ANNUAL REPORT
2019/2020

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
Gawa Bidla
Brian Gilfix (Medical Biochemistry)
David S. Rosenblatt
David Watkins

CLINICAL SUPPORT STAFF
Maria Galvez
Leah Ladores
Keo Phommarinh
Sina Yak

RESEARCH SUPPORT STAFF
GRADUATE STUDENTS
Lina Sobhy Abdrabo

UNDERGRADUATE AND SUMMER STUDENTS
Marilou Charron (Co-supervise with Yann Joly)
Shira Perton (Observer from New York)
Krithika Ragupathi (Co-supervised with Jean-Baptiste Riviere)
Mark Sorin

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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 Research Institute of the McGill University Health Centre (MUHC). 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.

Ongoing projects in the laboratory:

Using genome and RNA sequencing in patients with undiagnosed inborn errors of vitamin B_{12} metabolism following somatic cell studies

Assay of MTHFD1 specific activity is patients with variants in the *MTHFD1* gene

The hunt for causal mutations in patients with known inborn errors of cobalamin metabolism in whom both causal mutations have not been found.

In addition, ongoing collaborations continue with groups at the NIH (Charles Venditti) and at Baylor College of Medicine (Ross Poché) on mouse and zebra fish models of inborn errors of cobalamin metabolism. Our laboratory provides specialized assays for vitamin B_{12} function in cell lines derived from mice with defects in the pathway.

Other ongoing projects (Brian Gilfix) include the development of high resolution melting for targeted mutation testing in alpha-1-antitypsin deficiency. In addition, Dr. Gilfix is collaborating with Dr. Paul Goodyer to develop an *in vitro* model to study the effects of aminoglycoside antibiotics on certain classes of detrimental mutations in genes associated inborn errors of vitamin B_{12} metabolism. This is with the view to develop possible treatments for a number of inborn errors.

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. Funding Extension until 2021.

NIH, Co-Investigator-2019-2024: Ronin (Thap11) in Neural Crest Development. PI is Ross Poché, Baylor College of Medicine

ORIGINAL PUBLICATIONS

1. Wehbe Z, Behringer S, Altabi KI, Watkins D, Rosenblatt DS, Spierkerkoetter U, Tucci S. The emerging role of the mitochondrial fatty acid synthase (mtFSII) in the regulation of energy metabolism. Biochim Biophys Acta Mol Cell Biol Lipids 1864:1629-1643, 2019
2. Abdrabo LS, Watkins D, Wang SR, Lafond-Lapalme J, Riviere JB, Rosenblatt DS. Genome and RNA sequencing in patients with methylmalonic aciduria of unknown cause. Genet Med 22:432-436, 2020
3. Watkins D, Venditti CP, Rosenblatt DS. Vitamins: cobalamin and folate. In Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 6th Edition (Rosenberg RN, Pascual JM, eds) (in press) 2020.
4. Watkins D, Riosenblatt DS. Immunodeficiency and inborn disorders of vitamin B_{12} and folate. Current Opin Clin Nutr Metab Care 23:241-246, 2020
5. Rashka C, Hergalant S, Oussalah A, Camadro JM, Motorine Y, Hassan Z, Baumgartner MR, Rosenblatt DS, Feillet F, Guéant JL, Coelho D. Transcriptomic analysis of fibroblasts from patients with cblC and cblG inherited defects of cobalamin metabolism reveals global dysregulation of alternative splicing. Hum Mol Genet doi:10.1093/hmg/ddaa027 2020
6. Bidla G, Watkins D, Chéry C, Froese DS, Ells C, Karachian M, Saskin A, Christensen KE, Gilfix BM, Guéant JL, Rosenblatt DS. Biochemical analysis of patients with mutations in *MTHFD1* and a diagnosis of methylenetetrahydrofolate dehydrogenase 1 deficiency. Mol Genet Metab 130:179-182, 2020
7. Yeganeh M, Basha T, Abdrabo LS, Wang SR, Rivière JB, Lejtenyi D, Rosenblatt DS, McCusker C, Alizadehfar R, Mazer BD. Primary antibody deficiency associated with ring chromosome 18. LymphoSign J 7:25-36, 2020
8. Gilfix BM. Congenital disorders of glycosylation and the challenge of rare diseases. Human Mutation 40:1010-2, 2019
9. Brasell EJ, Chu LL, Akpa MM, Esker-Oren I, Alroy I, Corsini R, Gilfix BM, Yamanaka Y, Hueryas P, Goodyer P. The novel aminoglycoside, ELX-02, permits $CTNS^{W138X}$ translational read-through and restores lysosomal cystine efflux in cystinosis. PLoS One 14(12):e0223954, 2019
10. Chen T, Gilfix B, Rivera JA, Sadeghi N, Richardson K, Hier MP, Forest VI, Fishman D, Caglar D, Pusztaszeri M, Mitmaker EJ, Payne RJ. The Role of the ThyroSeq

v3 Molecular Test in the Surgical Management of Thyroid Nodules in the Canadian Public Healthcare Setting. Thyroid doi: 10.1089/thy.2019.0539, 2020

11. Mattman A, Gilfix BM, Chen SX, DeMarco ML, Kyle BD, Parker ML, Agbor TA, Jung B, Selvarajah S, Barakauskas E, Vaags AK, Estey MP, Nelson TN, Speevak MD. Alphai-1-1antitrypsin: molecular testing in Canada: A seven year, multi-centre comparison. Clin Biochem (submitted) 2020

GRADUATE STUDENT SUPERVISED

Lina Sobhy Abdrabo M.Sc. 2016-2019

Title: Next generation sequencing to discover genes underlying methylmalonic aciduria

FINANCIAL REPORT – 2019/2020

Starting Balance		**$ 123, 595**
*Salary Support and Benefits	$ 68,545	
Conferences, Travel, Special Events	$ 6,868	
Phones, Computers, Printing, Couriers	$ 472	
Total Expenses		**$ 78,885**
**Balance		**$ 44,410**

Research Associate: David Watkins (adjusted to include retro salary/benefits expense of $9117 (For FY20) transferred to 252879 June 1, 2020)