NEWS RELEASE

Cholesterol levels in the pancreatic beta cells discovered to play a key role in insulin secretion and development of diabetes

(Vancouver – February 18, 2007) – Scientists at the Child & Family Research Institute and the University of British Columbia have discovered that high levels of cholesterol in the pancreatic beta cells damage the body's ability to secrete insulin and this may contribute to the development of type 2 diabetes.

The scientists found that a gene called ABCA1 is key to regulating cholesterol levels in the pancreatic beta cells, which produce and secrete insulin and are impaired in type 2 diabetes. The gene transports cholesterol out of the cell and it also plays a key role in making HDL cholesterol – the good kind – in the blood. When ABCA1 is defective, as shown in a mouse model, the body is unable to regulate cholesterol in the beta cells and therefore cannot properly secrete insulin.

The paper is published Sunday, February 18, 2007 in an advance online edition of the international scientific journal *Nature Medicine.* It will be published in the journal's print edition on March 1, 2007.

"These are the first data directly implicating cholesterol levels in the pancreatic beta cell as having a role in insulin secretion," says Dr. Michael Hayden, the study's co-principal investigator. He is director of the Centre for Molecular Medicine and Therapeutics, which is part of the Child & Family Research Institute (CFRI) and a University of British Columbia (UBC) research centre. Dr. Hayden is University Killam Professor in the UBC department of medical genetics.

"This points to ABCA1 in the beta cell as a new target for treating diabetes," says Dr. Hayden.

"No one has thought about cholesterol in the beta cell before," says Dr. Bruce Verchere, the study's co-principal investigator and head of the Diabetes Research Program at the Child & Family Research Institute. He is an associate professor in the department of pathology and laboratory medicine at the University of British Columbia.

"There's been a smoking gun out there that glucose and lipids contribute to the demise of the beta cells over time," says Dr. Verchere. "We're showing that cholesterol is an important part of the equation and that it has to be very tightly regulated."

The scientists studied special "knock-out" mice that lacked the ABCA1 gene in the beta cell. Compared to normal mice, the ABCA1-deficient mice showed increased cholesterol levels in the pancreatic beta cells and impaired ability to metabolize glucose. The mice also had reduced insulin secretion, which is a hallmark of type 2 diabetes. Studying the disease in mice is a model for understanding the disease in humans.

These data also help explain the mechanism of action for a drug called rosiglitazone. It is commonly prescribed for people with type 2 diabetes as it helps their bodies use insulin. The scientists found that this drug works in part by acting directly on the beta cells to increase the activity of ABCA1 and therefore regulate cholesterol levels inside the beta cells. However, if ABCA1 is absent from the beta cell, then the drug is less able to lower blood glucose levels.

Type 2 diabetes is a chronic, progressive disease in which the pancreas is unable to produce sufficient amounts of insulin and the body becomes unable to use insulin effectively. Eventually, type 2 diabetics

become dependent on daily injections of insulin. Insulin is a hormone required for metabolizing glucose from food. According to the Canadian Diabetes Association, more than two million Canadians are estimated to have type 2 diabetes.

“We now know that maintaining normal cholesterol levels in the pancreas, and particularly in the beta cells, is very important in preventing type 2 diabetes,” says Dr. Verchere. “It’s important to keep an eye on your cholesterol levels – not just for your heart health but quite possibly for your pancreas as well.”

The two scientists are colleagues in the Child & Family Research Institute. Dr. Hayden is a human geneticist and specialist in genes involved in cholesterol metabolism. His lab cloned the ABCA1 gene in 1999 and determined its importance in regulating the amount of good cholesterol in the blood. Dr. Verchere is an expert in diabetes and pancreatic beta cells and the recipient of the 2006 Canadian Diabetes Association’s Young Scientist Award. Drs. Hayden and Verchere began exploring the hypothesis of cholesterol’s role in diabetes when they joined the thesis advisory committee for Liam Brunham, the study’s first author. He is an MD/PhD student in Dr. Hayden’s lab and he is studying the role of ABCA1 in lipid metabolism.

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The Centre for Molecular Medicine and Therapeutics (CMMT) at BC Children’s Hospital is a research center supported collaboratively by the University of British Columbia, the Child & Family Research Institute, and the Government of British Columbia. Built on a 10-year history of research excellence, the CMMT is dedicated to advancing the fundamental understanding of the molecular function and structure of genes as the key to improved diagnosis, treatment, and prevention of health problems in children and adults. For more information, visit www.cmmt.ubc.ca.

The Child & Family Research Institute is dedicated to world-class research at the Children’s and Women Health Campus. It is the largest research institute of its kind in Western Canada and is supported by the BC Children’s Hospital Foundation. Research is conducted in the areas of community child heath, diabetes, applied health research and evaluation, infectious and inflammatory diseases, molecular medicine and therapeutics, oncology, reproductive health, nutrition, genetics, immunology, informatics, neurobiology and mental health. Incorporated in 1995, the Institute works in close partnership with the University of British Columbia, BC Children’s Hospital and Sunny Hill Health Center for Children, BC Women’s Hospital & Health Centre, which are agencies of the Provincial Health Services Authority. For more information, visit www.cfri.ca.

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For more information or to arrange an interview, please contact:
Jennifer Kohm, Communications Director, Child & Family Research Institute
telephone: (604) 875-2401 email: jkohm@cw.bc.ca