Proof-of-concept proposal

Development of a negative self-vaccine against Type 1 diabetes based on central tolerogenic properties of the thymus

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A thymus defect in type 1 diabetes (T1D)

**Thymus physiology**
- AIRE-regulated transcription of T1D related self-antigens in thymus epithelium
  - $IGF2 > IGF1 >> INS$
  - $GAD67 >> GAD65$
- Deletion of T cells with high affinity for T1D related self-peptide complexes.
- Selection of CD4+ CD25+ Foxp3+ tTreg, specific of T1D related self-peptides.

**Thymus physiopathology**
- Absence or decrease in expression/presentation of T1D related self-peptides in the thymus (BB rat, APECED/APS-1, ...)
- Enrichment of T-cell repertoire with ‘forbidden’ self-reactive effector T cells (Teff).
- Decrease in selection of tTreg with specificity to T1D related self-antigens.

**Bridge between self-reactive Teff and target T1D antigens**
- Role of environmental factors (viruses, diet, vitamin D deficiency, stress...)

Islet β cells
The concept of « negative self-vaccination »:
Thymus T1D self-antigens for reprogramming tolerance to β cells

In the thymus

SELF-TOLERANCE TO β CELLS
Clonal deletion and anergy of self-reactive T cells
Generation of specific tTreg

In pancreatic islets

AUTOIMMUNITY TO β CELLS
Activation of self-reactive T cells
Induction of memory T cells

TCR
Self-antigens
IGF-2, GAD67

T1D related antigens
Insulin, GAD65

= « Altered » self
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