ANNUAL REPORT
2017/2018

THE HESS B. AND DIANE FINESTONE LABORATORY
IN MEMORY OF
JACOB AND JENNY FINESTONE

Submitted by: Dr. David S. Rosenblatt, Holder, Dodd Q. Chu and Family Chair in Medical Genetics, Professor of Human Genetics, Medicine, Pediatrics and Biology, McGill University

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MEMBERSHIP

PHYSICIANS AND SCIENTISTS
David S. Rosenblatt
David Watkins

CLINICAL SUPPORT STAFF
Maria Galvez
Leah Ladores (medical leave)
Keo Phommarinh
Jocelyne Tossa

RESEARCH SUPPORT STAFF
GRADUATE STUDENTS

Lina Sobhy Abdrabo
Jordan Chu
Mihaela Pupavac

UNDERGRADUATE AND SUMMER STUDENTS
Courtney Ells

SUMMER STUDENTS
Camilah Arbabian

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The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone was 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.

RESEARCH

The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone is located at the Glen Site of the McGill University Health Centre. Our facility 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 the MUHC has a CLIA certified cellular and molecular diagnostic laboratory, advances in knowledge from research can be immediately translated to clinical diagnostics.

2017-2018 has seen a number of scientific highlights:

In a well-publicized article in *Nature Communications*, we described a distinct and totally new mechanism whereby an epimutation causes abnormal regulation of the *MMACHC* gene. Based on the study of patients with the *cblC* inborn error of vitamin B_{12} metabolism and their families, we and our colleague Jean-Louis Guéant from the Inserm unit at the Univeristy of Lorraine, identified an epimutation affecting the *MMACHC* gene that was present in three generations and in the sperm of the fathers of two of seven patients. It was found that this epimutation resulted from aberrant reading of the adjacent gene. The epimutation causes *MMACHC* to shut down and become inactive, having the same effect as a mutation in the gene itself. This mechanism may be involved in many more disease-causing genes.

Mihaela Pupavac received her Ph.D in Human Genetics in 2017. The major focus of her work was the discovery of a novel inborn error of vitamin B_{12} metabolism that is caused by mutations in *ZNF143*, which codes for a transcription activator. Cells from this patient accumulate the vitamin bound to its transporter (transcobalamin, TC) in lysosomes or pre-lysosomal compartments in the cell. She also published an article on **RaDiCAL** (Rare Disease Collaboration for Autosomal Loci). This supports the use of single patients with Mendelian disorders to discover new genes using next generation sequencing approaches. With

collaborators in Canada and the United States, Mihaela showed how "Matchmaking" can be used to make a diagnosis in a rare genetic disease. In this case a diagnosis was provided for an autosomal recessive mitochondrial disease caused by mutations in the *TRIT1* gene.

Jordan Chu received his M.Sc. in Human Genetics in 2017. With Mihaela, he compared the results that have been obtained over decades using a somatic cell genetic approach with those that can now be obtained using next generation sequencing panels. This has validated the utility of both techniques. He also identified sixteen novel mutations in the *MUT* gene responsible for *mut* methylmalonic aciduria.

RESEARCH OPERATING FUNDS

CIHR Operating Grant, PI – 2016-2019. This grant is for the use of next generation sequencing to discover disorders of vitamin B_{12} metabolism.

ORIGINAL PUBLICATIONS

*Chu J, Pupavac M, Watkins D, Tian X, Feng Y, Chen S, Fenter R, Zhang VW, Wang J, Wong LJ, Rosenblatt DS. Corrigendum to "Next generation sequencing of patients with *mut* methylmalonic aciduria: validation of somatic cell studies and identification of 16 novel mutations." *Mol Genet Metab* 120:295, 2017

*Pupavac M, Zawati M, Rosenblatt DS. A RaDiCAL gene hunt. J Taibah University Med Sci doi.org/10.1016/j.jtumed.2016.11.007, 2017

*Kernohan KD, Dyment DA, Pupavac M, McBride A, Hartley T, Huang L, Sell E, Majewski J, Rosenblatt DS, Shoubridge EA, Mhanni A, Myers T, Farrow E, Kaussman J, Safina N, Care4Rare Consortium, Saunders C, Boycott KM, Thiffault I. Matchmaking facilitates the diagnosis of an autosomal-recessive mitochondrial disease caused by biallelic mutation of the tRNA isopentyltransferase (*TRIT1*) gene. *Hum Mut* 38:511-516, 2017

Quintana AM, Yu HC, Brebner A, Geiger EA, Appel B, Cheung W, Pupavac M, Shen SH, Watkins D, Skovby F, Pastinen T, Rosenblatt DS, Shaikh TH. Mutations in *THAP11* cause an inborn error of cobalamin metabolism and developmental abnormalities. *Hum Mol Genet* 26:2838-2849, 2017

Guéant JL, Chéry C, Oussalah A, Nadaf J, Coelho D, Josse T, Flayak J, Robert A, Koscinski I, Gastin I, Filhine-Tresarrieu P, Pupavac M, Brebner A, Watkins D, Pastinen T, Montpetit A, Hariri F, Tregouët D, Raby B, Chung WK, Morange PE, Froese DS, Baumgartner MR, Benoist JF, Ficicioglu C, Marchand V, Motorine Y, Bonnemains C, Feillet F, Majewski J, Rosenblatt DS. A *PRDX1* mutant allele causes a *MMACHC* secondary epimutation in cblC patients. *Nature Comm* doi: 10.1038/s41467-017-02306-5, 2018

CHAPTERS

*Watkins D, Rosenblatt DS. Inherited defects in cobalamin metabolism. In: Vitamin B_{12}: Advances and Insights, Obeid R (ed) CRC Press, Boca Raton, 2017

*Watkins D, Morel CF, Rosenblatt DS. Inborn errors of folate and cobalamin transport and metabolism. In: Pediatric Endocrinology and Inborn Errors of Metabolism 2nd Edition (Sarafoglou K, Hoffmann GF, Roth KS, eds) McGraw –Hill, New York, pp. 287-307, 2017

*2017 Publication also cited in 2016/2017 Report

TEACHING

David Watkins

Biology 575

Department:	Biology/Human Genetics
Format:	Lecture
Title:	***Inborn Errors of Cobalamin Transport and Metabolism***
Role:	Lecturer
Level:	Undergraduate/Graduate
Time:	2 1.5-hour class lectures

David Rosenblatt

PIAT-Medical Students-Genomics- 1.5 hours

CME Wednesday E-Learning Series: 1 hour lecture

GRADUATE STUDENTS SUPERVISED

Mihaela Pupavac	Ph.D.	2012-2017
	Title: Next generation sequencing to discover genes for Mendelian disorders	
Jordan Chu	M.Sc.	2014-2017
	Title: Study of patients with atypical inborn errors of cobalamin metabolism	
Lina Sobhy Abdrabo	M.Sc.	2016-
	Title: Next generation sequencing to discover genes underlying methylmalonic aciduria	

FINANCIAL REPORT – 2017/2018

Starting Balance		**$ 129,819**
*Salary Support and Benefits	$ 88,509	
Conferences, Travel, Special Events	$ 9,987	
Phones, Pagers, Computer, Printing, Couriers	$ 2,311	
Materials and Supplies	$ 502	
Total Expenses		**$ 101,309**
**Balance		**$ 28,510**

**Students: Abdrabo, Chu, Ells, Pupavac; Research Associate: Watkins*

***Capitalized*