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Background:
Over the past decade, GWAS have successfully identified common variants at genomic loci associated with increased risk of T2D development. One risk locus is a relatively common intronic SNP in the NOTCH2 gene (rs10923931), consistently found in a wide variety of populations. NOTCH2 is part of a family of receptors critical for cell-fate decisions in normal development. Recently, it was found that the signaling is reactivated in response to obesity in several insulin-sensitive tissues. The role of Notch signaling in β-cell proliferation and maturation is unclear. Investigators will look at the role of NOTCH2, and the particular risk variant, on β-cell development and function.

Objectives:
First, use CRISPR to generate null NOTCH2 alleles, on the background of a reporter IPS line encoding GFP in the insulin locus to allow tracking of the cells in vitro and in vivo. After differentiation to β-cells in vitro and in vivo, test the repercussions of loss of NOTCH2 on β-cell biology.
Second, determine the mechanism of reduced NOTCH2 expression and other possible molecular repercussions of the rs10923931 SNP, and determine effects on β-cell Notch activity and downstream effects on β-cell proliferation and maturation.

Future Work:
Investigators predict that NOTCH2 T2D risk variants decrease proliferation of pancreatic progenitors and/or fully developed cells due to reduced β-cell NOTCH2 expression, which in turn reduces β-cell Notch activity. Future work will focus on translational studies, to cross-reference individual genomic information to β-cell mass data from PET imaging. In addition, investigators will test whether the NOTCH2 variant is associated with lower insulin/C-peptide in T2D patients, and whether the NOTCH2 variant will predict early need for insulin therapy in susceptible patients.