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In Pilot Study, a Peptide Controls Blood Sugar in People with Congenital Hyperinsulinism

--Children's Hospital of Philadelphia Researchers Develop First Potential Medicine for Patients with Most Severe Form of this Disease--

Philadelphia, Aug.1, 2012 –A pilot study in adolescents and adults has found that an investigational drug shows promise as the first potential medical treatment for children with the severest type of congenital hyperinsulinism, a rare but potentially devastating disease in which gene mutations cause insulin levels to become dangerously high.

"There is currently no effective medicine for children with the most common and most severe form of hyperinsulinism," said study leader Diva D. De Leon, M.D., a pediatric endocrinologist at The Children's Hospital of Philadelphia. "Our new research shows that this investigational drug, a peptide called exendin-(9-39), controls blood sugar levels in people, a very promising result."

The study appeared today online ahead of print in the journal *Diabetes*.

In congenital hyperinsulinism (HI), mutations disrupt the insulin-secreting beta cells in the pancreas. Uncontrolled, excessive insulin levels thus sharply reduce blood glucose levels, a condition called hypoglycemia. If untreated, hypoglycemia may cause irreversible brain damage or death in children. Congenital HI occurs in an estimated one in 50,000 U.S. children, with a higher incidence among Ashkenazic Jews and certain other groups.

The standard treatment for some forms of congenital HI is diazoxide, a drug that controls insulin secretion by opening potassium channels in beta cells. However, this drug does not work in the most common types of HI, in which mutations prevent these potassium channels from forming.

When abnormal beta cells occur only in a discrete portion of the pancreas, precise surgery on the tiny organ can remove the lesion and cure HI. The Congenital Hyperinsulinism Center at The Children's Hospital of Philadelphia is a world leader in diagnosing such lesions and performing the curative surgery on newborns.

However, in roughly half of congenital HI cases, abnormal cells are diffused through the pancreas, and surgeons must remove nearly the entire pancreas. This leaves the majority of patients at high risk of developing diabetes.

The current study, which builds on previous research by De Leon and colleagues in animals, uses exendin-(9-39), which blocks the action of a hormone receptor, glucagon-like peptide-1 (GLP-1), in beta cells. The GLP-1 receptor is currently the target of drugs that treat diabetes, using the opposite effect from that investigated in this HI study.

The current pilot study included nine subjects, aged 15 to 47 years old, who had hyperinsulinism caused by mutations in potassium channels. None were being treated for HI at the time of the study, but all were at risk of hypoglycemia during periods of fasting.

In all nine subjects, the drug controlled blood glucose levels during fasting. Exendin also controlled insulin secretion in cell studies of beta cells taken from newborns with HI. The current research did not focus on the biological mechanisms that occurred, but De Leon said the results are encouraging enough to progress to a clinical study in children with HI over the next year.

Financial support for this study came from the National Institutes of Health (grant 1R03DK07835), the Lester and Liesel Baker Foundation, and the Clifford and Katherine Goldsmith Foundation. De Leon's co-authors, all from Children's Hospital, were Charles A. Stanley, M.D., Andrew C. Calabria, M.D., Changhong Li, M.D., and Paul R. Gallagher In addition to their positions at Children's Hospital, De Leon, Stanley and Li also are in the Perelman School of Medicine at the University of Pennsylvania.

"The GLP-1 Receptor Antagonist Exendin-(9-39) Elevates Blood Fasting Glucose Levels in Congenital Hyperinsulinism due to Inactivating Mutations in the ATP-sensitive Potassium Channel," *Diabetes*, published online Aug.1, 2012, to appear in print, October 2012. doi: 10.2337/db12-0166.