Verification of β-cell Specific Tamoxifen-Induced *Dec1* Knockout in Mice

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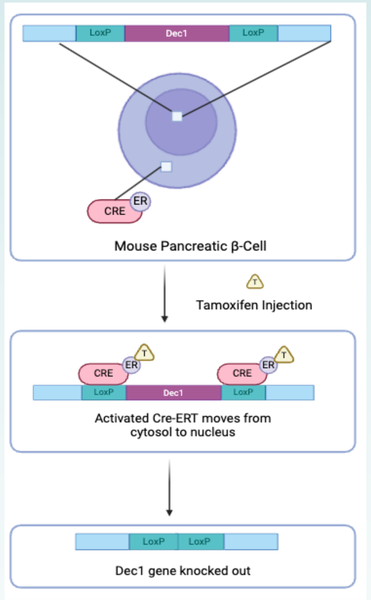
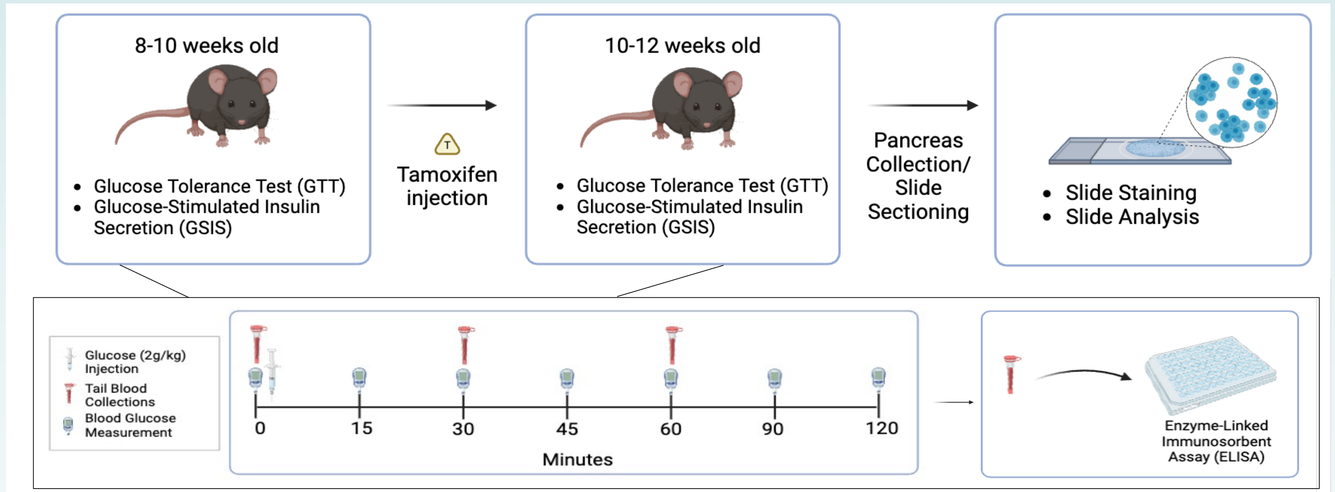
Background

- 38.4 million people of all ages—or 11.6% of the U.S. population—has diabetes (Center for Disease Control 2021).
- Many metabolic pathways, including Glucose Metabolism, are tied to the Core Circadian Clock mechanism.
- Disruptions of circadian rhythm oscillations in glucose metabolism are involved in the pathogenesis of Type 2 Diabetes.
- Dec1, a transcriptional repressor found in mature β-cells, inactivates Core Clock genes, such as CLOCK-BMAL1, that control rhythmic gene expression in many metabolic pathways.
- Previous experiments show Dec1 Whole-Body Knockout (KO) mice have hypo-insulinemic diabetes, and their islets exhibit an immature phenotype.
- Tamoxifen-induced mouse strains allow for precise timing of gene knockout in specific tissue.
- In this experiment, *Dec1* was knocked out at 8-10 weeks in Mouse Insulin Promoter (MIP)-CreERT Dec1 fl Mouse β-cells.



Methodology



- Mouse Insulin Promoter (MIP)-CreERT Dec1 fl Male Mice [6 Cre (+) fl/fl, 1 Cre (-) fl/+].
- Tamoxifen Injection (200 ug/g) every other day for 5 days.
- Mouse Ultrasensitive ELISA to determine insulin secretion.

Objectives

To determine the effect of Dec1 in insulin secretion and blood glucose responsiveness of adult mice by:

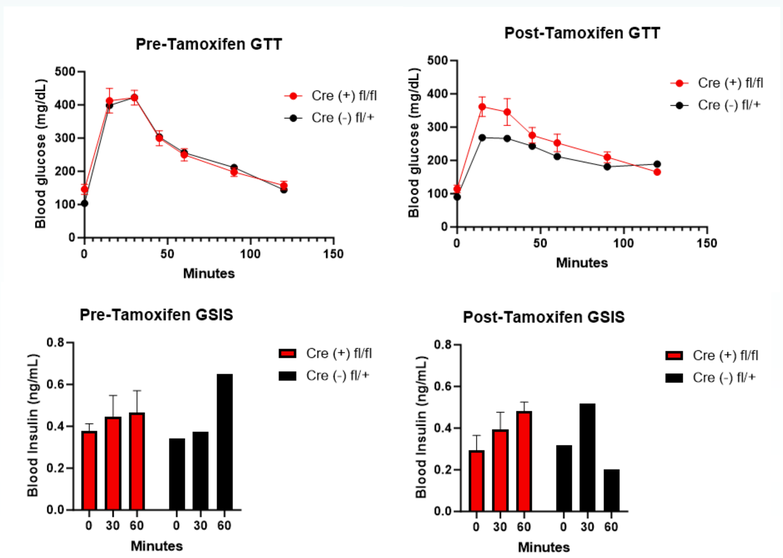
- Glucose Stimulated Insulin Secretion (GSIS)
- Glucose Tolerance Test (GTT)
- Troubleshoot Tamoxifen administration
- Verification of removal of Dec 1 protein in pancreatic β-cells slides

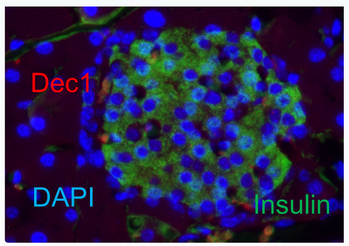
Hypothesis

β-cell knock-out of Dec1 in adult mice will result in a diabetic phenotype, meaning:

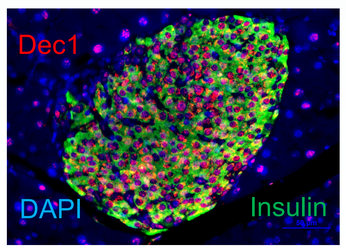
- Cre (+) fl/fl mice will have lower rate of glucose clearance, shown in GTT.
- Cre (+) fl/fl mice will have a lower rate of insulin secretion, analogous to Dec1 KO hypo-insulinemic diabetes, shown in GSIS.

Results





Tamoxifen Injected Cre (+) fl/fl Islet



Untreated Wild-Type Islet

Conclusion

- All Tamoxifen-injected mice have less relative Dec1 protein, compared to untreated Wild-Type mouse islets. However, there is no difference between Cre (+) and Cre (-) mice.
- GTT and GSIS show inconclusive results because of a small sample size.
- Further experiments must be done to verify and troubleshoot the knockout of *Dec1* of mouse β-cells with the use of Tamoxifen.

Acknowledgements

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