Optimization of GLP-1 Coated Micelle Formulation for Pancreatic Beta-cell-selective Induction of Autophagy

Anish P. Patel[1,2], Alissa N. Novak[3], Tanmaye N. Chakravarthula[4], Nathan J. Alves[4], and Amelia K. Linnemann[2,3]

[1]Indiana University School of Medicine; [2]Indiana Center for Diabetes and Metabolic Diseases, Indianapolis, IN; Departments of [3]Pediatrics and [4]Emergency Medicine, Indiana University School of Medicine

Background and Hypothesis: Type 1 Diabetes (T1D) is a progressive disease in which the insulin-producing beta-cells of the pancreas are damaged by autoimmune attack, often associated with accumulation of reactive oxygen species (ROS) in the early pathogenesis of disease. Autophagy is an endogenous response to protect against ROS-induced damage and promote beta-cell survival. Previous research has demonstrated that beta-cell autophagy is impaired in T1D, making autophagy a potential therapeutic target. We hypothesize that rapamycin, an mTOR inhibitor that stimulates autophagy, can be selectively delivered to and internalized by islet beta-cells through the encapsulation of drug in GLP-1 coated polymeric micelles.

Project Methods: We first validated and optimized the formulation of the GLP-1 coated micelles by evaluating key steps in the process: initial solvent removal and dissolution of GLP-1-conjugated lipid components. The solvent removal step involved assessment of evaporation and lyophilization, and the dissolution step involved determining solubility of conjugated lipid in methanol, chloroform, and a mixture of the two solvents.

Results: We utilized high-performance liquid chromatography to validate solubility in a 70:30 mixture of methanol and chloroform, and we have determined that yield of conjugated lipid in the final micelle solution can be increased from 4% to 80% by using lyophilization as the solvent removal technique in place of evaporation.

Potential Impact: The next step in this project will be to treat beta-cells with GLP-1 coated micelles containing rapamycin *in vitro* and to evaluate uptake and action of rapamycin within the beta-cell. The overall aim of this project is to establish the use of a targeted nanoparticle drug system in the preclinical setting with the goal of future T1D treatment application.