ANNUAL REPORT
2005/2006

THE HESS B. AND DIANE FINESTONE LABORATORY
IN MEMORY OF JACOB AND JENNY FINESTONE
http://www.mcgill.ca/finestone/

Submitted by: Dr. David S. Rosenblatt, Director
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MEMBERSHIP

PHYSICIANS AND SCIENTISTS
Ken Dewar
Eleanor Elstein
William D. Foulkes
T. Mary Fujiwara
Brian M. Gilfix
Thomas J. Hudson
Kenneth Morgan
David S. Rosenblatt
Marc Tischkowitz
Patricia N. Tonin
David Watkins

ADMINISTRATION
Maryse Bibeau
Razia Chanda
Maria Fiorito
Vanessa Flannery
Claire Goguen
Yasmin Karim
Jenny Kouli
Danielle Veyre
Anna Wong

CLINICAL SUPPORT STAFF
Suzanne Dufrasne
Maria Fiorito
Stephanie Fox
Maria Galvez
Angela Hosack
Antonia Klitorinos
Maria Lalous
Jocelyne Lavallée
Laura Palma
Nora Wong
Sonya Zaor

RESEARCH SUPPORT STAFF
Suzanna Arcand
Danielle Frappier
Nancy Hamel
Kimberley Kotar
Mathieu Lemire
Lili Li
I-Ching Lu
Nicole Roslin
Nelly Sabbagian
Daniel Yavin
Zhen Shen, MD

POST-DOCTORAL FELLOWS/CLINICAL FELLOWS
Yohan Bosse
Sarah Gail Buxbaum
Luca Cavallone
P. Campeau, MD
Long-Qi Chen
Patrick Dion
Nicholas Dupre
Li Fan
Claudia Gaspar
Richard Le Blanc
Fabric Larribe
J. Concepción Loredo-Osti
Alexandre Montpetit
Laura Oksanen
Tomi Pastinen
Michael Quinn
Polynnia Saliatsatos
David Serre
André Toulous
Ahmet Yilmaz
GRADUATE STUDENTS
Faith Au-Yeung  Jordan Lerner-Ellis
Amanpreet Badhwar  Anastasia Levechenko
Ashley Birch  Amanda Loewy
Marie-Hélène Benoit  Ioli Makriyianni
Anna Breznan  Susan McVety
Neal Cody  Alexandre Marcil
Patrick Cossette  Christianne Messaed
Daniel Darmond  Emmanuel Mongin
Adrian Diaz  Emily Moras
Qingling Duan  Emil Nashi
Julie Gauthier  Nicole Palmour
Abigail Gradinger  Guillaume Pare
Heidi Howard  Vanessa Rossiny
Tamya Khalil  Saravanan Sundararajan
Kathleen Klein  Paulina Wojnarowicz
Peter Lee  Lama Yamani

SUMMER STUDENTS
Caroline Belair  Amanda Lowey
Junhui Liu

INDEPENDENT STUDIES STUDENTS
Joanna Grater  David Novak
Carter Li  Paulina Wojnarowicz
The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone was established to promote the field of medical genetics at McGill University. Dr. David S. Rosenblatt has been Director of the laboratory since its inception. The laboratory was established with the help of an endowment to McGill University and funding is used to advance the academic goals of the Division of Medical Genetics in the Department of Medicine of the McGill University Health Centre (MUHC). As such, this report also serves as the Annual Report of the Division of Medical Genetics of the Department of Medicine of the MUHC. It is available on the Internet (http://www.mcgill.ca/finestone). Since the University Division in Medicine also has included the Division at the Jewish General Hospital, this report also encompasses parts of that activity. Within the past few years, major advances have occurred with the creation of the Department of Medical Genetics at the Jewish General Hospital.

**Highlights: Research**

Dr. Ken Dewar and his group sequenced the entire 4 Mb genome of the human bacterial pathogen *Clostridium difficile*, in an attempt to understand its genome structure and virulence factors. This organism has been responsible for significance morbidity and mortality in Quebec hospitals.

Dr. Thomas Hudson and his laboratory played a prominent role in the International HapMap Consortium. The publication of this work represented a major international research accomplishment of 2005.

Dr. David Rosenblatt and his laboratory discovered the *MMACHC* gene responsible for the cblC form of combined homocystinuria and methylmalonic aciduria, the most common inborn error of vitamin B$_{12}$ (cobalamin) metabolism.

**Highlights: Awards**

Dr. Thomas Hudson:

Investigator Award  
Canadian Institute of Health Research  
July 2002-August 2007

Achievement of the Year in Healthcare  
Maclean’s magazine, December 2005

Award for Research in Immunology  
Canadian Society for Allergy and Clinical Immunology, September 2005
Highlights: Teaching

Dr. Mary Ann Thomas completed her CCMG training in cytogenetics and has taken up a staff position in Medical Genetics at Calgary. Dr. Fatma Bastaki completed her RV year, successfully passed the examination of the Royal College of Physicians and Surgeons of Canada, and returned to a hospital position in Dubai. Dr. Teresa Rudkin decided to transfer from Medical Genetics in order to complete training in Family Medicine. Dr. Nicolas Ah Mew completed his RIV year and served as Chief Resident. Dr. Philippe Campeau completed his RIII year and served as Assistant Chief Resident. Dr. Maha Al-Awadi and Dr. Khalid Al-Thihli completed their RII year in the Medical Genetics residency as did Dr. Mouna Ben Amor.

Highlights: Clinical

After more than five years, the committee to search for a Program Director for medical genetics of the MUHC has actually met, and there are several highly competent applicants for the position.

The recruitment of Dr. Marc Tischkowitz has made a major contribution to both the basic and clinical areas of cancer genetics and general medical genetics. He is based at the Jewish General Hospital and began working in August 2005.

Clinical Statistics:

Suzanne Dufrasne, M.Ps, Psychologist:
Huntington Disease
Number of new patients seen: 20
Number of sessions: 40
Number of counselling phone calls: 68
Total cases seen: 128

Stephanie Fox, MSc, MS, Genetic Counsellor:
Hereditary Cancer Clinic:
Counselling as of September 6th, 2005

Number of new patients seen: 62
Number of follow-up patients seen: 46
(Number of counselling phone calls: 20)
Total cases seen: 108

Number of breast cancer cases: 50
Number of colon cancer cases: 38
Number of other cancer cases: 7
Number of hemochromatosis cases: 7
Number of other cases: 6
Total: 108
Predictive Testing for Huntington Disease:
Counselling as of January 2006
Number of counselling sessions for Huntington disease: 5
Number of results sessions for Huntington disease: 4

Laura Palma, MSc, Genetic Counsellor
Hereditary Cancer Clinic
Counselling as of July 4th, 2005
Total # new patient (NP) visits: 70
Total # follow-up (FU) patient visits: 45
115

Total # follow-up (FU) (letters only)*: 10 * this applies to patients who were not seen in clinic for FU but received a FU results letter

Description of patient visits by type (total = 115)

<table>
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<th>Type</th>
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</tr>
<tr>
<td>colon cancer cases</td>
<td>22</td>
</tr>
<tr>
<td>breast AND colon cases</td>
<td>5</td>
</tr>
<tr>
<td>other cancer cases</td>
<td>4</td>
</tr>
<tr>
<td>other cases**</td>
<td>20</td>
</tr>
</tbody>
</table>

115

** This includes counselling for other genetic conditions which may/may not predispose to cancer (e.g. Cowden syndrome, pheochromocytoma, hemochromatosis, MEN1, tuberous sclerosis etc.)

Prevention Clinic, Fridays (last Friday of every month), 1:00-4:00p.m.
Total # follow-up (FU) patients seen: 60

Research Interests and Accomplishments of Individual Members:

Dr. Eleanor Elstein has an active clinic, which evaluates inherited cardiac diseases as well as systemic genetic diseases that have cardiac manifestations.

Dr. Ken Dewar and his laboratory are using genomics technologies to study genome structure and variation. They are participating in an NIH funded project to develop SNP-based genetic mapping tools for the vervet monkey, and have begun a Genome Canada/Genome Quebec project to generate the corresponding genome wide physical map. Preliminary results demonstrate the ability to delineate chromosomal breakpoints and to identify vervet BAC clones associated with evolutionary recently derived centromeres and pericentromeric regions. The
group is also interested in understanding genome structure and virulence factors in the human bacterial pathogen *Clostridium difficile*, which led to the sequencing of the entire 4 Mb genome during the past year.

**Dr. William Foulkes’** interests continue to be focused on hereditary cancer, specifically breast, colorectal and prostate cancer. His main contribution in 2005 was to extend his work on the basal phenotype of BRCA1-related breast cancer. In addition, he published several papers on Lynch (HNPCC) syndrome, in collaboration with colleagues both in Montreal and overseas. He was the co-organiser of a major conference on hereditary breast and ovarian cancer that was held in Montreal in October 2005 ([www.hboc.ca](http://www.hboc.ca)).

**T. Mary Fujiwara** has research interests which include the study of the distribution and maintenance of genetic variability, including deleterious alleles in well-defined populations, in particular, the Hutterite population of North America – an inbred population isolate. During the current reporting period, she continued collaborations on mapping Mendelian diseases, and further delineated the clinical variability of a cerebellar hypoplasia called disequilibrium syndrome. This work was done in collaboration with Kenneth Morgan, although he is not a co-author on all the publications. She also collaborates with Daniel Bichet (Hôpital Sacré-Coeur de Montréal) on a worldwide collection of families with nephrogenic or neurohypophyseal diabetes insipidus. During the current reporting period, they were invited to write a review for the *Journal of the American Society of Nephrology*.

**Dr. Brian Gilfix** and his team are focused on two main areas of research: 1) Homocysteine and its Metabolism/Inborn Errors of Metabolism (Homocystinuria)-they have a large cohort of patients in the Adult Genetics Clinical with homocystinuria. His team is using this opportunity to explore new treatments of homocystinuria and investigate the effect of elevated homocysteine on other risk factors for cardiovascular disease; 2) Development of Laboratory Methods in Molecular Diagnostics and HPLC-they are developing and implementing assays based on hybridization probes to replace standard assays based on restriction fragment length polymorphism used to genotype for single nucleotide polymorphisms in the clinical laboratory. The benefit of this is decreased net cost and faster turn-around-time.

**Dr. Thomas Hudson** directs the McGill University and Genome Quebec Innovation Centre which is the largest genomic and proteomic facility in Canada. As mentioned above, Dr. Hudson played a major role in the International Haplotype Map Consortium and received great recognition for this work. His laboratory also is heavily involved in the study of the genetics of common disease. Dr. Hudson is one of Canada’s premier scientists.

**Dr. Ken Morgan** has research interests in population genetics, pedigree analysis, and genetic modelling. He leads a Genetic Analysis Group that participated in two Networks of Centres of Excellence programs: the Canadian Genetic Diseases Network (CGDN) and the Mathematics of Information Technology and Complex Systems. His group is involved in the genetic analysis of Mendelian and complex traits in humans and mice. Accomplishments related to human genetics include: 1) mapping Mendelian diseases in the Canadian Hutterite population with collaborators in Calgary and Winnipeg, and further clinical delineation of a cerebellar hypoplasia; 2)
collaboration with Alexey Pshezhetsky, Hôpital Ste-Justine, in mapping the locus for mucopolysaccharidosis IIIC (Sanfilippo syndrome); 3) former postdoc Loredo-Osti developed methodology for segregation analysis of a quantitative trait in sibships to find evidence for a major gene for urine calcium excretion in families ascertained for kidney stones, a collaboration with Alain Bonnardeaux, Hôpital Maisonneuve-Rosemont; 4) collaboration with David Rosenblatt and mentoring of his student, Jordan Lerner-Ellis, in mapping the locus for methylmalonic aciduria and homocystinuria, cblC type, and identification in mutations in the MMACHC gene; 5) collaboration with Susie Tenenhouse (Montreal Children’s Hospital) and collaborators in Boston to identify mutations in the gene encoding a sodium-phosphate cotransporter that cause hereditary hypophosphatemic rickets with hypercalciuria.

**Dr. David Rosenblatt** and his laboratory continue to be the major international referral source for the diagnosis of patients with inherited disorders of folate and vitamin B₁₂. They are involved in studying the biochemical and molecular bases of these diseases. Jordan Lerner-Ellis, a Ph.D. student, succeeded in discovering the MMACHC gene responsible for combined homocystinuria and methylmalonic aciduria, the most common inborn error of vitamin B₁₂ metabolism. This work was published in Nature Genetics and received considerable publicity. It has allowed for carrier detection and more rapid prenatal diagnosis in those families in which mutations are known. Emily Moras has discovered a novel mitochondrial protein binder for cobalamin. Abigail Gradinger has been looking at the frequency of mutations in the MCEE gene among patients with elevated excretion of methylmalonic acid.

**Dr. Marc Tischkowitz** took up a position in September 2005 as Assistant Professor in the Departments of Human Genetics and Oncology at McGill University Faculty of Medicine. Prior to his current post, Dr Tischkowitz was a Consultant (Attending Physician) in Clinical Genetics at the North East Thames Regional Genetics Unit, Great Ormond Street Hospital, UK. He has medical training in both Clinical Genetics and Medical Oncology and his primary interests are molecular studies of cancer predisposition genes and the clinical management of familial cancer predisposition syndromes. He has a strong scientific background, which he has built upon since his undergraduate years. From 1999 to 2002 he undertook a PhD on the chromosome breakage syndrome Fanconi anemia and through this he has developed an interest in DNA repair mechanisms. He is currently in the process of establishing a research group to undertake innovative and effective research in the field of hereditary predisposition to cancer.

**Dr. Patricia Tonin** has two major areas of research interest. The first involves the identification of genetic factors that are implicated in the development and/or progression of human epithelial ovarian cancer. The second involves the study of genetic factors that predispose to hereditary forms of breast cancer: 1) The Molecular study of Human Epithelial Ovarian Cancer—Our knowledge of the molecular events associated with the development and progression of epithelial ovarian cancer has been limited by the lack of a suitable model system. Also, since the disease is often diagnosed at a late stage when numerous complex chromosomal changes have already taken place, the early molecular events remain largely unknown. Deletions of chromosome 3p and 17q (distinct from the BRCA1 locus) are frequent events in ovarian tumours of epithelial origin. Dr. Tonin has shown deletions in low grade, early stage tumours and therefore has hypothesized that these chromosomal regions harbour tumour suppressor genes whose function
is lost early in the development and/or progression of ovarian cancer. The goals of the CIHR funded projects are to refine the localization and then clone the putative chromosome 3p and 17q tumour suppressor genes. Previously, her team published a deletion map of chromosome 3p deletions observed in a large series of epithelial ovarian tumours. In addition they are applying a candidate gene approach and have excluded known candidates, such as TGF-β-RII. They described a chromosome 3 transcriptome based on the comparison of expression profiles of ovarian cancer cell lines with normal surface epithelial cells using high through put oligonucleotide expression microarrays. In this study they were able to establish the sensitivity of detection and show that subtle changes in gene copy number are detectable by microarray analysis. In an effort to characterize the putative TSG on chromosome 3p implicated in ovarian tumourigensis, they established the relationship between chromosome losses frequently associated with specific regions of the human genome (BRCA2 and 13q, TP53 and 17p, BRCA1 and 17q, and Xp11) with that of 3p regions lost in ovarian cancer. They established chromosome 3p loss occurs independently from TP53 mutagenesis. They reported a comprehensive analysis addressing the fidelity of expression microarrays, such as Affymetrix GeneChips®, showing that rigorous investigation of target sequences representing genes on these microarrays should be pursued prior to engaging in experiments of target genes. Most recently her team has begun to translate their findings to identify markers for epithelial ovarian cancers; 2) Breast Cancer Susceptibility Genes: BRCA1 and BRCA2 - Hereditary breast cancer accounts for approximately 5% to 10% of all breast cancers and large majority of hereditary cancer families are attributed to germline mutations in BRCA1 and BRCA2, which confer an increased susceptibility to both breast and ovarian cancer. Dr. tonin and her team are continuing to further define the spectrum of mutations in the BRCA1 and BRCA2 cancer susceptibility genes in the French Canadian population of Quebec. Most recently they reported a new recurrent BRCA2 mutation in the French Canadian population at risk for hereditary breast and ovarian cancer and determined that it is likely identical by descent. This latest discovery has redefined mutation screening protocols and improved genetic testing, and consequently genetic counselling, for this population.
MEETINGS AND PRESENTATIONS

KEN DEWAR
April 22-2006
15th Annual Scientific Meeting of the Canadian Genetic Diseases Network, Saint-Sauveur, QC
Title: Genome sequencing and analysis of a Quebec isolate of *Clostridium difficile*

SUZANNE DUFRASNE
November 22, 2005
Hôpital Ste-Justine / Université de Montréal
Predictive Testing for Huntington Disease
Module for Masters degree students in Genetic Counselling

WILLIAM FOULKES
September 19, 2005
National Council of Jewish Women of Canada
Gelber Conference Centre, Montreal, QC
Title: Role of genetic factors in cancer & familial diseases

September 28, 2005
CCMG 2005 Annual Meeting
Château Bromont, Bromont, QC
Title: Genetics of colorectal cancer: What’s new?

October 12, 2005
10th McGill International Symposium on Reproductive Endocrinology & Infertility and Women’s Health Centre Mont-Royal, Montreal, QC
Title: Genetic influence of breast and gynecological cancers in pre-menopausal women

October 20, 2005
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes BRCA: Today & Tomorrow Marriott Château Champlain, Montreal, QC
Title: Overview - 10 years of BRCA1 and BRCA2
Title: Outcome following BRCA1/2 related breast cancer

February 2, 2006
5th International From Gene to Cure Congress Vrije Universiteit Amsterdam, Amsterdam, Netherlands
Title: Genetic Risk Assessment & Title: Prevention of Hereditary Breast Cancer
**STEPHANIE FOX**

September 29-October 2, 2005  
CAGC annual meeting (Canadian Association of Genetic Counsellors) Montreal, Quebec

October 20-21, 2005  
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes  
Presented workshop: Taking a history for cancer risk  
Montreal, Quebec

November 12-15, 2005  
NSGC annual meeting (National Society of Genetic Counsellors) Los Angeles, California

**BRIAN GILFIX**

November 29, 2005  
Montreal General Hospital

November 30, 2005  
Royal Victoria Hospital  
Medical Grand Rounds  
**Title**: A mini-symposium on the gene that rusts

**THOMAS HUDSON**

August 12, 2005  
Club Kiwanis Chicoutimi, QC  
**Title**: Medical Genetics: progress and hopes

September 20, 2005  
Conference: From Biobanks to Biomarkers: Translating the Potential of Human Population Genetics Research to Improve the quality of Health of the EU Citizen, Hinxton, Cambridge, UK,  
**Title**: Unraveling the causes of chronic diseases

December 6, 2005  
Guest speaker: Council of Community-Based Pediatricians, CME Meeting  
**Title**: Genetics for pediatricians

December 20, 2005  
Invited speaker: The National Sciences Foundation of China, Beijing  
**Title**: From haplotypes to chronic diseases: the power of international consortia

**KENNETH MORGAN**

March 30-31, 2006  
**Title**: First Canadian genetic epidemiology and statistical genetics workshop  
Member of organizing committee and co-chairman  
Toronto, ON
LAURA PALMA  
September 29-October 2, 2005  
CAGC annual meeting (Canadian Association of Genetic Counsellors) Montreal, Quebec  
Member of local organizing committee  

October 20-21, 2005  
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes  
Presented workshop: Taking a history for cancer risk  
Montreal, Quebec  

November 12-15, 2005  
NSGC annual meeting (National Society of Genetic Counsellors) Los Angeles, California  

DAVID ROSENBLATT  
September 18-23, 2005  
Gordon Research Conferences  
**Discussion Leader:** B$_{12}$ in medicine and toxicology  
Queen’s College  
Oxford, England  

Feb 15-16, 2006  
Banbury Conference  
Long Island, Cold Spring Harbor.  

March 6, 2006  
MUHC-Montreal Children’s Hospital Research Institute Research Seminar  
**Title:** What’s new in the genetics of vitamin B$_{12}$?  
Montreal Children’s Hospital  

MARK TISCHKOWITZ  
October 20, 2005  
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes  
BRCA: today & tomorrow  
Marriott Château Champlain, Montreal, QC  

PATRICIA N. TONIN  
January 13, 2006  
Montreal Children’s Hospital  
**Topic:** Towards the identification of chromosome 3p tumour suppressor genes implicated in ovarian cancer  
Seminar
ORIGINAL PUBLICATIONS


RESEARCH OPERATING FUNDS – 2005-2006

AGENCY

Dewar, Ken
Genome Canada/Genome Quebec, Group Grant – 2001-2005
National Institutes of Health - (P.I.) - 2004-2008

Foulkes, William
FRSQ – Group Grant – 2000-2005
Valorisation-Recherche Quebec – Group Grant – 2002-2006

Hudson, Thomas
Canadian Foundation for Innovation, Infrastructure Grant - Project Leader – 2002-2006
Genome Canada - PI – 2006-2008
CIHR, Operating Grant – PI - 2001-2006
CIHR – Operating Grant – 2003-2008
Juvenile Diabetes Foundation International, Group Grant – 2001-2006
Genome Canada – PI, 2006-2009
Ontario Genomics Institute/Genome Quebec – PL – 2001-2005
Genome Canada/Genome Quebec – Group Grant – 2001-2005
CIHR - Group Grant – 2001-2006
Valorisation-Recherche Quebec – Group Grant – 2002-2006
Burroughs Wellcome Fund, PI – 2002-2007
CIHR – Operating Grant – 2002-2005
National Institute of Allergy & Infectious Diseases – Co-investigator – 2004-2009
Networks of Centres of Excellence – Leader Theme I, 2005-2007
European Commission – Co-investigator – 2006-2008

Morgan, Kenneth
Networks of Centres of Excellence, Operating– Investigator, 1999-2009
CIHR – Investigator, Group grant – 2003-2008
CIHR, Co-applicant, 2003-2006
NSERC - Postdoctoral Fellowship to Fabrice Larribe, 2004-2005

Rosenblatt, David S.
CIHR – Operating – 2001-2006 (PI)
March of Dimes – Operating – 2001-2005 (PI)
Garrod Association– Operating – 2004-2005 (PI)
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<th>Tischkowitz, Mark</th>
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<td>Tonin, Patricia N.</td>
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