The incidence of type 1 Diabetes (T1D) is doubling every 20 years. The pathogenesis of T1D is poorly understood, but available data indicate that pancreatic beta cells are destroyed by an autoimmune attack and consequent inflammation (insulitis). Alternative splicing (AS) is a key post-transcriptional mechanism regulating gene expression and generating proteome diversity. It allows cells to adapt their transcriptome to intra and extracellular cues, and has a major impact in apoptosis and generation of new antigenic epitopes. There is a growing interest in AS in autoimmune diseases but nearly nothing is known on its role in T1D. We have recently shown by RNA sequencing that pro-inflammatory cytokines modify the expression of >30 splicing regulators and trigger a specific alternative splicing signature involving AS of >3000 genes in human islets. Importantly, we discovered that the diabetes candidate gene Glis3 affects beta cell apoptosis by regulating splicing of the pro-apoptotic protein Bim, and that the previously called “neuron specific” splicing factor Nova1 has a major role in beta cell AS. Based on these data, we hypothesise that early islet inflammation activates specific AS regulatory networks that regulate beta cell viability and/or susceptibility to immune-induced stress and lead to the generation of neoantigens. Against this background, the goal of the present project is to use advanced bioinformatics and molecular biology techniques to define the regulatory splicing networks that modulate beta cell AS under basal and inflammatory conditions.