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MUHC and McGill scientists identify gene for debilitating vitamin B₁₂ disease

Montreal, 30 November 2005—Scientists at the MUHC and McGill University have identified a gene responsible for a disease that impairs the body's ability to handle vitamin B₁₂ and that may contribute to heart disease, stroke and dementia. The details of the CIHR and March of Dimes funded research are published in this week's issue of *Nature Genetics*. The research, which began more than 20 years ago, will allow doctors to perform earlier diagnosis, assess 'carriers' of the disease—Combined Methylmalonic aciduria (MMA) and Homocystinuria—and open the door to new and improved treatments for this debilitating disease.

"Although this disease sometimes starts in adolescence or adulthood, we usually diagnose this rare inability to process vitamin B₁₂ in the first few months of life," says Dr. David Rosenblatt, Chairman of Human Genetics at McGill, Director of Medical Genetics in Medicine at the MUHC, Chief of Medical Genetics at the Jewish General Hospital and lead researcher of the new study. "Babies may have breathing, feeding, visual and developmental difficulties, older patients may develop sudden neurological disease."

Vitamin B₁₂, which is found in all animal products—including dairy, eggs, meat, poultry, and fish—but not in plants, is vital for synthesis of red blood cells and maintenance of the nervous system. Vitamin B₁₂ also helps control homocysteine levels in the human body. Homocysteine control is important because in excess this compound can increase the risk of heart disease, stroke, and dementia.

17 year-old Michael—a typical MMA and Homocystinuria patient—was diagnosed at 6-months of age, and has battled numerous medical challenges as a result of his condition. Michael is developmentally delayed, visually impaired and does not talk; he has suffered seizures since he was three years old, had a stroke by the age of seven and has since developed rheumatoid arthritis and scoliosis. Michael's diagnosis, which led the way to treatment involving injections of vitamin B₁₂, was conducted at Dr. Rosenblatt's laboratory at the MUHC—one of only two centres in the world that perform these tests.

After more than 20-years of data collection, Dr. Rosenblatt, his student Jordan Lerner-Ellis and their team have now unlocked some of the secrets of this rare but debilitating condition. "Using over 200 patient samples, representing the majority of the world's 350 known cases, we have identified the responsible gene, called MMACHC," says Dr. Rosenblatt. "In collaboration with the laboratory of Dr. James Coulton, Department of Microbiology and Immunology at McGill, we used computer modelling to demonstrate the similarity between the protein encoded by the MMACHC

gene and a protein involved in bacterial vitamin B₁₂ metabolism.” This new link between bacterial and mammalian species may help us better understand how humans use vitamin B₁₂. Ultimately these discoveries have enabled us to develop early diagnosis and carrier assessment tests for the disease—something that was not previously possible.

“This discovery offers earlier diagnosis and treatment options for genetic diseases such as Methylmalonic aciduria and Homocystinuria. This represents a step toward improving the lives of those afflicted with such rare and devastating genetic diseases,” says Dr. Roderick McInnes, Scientific Director of CIHR’s Institute of Genetics. This breakthrough represents hope for Michael and his family, and many others that have been touched by this disease. “Michael is a very loving and caring child, who has had to overcome many challenges,” says his mother Karen. “We are overjoyed that this research may one day give courageous children like Michael a fighting chance at a better quality of life.”

About medical genetics:

Alterations in our genes are responsible for thousands of hereditary diseases and influence the development of thousands more. Once the genes involved in a particular disease are discovered, scientists become better able to precisely diagnose disease, predict its course, and create more effective treatments with fewer side effects. Medical genetics can even be used to assess patients’ risk of developing certain diseases, allowing them to take preventive medicines and make lifestyle changes, like diet and environment, which may help prevent or delay their development.

Medical genetics research is advancing at an incredible rate. This year alone, MUHC scientists have identified genes contributing to breast cancer, colon cancer, lung cancer, tuberculosis, migraines, cytomegalovirus (associated with herpes, chicken pox and mononucleosis) and rare but devastating diseases such as retinitis pigmentosa. The current work on Methylmalonic aciduria and Homocystinuria was a product of the CIHR group in Medical Genetics, comprised of scientists at the MUHC, McGill University, the University of Calgary and collaborators at the Hospital for Sick Children in Toronto.

The McGill University Health Centre (MUHC) is a comprehensive academic health institution with an international reputation for excellence in clinical programs, research and teaching. The MUHC is a merger of five teaching hospitals affiliated with the Faculty of Medicine at McGill University—the Montreal Children’s, Montreal General, Royal Victoria, and Montreal Neurological Hospitals, as well as the Montreal Chest Institute. Building on the tradition of medical leadership of the founding hospitals, the goal of the MUHC is to provide patient care based on the most advanced knowledge in the health care field, and to contribute to the development of new knowledge. www.muhc.ca

McGill University is Canada's leading research-intensive university and has earned an international reputation for scholarly achievement and scientific discovery. Founded in 1821, McGill has 21 faculties and professional schools, which offer more than 300 programs from the undergraduate to the doctoral level. McGill attracts renowned professors and researchers from around the world and top students from more than 150 countries, creating one of the most dynamic and diverse education environments in North America. There are approximately 23,000 undergraduate students and 7,000 graduate students. It is one of two Canadian members of the American Association of Universities. McGill's two campuses are located in Montreal, Canada. www.mcgill.ca

The March of Dimes is a national voluntary health agency whose mission is to improve the health of babies by preventing birth defects, premature birth and infant mortality. Founded in 1938, the March of Dimes funds programs of research, community services, education, and advocacy to save babies and in 2003 launched a campaign to reduce the rate of premature birth. For more information, visit the March of Dimes Web site at www.marchofdimes.com.

The Canadian Institutes of Health Research (CIHR) is the Government of Canada's agency for health research. CIHR's mission is to create new scientific knowledge and to catalyze its translation into improved health, more effective health services and products, and a strengthened Canadian health care system. Composed of 13 Institutes, CIHR provides leadership and support to close to 10,000 health researchers and trainees across Canada. www.cihr-irsc.gc.ca

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