2009
Scientific Reviewer USAMRMC - Breast Cancer Research Initiative, Endocrinology panel 2, 2008
Scientific Reviewer Personnel Awards panel MHRC - 2007
Member of the College of Reviewers for the Canada Research Chairs Program: 2000 to present

**Community Service**
Member, UICC International Fellowships Review Panel (ICRETT Panel, disciplines biochemistry. Molecular biology, biophysics) 1999 to present
Member of the Clinical Endocrinology Subcommittee of the Clinical Research Section of the 2006 AACR Program Committee.
Keynote Speaker at Guardian Angels Youth Cancer Awareness Program, October, 2006
Epigenetic is a term used to describe changes in gene expression that are stable between cell divisions. Chromatin modifying enzymes including lysine acetyltransferases (KATs), histone deacetylases (HDACs), histone kinases, histone phosphatases, lysine/arginine methyltransferases, lysine/arginine demethylases, ATP-dependent chromatin remodeling complexes and DNA methyltransferases mediate chromatin remodeling and are components of a complex epigenetic network regulating gene expression during development, differentiation and disease. Multistep tumorigenesis is a progression of events resulting from alterations in the processing of the genetic information. These alterations result from stable genetic changes (mutations) in tumor suppressor genes and oncogenes (e.g. \textit{ras}) and potentially reversible epigenetic changes. DNA methylation and histone post-translational modifications (PTMs) are two epigenetic mechanisms that are altered in cancer cells.

The mammalian cell’s nucleus is highly organized, with transcription factors and factories, chromatin modifying enzymes, and chromosomes having defined sites. Altered nuclear structure and function (gene expression) underlie the development and progression of cancer.

Dr. Davie’s research program has three research themes designed to understand the roles of chromatin dynamics and nuclear structure in gene expression in normal and cancer cells: i) to characterize histone PTMs and chromatin modifying enzymes associated with transcribed chromatin; ii) to investigate the mechanisms by which signal transduction pathways control chromatin dynamics; iii) to explore the role of the nuclear matrix in chromatin dynamics and to identify nuclear matrix proteins informative in cancer diagnosis.

Publications Since 2006


**Organizer/Chair of International Meetings**
Organizer, Canadian Society for Biochemistry and Molecular & Cellular Biology (CSBMCB) Meeting on Chromatin Structure and Function, Banff, March 5-9, 2008
Organizer, FASEB Summer Conference on "Nuclear Structure and Cancer", June 16-21, 2007 at Saxtons River, Vermont
Co-Organizer, FASEB Summer Conference on "Nuclear Structure and Cancer", June 14-19, 2009 at Saxtons River, Vermont
Invited Co-Chair, US National Cancer Institute think tank on nuclear structure and cancer, Feb 2006

**Invited Speaker at Symposia/Meetings**
FASEB Summer Conference on "Nuclear Structure and Cancer", June 14-19, 2009 at Saxtons River, Vermont
6th Meeting of the Canadian Oxidative Stress Consortium, May 7-10, 2009 at Winnipeg, Manitoba
2nd International Conference on Functional Annotation of the Mammalian Genome, April 25-27, 2009 at Banff, Alberta
6th Centre for Genomic Regulation Symposium, “Genomic Regulation: Executing the Code” November 9-10, 2007 at Barcelona, Spain
48th Advances in Enzyme Regulation Symposium, Sept 2007 at Bologna, Italy
Gordon Conference on “Bones and Teeth”, July 15-20, 2007 at University of New England, Biddeford, ME
FASEB Summer Conference on "Nuclear Structure and Cancer", June 16-21, 2007 at Saxtons River, Vermont
FASEB Summer Conference on “Histone Deacetylases”, June 2-7, 2007 at Snowmass Village, Colorado
International Symposium on “Regulation of Enzyme Activity and Synthesis in Normal and Neoplastic Tissues”, September 24-25, 2007, University of Bologna, Italy
Workshop on Nuclear Structure and Function, January 9-10, 2007 at School of Biological Sciences, University of Concepción, Concepción, Chile
NCI meeting on the Nuclear Microenvironment and Cancer, Washington D.C., February 2006 (co-organizer)
Invited Research Seminars
Center for Epigenetics, University of Florida, Gainesville, Florida, April 2009
Cell Differentiation and Development Center, Marshall University, Huntington, West Virginia, February 2009
Department of Biochemistry, Schulich School of Medicine & Dentistry, University of Western Ontario, London, November 2008
Department of Molecular Biology, College of Agriculture, University of Wyoming, Laramie, Wyoming, October 2008
Department of Medical Genetics, University of Alberta, Edmonton, April 2008
University of Manitoba Continuing Medical Education, Winnipeg, Sept 2007
Prostate Centre at Vancouver General Hospital, Vancouver, June 2007
University of Montreal. Montreal, Quebec, February 2006

Professional Service
Member, Site Visit Team to review a NCIC Program Project application, 2009
Member, Grant Review Committee Biochemistry and Molecular Biology, CIHR, 2008, 2009
Chair, Grant Review Panel D, NCIC, 2005, 2007, 2008
Member, CFI New Opportunities Fund, College of Reviewers, 2004-
Member, CRC, College of Reviewers, 2004-
Member, MHRC Research Advisory Committee, 2008
Member, US NCI Prevention Control Group, 2008
Member, Steering Committee for the Manitoba HPV Prevention Secretariat, 2008
Member, Scientific and Medical Advisory Committee, Prostate Cancer Research Foundation of Canada, June 2008
Member, Molecular and Cellular Oncology P01 Special Emphasis Panel, US National Cancer Institute, Washington DC, June 4-5, 2008
Member, US Congressionally Directed Medical Research Programs review panel for the pre-doctoral traineeship award in breast cancer, March 2008
Member, Institute of Cardiovascular Sciences Awards Committee, 2007, 2008
Member, Grant Review Committee, Genetics, CIHR, 2007
Member, review NIH Program Project application, March 2007
Member, NorCOMM Scientific Advisory Board (Genome Canada), 2005-present

Review Team Membership
Chair, Senate Committee of University Research review of Institute of Cardiovascular Sciences, 2008
Member, Academic Program Review Committee to review Department of Biochemistry and Microbiology at the University of Victoria, March 19-20, 2008
Member, Senate Committee of University Research review of Centre for Life Course Health, 2007
**Member of the Editorial Board**

Editor, Biochemistry and Cellular Biology, 1999 - present
Clinical Epigenetics (current)
Journal of Cellular Biochemistry (current)
International Journal of Cell Biology (current)
International Journal of Biochemistry and Cell Biology
Molecular Biology Reports (current)
Gene Therapy and Molecular Biology
Critical Reviews in Eukaryotic Gene Expression (2005-08)

Dr. Davie and members of his lab
The research conducted in my laboratory is directed toward understanding the regulation of cell growth and differentiation during development. These investigations are of primary importance to childhood cancers. In Manitoba, cancer is the most common cause of death in childhood and adolescence, excluding accidents. Current treatment strategies, which primarily involve radiation and chemotherapy, do not directly target the cancer cell. In contrast, biological response modifiers have been used to treat several types of malignancy by harnessing normal developmental programs specific to these relatively undifferentiated cancer cell populations. The primary aim of my research program is to facilitate our understanding of the processes of differentiation of cells through changes in their internal milieu and external environment. I propose to accomplish this through an improved understanding of two important regulatory molecules: (i) the hypoxia-inducible cell death protein, BNIP3 (in collaboration with Dr. Spencer Gibson) in brain tumours of children and adults; and (ii) the DLX homeodomain proteins that are transcription factors in the developing brain, retina, pancreas and intestine. The ultimate goal is to develop novel therapeutic approaches complementing current treatment strategies by modifying neuronal differentiation programs in paediatric malignancies, including neuroblastoma, retinoblastoma and brain tumours.

Publications Since 2006


Abstracts and Conference Presentations since 2006


**Invited Seminars and Presentations at Symposia/Meetings**


5. Visiting Professors in Medical Education Series, Faculty of Medicine, University of Calgary, Calgary, Alberta. “The Advanced Degrees in Medicine Program at the University of Manitoba”, September 17, 2008.

6. Genes and Development Research Group Seminar, Faculty of Medicine, University of Calgary, Calgary, Alberta. “Regulation of brain development and neurodevelopmental disorders by homeobox genes.” September 17, 2008.


8. Genes and Development Research Group Seminar, Faculty of Medicine, University of Calgary, Calgary, Alberta. “Regulation of brain development and neurodevelopmental disorders by homeobox genes.” September 17, 2008.


10. Children’s Mercy Hospital and Department of Pediatrics, University of Missouri, Kansas City School of Medicine “DLX homeobox genes in forebrain development and relevance to autism”, Dec. 4, 2007.


**Professional Service**

**Grant review committees**

1. Leukemia and Lymphoma Society of Canada, panel member, 2009-present
2. National Brain Tumor Society (USA), Scientific Advisory Committee and panel member, 2009-present.
3. Austrian Science Foundation, external reviewer, 2008-present.
4. Brain Tumor Society (USA), Low Grade Gliomas, panel member, 2007-2008.
6. National Cancer Institute of Canada (NCIC), Clinical Research Fellowship, panel member, 2006-present.
8. Brain Tumor Funders’ Collaborative, Scientific Advisory Committee and panel member, 2005-present.
11. Natural Sciences and Engineering Research Council (NSERC), external reviewer, 2003-present.

**Journal Reviewer**

Acta Neuropathologica
Acta Paediatrica
Brain Research
Cancer Research
Clinical Cancer Research
Development
Developmental Dynamics
Journal of Engineering in Medicine
Molecular Brain Research
Neuroscience
Discovering Signal Transduction Pathways Regulating Cell Death

In maintaining integrity and homeostasis of multicellular organisms, the balance between cell death and survival is fundamentally important. When this balance is altered diseases occur such as cancer. One protein important in regulation of cell death is the Bcl-2 BH-3 only member BNIP3. BNIP3 expression is induced under low oxygen (hypoxia) conditions and is over expressed in solid tumors in hypoxic regions. When BNIP3 is over expressed in cancer cells it induces cell death mediated by mitochondrial dysfunction. This cell death instead of being apoptotic is autophagic (a new form of programmed cell death). This paradox of BNIP3 killing cancer cells and being over expressed in live cells within tumors is a focus of our research. To date three explanations could account of these differences. The first difference is growth factors block BNIP3 cell death function and tumors have deregulated growth factor signaling leading to cell survival (see below). Secondly, BNIP3 is also localized in the nucleus of tumor cells prevent its interaction with the mitochondria blocking its cell death function. Finally, the BNIP3 gene is mutated to an inactive protein. This protein acts in a dominant negative fashion blocking hypoxia induced cell death. The importance of these mechanisms for cancer progression and treatment is under active investigation.

Cell survival is as important as cell death. The epidermal growth factor receptor (EGFR) is expressed at high levels in several cancers such as breast cancer. We discovered that pretreatment of breast cancer cell lines with epidermal growth factor (EGF) effectively blocked drug and death receptor induced apoptosis. This protection from apoptosis is mediated by a serine threonine kinase called AKT through up-regulation of the Bcl-2 anti-apoptotic family member Mcl-1. Besides breast cancer, we have found that a lipid, lysophosphatic acid (LPA) blocks apoptosis in chronic lymphocytic leukemia (CLL) cells using a similar mechanism. We are currently investigating the regulatory elements controlling Mcl-1 expression.

Molecular-based therapies could alter the balance between cell death and survival towards killing cancer cells. Tumor necrosis factor related apoptosis-inducing ligand (TRAIL) selectively kills cancer cells while normal cells are resistant to TRAIL-induced apoptosis. In collaboration with Dr. James Johnston, we are investigating the potential of TRAIL as a therapy for chronic lymphocytic leukemia (CLL) alone or in combination with chemotherapy.
In addition, we previously discovered that chemotherapeutic drugs increase TRAIL death receptor (DR4/5) expression and this contributes to drug-induced apoptosis. We are defining the regulatory elements controlling DR4/5 expression in CLL cells to enhance the clinical effectiveness of TRAIL.

The goal of this research is to define the signal transduction pathways leading to cell death or survival. This will elucidate pharmaceutical targets that could alter the cellular balance in favour of cell death. This research will be the foundation to establish clinical trials using molecular targeted therapies to increase effectiveness of chemotherapy in cancer.

**Publication since 2006**


**Invited Seminars and Presentations at Symposia/Meetings**
1. Department of Pharmacology and Toxicology, University of Manitoba, March 2009
2. Department of Pathology, University of Calgary, September, 2008
4. Winship Cancer Institute, Emory University, Atlanta, GA, November, 2007
5. Updates in CLL Conference, Ontario Cancer Institute, Toronto, ON, November 2007
6. Karmanos Cancer Institute, Wayne State University, School of Medicine, Detroit MI, April 2007
7. Department of Medical Genetics, University of Calgary, Calgary, AB, March 2007
8. Division of Hematology, Mayo Clinic, Rochester, MN March 2007
9. Department of Oncology, Queens University, Kingston, Ontario, January 2007
10. Ontario Cancer Institute, Princess Margaret Hospital, April, 2006
11. Human Genome Sciences Inc., Gaithersburg, MB, June, 2006
12. American Society for Hematology, Orlando, 2006
13. NCIC CTG Annual Fall Meeting, Montreal, 2006

**Professional Service**
1. Interim, Provincial Director, Research, CancerCare Manitoba
2. Administration
3. Director of Translational Research
4. Scientific Director of the Manitoba CLL Tissue Bank
5. Radiation Safety Officer for Manitoba Institute of Cell Biology
6. Attend Manitoba Institute of Cell Biology Senior Investigator Meetings
7. Attend Departmental Council Meetings
8. Organizer of Signal Transduction Journal Club
9. Administrator of the Invited Speakers Program- Molecular Biology series
10. Member of Standard Operating Practices Committee at Manitoba Institute of Cell Biology
11. Attended workshops on PCR techniques and Laboratory Animal Care and Use.
12. Attended the National Cancer Research Initiative meeting for Young Investigators representing Manitoba.
13. External Reviewer for the Saskatchewan Health Research Foundation for Establishment grant.

**External Service:**
1. Reviewer for manuscripts for peer-reviewed scientific journal: Oncogene, Molecular Biology of the Cell, Blood, Cancer, Cancer Research, British Journal of Cancer, Cell Death and Differentiation and Carcinogenesis,
2. Participated in a teleconference to nominate members of the Cancer A and B grant committees for Canadian Institutes of Health Research
3. Reviewer for grant submitted to the Alberta Heritage Foundation
**Member of External Committees**

NCIC Personnel Awards Committee 2008-present
Leukemia and Lymphoma Society of Canada 2007-present
  Grant Panel Member
Lymphoma Foundation of Canada 2006-present
  Scientific Advisory Board
National Institutes of Health, 2006-present
  BMCT Study Section Committee member
NCIC CTG, Correlative Science 2006-present
  Hematology Committee member
Canadian Institutes of Health Research 2005-present
  New Investigator committee (NIA)
National Cancer Institute of Canada 2005-present
  Health Research Ethics Board
Functional Analysis of the Mammalian Genome

Now that the human genome has been decoded, the next major challenge to the Genome Initiative will be to bridge the gap between these rapidly expanding DNA sequence databases and gene function. To utilize the sequence information for large-scale functional studies, we have developed a process called tagged-sequence mutagenesis to disrupt genes expressed in mouse embryo-derived stem (ES) cells and to characterize each mutation by direct DNA sequencing. Comparison of these sequence tags (PSTs) with the existing databases identifies disruptions of known genes or genes which may be related by homology or functional domains. The ability to induce, characterize and maintain mutations in ES cells circumvents many limitations associated with conventional mammalian genetics, and will greatly increase the number of mutant alleles (typically loss of function mutations) by which gene functions can be studied in mice and in cell lines derived from such mice. The process will facilitate a functional analysis of a mammalian genome in vivo and will provide animal models for human genetic diseases. Our initial goal is to develop an Embryonic Stem Cell Library of 20 - 40,000 defined gene mutations. ES cell clones containing specific mutations in genes of interest will be made available to investigators as a national resource.

Functional Analysis of TLS, EWS, and ALR in Normal Development and in Oncogenic Transformation

Mutations (from the ES cell library) transmitted to the germline will focus on genes known or suspected to be involved in tumor progression. Understanding the normal function of a gene in mammalian development is a powerful approach to understanding how the oncogene contributes to the respective cancer. The focus of the lab is on genes which are translocated in the development of human cancers; specifically, the TLS, EWS and ARL genes. While the translocations and the associated cancers for these genes are highly characterized, little is known about function of the genes themselves or how they contribute to tumor development. Our approach is to analyze developmental defects in mice that are deficient for each specific gene (and are otherwise genetically identical to wild-type mice). For example TLS is a gene that is translocated in many human soft tissue sarcomas and myelogenous leukemia. Functional analysis of mice that are homozygous for the TLS/FUS mutation has revealed TLS plays a critical role in embryogenesis. We are now in a position to examine the function of this gene as it directly relates to the diseased or cancerous state found in humans. Furthermore, we have derived cell lines from the TLS deficient mice that will enable a molecular analysis of the TLS protein, the proteins it interacts with, its regulatory mechanisms, and the signaling pathways it is involved in.
Publications Since 2006


Chapters and Invited reviews


Invited Seminars and Presentations at Symposia/Meetings


Professional Service
2. NIH Ewing Sarcoma Initiative. 2002-present
4. International Mouse Mutagenesis Consortium. 2001-present
5. International Knockout Mouse Project Consortium. 2004-present
6. Federation of International Mutant Mouse Resources. 2005-present
7. Canadian Mouse Consortium, founding member. 2004-present
8. International Knockout Mouse Consortium, founding member. 2004-present

Professional Activities
1. Director, Mammalian Functional Genomics Centre. 1999-present
2. Canadian Institutes of Health Research, Reviewer for G, CPT and MCC Panels. 1999-present
3. Chair, CIHR Institute of Genetics New Principal Investigator Symposium. 2001-present
4. Scientific Director, Gene Modeling Centre, University of Manitoba. 1999-present
5. Scientific Advisory Board Member, Genome BC, Pathogenomics of Innate Immunity. 2006-present
6. CIHR Institute of Genetics Advisory Panel. 2001-present
7. Scientific Advisory Board Member, Genome Quebec, Gene Regulators in Disease. 2006-present
8. Scientific Advisory Board Member, BC Transgenics Centre. 2007-present
9. Scientific Director, Genetic Modeling Centre, University of Manitoba. 2007-present
10. Manitoba Health Research Council, Research Advisory Committee. 2008-present
Elevated homocysteine levels are associated with increased risk of atherosclerotic vascular disease and of venous thrombosis. We have shown that homocysteine induces expression of tissue factor, the trigger for the coagulation cascade, by human monocytes. This is a plausible explanation for the thrombotic tendency associated with homocysteine, which we are now looking to confirm in patient studies. We are also investigating the biochemical mechanism by which homocysteine activates the monocytes, which may have important implications for the management of hyperhomocysteinemia. A second area of interest is the laboratory assessment of hemostasis and thrombophilia.

**Publications Since 2006**
Our platelet research laboratory studies basic mechanisms of platelet function and investigates patients with inherited platelet function abnormalities, in conjunction with the clinical Haemostasis Laboratory. Our projects include: 1) Investigating the role of CD63, a member of the tetraspanin superfamily present on platelet dense granule and lysosomal granule membranes, and expressed on the platelet surface following activation, where it associates with the platelet integrin alphaIIb/beta3, and with the contractile platelet cytoskeleton. It plays a role in platelet spreading on adhesive surfaces. We are presently investigating how it modulates integrin-mediated signaling. Understanding the role of CD63 has implications beyond platelet function, as it, and similar molecules, may be involved in tumor cell migration and metastases. 2) Studies of patients with inherited platelet function disorders, with a particular interest in families with a congenital deficiency of platelet dense granules, Storage Pool Deficiency. 3) Studies of the platelet defect in patients with Noonan Syndrome. 4) In collaboration with colleagues at the Toronto Hospital for Sick Children, we have created a national registry of patients with inherited platelet disorders, an opportunity to improve our understanding of these rare conditions, aid in their diagnosis, and evaluate treatment options.

Publications Since 2006
Refereed Journal Articles


**Book Chapters/Review Articles/Monographs**


**Abstracts and Conference Presentations**


**Invited Seminars and Presentations at Symposia/Meetings**


3. “Assessment of Bleeding in Infants and Children”. Department of Family Medicine, University of Manitoba, Winnipeg, Manitoba, October 31, 2008.


10. “Platelet function testing – Myths” Dalhousie University Hematology Symposium, Halifax, September 29, 2007
12. “Inherited platelet disorders” Pediatric Hemostasis & Thrombosis Update. Department of Paediatrics, Faculty of Medicine, University of Toronto. September 29, 2006
13. “Laboratory diagnosis of platelet abnormalities” Pediatric Hemostasis & Thrombosis Update. Department of Paediatrics, Faculty of Medicine, University of Toronto. September 30, 2006

**Professional Service**

**University of Manitoba**
1. Section Head, Pediatric Hematology/Oncology/BMT, 1993-present
2. Faculty of Medicine Promotion Committee, 2006-present
3. Dept of Pediatrics and Child Health Promotions Committee: Chair, 2004-present
4. Department of Pediatrics Executive and Planning Committee, 1997-present
5. Hematology/Medical Oncology Fellowship Training Program Committee, 1994-present

**WRHA**
1. Director, Haemostasis Laboratory, Health Sciences Centre 1994-present

**CancerCare Manitoba**
1. CCMB LG Israels Memorial Lecture Committee, 2004-present
2. CCMB Medical Council, 2004-present
3. Simon and Sarah Israels Thesis Prize Review Committee: Chair, 2004-present
4. CancerCare Manitoba Foundation Board of Directors, 2003-present
5. CancerCare Manitoba Foundation Project Grants and Awards Committee, 2003-present
External
3. External Review: Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of British Columbia, Vancouver, October 2006.
4. Canadian Council of Pediatric Hematology/Oncology Program Directors Executive Committee, 2005-present
5. Royal College of Physicians and Surgeons – Specialty Committee (Nucleus) in Pediatric Hematology/Oncology, 2004-present
6. Royal College of Physicians and Surgeons – Pediatric Hematology / Oncology Examination Committee, 2005-present
7. External Grant Reviews: Heart and Stroke Foundation of Canada, CIHR, Canadian Blood Services/Bayer, Health Sciences Centre Research Foundation, C17 Research Network
My primary research interest is in chronic lymphocytic leukemia (CLL) and I am involved in a number of translational research programs related to this disease. These studies involve the epidemiology and basic science of CLL, in addition to clinical trials. To further these activities, we have developed the CLL Clinic at CancerCare Manitoba and the Manitoba CLL Tumor Bank, which is housed in the MICB. Our epidemiological studies have demonstrated that the incidence of CLL is much higher than previously reported with elderly male patients having a particularly poor prognosis. Our ongoing laboratory studies are evaluating new therapies and prognostic markers in CLL and examining the effects of age and gender on the biology of this cancer.

**Publications Since 2006**


**Book Chapters**

**Invited Seminars and Presentations at Symposia/Meetings**


**Professional Services**
Assistant Head (Clinical), Manitoba Institute of Cell Biology
Clinical Director, Manitoba CLL Tumour Bank
Cancer Biology Graduate Course Coordinator (36.720) (with Dr. Michael Mowat)
Molecular Biology Course Coordinator for Clinical Hematology/Oncology residents
Chairman for the Planning Committee for the annual Canadian CLL Meeting
Member of the Planning Committee for the annual Canadian Lymphoma Meeting
Coordinator for Hematology/Oncology Section Rounds
Chairman of the LG Israels Annual Memorial Lecture Committee
Manuscript reviewer for Blood, Cancer, Leukemia Lymphoma and Leukemia Research
Scientific reviewer for Alberta Cancer Board
Our research focuses on mechanisms of c-Myc-dependent locus-specific and karyotypic instability. Our in vitro models include primary, immortalized and tumor cell lines with normal, experimentally inducible and constitutive c-Myc deregulation, respectively. Our current in vivo models of c-Myc-dependent genomic instability and neoplasia focus on mouse plasmacytoma.

We were the first to demonstrate that the deregulated expression of the proto-oncogene c-Myc induces dynamic karyotypic alterations; they include numerical chromosomal changes, telomere-centromere-fusions and the enhanced formation of extrachromosomal elements (Mai et al., 1996a). Moreover, we have shown that experimental deregulation of c-Myc mediates rearrangements, chromosomal and extrachromosomal amplification of specific genes. Among these genes are dihydrofolate reductase (DHFR), (Mai, 1994; Mai et al., 1996b), CCND2 (cyclin D2) (Mai et al., 1999), ribonucleotide reductase R2 (R2) (Kuschak et al., 1999), and the carbamoyl-phosphate synthetase-aspartate transcarbamoyl-dihydroorotase (CAD) (Fukasawa et al., 1997) gene. Other genes, such as syndecan-1 and 2, glyceraldehyde-3-phosphate-dehydrogenase, ribonucleotide reductase R1, and cyclin C, remain unaffected irrespective of c-Myc protein levels (Mai et al., 1996b). We identified a mechanism that leads c-Myc-mediated gene amplification. It involves c-Myc-dependent illegitimate locus-specific de novo replication initiation (Kuschak et al., 2002).

A novel mechanism of c-Myc activation involves c-Myc transcription from extrachromosomal elements (EEs) (Wiener et al., 1999). Analyses into the functions of EEs have demonstrated that they carry modified histones and are transcriptional competent. Furthermore, they are able to replicate their DNA (Smith et al., 2002). c-Myc-induced EEs therefore are functional mini-chromosomes with the ability to actively contribute to cellular transformation. Our recent work focuses on the three-dimensional organization of the nucleus and the role of c-Myc in nuclear remodelling and cell transformation. Highlights are summarized below.

**Research Highlights**

*The three-dimensional (3D) nuclear telomere organization:* We undertook a study of normal cells, of immortalized and primary tumor cells and cell lines to investigate by 3D imaging how telomeres are organized in the interphase nucleus and whether there was a change in this organization during cell cycle and during cellular transformation. Telomeres of normal cells are organized in a cell cycle-dependent manner.
They occupy a wider nuclear space in G0/G1 and S phases than in the late G2 phase where they are organized into a telomeric disk (TD) first described in Chuang et al., 2004. In contrast to the ordered organization of non-overlapping telomeres in normal cells, telomeres of tumor cells display an aberrant order and frequently form aggregates (Chuang et al., 2004). We have filed a patent about these findings. It also includes new analytical tools.

**Analysis of the 3D space occupied by telomeres.** To define the 3D nuclear space occupied by telomeres, new software (TeloView™) was developed in collaboration with Dr. Garini’s group at the Quantitative Imaging Group, University of Technology, Delft (The Netherlands). TeloView™ allows one to determine the nuclear localization of all telomeres in the interphase nucleus. A detailed summary of the algorithms is described in Vermolen et al., 2005. Recent developments within this program now allow us to determine the numbers of telomeric aggregates found per nucleus. This ability to quantitatively assess the number of aggregates per nucleus enhances the program features rendering it fully independent of the users’ assessment.

**c-Myc deregulation affects the 3D organization of the nucleus.** We have recently found that c-Myc deregulation promotes the formation of telomeric aggregates (TAs). This structural change is accompanied by chromosomal rearrangements (CRs) as evident in the subsequent metaphases. We showed that c-Myc mediates the formation of CRs via TAs and/or positional changes of chromosomes (Louis et al., 2005; Mai and Garini, 2005, Mai and Garini, 2006). Moreover, we have found that chromosomes can alter their positions transiently as a result of c-Myc deregulation (Louis et al., 2005).

**c-Myc-dependent formation of telomeric aggregates requires myc boxII.** In order to understand the Myc-induced formation of telomeric aggregates, we have studied myc mutant proteins. In wild-type p53 carrying, spontaneously immortalized and non-tumorigenic mouse proB cells (BA/F3) aggregates form only in the presence of wild-type c-Myc deregulation. If myc box II is absent, no such aggregates are observed (Caporali et al., 2007). This finding is directly relevant for c-Myc-dependent tumor formation as only wild-type but not myc box II mutant overexpressing cells promote tumor formation in SCID mice (Fest et al., 2005).

**Centromeres reorganize during cellular transformation.** The positions occupied by centromeres in nuclei of mouse lymphocytes vary during the cell cycle and during cellular transformation (Sarkar et al., 2007). One pathway to this nuclear remodeling involves c-Myc deregulation. The impact of this pathway on nuclear organization is currently explored.

**Centromeres reorganize during cellular transformation.** The positions occupied by centromeres in nuclei of mouse lymphocytes vary during the cell cycle and during cellular transformation (Sarkar et al., 2007). A program to measure centromere positions in the interphase nucleus was developed by Rahul Sarkar, in collaboration with Dr. Garini’s group, and patented (Sarkar et al., 2007).
The impact of this pathway on nuclear organization was demonstrated in recent experiments. Amanda Guffei in the lab showed in mouse cells that c-Myc deregulation mediates centromeric nuclear remodeling (Guffei et al., 2007). She also showed that this remodeling leads to the fusion of centromeric ends via their telomeric sequences; this new organization gives rise to Roberstonian translocation chromosomes (Guffei et al., 2007). Her work was featured on the journal cover.

A recent Perspectives Article by our group summarizes our current knowledge about the centromere in cell division, speciation and cancer (Silva et al., 2008)

c-Myc cooperates with Tip60 to accelerated lymphomagenesis in mice. In collaboration with Bruno Amati, we showed that Tip60 haploinsufficiency and c-Myc deregulation lead to accelerated lymphoma development in mice. Landon Wark in the lab was working on this project, which was published in Nature (Gorrini et al., 2007).

Genomic instability. I was a guest editor for a special issue in Seminars in Cancer Biology (February 2007 issue) that featured non-random genomic instability in cancer: a fact, not an illusion. The issue includes articles on mechanisms leading to instability in cancer cells, on modeling of non-random deletions, on large common fragile sites and gene amplification, specificity, selection and significance of gene amplification, on the formation of extrachromosomal elements, on microRNAs and genomic instability, on mechanisms leading to non-random nonhomologous translocations in leukemia, and on the spatial genome organization in the formation of chromosomal translocations.

New insights into Hodgkin's lymphoma. In collaboration with Dr. Hans Knecht (Sherbrooke, QC), we have gained insights into the biology of Hodgkin’s lymphoma and shown that the mononucleated Hodgkin cell gives rise to the multinucleated Reed Sternberg cell through dynamic telomere dysfunction and aberrant cell divisions (Knecht et al., 2009).
Publications since 2006:


**Invited Seminars and Presentations at Symposia/Meetings**

2. Anti-estrogen resistant breast cancer cells differ in their 3-dimensional chromosomal arrangements from their parental cells. AACR, Denver, 2009 (Johannes von Vopelius-Feldt, Andreea Nistor, Sabine Mai, Sabine Hombach-Klonisch).
3. Nuclear architecture in human thyroid carcinoma revealed by three-dimensional (3D) telomere imaging: New insight into genomic instability and potential diagnostic application. AACR, Denver, 2009. (Thomas Klonisch, Landon Wark, Sabine Hombach-Klonisch, Cuong Hoang-Vu, Sabine Mai)
4. Telomere-poor “ghost” nuclei define Reed-Sternberg cells as end-stage cells. AACR, Denver, 2009 (Sawan B, Lichtenzstejn Z, Lichtenzstejn D, Mai S, Knecht H.)


18. April 2006. AACR, Washington DC, USA.

- c-Myc alters the three-dimensional order of telomeres and chromosomes in the interphase nucleus. Sherif F. Louis, Bart Vermolen, Fabien Kuttler, Yuval Garini, Sabine Mai. Proc Amer Assoc Cancer Res 2006;47:[4240]

Grant Panels and Advisory Committees
Genomic Centre for Cancer Research and Diagnosis: User Committee
CIHR Strategic Training Program "Innovative Technologies in Multidisciplinary Health Research Training" selection committee
CIHR Strategic Training Program "Innovative Technologies in Multidisciplinary Health Research
NCIC/CCSRI: Panel J Member
Advisory Board Member, Industrial Technology Centre, Virtual Reality Centre
6th Canadian Symposium of Telomeres and Telomerase at The Narrows Lodge, Lake Manitoba
One area of research in my laboratory is the study of programmed cell death or apoptosis, a form of cell suicide. As a result of genetic changes, cancer cells have a reduced or slowed ability to undergo apoptosis which can also make them more resistant to anti-cancer drug treatment. To better understand programmed cell death, we have taken a genetic approach. Several mutant cell lines have been isolated that are defective in apoptosis. This was done by using a specially constructed virus that, after it infects a cell, can interfere with the genes that control cell death. The underlying genes disrupted in the mutant cell lines by the virus are now being studied to understand their role in programmed cell death. By understanding the genetic basis of resistance to cell death, completely new treatments can be devised.

One gene that came out of this screen is the Dlc-2 (Deleted in liver cancer two) tumor suppressor gene. We are studying the role of this gene, and its closely related paralog Dlc-1, in tumor cell progression and drug response. To carry out these experiments we have developed conditional knockout mouse models of these genes. With these mouse models, we are studying the role of the Dlc genes in lung, liver and breast cancer progression.

Publications Since 2006

Professional Service
Grant Review Committees
National Cancer Institute of Canada, Panel J: Pathology and Tumour Markers 2005-2008
CIHR Research Advisory Group, U. of Manitoba 2005-present

Department Service
Biochemistry & Medical Genetics
Graduate Affairs Committee, Biochemistry & Medical Genetics 2007-present
Member, PhD Candidacy examination committees, 2005 to 2009
Member, Graduate Student Admissions Committee, 2009-present

Administrative Service - MICB
Executive committee MICB
CIHR Innovative Technologies In Multidisciplinary Health Research Training
Programme selection committee.
Chair, CancerCare MB library committee.

Awards to trainees
Golom Sabbir, (postdoctoral fellow), top poster awards 1. CancerCare Manitoba

Members of Dr. Mowat’s lab
My overall research focuses on the study of gene expression during human breast tumorigenesis and breast tumor progression.

Designing therapies slowing down or inhibiting estrogen signalling in breast cells has already saved thousands of women. Unfortunately, resistance to a specific drug can occur in some patients and alternative treatments remain needed. It appears that a combination of drugs, targeting different critical points of estrogen signalling at different times, will provide a more efficient protection and overcome the potential resistance to a single drug.

The original face of the products of the SRA1 gene consisted of a non-coding functional RNA (SRA), able to activate estrogen receptors action. We have however demonstrated that this RNA also leads to the production of a protein (SRAP), which also acts as modulator of estrogen receptor action. We found that the action of this newly discovered SRAP is depending upon the receptor ligand, the cell context and the target genes considered.

The bi-faceted SRA RNA/SRAP system, consisting of a functional RNA and its corresponding protein, is therefore a newly discovered mechanism used by breast cells to modulate estrogen action. We hypothesize that characterization of SRA RNA/SRAP mechanism of action could provide new windows of opportunity to design innovative therapeutic or preventive strategies to fight breast cancer.

**Publications Since 2006**


Invited Seminars and Oral presentations at Symposia/Meetings
1. BIT’s World Cancer Congress, Nuclear Receptor Symposium, Shanghai, China (2008)
2. BIT’s World Cancer Congress, Endocrinology Session, Shanghai, China (2008)
4. INSERM, Montpellier, France (2007)

Panels
1. Operating grant competition of the National Cancer Institute of Canada (NCIC)
2. PhD and Post-doctoral Awards, US-Army Medical Research and Materiel Command (USAMRMC)
This laboratory conducts research in the areas of molecular endocrinology and breast cancer biology. Current research focuses on the molecular mechanisms by which human breast cancer cells destroy bone.

**Publications Since 2006**


External Reviewer
Medical Research Council of Canada, Manitoba Health Research Council, Health Sciences Center Research Foundation (Winnipeg), Swedish Cancer Foundation, U.S. National Science Foundation, U.S. Department of Energy, Australian National Health & Medical Research Council

Scientific Journals

Dr. Shui resigned in June of 2009 as a Senior Investigator of MICB
Peter is Chief Physician at the BC Cancer Agency Vancouver Island Centre, breast pathologist, scientist with focus on molecular pathology, and leader in biobanking. In the latter role he is the director of the BCCA’s Tumor Tissue Repository program (since 2005) and director of the CIHR Manitoba Breast Tumor Bank (since 1993) and co-leader of local (VIC-PREDICT program, since 2006), provincial (MSFHR BC BioLibrary, since 2007) and national (CIHR Canadian Tumor Repository Network, since 2003) biobanking framework programs and is a member of the executive of the NCIC-CTG Correlative Sciences and tumor banking committee. Peter is also a senior scientist at the Manitoba Institute of Cell Biology. His own research program has pioneered molecular approaches to analysis of human breast tumors and has contributed to the discovery and delineation of several potential biomarkers and therapeutic targets in breast cancer. These include delineation of potential relevance of components of the Estrogen Receptor network, discovery of the S100A7-Jab1 pathway, and definition of CAIX & CAXII as tissue biomarkers of hypoxia in breast tumors.

**Publications Since 2006**


Dr. Leigh Murphy and Dr. Peter Watson
The Genomic Centre for Cancer Research and Diagnosis (GCCRD) has one project manager (Dr Rhea Vallente), a full time technician (Landon Wark) and one full time computer technician (Daniel Lichtenzstejn) to perform training of new personnel, to assist with imaging and to maintain and/or upgrade the GCCRD equipment, software and data (back-ups, networking and archiving).

"The GCCRD is overseen by a user committee. It consists of Dr. Sabine Mai (GCCRD Director), Dr. Jim Davie (GCCRD Co-Director), Drs. James Johnston, Spencer Gibson, Michael Mowat and Leigh Murphy (MICB Director)."

One of the GCCRD mandates is education. We have been involved in running weekend and summer workshops with students from the Pembina Trails School Division. 142 high school students were trained since the program started in 2002, the training was done in basic plasmid preparation techniques, restriction digestions, gel electrophoresis experiments, chromosome harvesting techniques, Fluorescent in situ hybridization and imaging. Eighteen of the students were from our international exchange program that involves high schools in Germany and Australia. Last year we trained 29 high school students, 7 of them from Australia. More than 400 high school students have come through since 2000 (tours, weekend workshops and summer training).

In 2002, we obtained a CIHR Strategic Training Program Grant entitled: “Innovative Technologies in Multidisciplinary Health Research Training.” This training grant provides us with $1.8 million over 6 years. Dr. Sabine Mai is the Principal Investigator on this grant. Co-mentors are from the University of Manitoba, the OCI (Toronto, ON), the NIH (Bethesda, Maryland, USA), the Karolinska Institute (Stockholm, Sweden), the University of Rennes (France), and the German Cancer Research Centre (Heidelberg, Germany). The GCCRD serves as the training base for innovative technologies as outlined in the grant and on our training website (http://www.itmhrt.ca). Zelda Lichtensztejn coordinates the workshops and all educational aspects that are part of the Strategic Training Program. We have held three workshops per year at MICB since implementation of the program. These are 16 workshops until to date. Participants have come from MICB, the University of Manitoba, the University of Toronto, the United Kingdom, France, the Netherlands, Sweden, France, Germany, Brazil, the United States, The Philippines, Denmark, Switzerland, and Thailand.
Throughout the year, the GCCRD is involved in tours through the facility. Daniel Lichtenstejn is involved in organizing tours. On average, 1-3 tour groups per month come through the centre. Tour groups consist of up to 20 individuals. Tours involve high school students (e.g. Balmoral Hall, St. John’s Raven’s Court and Kildonan East Collegiate), as well as representatives from industry and politics, and interested public.

**General Objectives/Mission of the Centre**
The Centre has been created as a regional/national facility for research in genomic instability and mechanisms of neoplasia. The objectives are focused on research in early detection of cancer and novel cancer treatments and on teaching and training of highly qualified personnel.

The Genomic Centre has been designed as a high-technology facility for digital imaging and analysis. The activities have been divided into two separate areas, basic research and technical services, to promote a better interaction between different fields of research.

The Basic Research support is developed in collaboration with scientific groups from Canada, USA and Europe. The technical services are offered on a fee basis, and they are mainly focused on fluorescent in situ hybridization, immunohistochemistry and microdissection of biological material. The Centre does not carry out clinical diagnostics, but collaborations with laboratories of clinical genetics are strongly encouraged.

**Description of Each Workstation**
Even though the workstations are organized independently, they are interconnected by our own server and have internet access. Below follows a description of each system indicating the current available features and applications. The workstations will be modified as upgrades and new software versions are added and this will further increase the current technical capabilities of each system.

**Fluorescent Workstation #1 MetaSystems Group Inc.**
The *Isis* software is used for fluorescent in situ hybridization (FISH), multicolor-FISH (M-FISH) and comparative genomic hybridization (CGH) for the analysis of chromosomes, interphase nuclei and tissue sections. Our system allows for the analysis of up to nine individual fluorophores for M-FISH. MetaSystems Group Inc. software features fully automated image acquisition for M-FISH, automated filter exchange with real-time image display, plus automatic and interactive time control for each colour channel.

The *In Focus* application offers quasi 3-dimensional analysis of FISH-probed and fluorescent immunostained cells and tissues.

MetaSystems Group Inc. offers a case database for both *Isis* and *Ikaros*, and the system can also perform statistical analysis.
*Applications:* fluorescent *in situ* hybridization (FISH); karyotyping, both fluorescent and bright field; multicolor-FISH (M-FISH); comparative genomic hybridization (CGH); stepwise analysis of cells and tissues after FISH or fluorescent immunostaining.

**Fluorescent Workstations #2 EMPIX**
The Empix system features fully automated image acquisition for each type of fluorescent analysis, automated filter exchange with live image computer screen plus automatic and interactive time control for each colour channel. It features joystick motorized stage movement as well as fully motorized functions that are completely software driven.

*Applications:* photography of light microscopy samples (H/E stained samples, Giemsa-stained karyotypes and chromosomes etc.); visualization and quantification of protein, DNA and RNA within the same cell(s); image overlay and analysis; cell morphology studies; densitometry.

**Fluorescent Workstations #3 Deconvolution (Zeiss)**
The system features fully automated image acquisition for each type of fluorescent analysis, automated filter exchange with live image computer screen plus automatic and interactive time control for each colour channel. It features joystick motorized stage movement as well as fully motorized functions that are completely software driven.

*Applications:* photography of fluorescent samples for 3D analysis; visualization of protein, DNA and RNA within the same cell(s); image overlay and analysis; cell morphology studies.

**Fluorescent Workstation #4 Live Cell Analysis (Zeiss)**
The system features fully automated image acquisition for each type of fluorescent analysis, automated filter exchange with live image computer screen plus automatic and interactive time control for each colour channel. It features joystick motorized stage movement as well as fully motorized functions that are completely software driven.

The Zeiss microscope is also equipped with a heated stage and chamber (Bioptechs Inc.), allowing us to combine cell culture with microscopy and imaging, and other live cell analysis.

*Applications:* photography of light microscopy and fluorescent samples (H/E stained, Giemsa-stained karyotypes and chromosomes etc.); visualization of protein, DNA and RNA within the same cell(s); image overlay and analysis; cell morphology studies; densitometry; live cell analysis.

**Fluorescent Workstation #5 Applied Imaging**
*Applications:* high-resolution photography of cells, tissues, and chromosomes by light microscopy; high-resolution image acquisition and analysis of immunostained cells or tissues; measurement of relative distance/length and relative fluorescent intensity of fluorescent signals in cells or on chromosomes; CGH.
**Fluorescent Workstation #6 SKY (Applied Spectral Imaging Inc.)**
The Applied Spectral Imaging system works through complementary software applications. Spectral Imaging (SI) version 5.5 software is dedicated to image acquisition and the SkyView 2.1.1 version software allows the user to analyze the images acquired in SI 5.5. The Applied Spectral Imaging system features fully automated image acquisition for spectral analysis of cells and tissues.

*Applications:* spectral karyotyping (SKY); spectral signatures of cell and tissue; spectral FISH; spectral imaging.

**Workstation #7 Laser Chromosome Microdissection**
The system is equipped with a PC-10 Micro-pipette puller which is used to make micro pipettes, micro-manipulators, and micro-needles for dissecting material.

*Applications:* laser micro-dissection of tissues, cells and chromosomes.

**Workstation #8 Histology and Pathology and Data Archiving**
*Applications:* At this workstation, pathology samples can be imaged. Also, projection and microscope slides can be scanned, directly imaged and archived. This capability allows the researcher to create a database comprising as many as 100,000 slides for future use. This microscope system is also provided for teaching purposes. It has the capability to image samples using bright field, phase contrast, fluorescent and polarized light.

**Fluorescent Workstation #10 Scanning Microscope**
*Applications:* Fluorescent *in situ* hybridization (FISH); karyotyping, both fluorescent and bright field; multicolor-FISH (M-FISH); comparative genomic hybridization (CGH); FISH spot counting; ploidy analysis; rare cell detection e.g./ tumour cells; Zeiss Microcom Cryostat HM560.

**Fluorescent Workstation #11: ApoTome**
*Equipment and Software:*
1. Zeiss AxioImager Z1 microscope
2. Zeiss Axio Cam HRm
3. Zeiss Apotome system
4. Zeon computer with dual monitors
5. AxioVision version 4.4

*Applications:* The Apotome allows the fast, high-quality production of optical sections through fluorochromed biological specimens.

**Website**
The GCCRD website has been updated and can be viewed at the following URL: [http://www.umanitoba.ca/institutes/manitoba_institute_cell_biology/GCCRD/Index3.htm](http://www.umanitoba.ca/institutes/manitoba_institute_cell_biology/GCCRD/Index3.htm)
Manitoba Breast Tumour Bank
Overview

The Manitoba Breast Tumour Bank is a collection of tissue and related clinical data. The Bank operates within the Department of Pathology of the Winnipeg Regional Health Authority and University of Manitoba, and CancerCare Manitoba. The Bank was originally established by the National Cancer Institute of Canada in 1993 with funds from the Canadian Cancer Society and is now supported by CancerCare Manitoba Foundation in partnership with the University of Manitoba and the Canadian Institutes of Health Research (CIHR). The Bank provides an important resource both for breast cancer research at the University of Manitoba and for researchers across Canada and internationally.

During the assessment of each breast biopsy specimen small tissue samples are taken by Pathologists to process and examine under a microscope and these samples are then stored as a ‘clinical archive’. After all diagnosis has been completed the Bank organizes these tissues and related clinical data into ‘cases’ for both future research and future clinical purposes and stores these ‘cases’ in CancerCare Manitoba. Researchers can apply to study these cases only through a review process and if they obtain approval for their research project from an institutional ethics review board. If approved, researchers are provided with tissue sections and the related clinical information from a set of typically 100 or more ‘cases’. These cases are carefully selected from the computer database on the basis of selection criteria such as size and type of tumor that are relevant to the research question under study. All cases are distinguished by a Tumor Bank number but are anonymous due to the absence of any tag that might allow it to be traced to an individual patient. Researchers are charged to cover the costs of storage and release but no tissue or information is sold. The Bank has supported over 50 research studies on breast cancer across North America and Europe.

The Bank stores three types of information on each case within a secure location in CancerCare Manitoba. This information relates to the tissue, clinical, and follow-up information. Tissue information includes the composition of the tissue, the size and type of tumor. Clinical information includes the patient age, clinical symptoms and the results of clinical tests such as x-rays. Follow-up information includes the type of treatment after surgery and the response to this treatment. Information is never released from the Bank with any label that might allow it to be traced to an individual. Information is only released as part of a set of anonymized cases, where each case is labeled by an anonymous tumor bank number and consists of a section of tissue with related information.
**Update**

With the renewal of the Manitoba Breast Tumor bank by CIHR in 2006, came an expanded mandate to collect from other disease sites. Therefore the most significant news to report for 2008 is that standard operating protocols for collection and banking of Head and Neck Cancers and Lung Cancers have been established and we have started to collect Head and Neck and Lung Cancer specimens.

**Operations: Consent.** Informed consent continues to be obtained for use of samples and data for research. Potential clients are first asked by the clinic staff if they are willing and interested in being approached to participate in a Tissue Bank research study. Those clients who sign a preliminary invitation to participate form are then contacted by the consent nurse to discuss and consider participation in the MTB project. This informed consent process was initiated initially for breast tissue collection in Dec 13th 2004. The total number of consented subjects for breast as of Dec 2008 is 2,184.

**Operations: Supplies and Expenses.** During the previous 12 months of full operation (April 1st to March 31st) in our lab area within CancerCare Manitoba, the MTB supplies expenses have been $ 53,190.

**Operations: Access, Release, and Revenue.** We have released breast cases in support of research studies to 7 local laboratories who have been charged $18,406.10 + $2,242.27(to bill) for the cost recovery of laboratory materials used in the process of release. We have also released material to 5 external laboratories (investigators in Newfoundland, Alberta, Ontario and BC x2) who have been invoiced for a total of $37,696.59 for materials received. We also have some applications from additional external laboratories that are currently in different stages of processing (x3 applications under review or approved from Saskatchewan x1, BC x1 and Manitoba x1; and 3 potential applicants provided with letters of support, Ontario x1 and Nova Scotia x2).

**Operations: Personnel.** The overall operation of the MBTB continues to be directed by Dr. Peter Watson and co-directed by Dr Leigh Murphy. The director and co-director have been assisted by the MTB coordinator, Michelle Parisien, and the following personnel; Pathologist Dr. Carla Penner (0.3 FTE, MICB funded), Tissue lab manager Sandra Troup (CIHR funded), Assistant tissue manager, Andrea Fristensky (1 FTE MICB and CIHR funded), and Clinical consent manager, Kendra-Ann Seenandan (0.5 FTE, U of M Research infrastructure grant funded), and data coordinator Kathy Bowler (1 FTE MICB funded).


**The Molecular Profiling Unit**

The Molecular Profiling Unit contains technology platforms that are used to investigate gene expression at the RNA and protein levels, in multiple breast tumor biopsy sample using high through-put systems.
The unit contains several Ventana auto-staining machines for high through-put immunohistochemistry (IHC) and in situ hybridization (ISH) analyses of multi-tissue sections; an automated Tumor Imaging System which captures and documents high resolution images of the contents of the tumor sections that have been processed on the Ventana previously; a Nucleic Acid Workstation for the automated extraction of RNA and DNA from multiple samples; a DNA microchip reader which allows the measurement of expression of every gene in the human or mouse genome at the level of RNA in any tissue sample. So the capability of the unit is to profile multiple tumour samples either at the level specific gene families through hypothesis driven research, or to more globally profile at the gene expression level to identify new patterns of gene expression which are associated with risk of disease, disease outcome and response to treatment. The unit has made further progress associated with molecular profiling of estrogen receptor isoforms in human breast cancer, identifying potentially better markers of responsiveness to endocrine therapies, identifying potential markers of risk of invasive breast cancer. The unit will cooperate with other platforms within the Breast Cancer Research Centre and MICB generally, and perform molecular profiling required by the research programs within and associated with the MICB.

**Nygard International Molecular Biology Breast Cancer Research Unit**

The proteomics facility in the Nygard International Breast Cancer Research Unit is equipped with CiphergenProteinChip mass spectrometer, HPLC, FPLC, protein electrophoresis (1D and 2D) and Imager system to study the molecular biology of cancer, especially to identify biomarkers of breast cancer and prostate cancer. The Facility is involved in protein purification and identification activities required in on-going breast cancer research projects.

**Professional Associate (J-M Sun):** Dr. Sun manages the facility and supervises the performance, operation and maintenance of the instruments, provides advice in the use of mass spectrometry and image methods for the analysis and characterization of protein.

**Technician (S Teow):** Shumein Teow is trained to operate and maintain the equipment within this Proteomics Facility, including the CiphergenProteinChip mass spectrometer, HPLC, FPLC and protein electrophoresis system. She performs cell and tissue sample preparation, protein isolation, purification and analysis under the supervision of Dr. Sun.

**Technician (Xuemei Wang):** Xuemei Wang performs two dimensional protein electrophoresis and imager analysis of samples from breast cancer and prostate cancer cells under the supervision of Dr. Sun. She is also involved in projects involving protein isolation, electrophoresis and analysis under the supervision of Dr. Leygue in Breast Cancer Research Program.
Introduction. The Manitoba Institute of Cell Biology is an international leader and major innovator in Functional and Cancer Genomics. With the recent completion of the human genome, the next major hurdle for the Human Genome Project will be to discover what these genes do. Given that we know there are as many as 5,000 human diseases with a genetic determinant, this new field of functional genomics will have a tremendous impact on health care and prevention. Our disease focus is clearly cancer.

The Manitoba Institute of Cell Biology has been leading the field by establishing the first Mammalian Functional Genomics Centre in Canada. The approach combines the wealth of sequence information available from the Genome Project with powerful cutting-edge genetic technologies in mice. The result is a national resource that will provide over 40,000 genetic "knock-out" mutations in mouse stem cells. Each mouse stem cell has a single gene missing as well as the capacity to actually form an intact mouse. Because mice are genetically 95% similar to humans they provide an ideal experimental model system for human disease. The mice that the Functional Genomics Centre can generate are 100% genetically identical to their mouse littermates - except for the one missing gene of interest. As such, any deficiency, defect or disease that might appear in the mutant mouse will be directly linked to the function of the single gene in question. The importance of discovering gene function in the context of the whole animal cannot be said too strongly for this is the context of disease itself - it cannot be modeled or predicted any other way. In this regard, the mutant mice themselves will not only provide insights into the genetic basis for the development of human diseases, but will also provide an experimental model to study the treatment and potential cures for human disease. On a practical note, development of the mice themselves initiates a chain of propriety that would be considered in all future discoveries as a result of the mice.

Programs. The MICB Mammalian Functional Genomics Centre, directed by Dr. Geoff Hicks, continues to provide international leadership in what is currently being dubbed as the next Human Genome Project. The centre has established a high throughput technology for the genome-wide creation of a library of transgenic knockout mice. Knockout mice are considered to be one of the most powerful approaches to discovering gene function and can be used to reveal how disease-related genes, like cancer-causing genes, work. It’s a critical first piece of the puzzle towards understanding what causes diseases in humans, and more importantly, how medicine can intervene or prevent the ensuing disease processes.
Dr. Hicks’ Knockout program aims to generate a knockout mouse for every single gene in the genome. The mice are freely available to the scientific community at large, thereby providing this powerful tool directly to the hands of every disease expert in the world. The impact of this project is considered to be so important that it has led to a worldwide effort to achieve the mouse resource as soon as possible, the *International Mouse Knockout Project*. Major funding for the centre was recently renewed by CIHR will provide the centre with an additional $2.0 M in operating funds over four years. Most notably, Dr. Hicks is also the lead investigator for a $23 Million Genome Canada application that will provide funding to support the Canadian initiatives related to the International Knockout Mouse Project. This Canadian led initiative is now recognized as one of the cornerstone international programs in Mammalian Functional Genomics.

The next step in the overall strategy is to generate and functionally analyze knockout mice. Dr. Hicks has established a leading edge Transgenics program located in both the MFGC and a state of the art transgenic mouse barrier facility located in the Faculty of Medicine’s Brodie Building. The later, known as the University of Manitoba Genetic Modeling of Disease Centre (GMC, Dr. Geoff Hicks is the Scientific Director), provides both the faculty and the province with a full suite of transgenic services. GMC services are provided in a cost-recovery fee basis to ensure all members of the Institute and Faculty can have ready access to this powerful approach to study disease genes and mouse models of human disease. Services provided include the generation of mice from ES cells, cryopreservation of ES cells, germ cells, and the rederivation of mouse models brought into the faculty from around the world. Dr. Hicks has also established the Canadian Mouse Consortium (www.MouseCanada.ca). The CMC integrates all the major mouse centres across Canada and will provide essential transgenic services to any Canadian disease-focused research program.

Finally, the MFGC also provides additional key service platforms to the Institute. These include a high throughput DNA sequencing facility, a flow-cytometry facility and a long term cryogenic cell storage facility. Once again, these are provided to MICB members as cost-recovery services that significantly reduce the operating costs of MICB research programs. As these services are used by all member of MICB, the Institute provides support for the on-going maintenance of the key instruments.

In summary, the MICB Mammalian Functional Genomics Centre is currently a leader in the field and creating an invaluable genetic resource. The Centre’s goal is to develop this resource to its fullest potential by focusing its efforts on the functional analysis of genes that are known, or suspected to be, determinants of cancer and human disease. We are hopeful that the true impact of the project will be to discover experimental mouse models of human disease that would greatly accelerate the development of pharmaceutical therapies, or even cures, for human cancer.

For more information, see the website at: [http://www.EScells.ca/](http://www.EScells.ca/)
DNA Sequencing Facility
The MICB DNA Sequencing Facility provides DNA sequencing for more than 45 labs at the MICB and University of Manitoba. Established and supervised by Dr. Don Dubik since March of 1998, the facility is self-sufficient and provides sequencing service at less than half the cost of most other Canadian facilities. The facility contains two sequencers: a single column ABI 310 and an eight column Beckman CEQ8000. The ABI 310 is the principle sequencer for the facility while the CEQ8000 is used by Dr. Hicks’ Functional Genomics Group.

For information about the MICB Sequencing Facility see our website at: http://www.umanitoba.ca/institutes/manitoba_institute_cell_biology/Sequence/Index2.htm

MICB Equipment Maintenance and Glass-washing Area
Salaries are provided for facility monitors and an equipment manager who oversees the use and operation of multi-lab equipment totalling well over $10M. Service contracts and a repair budget are also provided for joint used equipment. A wash-up area and salaries for two full-time staff are provided.

CLL Tissue Bank
Salaries and supplies for a Chronic Lymphocytic Leukemia (CLL) Tissue Bank are provided. The purpose of this bank is to facilitate basic scientific research in CLL. This tissue bank stores CLL samples as well as relevant scientific and clinical information related to each sample stored. The bank is accessed by MICB senior investigators interested in CLL research with the expectation of expanding the bank as a national resource with networks established across Canada with long-term national funding. Salaries for a technician, research nurse and supplies are provided by the Institute.

Confocal Microscope Facility
An advanced confocal microscope, one of only three in Canada, was purchased by MICB with the assistance of the Canadian Institutes of Health Research, the Canadian Foundation for Innovation and the Guardian Angel Benefit, a fundraising committee of the CancerCare Manitoba Foundation. The microscope is unique because it is capable of examining the biology and metabolic processes inside cells. With the help of laser light, it creates optical slices of cancer cells and allows detailed examination of various cell building blocks, including DNA within the nucleus of the cell.
**Electron Microscope Facility**

The electron microscope facility allows for the visualization of cellular structures and detection of specific proteins within cells. This technology has been utilized clinically for platelet disorders as well as research projects. The facility has been used by senior investigators at MICB (Drs. Israels, Gibson and Eisenstat) for their research on primary cells, cell lines and tissues using transmission electron microscopy. We share a new digital camera and image analyser system with the Department of Human Anatomy and Cell Science.
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