THE HARTWELL FOUNDATION

2008 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Louise C. Laurent, MD, Ph.D.**
Assistant Professor
Department of Reproductive Medicine

Institution: **University of California, San Diego**

Proposal: **Reprogramming of Fibroblasts Using MicroRNAs for Autologous Cell Replacement Therapy for Juvenile Diabetes**

As an effective alternative to existing therapies for Type-1 (juvenile) diabetes, Dr. Laurent proposes an unprecedented strategy for improving patient-specific (autologous) pancreatic islet cell replacement. In Type-1 diabetes, the immune system erroneously attacks and destroys the insulin-producing beta islet cells in the pancreas, but since the human body cannot regenerate islet cells, patients with Type-1 diabetes must find another source of insulin for life. While insulin injections and pumps have vastly improved the quality and length of life for patients, they do not fully reproduce the function of normal pancreatic islet cells, as many patients remain prone to dangerous swings in blood sugar and experience diabetes-induced disorders like blindness and neuropathy. Life-long insulin therapy is one of the leading causes of associated morbidity and mortality in Type-1 diabetes, and besides cost, creates many difficult challenges for young pediatric patients. Effective cell replacement therapy using transplanted islet cells from cadavers has shown promising results, but the source is too limited to treat more than a tiny fraction of affected patients. Worse, because cadaver cells can never be a perfect match with the affected patient, recipients of the cells must undergo debilitating life-long immunosuppression to prevent rejection of the transplant, which is a particular disadvantage to affected children. Exciting new stem cell-based therapies are the subject of current investigation, but create additional concerns, including their observed propensity to generate tumors. By contrast, Dr. Laurent proposes to innovatively collect skin fibroblast cells from an affected patient, manipulate microRNA levels to reprogram the cells into insulin-producing pancreatic islet cells, and then transplant the self-same (autologous) cells back into the patient. The use of preformed synthetic microRNA rather than viral vectors carrying genes coding for microRNA is a transformative innovation, which if successful, would create a safe and effective way to correct Type-1 diabetes and overcome the problems associated with current therapeutic approaches.