ANNUAL REPORT
2011/2012

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

TABLE OF CONTENTS

MEMBERSHIP 2
ANNUAL REPORT 2011/2012 3
RESEARCH 3
RESEARCH OPERATING FUNDS 4
INVITED PRESENTATIONS 4
ORIGINAL PUBLICATIONS 5
CHAPTERS 5
ABSTRACTS 6
TEACHING 7
FINANCIAL REPORT – 2011/2012 9

MEMBERSHIP

PHYSICIANS AND SCIENTISTS
David S. Rosenblatt
David Watkins

ADMINISTRATION
Laura Benner (Maternity Leave)
Danielle Veyre
Sandra Anastasio

CLINICAL SUPPORT STAFF
Maria Galvez
Leah Ladores

RESEARCH SUPPORT STAFF
Wayne Mah
Maira Moreno
Maria Plesa

GRADUATE STUDENTS
Isabelle Racine-Miousse
Laura Dempsey Nuñez
Peg Illson
Jaeseung Kim

UNDERGRADUATE AND SUMMER STUDENTS
Alison Brebner
Selim Fares (Visiting Student from Paris)
Francis Petrella

ANNUAL REPORT 2011/2012

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 honor 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. 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 the third floor of Livingston Hall at 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 immediate translated to clinical diagnosis.

2011-2012 has seen a number of major scientific highlights:

1) Dr. Rosenblatt has championed the concept of **RaDiCAL** (Rare Disease Collaboration for Autosomal Loci). He proposed the use of single patients with Mendelian disorders to discover new genes.

2) With Jacek Majewski at the McGill University-Genome Quebec Innovation Centre, and with colleagues at McGill and around the world, we used next generation sequencing technology to find the gene responsible for **three different diseases.** This has been a proof of principle that McGill can compete with the best in the world in gene discovery using this advanced technology.

3) With the group of Don Jacobsen at the Cleveland Clinic, we described the proteome of *cblC* cell lines.

4) With Loydie Jerome-Majewska, we showed different expression patterns of *MMACHC* and *MMADHC* in the developing mouse. It was particularly important to show *MMACHC* expression in the developing heart, since some patients with the *cblC* disorder have congenital heart disease.

5) We described novel mutations in patients with the *cblF* form of combined homocystinuria and methylmalonic aciduria.

RESEARCH OPERATING FUNDS

CIHR, Operating Grant, PI – 2009-2014

INVITED PRESENTATIONS

August 30- September 2, 2011
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism
Geneva, Switzerland

Title: Disorders of Folate Transport and Metabolism

March 31-April 3, 2012
SIMD Annual Meeting
Westin Charlotte
Charlotte, NC

Title: Combined Homocystinuria and Methylmalonic aciduria (cblC)

April 27, 2012
Harvey L Levy Symposium
Beyond Archibald Garrod: Understanding and Treating Metabolic Disorders
Children`s Hospital Boston Division of Genetics and Metabolism
Harvard Medical School
Boston, Massachusetts

Title: Combined Homocystinuria and Methylmalonic Aciduria (*cblC*): From Patient to Gene to Function-and Beyond-RaDiCAL Thoughts

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ORIGINAL PUBLICATIONS

Hannibal L, DiBello PM, Yu M, Miller A, Wang S, Willard B, **Rosenblatt DS**, Jacobsen DW. The MMACHC proteome: hallmarks of functional cobalamin deficiency in human. *Mol Genet Metab* 103:226-239, 2011.

Pupavac M, Garcia MA, **Rosenblatt DS**, Jerome-Majewska LA. Expression of Mmachc and Mmadhc during mouse organogenesis. *Mol Genet Metab* 103(4):401-405, 2011.

Alfares A, Dempsey Nunez L, Al-Thihli K, Mitchell J, Melançon S, Anastasio N, Ha KCH, Majewski J, **Rosenblatt DS**, Braverman N. Combined malonic and methylmalonic aciduria: exome sequencing reveals mutations in the ACSF3 gene in patients with a non-classic phenotype. *J Med Genet* 48(9):602-605, 2011.

Watkins D, Schwartzentruber JA, Ganesh J, Orange JS, Kaplan BS, Dempsey Nunez L, Majewski J, **Rosenblatt DS**. Novel inborn error of folate metabolism: identification by exome capture and sequencing of mutations in the MTHFD1 gene in a single proband. *J Med Genet* 48(9):590-592, 2011.

Campeau PM, Kim JC, Lu JT, Schwartsentruber JA, Abdul-Rahman OA, Schlaubitz S, Murcock DM, Jiang M-M, Lammer EJ, Enns GM, Rhead WJ, Rowland J, Robertson SP, Cormier-Daire V, Bainbridge MN, Yang X-J, Gingras M-C, Gibbs RA, **Rosenblatt DS**, Majewski J, Lee BH. Mutations in *KAT6B* encoding a histone acetylase, cause Genitopatellar syndrome. *Am J Hum Genet* 90: 282-289, 2012.

Miousse IR, Watkins D and **Rosenblatt DS**. Novel splice site mutations and a large deletion in three patients with the cblF inborn error of vitamin B12 metabolism. *Mol Genet Metab* 102:505-507, 2011.

Watkins D and **Rosenblatt DS**. Inborn errors of cobalamin absorption and metabolism. *Am J Med Genet Part C* 157:33-44, 2011.

CHAPTERS

Watkins D and **Rosenblatt DS**. Water Soluble Vitamins: Vitamin B12 and folic acid. In: Rudolph's Pediatrics 22nd Edition, Rudolph AM, Rudolph C, First L, Lister G and Gershon AA, (eds), McGraw-Hill, New York, 2011. Chapter 147.

Shevell M, Watkins D, **Rosenblatt DS**. Disorders of Cobalamin and Folate Metabolism and Epilepsy. In: The Causes of Epilepsy: Common and Uncommon Causes in Adults and Children,

Shorvon SD, Andermann F, and Guerrini R (eds), Cambridge University Press, Cambridge. 2011, Chapter 37 pp 252-257.

Watkins D, **Rosenblatt DS**, Fowler B. Disorders of Cobalamin and Folate Transport and Metabolism. In: Inborn Metabolic Diseases – Diagnosis and Treatment, 5th Edition, Saudubray J-M, van den Berghe G and Fernandes W (eds), Springer. 2011, Chapter 28 pp 385-402.

Watkins D and **Rosenblatt DS**. Disorders of folate and cobalamin transport and metabolism. The Online Metabolic and Molecular Bases of Inherited Disease, Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE and Ballabio A, (eds), McGraw Hill, New York. http://dx.doi.org/10.1036/ommbid.197 , 2011.

ABSTRACTS

Coelho D, Kim JC, du Moulin M, Buers I, Suormala T, Stucki M, Miousse IR, Fung S, Nürnberg P, Thiele H, Longo N, Pasquali M, Mengel E, Watkins D, Shoubridge EA, Majewski J, **Rosenblatt DS**, Baumgartner M, Rutsch F, Fowler B. A new cobalamin complementation class mimicking cblF is caused by mutations in ABCD4. Society for the Study of Inborn Errors of Metabolism, Geneva, Switzerland, August 30 – September 2, 2011.

Kim JC, Coelho D, Miousse IR, Fung S, du Moulin M, Buers I, Suormala T, Stucki M, Nürnberg P, Thiele H, Longo N, Pasquali M, Mengel E, Watkins D, Shoubridge EA, Rutsch F, Majewski J, Baumgartner M, Fowler B, **Rosenblatt DS**. Mutations in ABCD4 cause a new inborn error of vitamin B12 metabolism. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Watkins D, Ganesh J, Schwartzentruber JA, Dempsey Nunez L, Orange J, Majewski J, **Rosenblatt DS**. Exome sequencing a single proband reveals that mutations in the MTHFD1 gene are responsible for a novel inborn error of folate metabolism. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Trakadis YJ, Rupar T, Melançon S, Alfares A, Schrewe B, Watkins D, **Rosenblatt DS**, Braverman N. Transcobalamin deficiency: a treatable metabolic cause of severe pancytopenia and recurrent infections. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Miousse IR, Plesa M, **Rosenblatt DS**, Coulton JW. Phage display predicts regions on MMACHC that bind to its partner MMADHC in human cobalamin metabolism. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Raiman J, Miousse IR, Watkins D, **Rosenblatt DS**. A new patient with the *cblD* cobalamin disorder presenting with high homocysteine. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Moreno Garcia MA, **Rosenblatt DS**, Jerome-Majewska LA. The expression pattern of genes involved in the vitamin B12 metabolic pathway during embryogenesis. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Illson ML, Huang Q, Dempsey Nunez L, Brebner A, Gilfix BM, Watkins D, **Rosenblatt DS**, Wittwer CT. Mutation screening of two genes involved in intracellular vitamin B_{12} metabolism by high resolution melting analysis (HRMA). ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Dempsey Nunez L, Alfares A, Al-Thihli K, Mitchell J, Melançon S, Anastasio N, Majewski J, Ha KCH, **Rosenblatt DS**, Braverman N. Combined malonic aciduria and methylmalonic aciduria CMAMMA): exome sequencing reveals mutations in the ACSF3 gene in patients with a non-classical phenotype. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

Plesa M, Hancock MA, Deme J, Watkins D, **Rosenblatt DS**, Coulton JW. Development of SPR-MS for the identification of novel intracellular vitamin B12 metabolism binding partners. ICHG. American Society for Human Genetics, Montreal, October 11-15, 2011.

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
	Course Co-Supervisor with Dr. Nancy Braverman

Unit 1

Department:	Human Genetics
Format:	Small Group Teaching
Role:	Group Leader
Title:	***Genetics: Problem Solving***
Level:	Medical Students-First Year
Time:	1 2-hour group session

Unit 8

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

FINANCIAL REPORT – 2011/2012

Starting Balance		$ 96, 011
Advance Recovery		$ 25,000
		$ 121, 011
*Salary Support and Benefits	$ 68, 797	
Materials and Supplies	$ 16, 758	
Conference, Travel, Special Events	$ 6, 365	
Library & Membership	$ 4, 558	
Phones, Pagers, Computer, Printing, Couriers	$ 3, 260	
Miscellaneous	$ 1, 621	
Total Expenses		$ **101, 359**
**Balance		**$ 19,652**

Notes

** Rosenblatt, Veyre, Benner, Kim, Dempsey-Nunez, Illson, Fares*.