ANNUAL REPORT
2016/2017

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
Keo Phommarinh

RESEARCH SUPPORT STAFF
GRADUATE STUDENTS

Lina Sobhy Abdrabo
Jordan Chu
Mihaela Pupavac

UNDERGRADUATE AND SUMMER STUDENTS
Zvi Cramer
Courtney Ells

SUMMER STUDENTS
Camilah Arbabian
Armin Chandizi (Medical Student-Observer)

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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. 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 can be found 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 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.

2016-2017 has seen a number of scientific highlights:

1) As part of her Ph.D., Mihaela Pupavac discovered 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 (TC) in lysosomes or pre-lysosomal compartments in the cell. This work was published in Human Mutation.

2) Dr. Rosenblatt has continued to champion the concept of **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. An article on RaDiCAL and its approach was published (by Mihaela Pupavac et al.) in the Journal Taibah University Medical Sciences in an issue Guest Edited by David Thomas, a past Chair of the Department of Biochemistry at McGill.

3) The group has 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. Sixteen novel mutations were identified in the

MUT gene responsible for *mut* methylmalonic aciduria. This work was published in Molecular Genetics and Metabolism (by Mihaela Pupavac et al. and Jordan Chu et al.).

4) With collaborators in Canada and the United States, we have shown 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.

RESEARCH OPERATING FUNDS

CIHR Operating Grant, PI – 2016-2019. A three year project grant was received starting July 2016. This grant is for the use of next generation sequencing to discover disorders of vitamin B_{12} metabolism.

ORIGINAL PUBLICATIONS

*Pupavac M, Tian X, Chu J, Wang G, Feng Y, Chan S, Fenter R, Zhang VW, Wang J, Watkins D, Wong LJ, Rosenblatt DS. Added value of next generation gene panel analysis for patients with elevated methylmalonic acid and no clinical diagnosis following functional studies of vitamin B_{12} metabolism. Mol Genet Metab 117:363-368, 2016.

*Chu J, Pupavac M, Watkins D, Tian X, Feng Y, Chen S, Fenter R, Zhang VW, Wang J, Wong LJ, Rosenblatt DS. Next generation sequencing of patients with *mut* methylmalonic aciduria: validation of somatic cell studies and identification of 16 novel mutations. Mol Genet Metab 118:264-271, 2016.

*Watkins D, Rosenblatt DS. Lessons in biology from patients with inherited disorders of vitamin B_{12} and folate metabolism. Biochimie 126:3-5, 2016.

*Mah W, Sonkusare SK, Wang T, Azeddine B, Pupavac M, Carrot-Zhang J, Hong K, Majewski J, Harvey EJ, Russell L, Chalk C, Rosenblatt DS, Nelson MT, Séguin C. Gain-of-function mutation in TRPV4 identified in patients with osteonecrosis of the femoral head. J Med Genet 53:705-709, 2016.

Pupavac M, Watkins D, Petrella F, Fahiminiya S, Janer A, Cheung W, Gingras AC, Pastinen T, Muenzer J, Majewski J, Shoubridge EA, Rosenblatt DS. Inborn error of cobalamin metabolism associated with the intracellular accumulation of transcobalamin-bound cobalamin and mutations in *ZNF143*, which codes for a transcriptional activator. Human Mutation 37:976-982, 2016.

Waters PJ, Thuriot F, Clarke JTR, Gravel S, Watkins D, Rosenblatt DS, Lévesque S. Methylmalonyl-CoA epimerase deficiency: a new case, with an acute metabolic presentation and an intronic splicing mutation in the MCEE gene. Mol Genet Metab Rep 9:19-24, 2016

Pupavac M, Zawati M, Rosenblatt DS. A RaDiCAL gene hunt. Journal Taibah University Medical Sciences doi.org/10.1016/j.jtumed.2016.11.007, 2017

Kernohan KD, Dyment DA, Pupavac M, Cramer Z, McBride A, Bernard G, Straub I, Tetreault M, Hartley T, Huang L, Sell E, Majewski J, Rosenblatt DS, Shoubridge EA, Mhanni A, Myers T, Proud V, Vergano S, Spangler B, Farrow E, Kaussman J, Safina N, Care4Rare Consortium, Saunders C, Boycott KM, Thiffeault I. Matchmaking facilitates the diagnosis of an autosomal-recessive mitochondrial disease caused by biallelic mutation of the tRNA isopentenyltransferase (*TRIT1*) gene. Hum Mut 38:976-982, 2016

*2016 Publication also cited on 2015/2016 Report

CHAPTERS

Watkins D, Rosenblatt DS, Fowler B. Disorders of folate and cobalamin transport and metabolism. In: Inborn Metabolic Disease, 6th Edition. Saudubray JM, Baumgartner M, Walter J (eds) Springer, Berlin pp 385-399, 2016.

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 (In press)

Rosenblatt DS, Watkins D. Prenatal diagnosis of miscellaneous biochemical disorders. In: Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment, 7th edition. Milunsky A, Milunsky JM (eds) Wiley-Blackwell, pp 927-941, 2016.

Watkins D, Rosenblatt DS. Inherited defects in cobalamin metabolism. In: Vitamin B12: Advances and Insights. Obeid R (ed) Science Publishers (In press)

EDITORIALS AND COMMENTARIES

Rosenblatt DS, Watkins D, Rajabi F, Levy HL. Commentary on: Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. Nature Biothech 34:1103-1104, 2016 (Commentary).

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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

Unit 8

Department:	Human Genetics
Format:	Lectures
Role:	Lecturer-1 sessions
Titles:	***Introduction to Medical Genetics***
	Level: Medical Students
Time:	1 hour Lecture

PIAT-Medical Students-Genomics-2 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:

Our laboratory has served as hosts for 3 high school students for the Canadian Gene Researchers for a Week program.

FINANCIAL REPORT – 2016/2017

Starting Balance		**$ 131, 222**
*Salary Support and Benefits	$ 99, 326	
Conferences, Travel, Special Events	$ 4, 506	
Phones, Pagers, Computer, Printing, Couriers	$ 1, 200	
Materials and Supplies	$ 260	
Total Expenses		**$ 105.292**
**Balance		**$ 25, 930**

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

***Capitalized*