ANNUAL REPORT
2012/2013

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

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MEMBERSHIP

PHYSICIANS AND SCIENTISTS
David S. Rosenblatt
David Watkins

ADMINISTRATION
Laura Benner (Maternity Leave)
Ross Mackay
Danielle Veyre

CLINICAL SUPPORT STAFF
Maria Galvez
Leah Ladores

RESEARCH SUPPORT STAFF
Wayne Mah (with James Coulton)
Maira Moreno (with Loydie Jerome Majewski)

GRADUATE STUDENTS
Alison Brebner
Justin Deme (with James Coulton)
Laura Dempsey Nuñez
Peg Illson
Jaeseung Kim
Mihaela Pupavac

UNDERGRADUATE AND SUMMER STUDENTS
Jeehye Jung
Francis Petrella
Kush Prithipaul
Dylan Tanzer
Tracy Wang

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The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone was first established in 1988. The intent of the donor was to honour the memory of Jacob and Jenny Finestone, and the 80th birthday of Mr. Hess B. Finestone. A permanent endowment was created 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, and this annual report describes the activity of his laboratory. The year 2013 will be the twenty-fifth anniversary of the Finestone Laboratory. Material relating to members of the Department of Human Genetics at McGill and the Departments of Medical Genetics at the McGill University Health Centre and the Jewish General Hospital should be sought in the respective university or hospital annual reports.

RESEARCH

The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone is located on Livingston 3 of the Montreal General Hospital Site of the McGill University Health Centre. It is one of two major international referral laboratories for the diagnosis of patients with inherited disorders of folate and vitamin B_{12} 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 diagnostics.

2012-2013 has seen a number of major scientific highlights:

1) Dr. Rosenblatt has continued to champion the concept of **RaDiCAL** (Rare Disease Collaboration for Autosomal Loci). He has proposed the use of single patients with Mendelian disorders to discover new genes. With colleagues at McGill he has continued to use exome sequencing for new gene discovery.

2) With colleagues at McGill and in the United States, Switzerland and Germany, we used exome sequencing to discover a novel inborn error of cobalamin metabolism (***cblJ***), and showed that it is caused by mutations in the ***ABCD4*** gene. These studies showed that at least two different proteins are responsible for the transport of cobalamin across the lysosomal membrane.

3) Together with James Coulton in the Department of Microbiology and Immunology, we continued studies on the intracellular function of proteins involved in intracellular cobalamin metabolism. We determined the ability of MMACHC and MMADHC to interact, as well as their subcellular locations.

4) With Loydie Jerome-Majewska, we determined the expression of the methylmalonic aciduria related genes, *Mmaa*, *Mmab*, and *Mut* in placental and embryonic tissue during mouse development.

5) With Carl Wittwer of the University of Utah, we have developed the technique of high resolution melting analysis (HRMA) to look for variants in the *MMAA* and *MMAB* genes.

RESEARCH OPERATING FUNDS

CIHR Operating Grant, PI – 2009-2014

INVITED PRESENTATIONS

July 22-27, 2012
Gordon Research Conference (GRC)
Chemistry and Biology of Tetrapyrroles
Salve Regina University
Newport, Rhode Island

Title: Vitamin B_{12} Transport and Metabolism: lessons from Mendelian Disease

September 20-22, 2012
Vitamin B_{12} Symposium
Nancy, France

Title: Lessons in Biology from Patients with Inborn Errors of Vitamin B_{12} Metabolism

September 24, 2012
Medical Genetics Seminar
Hôpital Necker
Paris, France

Title: Lessons in Biology from Patients with Inborn Errors of Vitamin B_{12} Metabolism

October 24, 2012
The Children's Hospital of Philadelphia
Grand Rounds-Annual Palmieri Lectureship
Philadelphia, Pennsylvania

Title: Lessons in Biology from Patients with Inborn Errors of Vitamin B_{12} Metabolism

November 15-16, 2012
Neurometabolic disorders Related to B Vitamins
Orphan Europe Academy
Manchester, UK

Title: Disorders of Cobalamin Transport

February 19-24
Nutrition, Epigenetics and Human Disease
Keystone Symposia on Molecular and Cellular Biology
Santa Fe, New Mexico, USA
Scientific Organizer and Session Chair

Title: Discovering New Genes in the One-Carbon Pathway Using Exome Sequencing-A RaDiCAL Approach

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ORIGINAL PUBLICATIONS

Coelho D, Kim JC, Miouse IR, Fung S, du Moulin M, Buers I, Suormala T, Burda P, Frapolli M, Stucki M, Nürnberg P, Thiele H, Robenek H, Höhne W, Longo N, Pasquali M, Mengel E, Watkins D, Shoubridge EA, Majewski J, Rosenblatt DS, Fowler B, Rutsch F, Baumgartner MR. Mutations in *ABCD4* cause a new inborn error of vitamin B_{12} metabolism. *Nat. Genet.* 44:1152-1155, 2012.

Dempsey-Nunez L, Illson ML, Kent J, Huang Q, Brebner A, Watkins D, Gilfix BM, Wittwer C, Rosenblatt DS. High resolution melting analysis of the *MMAA* gene in patients with *cblA* and in those with undiagnosed methylmalonic aciduria. *Mol. Genet. Metab.* 107:363-367, 2012.

Deme JC, Miousse IR, Plesa M, Kim JC, Hancock MA, Mah W, Rosenblatt DS, Coulton JW. Structural features of recombinant MMADHC isoforms and their interactions with MMACHC, proteins of mammalian vitamin B_{12} metabolism. *Mol. Genet. Metab.* 107:352-362, 2012.

Moreno-Garcia M, Rosenblatt DS, Jerome-Majewska LA. The methylmalonic aciduria related genes, *Mmaa*, *Mmab* and *Mut*, are broadly expressed in placental and embryonic tissues during mouse organogenesis. *Mol. Genet. Metab.* 107:368-374, 2012.

Kim JC, Lee NC, Hwu WL, Chien YH, Fahiminiya S, Majewski J, Watkins D, Rosenblatt DS. Late onset symptoms in a patient with the *cblJ* inborn error of vitamin B_{12} metabolism:

diagnosis and novel mutation revealed by exome sequencing. *Mol. Genet. Metab.* 107:664-668, 2012.

Mah W, Deme JC, Watkins D, Fung S, Janer A, Rosenblatt DS, Shoubridge EA, Coulton JW. Subcellular location of MMACHC and MMADHC, two human proteins central to intracellular vitamin B_{12} metabolism. *Mol. Genet. Metab.* 108:112-118, 2013.

Prasad C, Cairney AE, Rosenblatt DS, Rupar CA. Transcobalamin (TC) deficiency and newborn screening. *J Inher Metab Dis* 35:727, 2012.

Watkins D, Rosenblatt DS. Lessons in biology from patients with inborn errors of vitamin B_{12} metabolism. *Biochimie* 95:1019-1022, 2013.

Keller MD, Ganesh J, Heltzer M, Paessler M, Bergqvist AGC, Baluarte JJ, Watkins D, Rosenblatt DS, Orange JS. Severe combined immunodeficiency resulting from mutations in *MTHFD1*. *Pediatrics* 131:e629-e634, 2013.

Prasad C, Melançon SB, Rupar CA, Prasad AN, Dempsey-Nunez L, Rosenblatt DS, Majewski J. Exome sequencing reveals a homozygous mutation in *TWINKLE* as the cause of multisystemic failure in three siblings. *Mol. Genet. Metab.* 108(3):190-4, 2013.

Gupta IR, Baldwin C, Auguste D, Ha KC, Andalousi EI, Fahiminiya S, Bitzan M, Bernard C, Akbari MR, Narod SA, Rosenblatt DS, Majewski J, Takano T. ARHGDIA: a novel gene implicated in nephritic syndrome. *J Med Genet.* 50(5):330-8, 2013.

CHAPTERS

Watkins D, Rosenblatt DS. Cerebral folate deficiency. *MedLink Neurology* http://www.medlink.com/MedLinkContent.asp, 2013.

Watkins D, Rosenblatt DS. Folic acid deficiency. *MedLink Neurology* http://www.medlink.com/MedLinkContent.asp, 2013.

ABSTRACTS

Kim JC, Coelho D, Miousse IR, Fung S, du Moulin M, Buers I, Suormala T, Burda P, Frapolli M, Stucki M, Nürnberg P, Thiele H, Robenek H, Höhne W, Longo N, Pasquali M, Mengel E, Watkins D, Shoubridge EA, Majewski J, Fowler B, Rutsch F, Baumgartner MR, Rosenblatt DS. Novel inborn error of vitamin B_{12} metabolism caused by mutations in ABCD4. RMGA: Journées Génétiques 2012, Montreal, May 22-24, 2012.

Dempsey-Nunez L, Illson ML, Kent J, Huang Q, Brebner A, Watkins D, Gilfix BM, Wittwer C, Rosenblatt DS. Spectrum of mutations in *MMAA* identified by high-resolution melting analysis. RMGA: Journées Génétiques 2012, Montreal, May 22-24, 2012.

Illson M, Dempsey Nunez L, Kent J, Zhou L, Watkins D, Gilfix B, Wittwer C, Rosenblatt D. Screening of the *MMAB* gene by high resolution melting analysis (HRMA). RMGA: Journées Génétiques 2012, Montreal, May 22-24, 2012.

Brebner A, Watkins D, Ficicioglu C, Pastinen T, Rosenblatt DS. Search for non-coding mutations in an atypical patient with combined homocystinuria and methylmalonic aciduria (*cblC*). RMGA: Journées Génétiques 2012, Montreal, May 22-24, 2012.

Rutsch F, Coelho D, Kim JC, Miousse IR, Fung S, du Moulin M, Buers I, Suormala T, Burda P, Frapolli M, Stucki M, Nürnberg P, Thiele H, Robenek H, Höhne W, Longo N, Pasquali M, Mengel E, Watkins D, Shoubridge EA, Majewski J, Rosenblatt DS, Fowler B, Baumgartner MR. A novel inborn error of vitamin B_{12} metabolism mimicking *cblF* is caused by mutations in *ABCD4*. May 17, 2012.

Rosenblatt DS, Brebner A, Miousse IR, Kim, JC, Watkins, D, Armour, C. Mild clinical and atypical somatic cell findings in a *cblF* patient detected by expanded newborn screening. ASHG Conference 2012. American Society of Human Genetics 2012, San Francisco, November 6-10, 2012.

Kim JC, Brebner A, Lee NC, Hwu WL, Chien YH, Fahiminiya S, Majewski J, Watkins D, Rosenblatt DS. Exome sequencing reveals a homozygous ABCD4 mutation in an adolescent with hyperpigmentation, ischemia, hyperhomocysteinemia, and methylmalonic aciduria. American Society of Human Genetics 2012, San Francisco, November 6-10, 2012.

Brebner A, Ficicioglu C, Watkins D, Pastinen T, Rosenblatt DS. Somatic cell and molecular studies on an atypical patient with combined homocystinuria and methylmalonic aciduria (*cblC*). American Society of Human Genetics 2012, San Francisco, November 6-10, 2012.

Dempsey-Nunez L, Illson ML, Kent J, Huang Q, Brebner A, Watkins D, Gilfix BM, Wittwer C, Rosenblatt DS. Somatic cell diagnostic studies may miss some patients with mutations in *MMAA* and *MMAB*, genes responsible for isolated methylmalonic aciduria. American Society of Human Genetics 2012, San Francisco, November 6-10, 2012.

Brebner A, Watkins D, Yu H-C, Sloan JL, Quintana A, Achilly NP, Geiger EA, Venditti CP, Shaikh TH, Rosenblatt DS. Mutations in the Transcription Factor *HCFC1* in Patients with the *cblX* Inborn Error of Vitamin B_{12} Metabolism. 2nd Annual Canadian Human and Statistical Genetics Meeting, Esterel, Qc, April 21-24 2013.

Pupavac M, Zawati MH, Nguyen MT, Joly Y, Majewski J, Rosenblatt DS. Rare Disease Collaboration for Autosomal Loci (**RaDiCAL**). 2nd Annual Canadian Human and Statistical Genetics Meeting, Esterel, Qc, April 21-24 2013.

TEACHING

David Watkins

Biology 575

Department:	Biology/Human Genetics
Format:	Lecture
Title:	***Inborn Errors of Folate and Cobalamin Transport and Metabolism***
Role:	Lecturer
Level:	Undergraduate/Graduate
Time:	3 1.5-hour class lectures

David Rosenblatt

Unit 8

Department:	Human Genetics
Format:	Lecture and Small Group Teaching
Role:	Lecturer-2 sessions
Titles:	***Introduction to Medical Genetics***
	Huntington Disease
Level:	Medical Students
Time:	2 lectures plus 3 2-hour sessions, 8 hours in total

FINANCIAL REPORT – 2012/13

Starting Balance		$ 92,310
Decapitalized		$ 19,651
		$ 111,961
*Salary Support and Benefits	$ 79,831	
Materials and Supplies	$ 3,578	
Conferences, Travel, Special Events	$ 17,942	
Memberships	$ 7,644	
Phones, Pagers, Computer, Printing, Couriers	$ 646	
Miscellaneous	$ 1,637	
Total Expenses		**$ 111,278**
**Balance		**$ 683**

Notes

** Rosenblatt, Brebner, Dempsey-Nunez, Illson, Pupavac, Petrella, Prithipaul, Tanzer, Veyre, Wang*