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Kathryn Kosiorek
Longwood University

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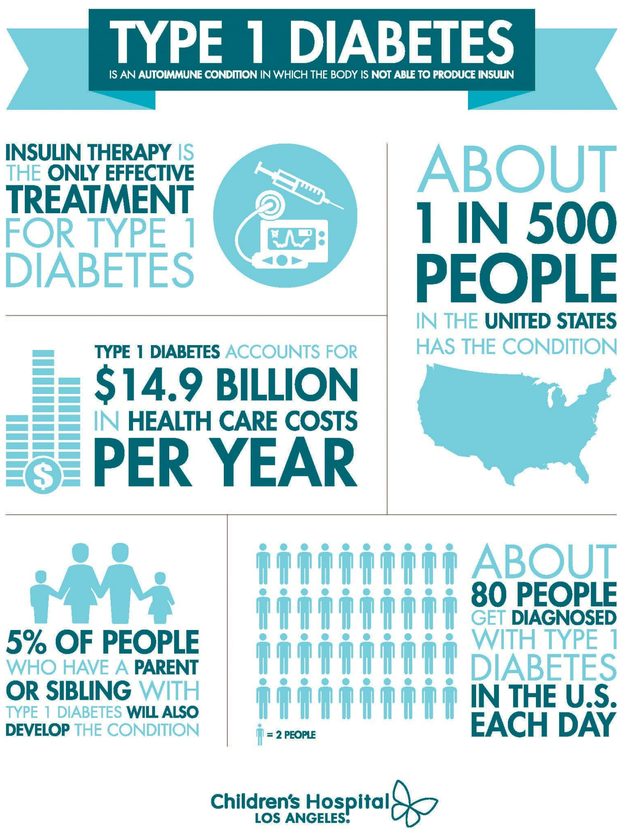
Double Gene Knockout of *PDX-1* and *HNF1β* Leads to Possible Novel Gene Therapy for Type 1 Diabetes

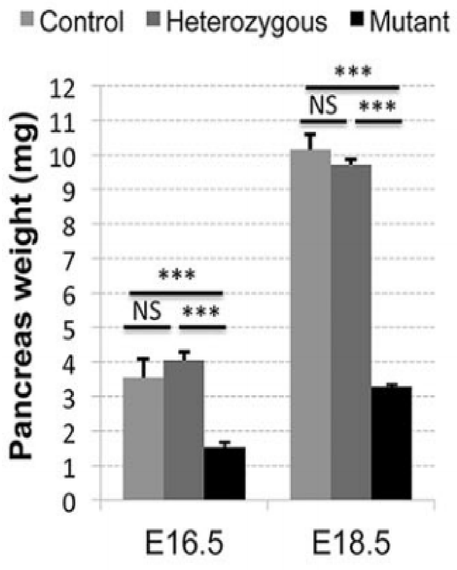
Kathryn Kosiorek
Department of Biological and Environmental Sciences

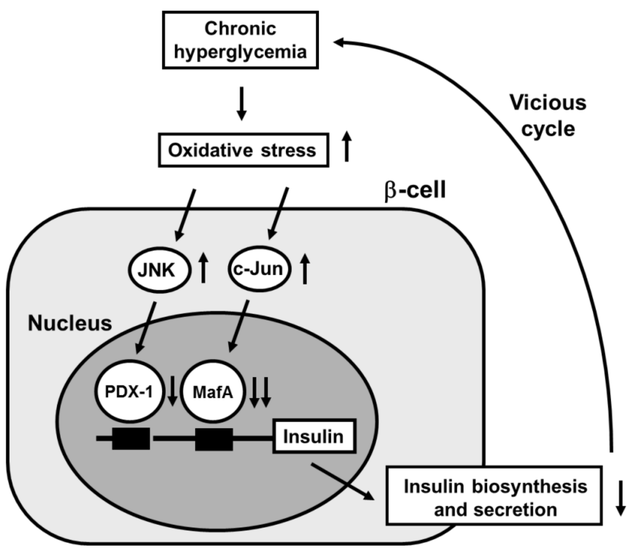
Background



◀ **Figure 1.** Occurrence of Type I Diabetes in the United States.

▼ **Figure 2.** Deletion of *HNF1*β gene causes severe pancreatic hypoplasia and decrease in pancreatic weight.[4]





◀ **Figure 3.** Signal transduction pathway leading to the activation of *PDX-1* causing insulin secretion.[2]

- Diabetes Mellitus is characterized by uncontrolled and elevated blood glucose which is the effect of inadequate levels of plasma insulin.[1]
- Type I Diabetes ultimately stems from the autoimmune destruction of beta cells due to malfunction or lack of the *PDX-1* gene.[4]
- The *PDX-1* gene is necessary for pancreatic development including the maintenance and survival of β-cells which produce and secrete insulin.[2]
- The HNF1β gene is partially responsible for pancreatic development and lack of this gene can cause pancreatic hypoplasia.[5]

Specific Aim

The specific aim of this study is to determine the relationship between *PDX-1* and *HNF1B*. Comparing these genes to each other and finding potential interactions may reveal essential components in recovering beta-cell function in those with Type I Diabetes.

Potential Pitfalls

- gRNA would not insert properly into the CRISPR-concatemer vector and therefore the gene knockout process would not be successful
- Transfection of the pancreatic islets by means of electroporation would not be successful
- Failure to quantify glucose responsiveness

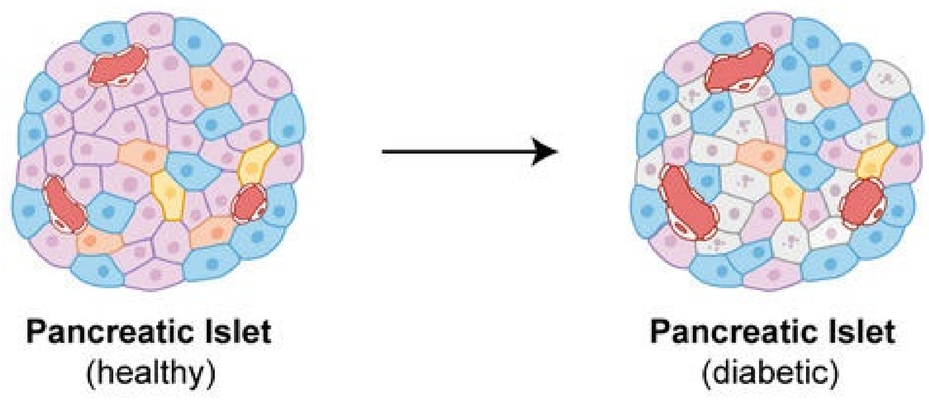


Figure 4. In comparison with a healthy pancreatic islet, a diabetic islet shows a depletion of beta-cells (violet) and therefore a loss of insulin secretion and ability to maintain target glucose levels.[3]

Potential Conclusions

- After performing this double gene knockout, it is expected to see a significant decrease in beta-cell function and a low amount of quantified glucose responsiveness.
- If the study provides the expected results, a therapy derived from this study would open up lots of new doors for precision medicine and overall improve the quality of life of individuals with Type I Diabetes.

Methodology

Split transgenic mice into 4 groups: control, single *PDX-1* knockout, single *HNF1B* knockout, and double knockout

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Perform single and double gene knockouts of *PDX-1* and *PDX-1/HNF1B* using a CRISPR-concatemer

→

Beta cell performance testing by quantifying the glucose responsiveness

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