

# Annual Report 2008/2009

## Annual Report Highlights: Research Teaching

### Annual Report 2008/2009

The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone was established in 1988 to honour the memory of Jacob and Jenny Finestone and the 80th birthday of Mr. Hess B. Finestone by providing a permanent endowment at McGill University devoted to the advancement of medical genetics. The specific objectives of the endowment are to a) fund research projects related to the field of medical genetics; b) fund trainees in the field of medical genetics; and c) publicize the field of medical genetics through the support of special lectures, visiting professorships and other appropriate means.

Dr. David S. Rosenblatt has been Director of the laboratory since its inception. In past years, this report has served as the Annual Report of the Division of Medical Genetics of the Department of Medicine. With the creation of free-standing Departments of Medical Genetics at both the McGill University Health Centre and the Jewish General Hospital, a longstanding goal of Dr. Rosenblatt, this and future Finestone reports will restrict themselves to the activities of the Director. Material previously found in this report should be sought in the respective university or hospital annual reports.

### Highlights: Research

Our laboratory, located at the Montreal General Hospital Site of the McGill University Health Centre, is one of two major international referral laboratories for the diagnosis of patients with inherited disorders of folate and vitamin B12 transport and metabolism. It is involved in studying the biochemical and molecular bases of these diseases. Since Dr. Rosenblatt directs a certified molecular diagnostic laboratory adjacent to the research laboratory, advances in knowledge from research can be immediately translated to clinical diagnosis.

2008-2009 has been another very productive year:

1. Along with collaborators in Germany and Switzerland, we described the *LMBRD1* gene responsible for the *cbIF* inborn error of vitamin B12 metabolism. This work marked the successful completion of a research goal going back to 1985, when Dr. Rosenblatt and colleagues described the biochemical defect in the first patient with this disease in the journal *Science*. This patient had been discovered following newborn urine screening in Quebec. The defect is caused because of a defect in a protein that is required to export vitamin B12 from the lysosome. Because of this, the vitamin levels increase inside the lysosome and the vitamin cannot get into the cell in order to be converted to its active forms. This work was published in *Nature Genetics* and will comprise a portion of the Ph.D. thesis of Isabelle R. Miousse.
2. We have shown that transcobalamin (TC) is an intracellular binder of vitamin B12 and that its level varies in cell lines from patients with different inherited disorders of vitamin B12 metabolism-in particular the *mut* and *cbIB* complementation classes. This work formed the basis of the M.Sc. thesis of Lama Yamani and was published in *Molecular Genetics and Metabolism*.
3. Transcobalamin deficiency can come to medical attention with findings similar to those of leukemia. We described such an infant in whom bone marrow transplantation was even being considered until the correct diagnosis was made. The work was published in the *Journal of Inherited Metabolic Diseases*.
4. Last year, with colleagues in Switzerland, we identified *MMADHC* as the gene responsible for the *cbID*

form of combined homocystinuria and methylmalonic aciduria. In the initial report in the New England Journal of Medicine, seven patients were studied and mutations in different parts of the gene were shown to be responsible for either homocystinuria alone (variant 1), methylmalonic aciduria alone (variant 2) or combined homocystinuria and methylmalonic aciduria, the classic form of *cbID*. This year, study of an additional three patients' added support to the hypothesis, that mutations affecting the N terminus of the MMACHC protein are associated with methylmalonic aciduria, whereas mutations affecting the C terminus are associated with homocystinuria. This work, published in the Journal of Pediatrics, increases the total number published cases of this disease to ten.

5. A number of years ago, using combined haplotype analysis and homozygosity mapping followed by sequencing of candidate genes, we identified *MMACHC* as the gene responsible for the *cbIC* disorder, which is associated with combined homocystinuria and methylmalonic aciduria. We discovered 42 different mutations in 204 individuals; many mutations were consistent with loss of function of the gene product. The c.271dupA mutation accounted for 40% of all disease-causing alleles, and almost always was found on a single haplotype. Patients homozygous for this mutation always had early-onset disease. Patients homozygous for another mutation, c394 C>T (R132X) always had late-onset disease. We also showed that a number of mutations had ethnic specificity; in particular c.331C>T (R111X) was found in patients of French Canadian or Acadian ancestry. Transduction of wild-type *MMACHC* into immortalized *cbIC* fibroblasts corrected the cellular defects in Cbl metabolism. The function of the gene product is not well understood. It contains a cobalamin-binding motif and a domain with homology to the bacterial protein TonB, which is involved in energy transduction for the transport of cobalamin and other molecules. Molecular modeling predicted that the domain in *MMACHC* folds similarly to TonB.

This year, sequencing of 118 additional patients from a mainly European cohort identified 11 novel mutations, as well as 21 that had been observed previously. Allelic expression analysis carried out on cell lines derived from patients who were compound heterozygotes for different combinations of mutations indicated that the early-onset c.271dupA and c.331C>T mutations were under-expressed when compared to the late onset c.394C>T mutation. This work is published in Human Mutation and will form part of the M.Sc. thesis of Natascia Anastasio.

6. We have shown that a human melanoma-derived cell line, which is a phenocopy for *cbIC*, shows methionine dependence due to aberrant methylation of the *MMACHC* promoter. This shows that a cancer cell line can mimic an inborn error of metabolism due to an epigenetic effect. This work is published in Molecular Genetics and Metabolism and is the basis of the M.Sc. thesis of Amanda Loewy.

## Teaching

Biology 575

Department: Biology/Human Genetics

Format: Lecture

Title: Inborn Errors of Folate and Cobalamin Transport and Metabolism

Role: Lecturer and Course Coordinator

Level: Undergraduate/Graduate

Time: 6 hours

Unit 8

Department: Human Genetics

Format: Lecture and Small Group Teaching

Role: Lecturer-2 sessions; Small Group Leader  
Title: Introduction to Medical Genetics  
Huntington Disease  
Level: Medical Students  
Time: 2 lectures plus 5 2-hour sessions, twelve hours in total

## Publications 2008/2009

### Research Operating Funds

Research Operating Funds

CIHR, Operating Grant, PI – 2006-2009

CIHR, Group Grant, Co-Investigator – 1975-2009

Canadian Gene Cure Foundation, PI-2007-2008

## Publications 2008/2009

### Original Publications Chapters

#### Original Publications

Yamani L, Gibbs BF, Gilfix BG, Watkins D, Hosack A, Rosenblatt DS. Transcobalamin in cultured fibroblasts from patients with inborn errors of vitamin B12 metabolism. *Mol Genet Metab* 95: 104-106, 2008

Prasad C, Rosenblatt DS, Corley K, Cairney AEL, Rupar CA. Transcobalamin (TC) deficiency-potential cause of bone marrow failure in childhood. *J Inherit Metabol Dis*, 31: 775, 2008.

Rutsch F, Gailus S, Miousse IR, Suormala T, Sagné, Toliat MR, Nurnberg G, Wittkamp T, Buers I, Shariffi A, Stucki M, Becker C, Baumgartner M, Robenek H, Marquardt T, Hohne W, Gasnier B, Rosenblatt DS, Fowler B, Nurnberg P. Identification of a putative lysosomal cobalamin exporter mutated in the *cb1F* inborn error of vitamin B12 metabolism. *Nat Genet*, 41:234-239, 2009.

Miousse IR, Watkins D, Lavallée J, Coelho D, Rupar T, Clarke JTR, Crombez EA, Vilain E, Cederbaum S, Bernstein JA, Cowan T, Lee-Messer C, Enns GM, Fowler B, Rosenblatt DS. Clinical and molecular heterogeneity in patients with the *cb1D* inborn error of cobalamin metabolism. *J Pediatr*, 154: 551-556, 2009

Loewy AD, Niles KM, Anastasio N, Watkins D, Lavoie J, Lerner-Ellis JP, Pastinen T, Trasler JM, Rosenblatt DS. Epigenetic modification of the gene for the vitamin B12 chaperone *MMACHC* can result in increased tumorigenicity and methionine dependence. *Mol Genet Metab* 96: 261-267, 2009

Lerner-Ellis JP, Anastasio N, Liu J, Coelho D, Suormala T, Stucki M, Loewy A, Gurd S, Grundberg E, Morel CF, Watkins D, Baumgartner MR, Pastinen T, Rosenblatt DS, Fowler B. Spectrum of mutations in *MMACHC*, allelic expression and evidence for genotype-phenotype correlations. *Human Mutat.*, doi: 10.1002/humu, 21001, 2009

#### Chapters

Watkins D, Shevell M, and Rosenblatt DS: Vitamins: cobalamin and folate in *The Molecular and Genetic Basis of Neurological and Psychiatric Disease* (4th ed). Rosenberg RN, DiMauro S, Paulson H, Ptacek L and Nestler E (eds). Wolters Kluwer/Lippincott Williams & Wilkins. 2008 pp 733-738

Watkins D, Whitehead VM and Rosenblatt DS. Megaloblastic anemia in Nathan and Oski's *Hematology of Infancy and Childhood* (7th ed). Orkin SH, Ginsburg D, Nathan DA, Look AT,

Fisher DE (eds). 2009, Chapter 11 pp 467-520

Morel C and Rosenblatt DS. Inborn Errors of Folate and Cobalamin Transport and Metabolism in Pediatric Endocrinology and Inborn Errors of Metabolism.

## **MEMBERSHIP**

### **PHYSICIANS AND SCIENTISTS**

David S. Rosenblatt

David Watkins

### **ADMINISTRATION**

Laura Benner

### **CLINICAL SUPPORT STAFF**

Maria Galvez

Jocelyne Lavallée

### **RESEARCH SUPPORT STAFF**

Suzanne Dufrasne

### **GRADUATE STUDENTS**

Natascia Anastasio

Junhui Liu

Amanda Loewy

Isabelle Racine-Miousse

Lama Yamani

### **SUMMER STUDENTS**

Lydia Vezina

Mireille Sayegh

Fei Li

Eleanor Foulkes

### **INDEPENDENT STUDIES STUDENTS**

Fei Li



## 2008/2009 Membership Page

### MEMBERSHIP

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David Watkins

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Natascia Anastasio  
Junhui Liu  
Amanda Loewy  
Isabelle Racine-Miousse  
Lama Yamani

#### SUMMER STUDENTS

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Mireille Sayegh  
Fei Li  
Eleanor Foulkes

#### INDEPENDENT STUDIES STUDENTS

Fei Li



## Meetings and Presentations 2008/2009

### Meetings and Presentations

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Miousse I.R., Watkins D., Coelho D., Suormala T., Lerner-Ellis J.P., Fowler B., Rosenblatt D.S.  
*Mutations dans MMADHC chez deux patients atteints de la forme cb1D l'erreur innée du métabolisme de la cobalamine.*

Journées génétiques, Québec. May 14-16, 2008.

Anastasio N., Lerner-Ellis J.P., Pastinen T., Liu J., Coelho D., Suormala T., Stucki M., Loewy A., Gurd S., Grundberg E.,

Morel C.F., Baumgartner M.R., Watkins D., Fowler B., Rosenblatt D.S. *Allelic expression of the MMACHC gene*

*and genotype-phenotype correlations in cb1C disease.* American Society of Human Genetics, Philadelphia. November 11-15, 2008. Abstract N. 1450W, page 291.

February 26, 2009

C. Ronald Scott Lecture

Title: *Vitamin B12: Can you teach an old vitamin new tricks?*

University of Washington

Seattle, WA

February 27, 2009

Markey Seminar Lecture

Title: *Novel biological insights in Vitamin B12 transport and metabolism: lessons from the clinic*

University of Washington

Seattle, WA

March 19, 2009

Title: *One carbon metabolism and the CNS: Lessons from inborn errors of folate and cobalamin metabolism*

Autism Speaks

Washington, DC

Financial Report 2008-2009

Starting Balance	\$112,006
De-capitalized from previous years	\$ 46,016
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	\$158,022
*Salary Support and Benefits	\$ 87,831
Computer Charges	\$ 1,508
Conference, Seminars, & Travel	\$ 16,766
Library & Membership	\$ 4,794
Materials, Supplies, Phones & Pagers	\$ 4,169
Renovations (Montreal Children's Hospital)	\$ 7,500
Miscellaneous	\$ 4,614
Total Expenses	\$127,182
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**Balance	\$ 30,840

*Notes*

\* *Rosenblatt, DufRASne, Veyre, Matos-Miranda, Benner, Vezina*

\*\* *Balance was capitalized*

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