THE HARTWELL FOUNDATION

2014 Individual Biomedical Research Award

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Turning Alpha Cells into Beta Cells to Cure Juvenile Diabetes

Juvenile diabetes is the result of an autoimmune response that inappropriately targets the insulin-producing beta cells of the pancreas, inevitably leading to the near-complete destruction of all beta cells. There are approximately 1 million children affected by juvenile diabetes in the United States and forty new children receive a diagnosis every day. With the development of stable, longer-acting forms of insulin and advances in medical device technology for its delivery, the disease is manageable, but there remains no cure. Life with juvenile diabetes requires around the clock vigilance by young patients and their parents. Only a special effort to match meals and physical activity with insulin injections will control high glucose levels and avoid long-term complications, which may include elevated risk of heart attack and stroke; circulation problems that cause blindness; kidney problems; and even lower limb amputations. The regulation of blood glucose levels occurs as the result of two hormones: insulin and glucagon. Insulin reduces blood glucose levels after a meal, while glucagon prevents dangerously low blood glucose levels that can occur when fasting or during physical activity. Glucagon instructs the liver to break down glycogen (the storage form of glucose) and release the resulting glucose into the blood. Achieving a balance between reduction of elevated glucose levels and the need to prevent potentially fatal low glucose levels is critical. At diagnosis, the underlying autoimmune attack has already destroyed most beta cells and any ability to produce insulin. The remaining alpha cells build up and release glucagon, which causes a serious side-effect of juvenile diabetes. The majority of scientific strategies focus on a means to prevent beta cell death and promote beta cell division. However, efforts to restore lost beta cell mass have been unsuccessful, largely because beta cells divide so slowly. Based upon Mark's seminal discovery in a mouse model that immature beta cells may arise from alpha cells through spontaneous trans-differentiation, he proposes to identify the biochemical signals that switch alpha cells into beta cells and determine whether such beta cells are adequately mature and functional. He will then go on to determine if the same process occurs in human pancreatic islets. His approach represents a shift in the current paradigm that after birth, beta cells arise exclusively through the division of existing beta cells. If successful, Mark will discern the factor(s) that transform(s) alpha cells into mature beta cells, harnessing the intrinsic potential for beta cell regeneration that exists within pancreatic islets. His approach has the added benefit of blocking a serious side-effect of juvenile diabetes by curbing the number of alpha cells, which will have the corollary benefit of reducing excess glucagon. If he is successful, restoring beta cells will represent a viable path to a cure for juvenile diabetes.