ANNUAL REPORT
2013/2014

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

Submitted by: Dr. David S. Rosenblatt

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MEMBERSHIP

PHYSICIANS AND SCIENTISTS
David S. Rosenblatt
David Watkins

ADMINISTRATION
Tracy Wang
Danielle Veyre

CLINICAL SUPPORT STAFF
Maria Galvez
Leah Ladores

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

GRADUATE STUDENTS
Alison Brebner
Justin Deme (with James Coulton)
Mihaela Pupavac

UNDERGRADUATE AND SUMMER STUDENTS
Francis Petrella
Tracy Wang (with Dr. Chantal Seguin)

ANNUAL REPORT 2013/2014

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. 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.

2013-2014 has seen a number of 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 the University of Colorado, the NIH and the University of Zurich, we described mutations in the **HCFC1** gene that codes for a restriction factor. These mutations result in combined homocystinuria and methylmalonic aciduria, a phenocopy of the *cblC* inborn error. Of great importance, because the *HCFC1* gene is located on the X chromosome, the genetic counseling of this disorder differs from that of the other inborn errors of cobalamin metabolism.

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.

4) With Loydie Jerome-Majewska, we determined that the *Mmachc* gene is required for implantation in the mouse.

RESEARCH OPERATING FUNDS

CIHR Operating Grant, PI – 2009-2014

INVITED PRESENTATIONS

November 5, 2013
Genomics in Metabolism
Copenhagen, Denmark
Title: Using next generation sequencing to discover novel steps in one-carbon metabolism

December 13, 2013
Journee Francophones de Nutition
Bordeaux, France
Title: Les maladie hereditaires du metabolism de la vitamine B_{12}: contribution a la connaissance du metabolism cellulaire.

ORIGINAL PUBLICATIONS

Yu HC, Sloan JL, Scharer G, Brebner A, Quintana A, Achilly NP, Manoli I, Coughlin CR, Geiger EA, Schneck U, Watkins D, Van Hove JLK, Fowler B, Baumgartner MR, **Rosenblatt DS,** Venditti CP and Shaikh TH. An X-linked cobalamin disorder caused by mutations in the transcription coregulator HCFC1. Am J Hum Genet 93:506-514, 2013

Moreno-Garcia MA, **Rosenblatt DS**, Jerome-Majewska LA. Vitamin B_{12} metabolism in man and in embryonic mouse models. Nutrients 5:3531-3550, 2013

Rosenblatt DS. Book Review: Victor McKusick and the History of Medical Genetics. J Med Genet 50:640, 2013

Paul E, Guttenberg M, Kaplan P, Watkins D, **Rosenblatt DS**, Kaplan BS. Atypical glomerulopathy associated with the cblE inborn error of vitamin B_{12} metabolism. Pediatr. Nephrol. 28:1135-1139, 2013

Armour C, Brebner A, Watkins D, Geraghty MT, Chan A**, Rosenblatt DS**. A patient with an inborn error of vitamin B12 metabolism (cblF) detected by newborn screening. Pediatrics 132:e257-e261, 2013

Fofou-Caillierez MB, Mrabet N, Chéry C, Dreumont N, Flayac J, Pupavac M, Paoli J, Alberto JM, Coelho D, Camadro JM, Feillet F, Watkins D, Fowler B, **Rosenblatt DS**, Guéant JL. Interaction between methionine synthase isoforms and MMACHC: characterization of cblG-variant, cblG and cblC inherited causes of megaloblastic anemia. Hum Mol Genet 22:4591-4601, 2013

Zawati MH, Parry D, Thorogood A, Nguyen MT, Boycott,KM, **Rosenblatt D**, Knoppers BM. Reporting results from whole-genome and exome sequencing in clinical practice: a proposal for Canada? J Med Genetics 51:68-70, 2014.

Trakadis YJ, Alfares A, Bodamer O, Boyukavci M, Christodoulou J, Connor P, Glamuzina E, Gonzalez-Fernandez F, Haim B, Echenne B, Manoli I, Mitchell J, Nordvall M, Prasad C, Scaglio F, Schiff M, Schrewe B, Touati G, Tchan MC, Varet B, Venditti C, Zafeiriou D, Rupar T, **Rosenblatt DS**, Watkins D, Braverman N. Update on transcobalamin deficiency: clinical presentation, treatment and outcome. J Inher Metab Dis 37:461-473, 2014

Battat R, Kopylov U, Szilagyi A, Saxena A, **Rosenblatt DS**, Warner M, Bessissaw T, Seidman E, Bitton A. Vitamin B12 deficiency in inflammatory bowel disease: the prevalence, risk factors, evaluation and management. Inflammatory Bowel Diseases 20:1120-1128, 2014

Moreno-Garcia MA, Pupavac M, **Rosenblatt DS**, Tramblay ML, Jerome-Majewska LA. The Mmachc gene is required for pre-implantation in the mouse. Mol Genet Metab 112:198-204, 2014

Lossos A, Teltsh O, Milman T, Meiner V, Rozen R, Leclerc D, **Rosenblatt DS**, Watkins D, Shaag A, Korman S, Heyman,SN, Gal A, Newman JP, Steiner-Birmanns B, Abramsky O, Kohn Y. Severe MTHFR deficiency: clinical clues to a potentially treatable cause of adult-onset spastic paraplegia. JAMA Neurology 71:901-904, 2014

D'Aco KE, Bearden D, Watkins D, Hyland K, **Rosenblatt DS**, Ficicioglu C. Severe methylenetetrahydrofolate reductase deficiency and 2 novel MTHFR variants in an adolescent with progressive myoclonic epilepsy. Pediatr Neurol 51:266-277, 2014.

Fischer S, Huemer M, Deodato F, Ballhausen D, Baumgartner M, Boneh A, Burlina AB, Cerone R,

Garcia P, Gökçay G, Gruenert SC, Grünewald S, Häberle J, Jaeken J, Ketteridge D, Lindner M, Mandel H, Martinelli D, Martins EG, Schwab KO, Schwahn BC, Sztriha L, Tomaske M, Trefz F, Vilarinho L, Rosenblatt DS, Fowler B, Dionisi-Vici C. Clinical presentation in a series of 88 patients with the cblC defect. J Inher Metab Dis doi:10.1007/s10545-014-9687-6, 2014

ABSTRACTS

Brebner A., Watkins D., Yu H-C., Sloan J.L., Quintana A., Achilly N.P., Geiger E.A., Venditti C.P., Shaikh T.H., Rosenblatt D.S. Mutations in the Transcription Factor *HCFC1* in Patients with the *cblX* Inborn Error of Vitamin B_{12} Metabolism.Garood Symposium 2013, Sherbrooke, Qc, May 31st –June 1st 2013.

Brebner A., Watkins D., Rosenblatt D.S. Novel Mutations in Patient with the *cblC* Inborn Error of Cobalamin Metabolism. International Congress of Inborn Errors of Metabolism, Barcelona, Spain, September 3rd-7th 2013.

Pupavac M, Wuh-Liang P, Chien YH, Rosenblatt DS, Lee NC. "Next Generation Sequencing to Discover Genes for Mendelian Disorders". Summer Institute in Taiwan Symposium. Hsinchu City, Taiwan. August 2013. Poster Presentation.

Pupavac M., Zawati M.H., Nguyen M.T., Joly Y., Majewski J., Rosenblatt D.S. Rare Disease Collaboration for Autosomal Loci (**RaDiCAL**). International Congress of Inborn Errors of Metabolism, Barcelona, Spain, September 3rd-7th 2013.

De Luen C, Knoll D, Bettany B, de Hora M, Rosenblatt D.S., Wilson C., Glamuzina E. Transcobalamin Deficiency: Diagnosis and Expanded Newborn Screening. International Congress of Inborn Errors of Metabolism, Barcelona, Spain, September 3rd-7th 2013.

Sloan J.L., Yu H-C., Scharer G., Brebner A., Quintana A., Achilly N.P., Manoli I., Coughlin II C.R., Geiger E.A., Schneck U., Watkins D., VanHove J.L., Fowler B., Baumgartner M.R., Rosenblatt D.S., Venditti C.P., Shaikh T.H. Mutations in a transcription regulator cause a novel X-linked cobalamin disorder (*cblX*) with a severe neurological phenotype. International Congress of Inborn Errors of Metabolism, Barcelona, Spain, September 3rd-7th 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: Lectures
Role: Lecturer-2 sessions
Titles: ***Introduction to Medical Genetics***
Huntington Disease
Level: Medical Students
Time: 2 lectures -1 hour each

FINANCIAL REPORT – 2013/14

Starting Balance		**$ 94,625**
*Salary Support and Benefits	$ 50,558	
Materials and Supplies	$ 4,287	
Conferences, Travel, Special Events	$ 17,100	
Memberships	$ 2,281	
Phones, Pagers, Computer, Printing, Couriers	$ 1,619	
Miscellaneous	$ 597	
Total Expenses		**$ 76,442**
**Balance		**$ 18,183**

** Michaud, Notte, Rosenblatt, Veyre, Wang*