Diabetes as autoimmune disease – *Type 1 Diabetes*

Evgenija Homšak,M.Ph., M.Sc., EuSpLM.
Department for laboratory diagnostics
University Clinical Centre Maribor
Slovenia

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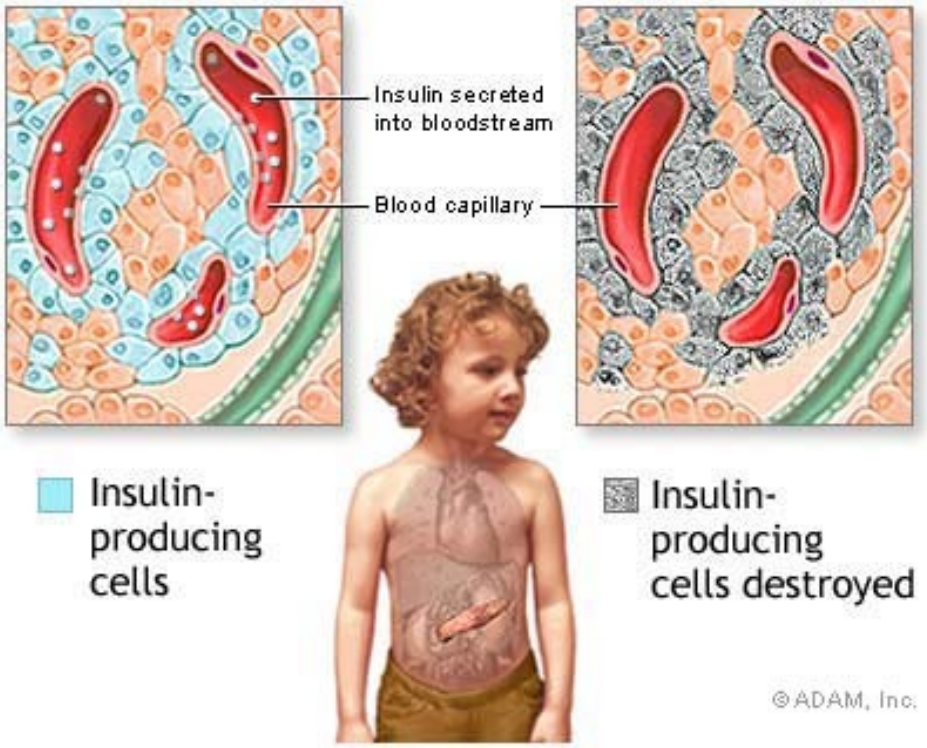
Type 1 Diabetes Melitus

- chronic immune mediated disease
- selective loss of insulin producing β cells
- in genetically susceptible subjects



Type 1 Diabetes Melitus (IDDM) Classification

- **1A (immune mediated)** – autoimmunity 95%
- **1B (non-immune mediated, idiopathic)**
  – lack of defined markers of autoimmunity 5%

5-10% of patient with diabetes mellitus

Epidemiology

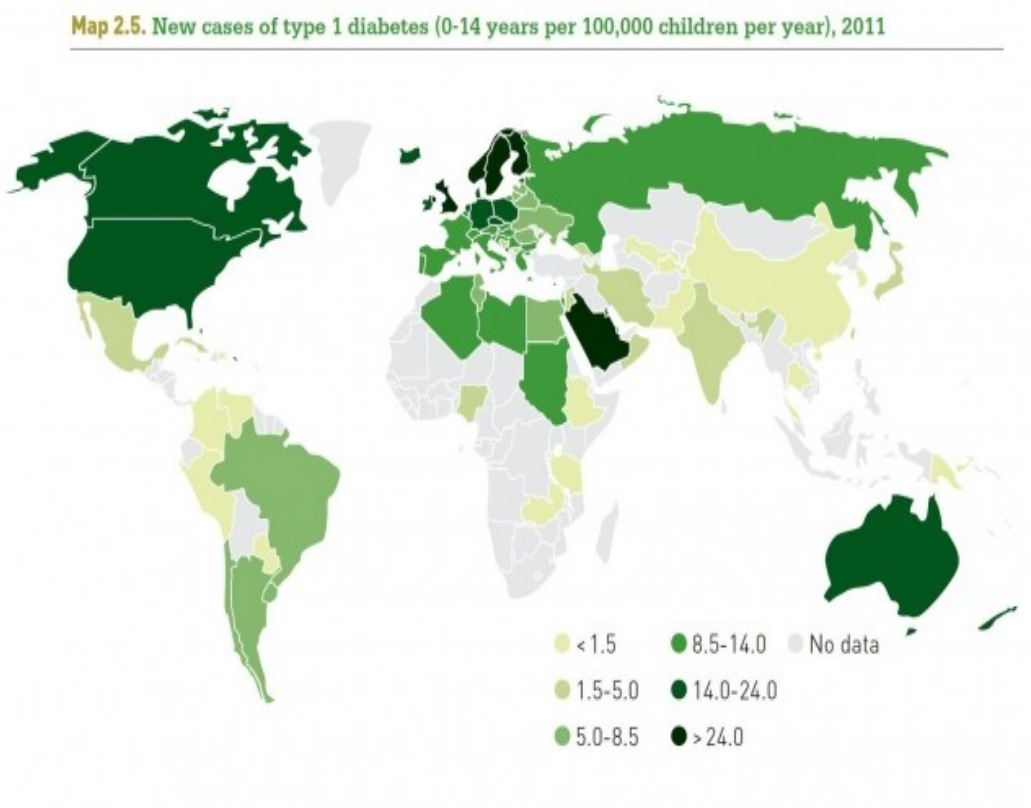
Present at any age, with equal affection of both sex.

- **Children**
  - most often occurs early in life with peak around the puberty
  - the most common type od DM (2/3) ≤ 19 age
- **Adults**
  - ¼ of new cases are diagnosed among adults
  - LADA- latent autoimmune diabetes in adult

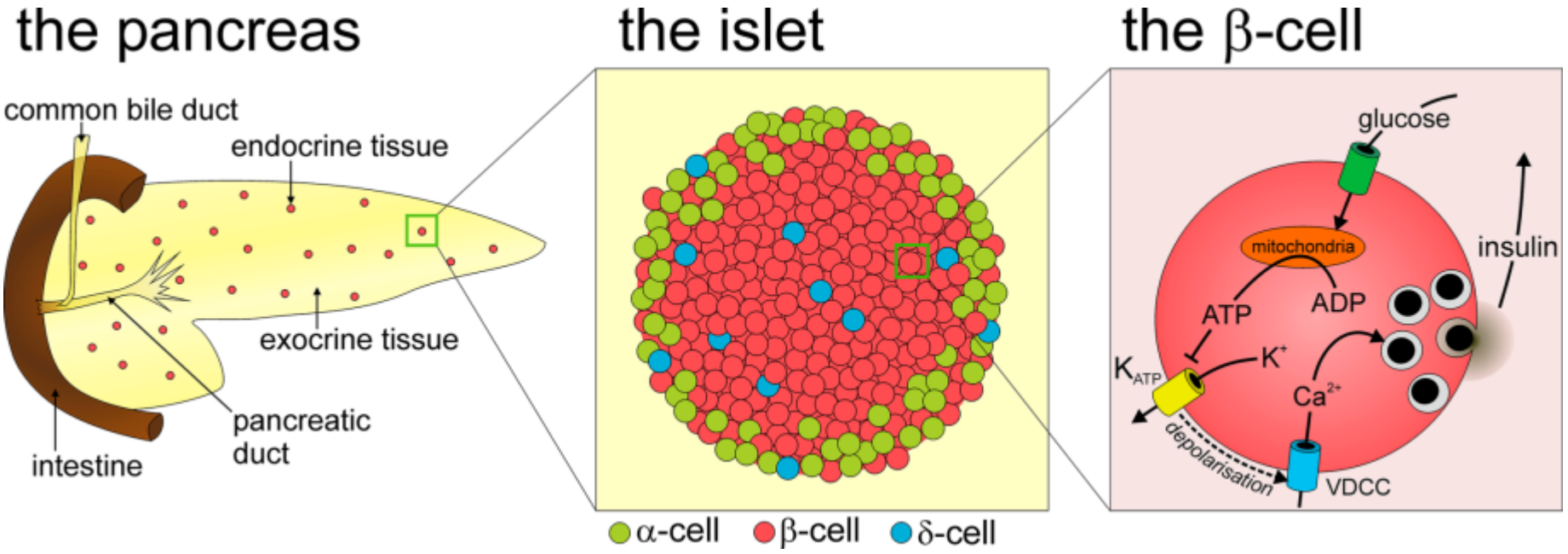
Incidence in children

- Incidence varies 50-100 fold around the world
  - 57,4 /100 000 in Finland
  - 0.6 / 100.000 in China
- Incidence of childhood T1DM growing rapidly,
  - especially in younger than 5 years
  - doubling time less than 20 years

(environmental contribution)

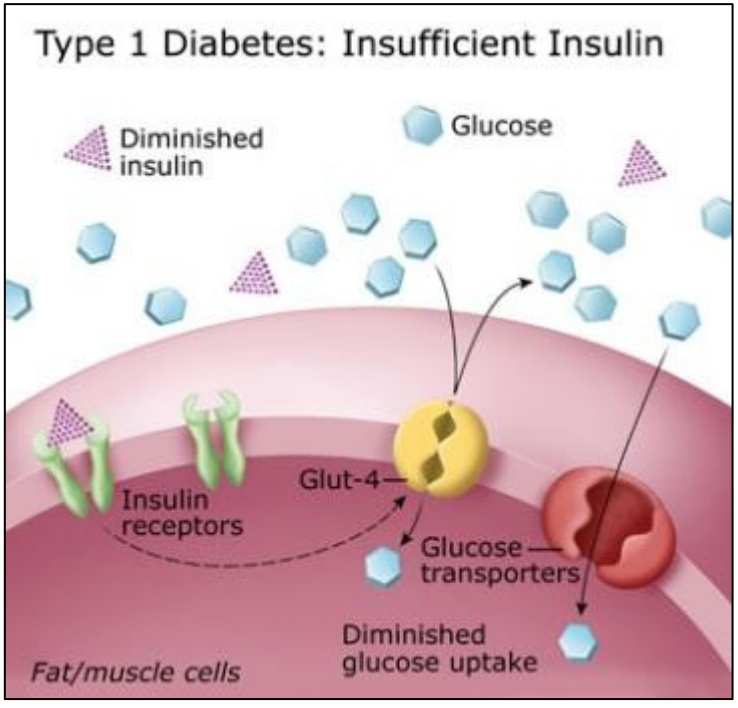


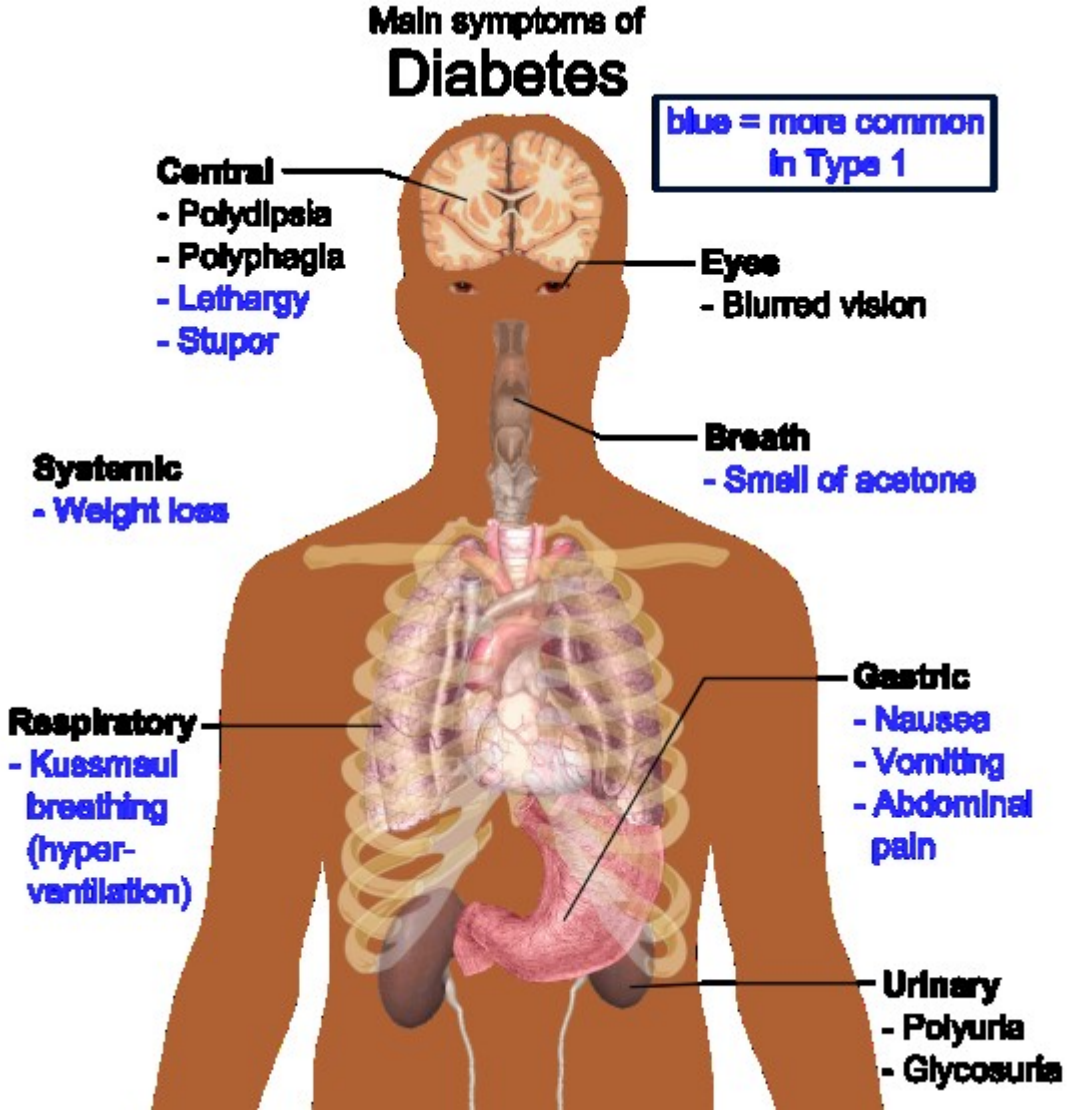
Symptoms of Clinical disease



Symptoms occur when remains only 20% of functional β cells

Symptoms of Clinical disease





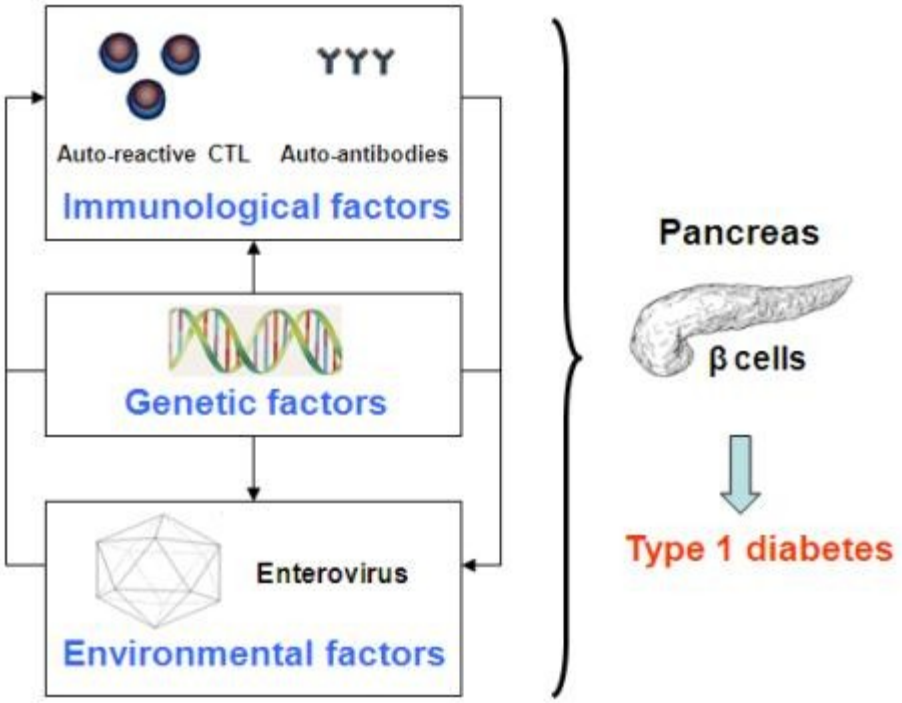
Etiology and pathogenesis of T1DM Why and how it happened?

Important for:

- early diagnosis
- to prevent
- to cure

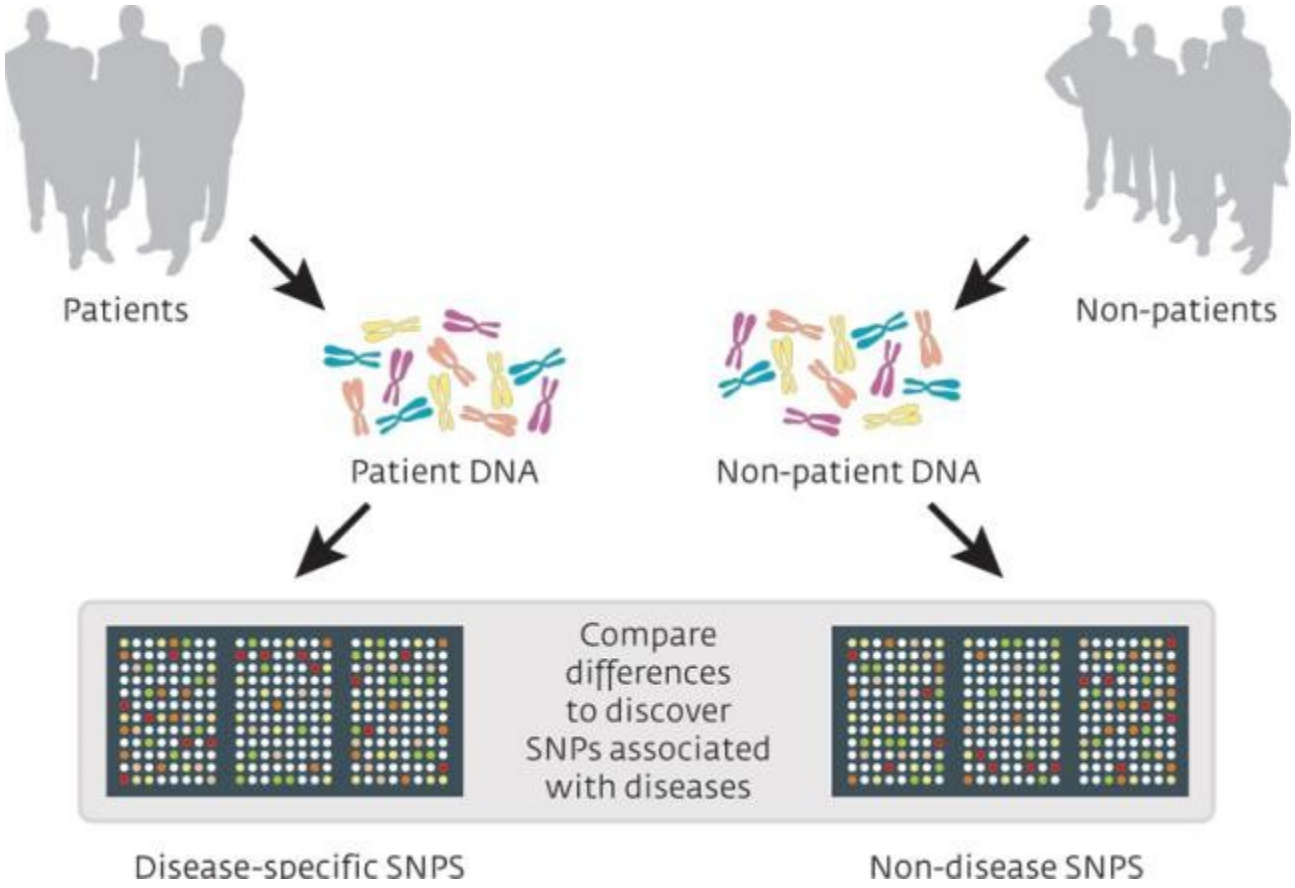
Etiology

- **Autoimmunity**
- Genetic predisposition
- Environmental factors, triggers and drivers



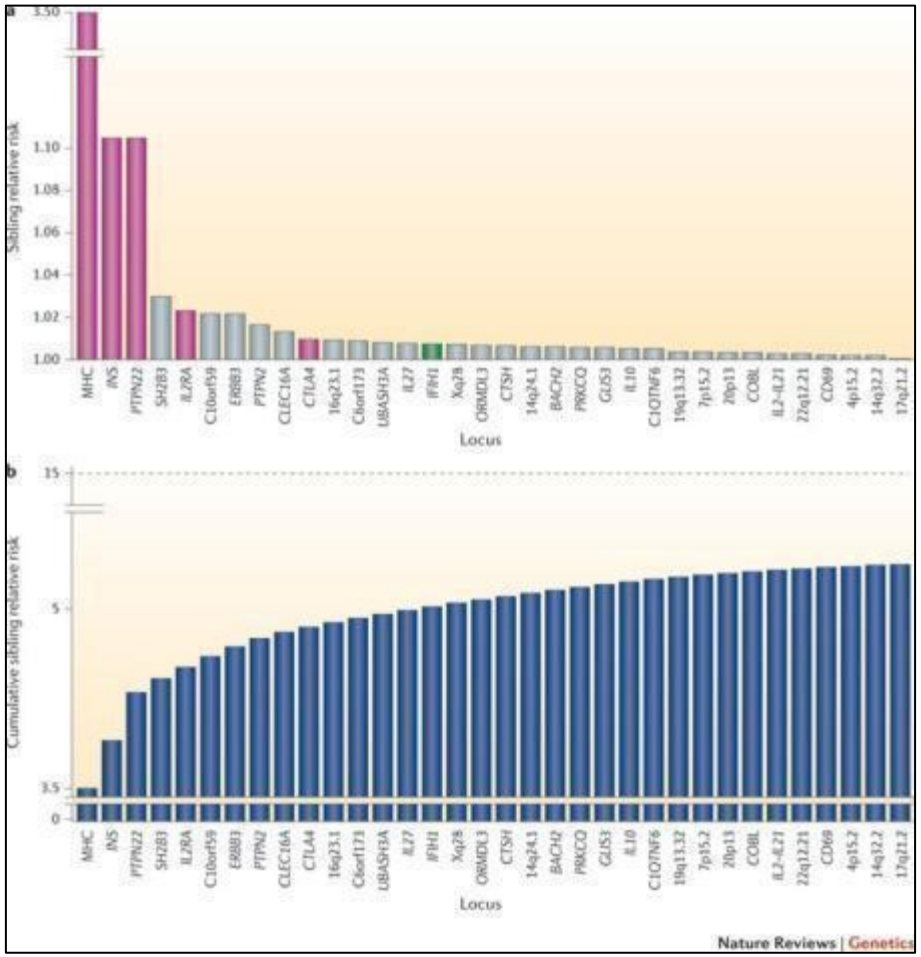
Genetic predisposition

- GWAS-more than 40 genetic factors associated with risk of T1DM

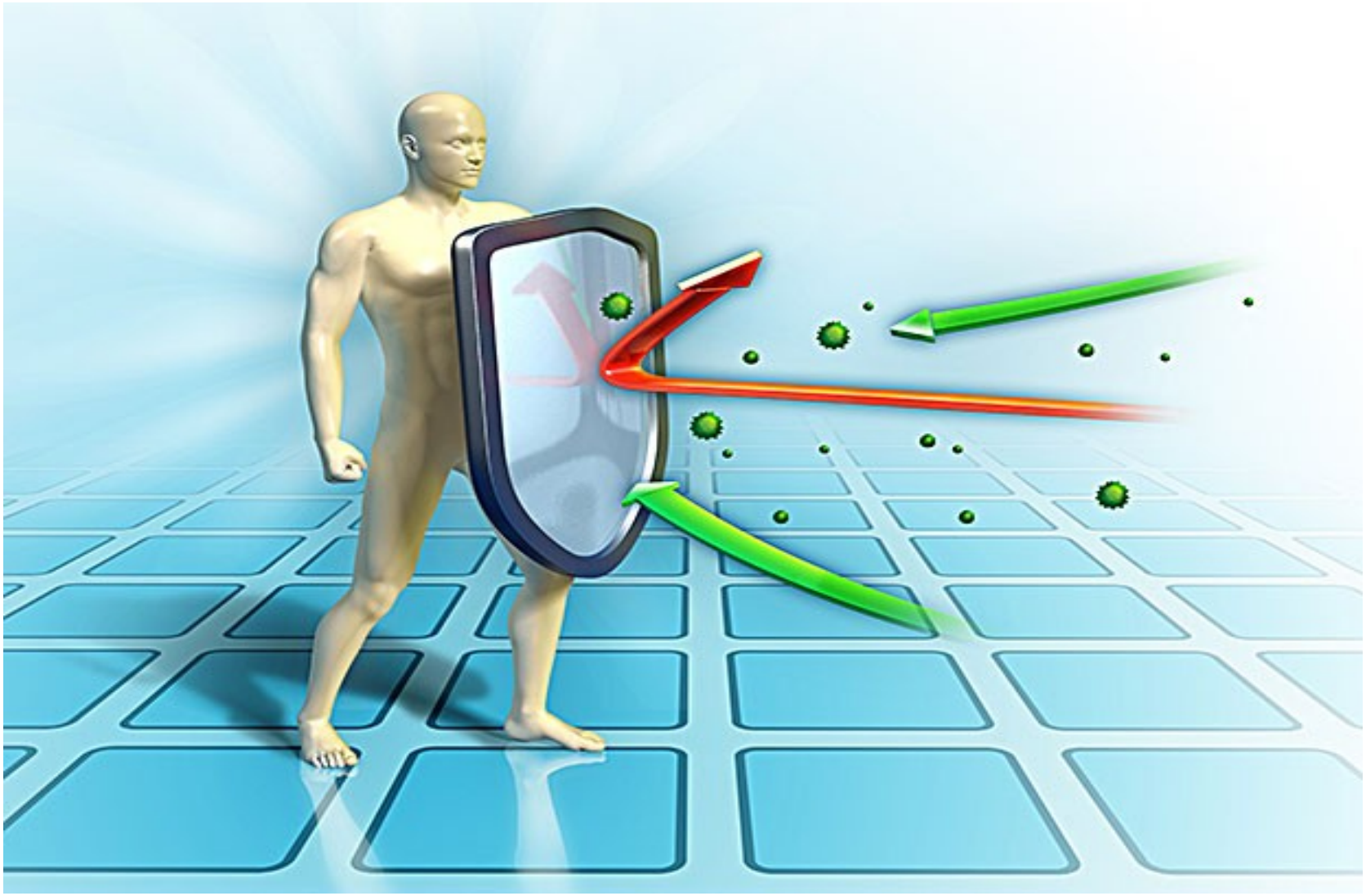


Genetic predisposition

- HLA genotype– MHC (90%)
  - Chromosome 6p21,3
  - DR3-DQ2/DR4-DQ8
  - Similarity with celiac disease
- Non-HLA
  - INS (10%) (chromosome 11p5,5)
  - PTPNN21 (protein tyrosine phosphatase)
  - CTLA4 – Treg
- intercommunication and influence between genes

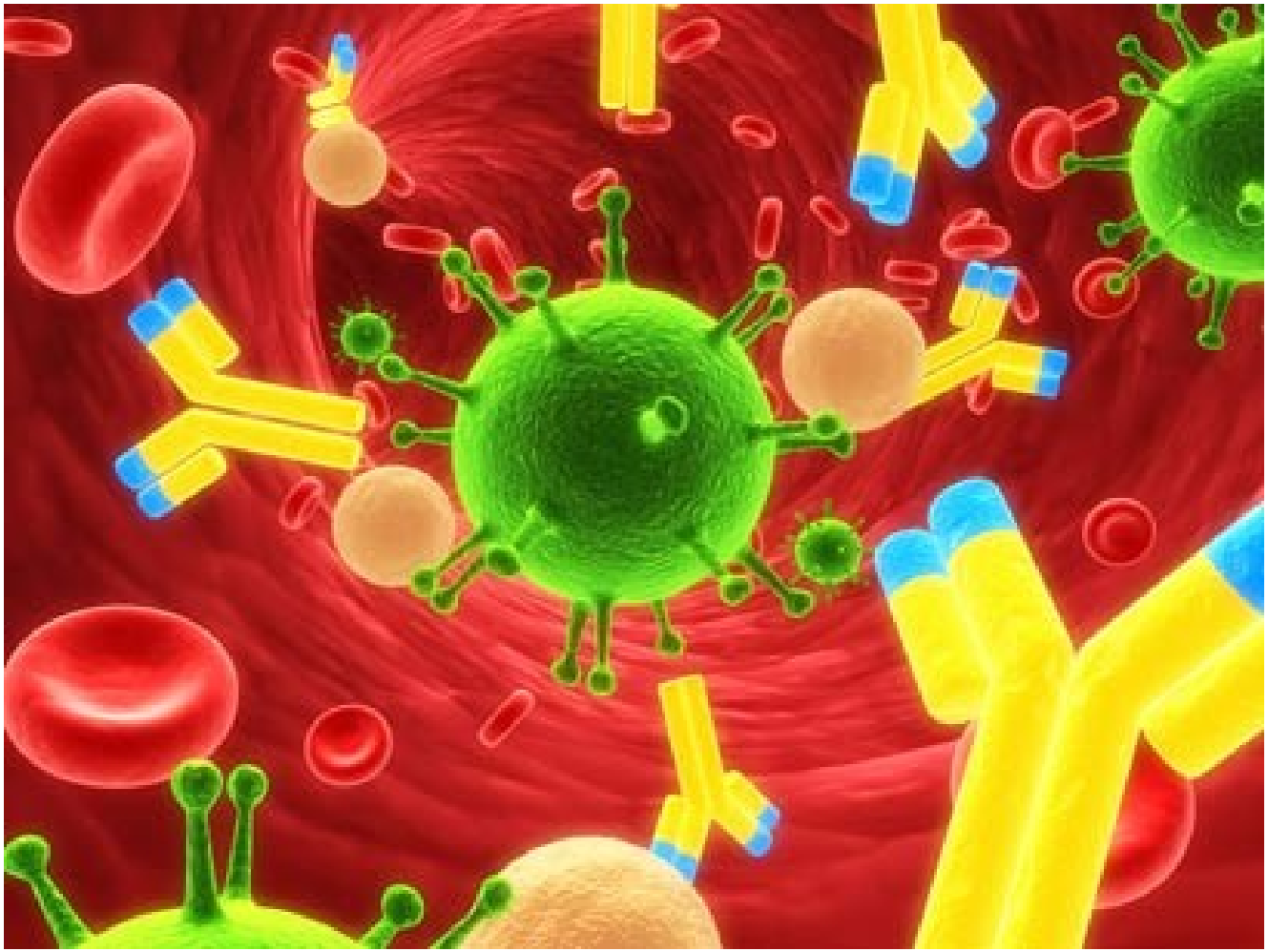


Immunity-useful defense



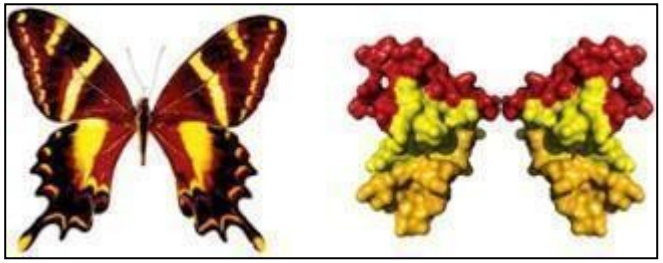
Autoimmunity - harmful defense

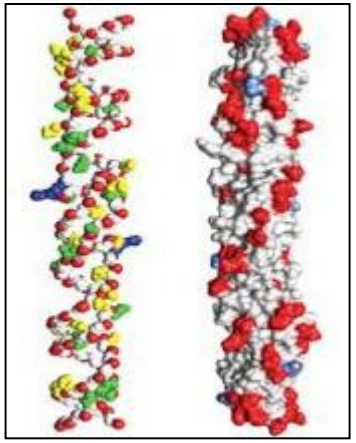
Autoimmunity – response against own cells and tissues



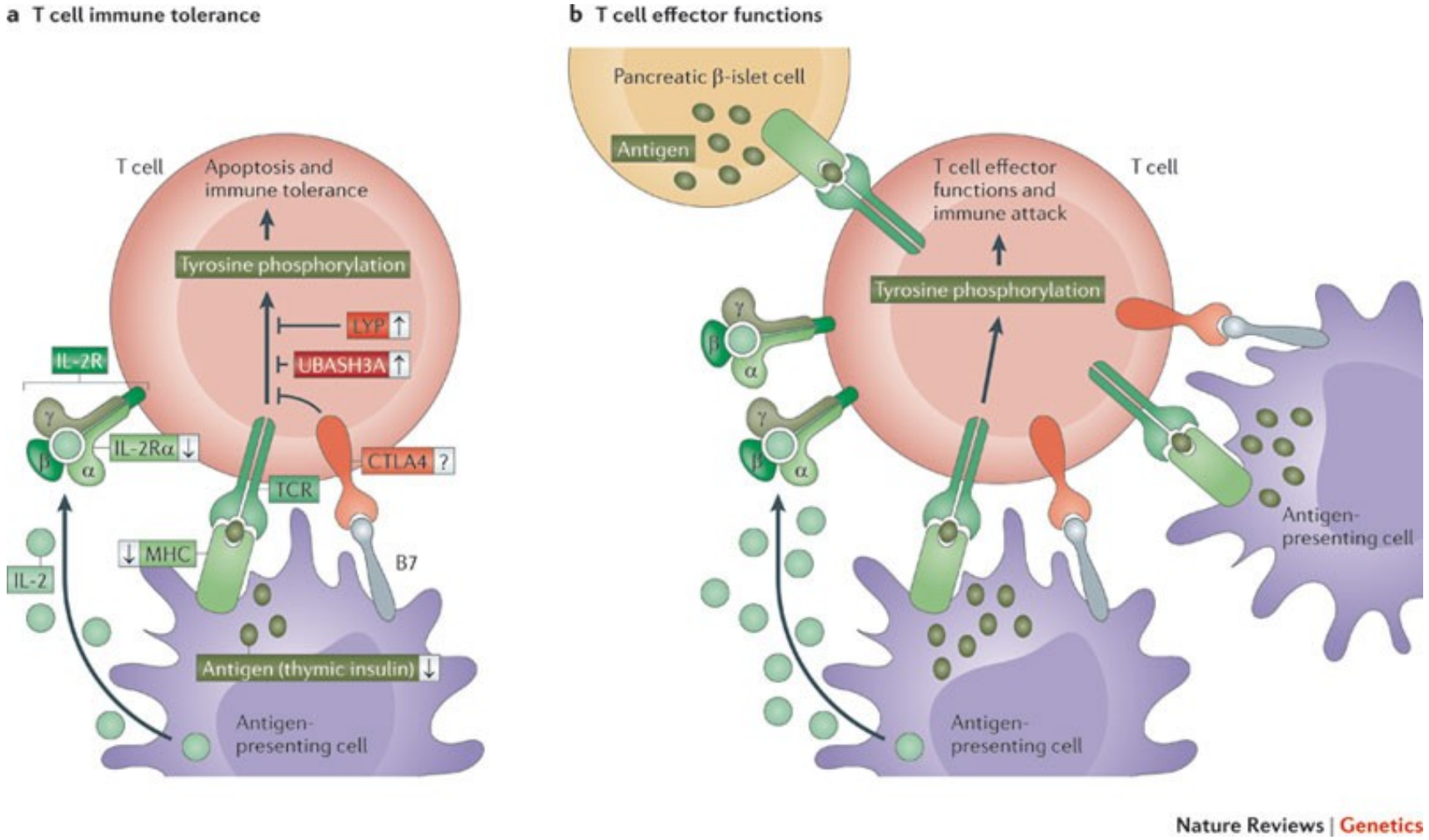
Similarity?

Recognition and differentiation their own from foreign



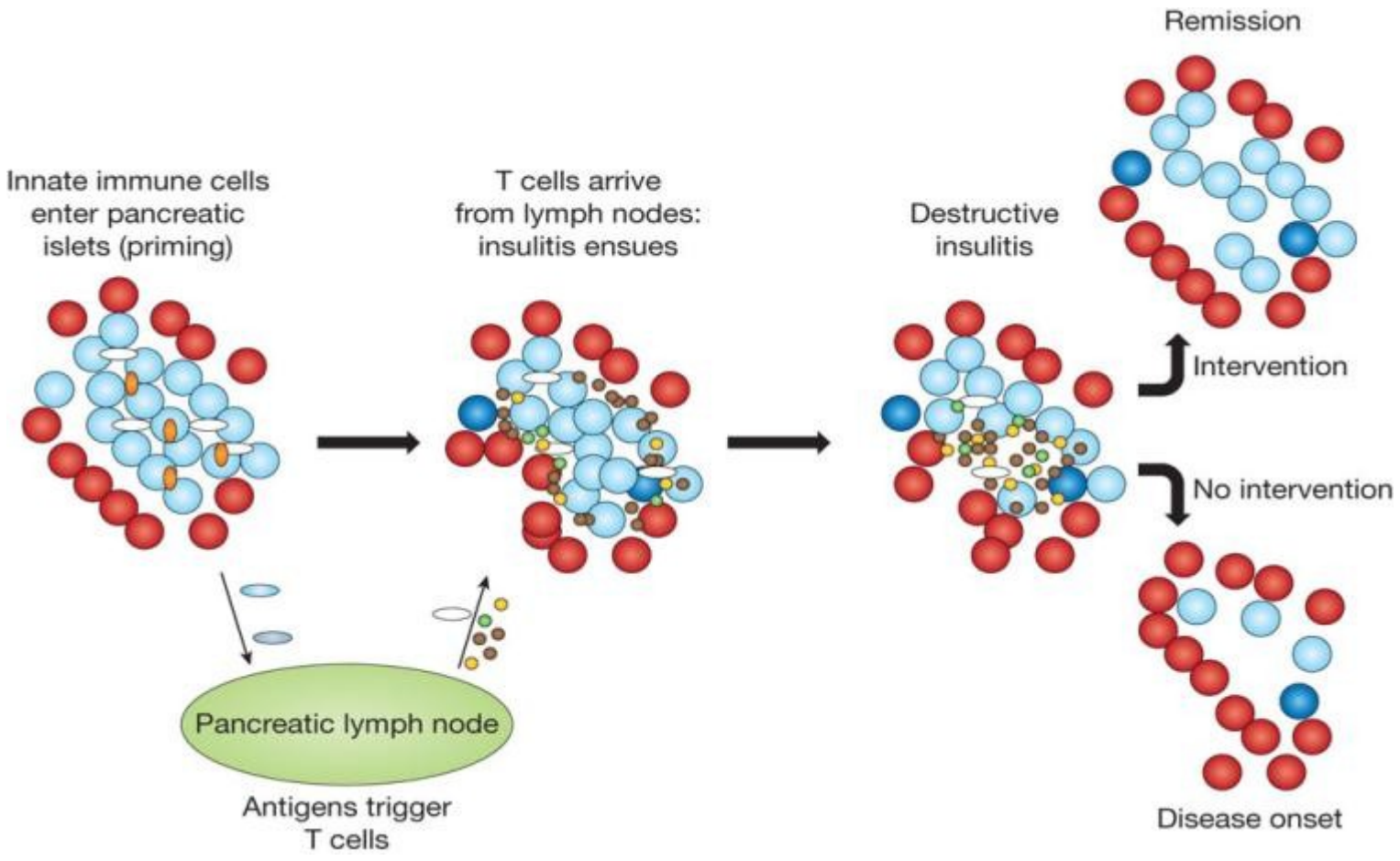


Immunotolerance/activity of LyT
(thymic developement and selection of LyT)



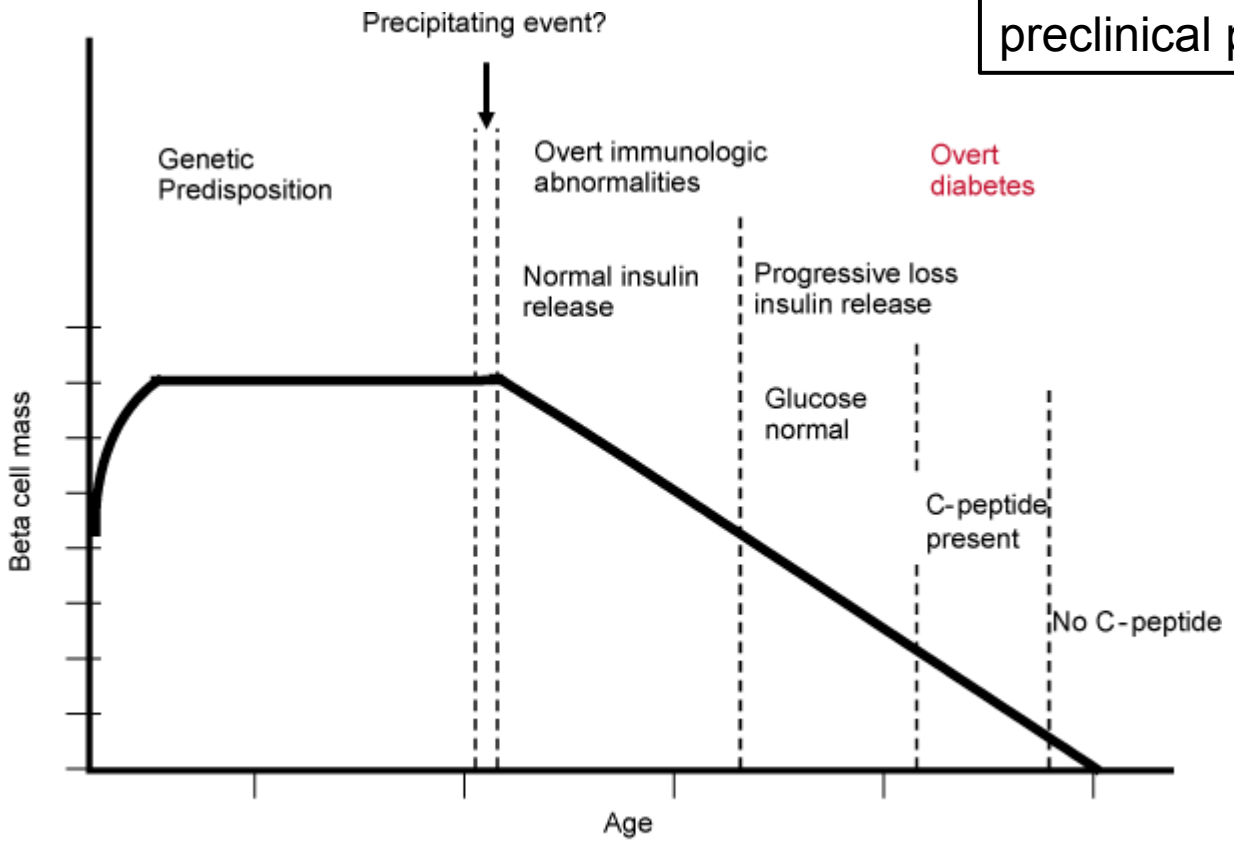
Histological evidence – insulitis

Infiltration of pancreas with Limphocites (LyT) and Ab



Progression of disease

Varied dauration of each preclinical phase



Modified from Eisenbarth GS. Type 1 diabetes mellitus. A chronic immune disease. N Engl J Med. 1986; 314:1360.

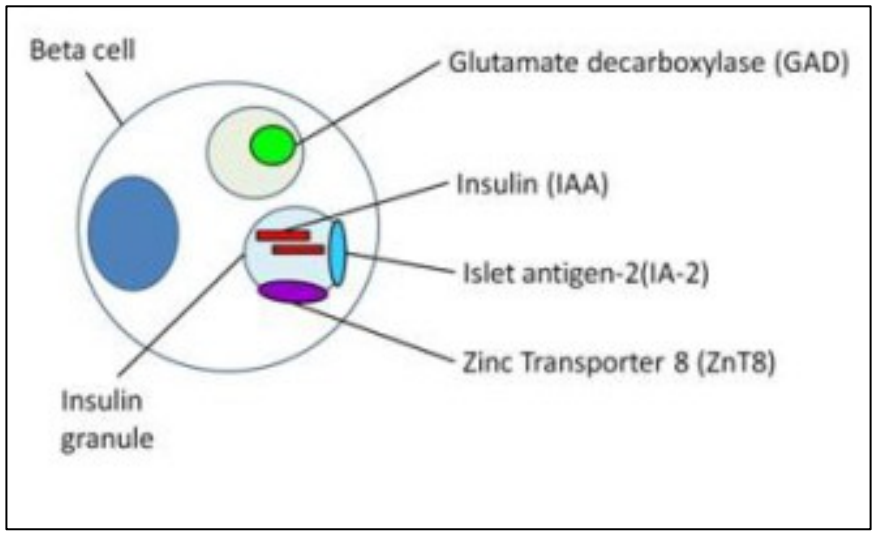
Figure 1. Stages in development of type 1A diabetes (7).

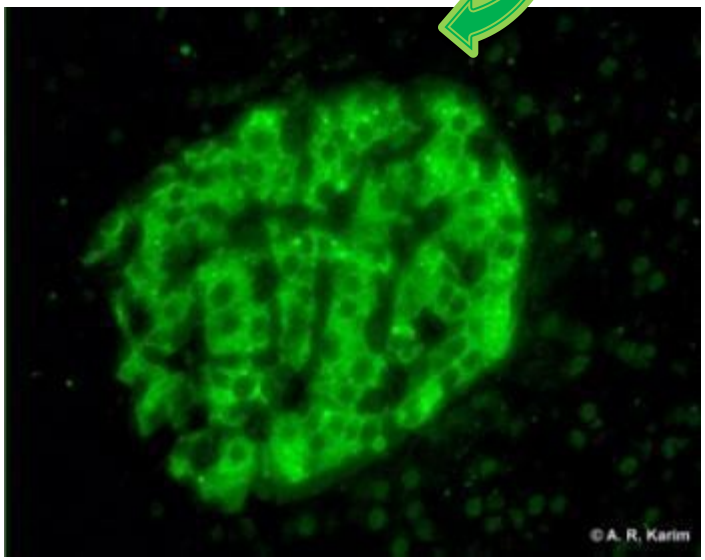
Individual specific

Environmental factors

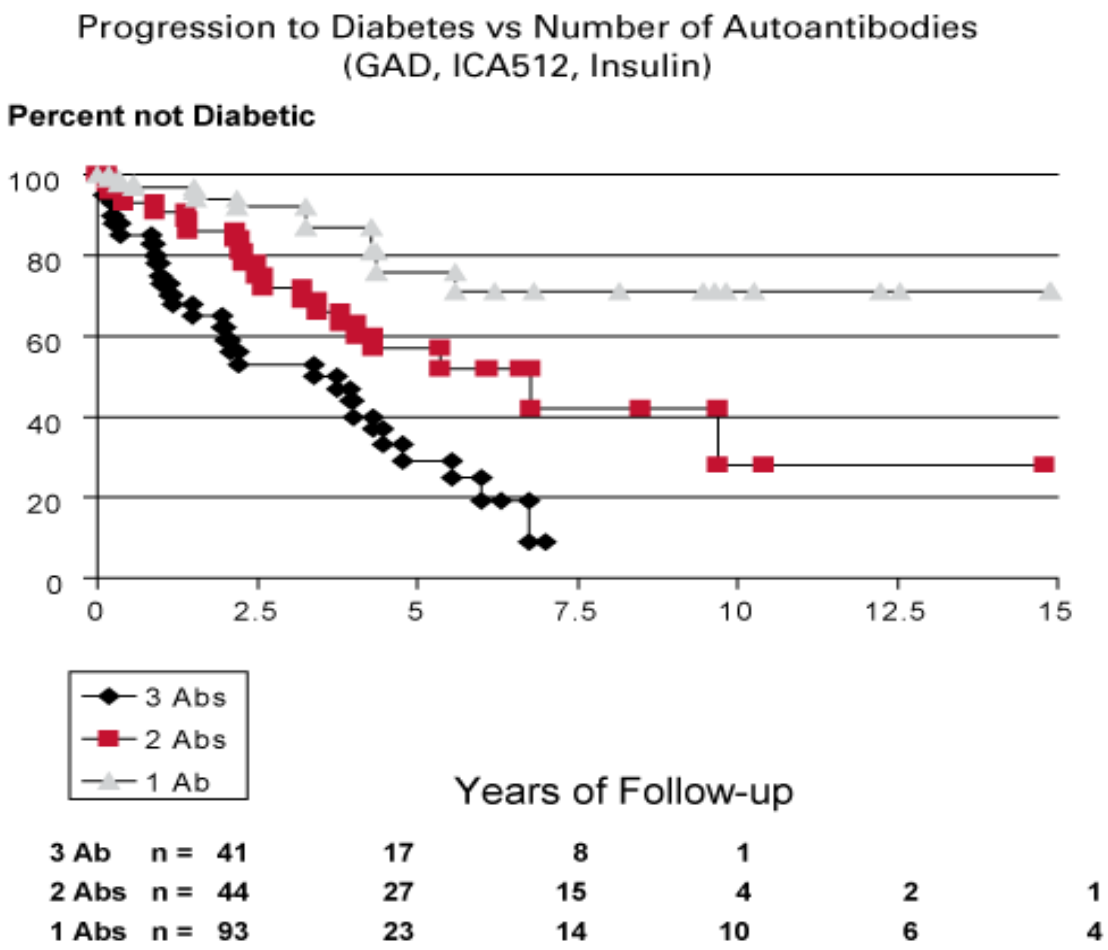
Presence of Auto-antibodies

- ICA – Islet cell antibodies
- GAD65- glutamic acid dekarboxilase
- IA-2 – tyrosine phosphatase related IA-2 molecule
  (insulinoma associate antigen 2- Ab)
- ZnT8A – Zn transporter protein
- IAA – insulin autoantibodies with epitope on B-chain



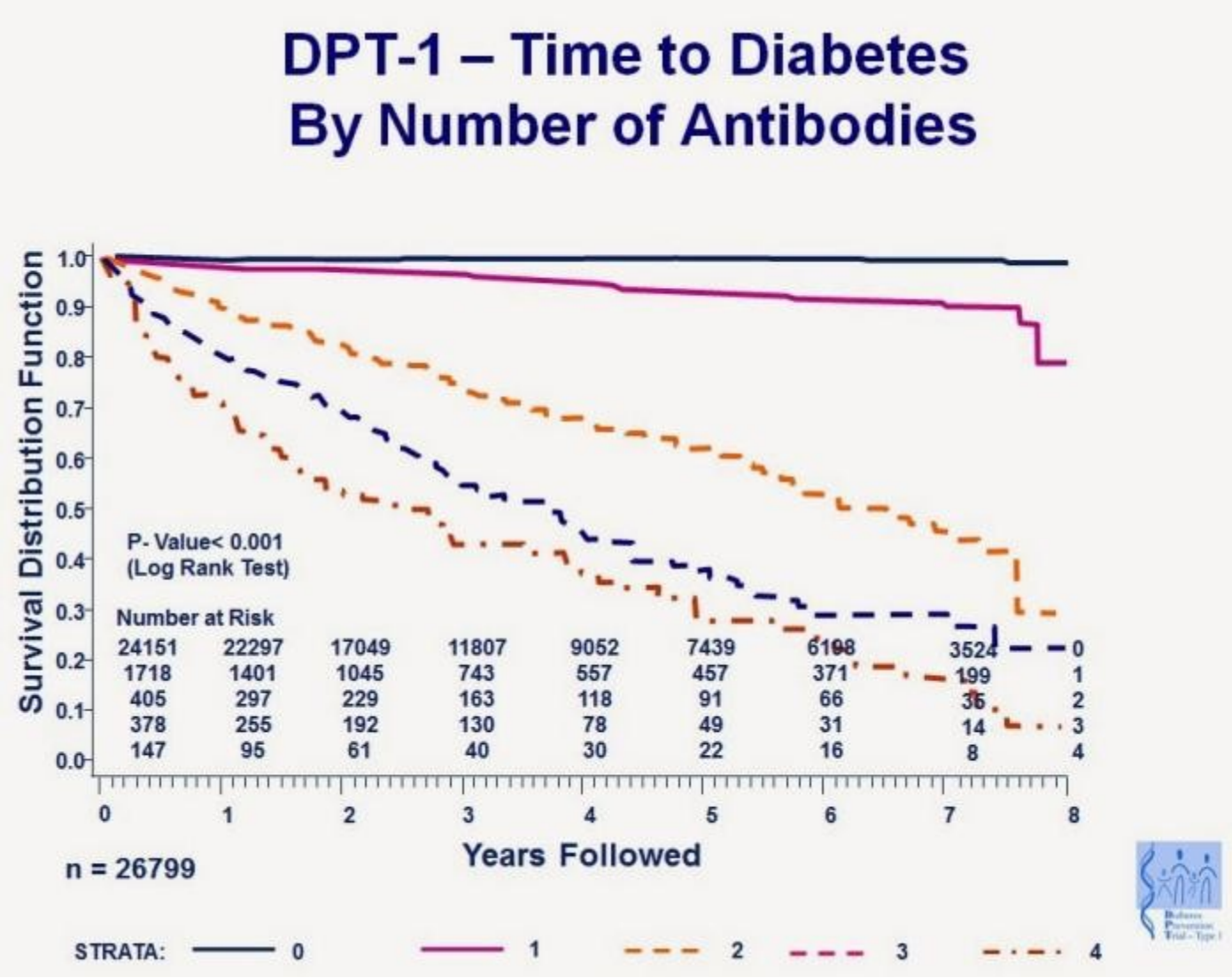


Progression of disease according to presence of Ab



From Verge et. al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes. 1996;45:926-33.

Prediction of disease development according to presence of Ab



Contribution to pathogenesis

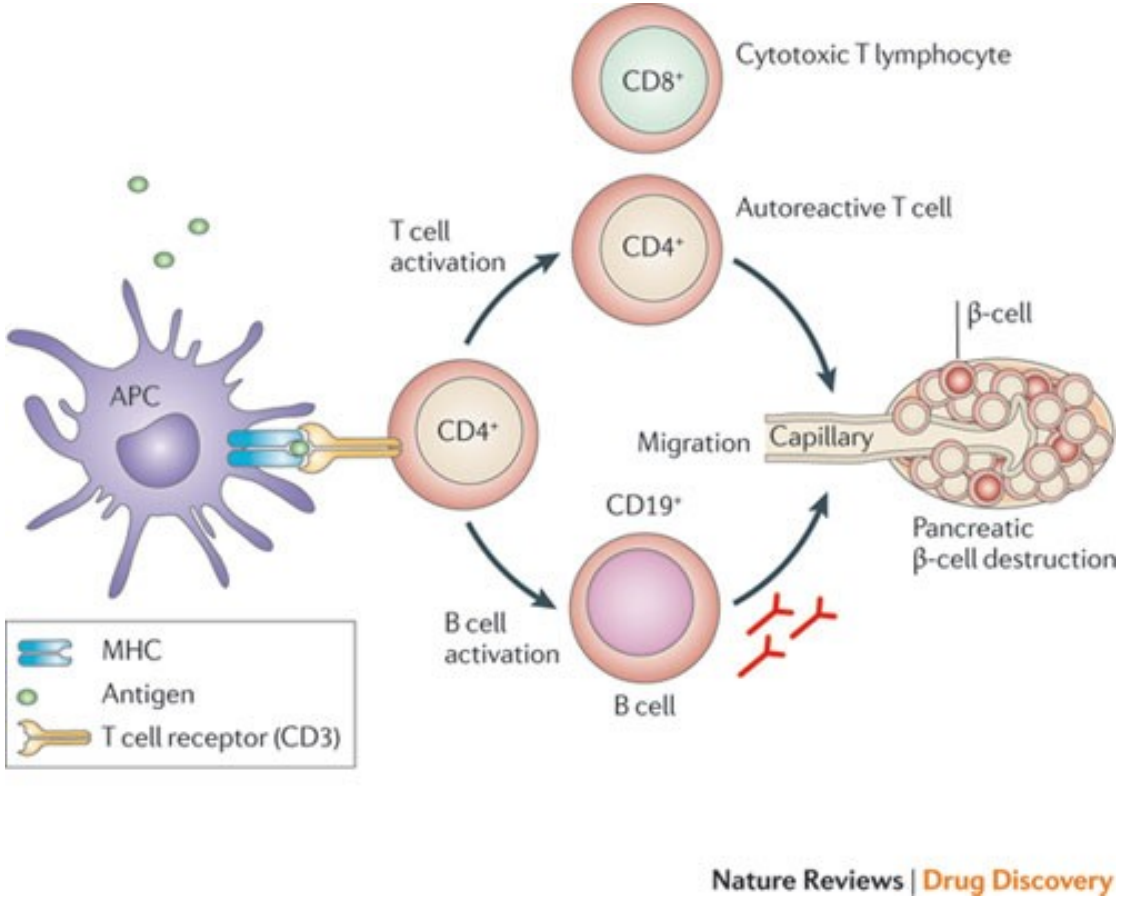
- **Is controversial**

- Transfer of auto-Ab alone did not reconstitue disease in the B less NOD mice
- Diabetes cannot be transferred using serum from diabetic humans
- The plasmapheresis provides little therapeutic benefit

- Still affect the time course of disease development

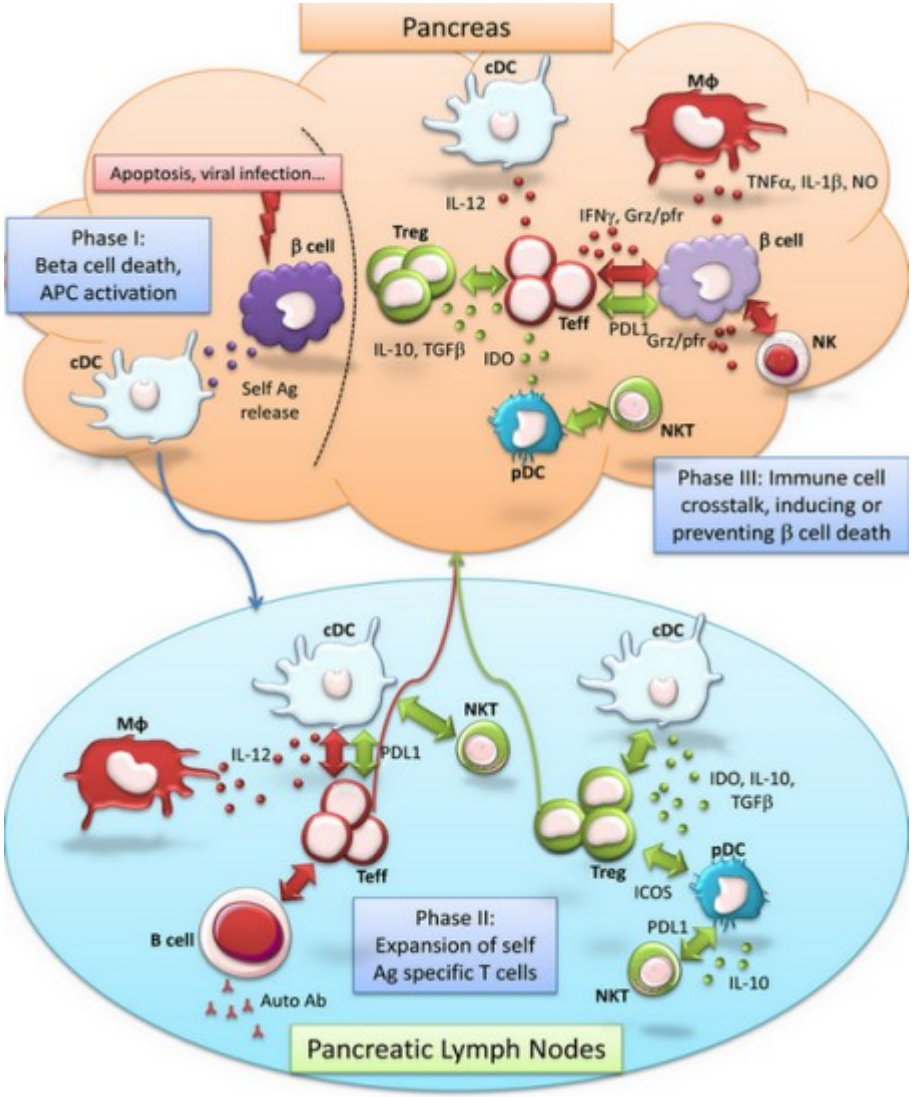
Pathogenesis

- Genetic predisposition (HLA: DR3-DQ2/DR4-DQ8)
- Environment factors, triggers :
  - food (milk casein, bovine insulin)
  - viruses (Coxsackie, rubella)
- Autoantigens
  - Insulin
  - GAD65
- Autoimmune inflamation, destruction, apoptosis
  - APC
  - LyT (CD4, CD8), Treg
  - LyB (APC, auto-Ab,)



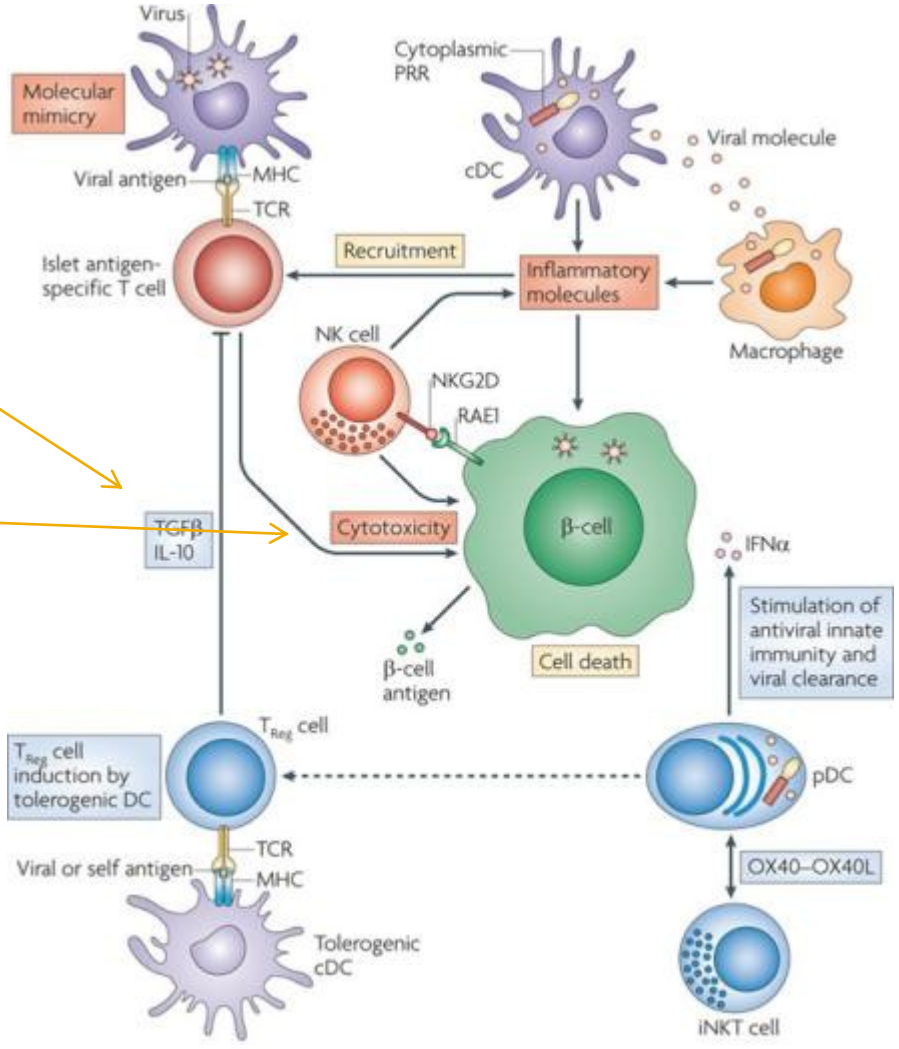
Pathogenetic autoimmune mechanism

- **Phase 1 (pancreas):**
  - B cell death
  - Self Ag release
  - APC activation
- **Phase 2 (lymph node):**
  - Expansion of self Ag specific Tcells
- **Phase 3 (pancreas):**
  - Immune cells inducing or preventing B cell death



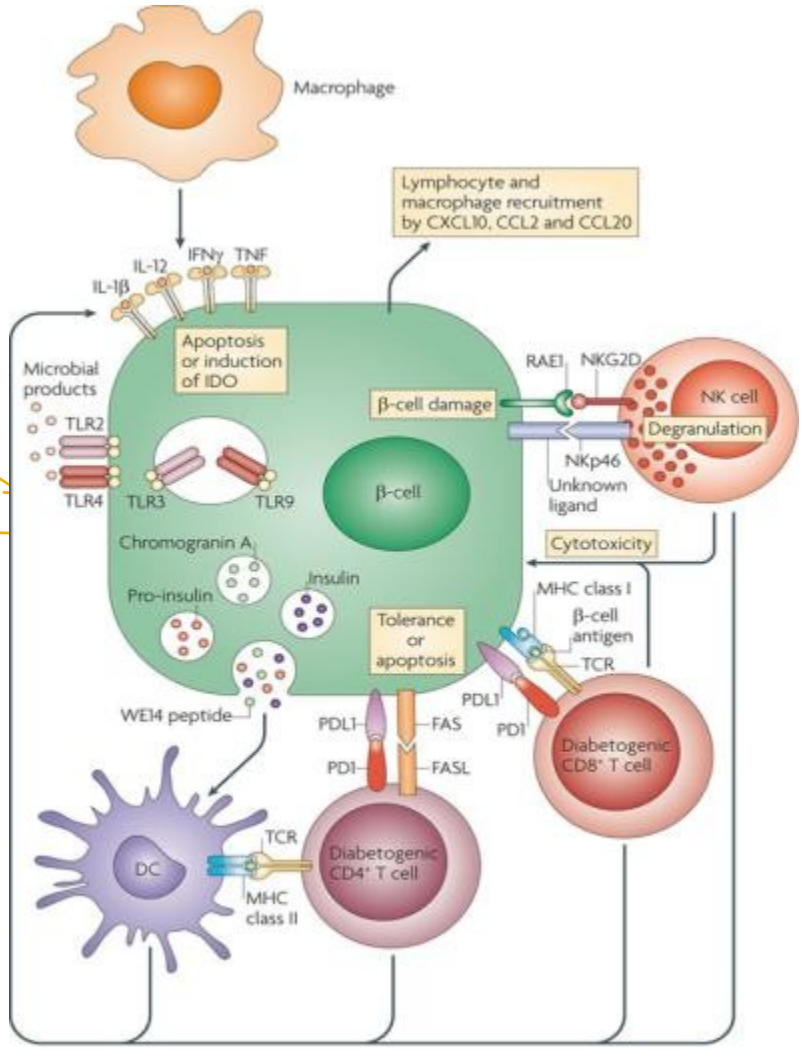
Role of crosstalking of immune cells in regulation

- Importance of Treg
  - Antiinflamatory citokine
  - Supression of cytotoxicity of β cells
- Genetic predisposition



Role of crosstalking of immune cells in beta cell death

- Attack from the auto-immune cells
- Cell death
  - Cytotoxic INFγ, TNFα, IL-1β
  - CD8- releasing perforines, granzymes;
  - Fas-mediated apoptosis
  - Free-radical (macrophages)
- Genetic predisposition
  - Immuno tolerance
  - apoptosis



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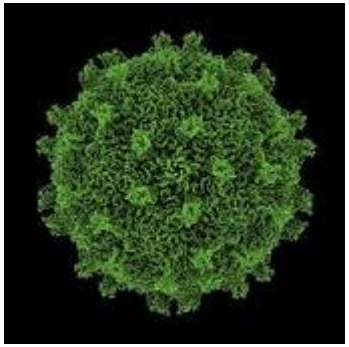
Environmental factors

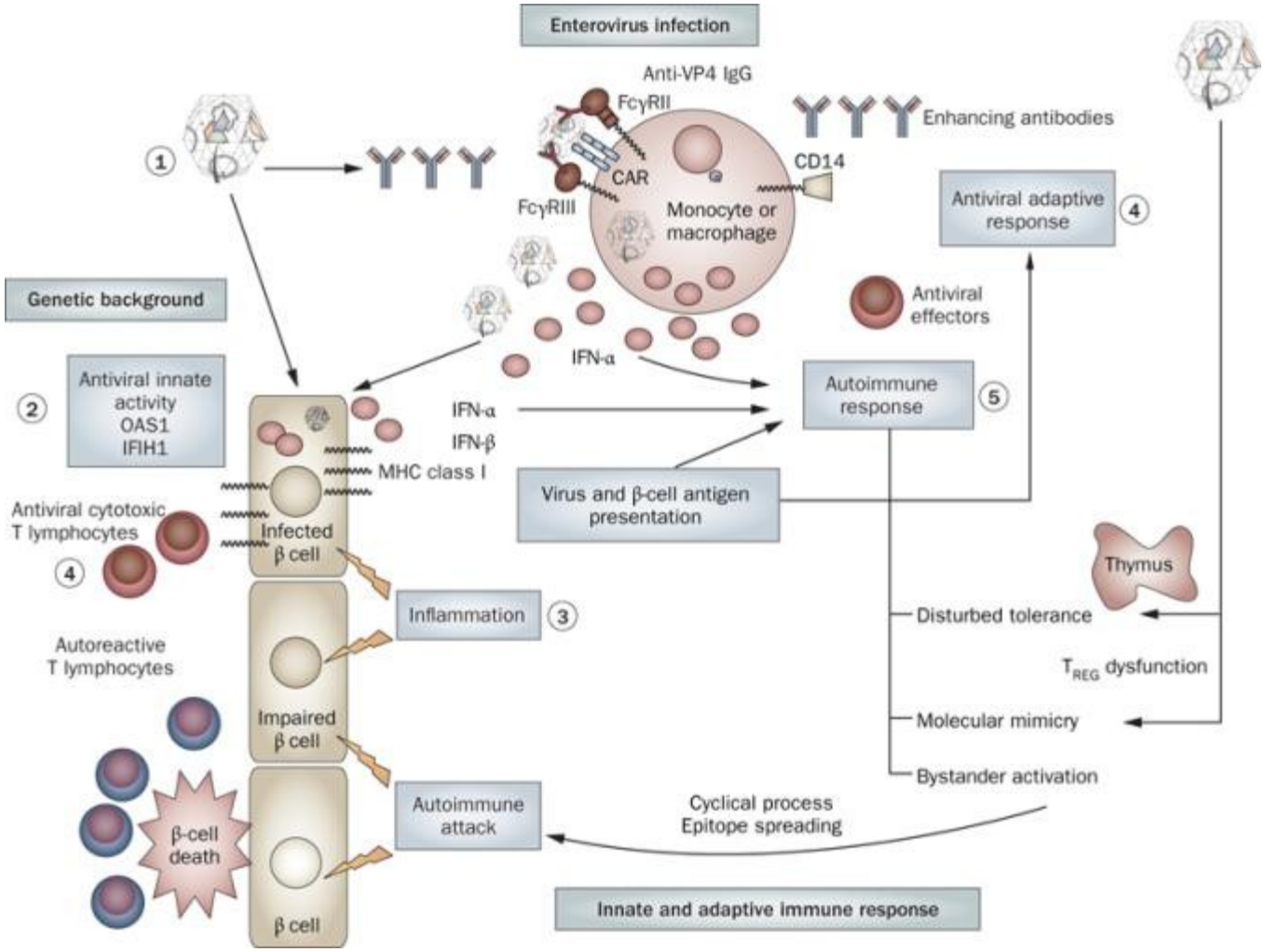
Only 20-40% concordance among monozigotic twins T1DM



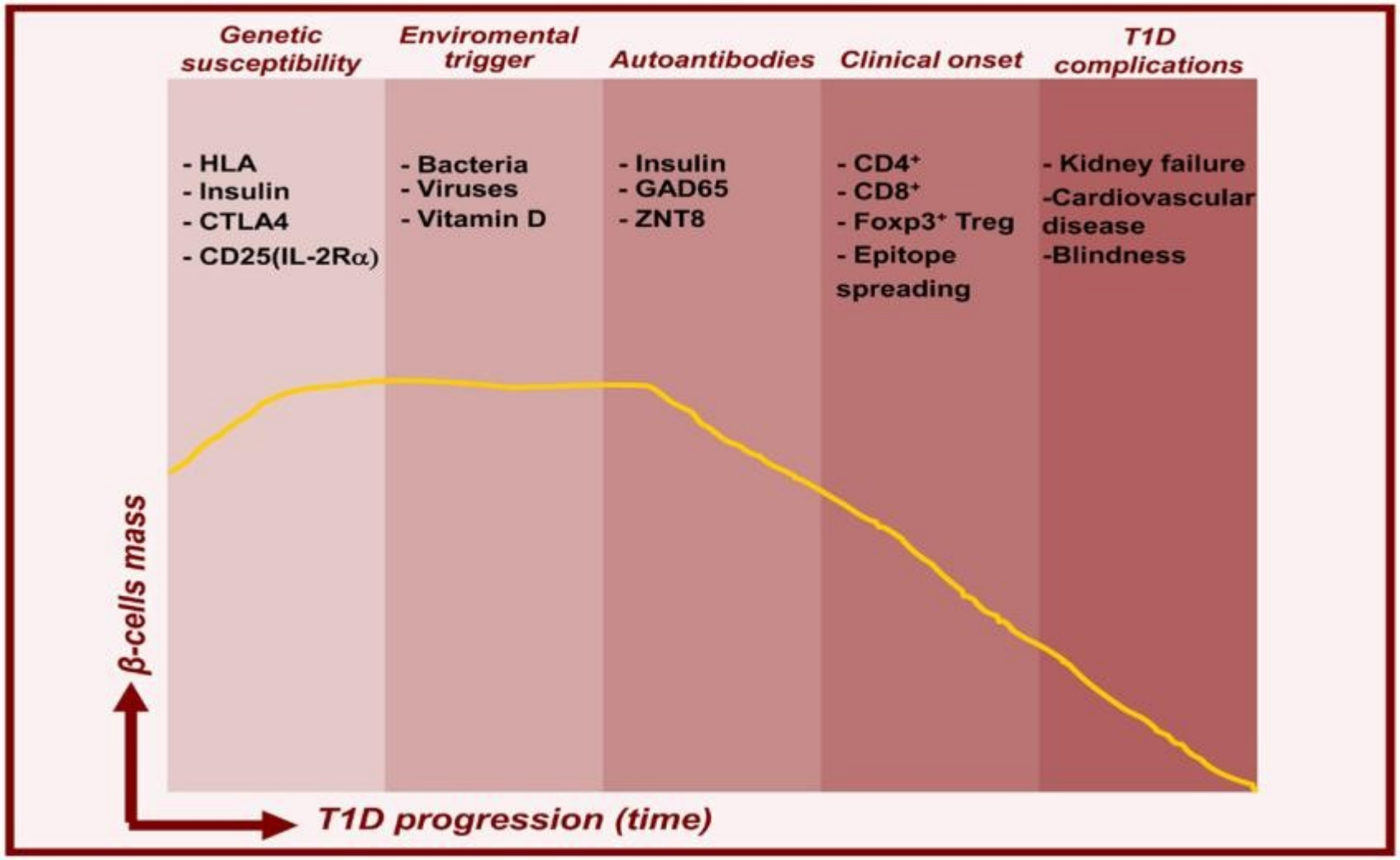
- **Entero-viruses**: Coxsackie, rubella
- **Food**: casein milk protein, bovine albumine
- ↓ **VitD**

- Have to be confirmed (controversial results in different studies)
- Possible future therapeutic target (options)

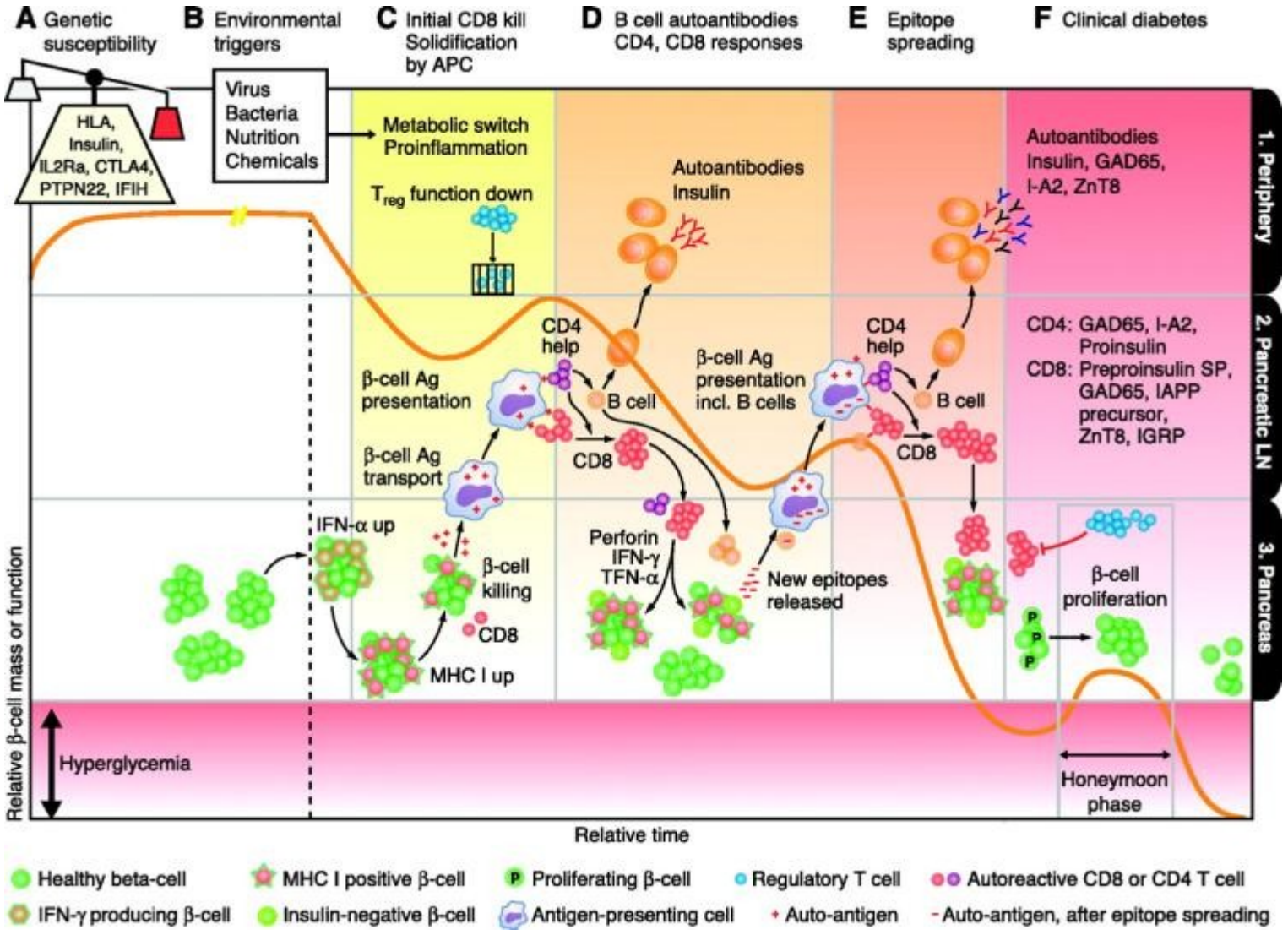
Enteroviruses as trigers



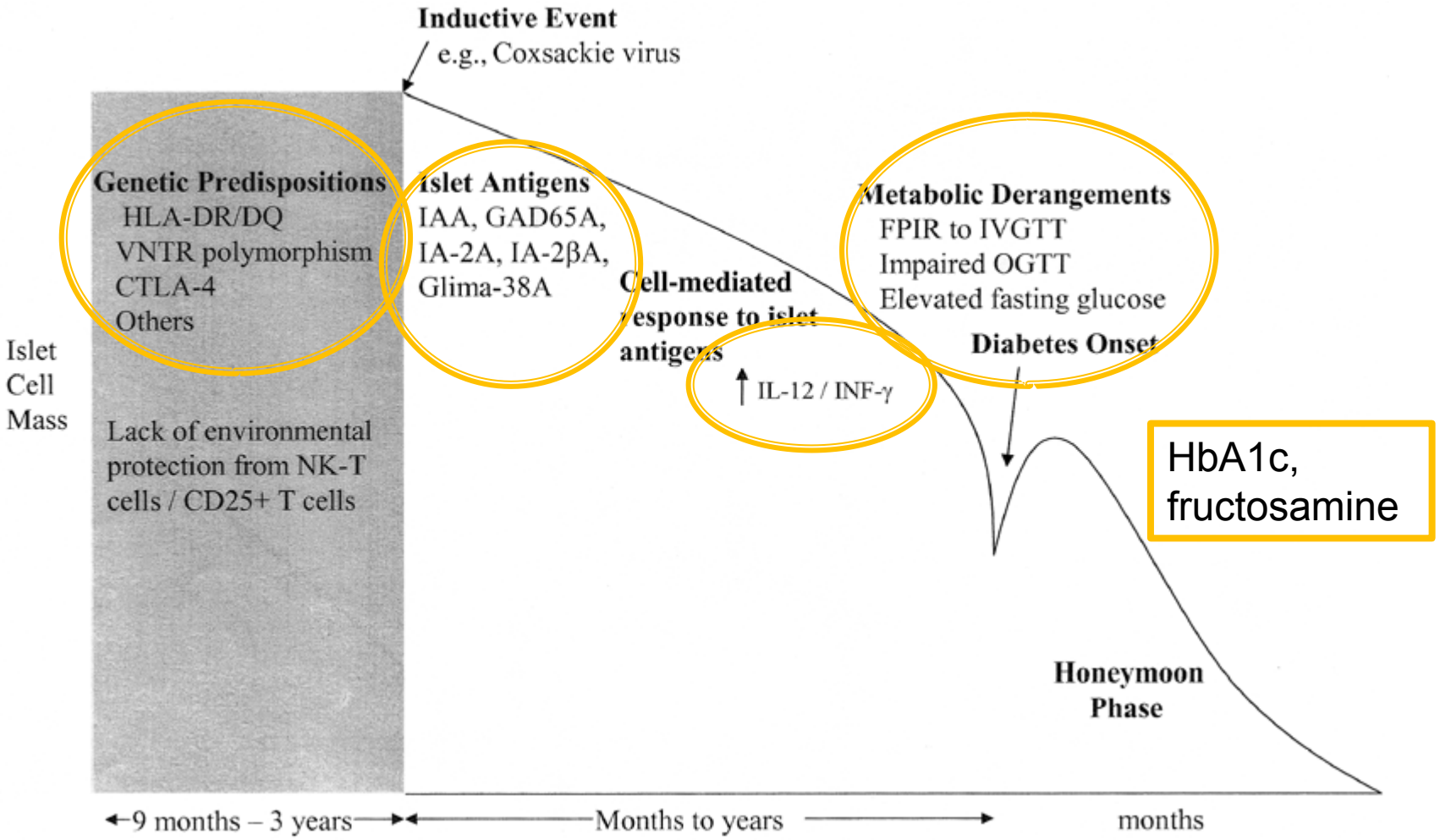
Pathogenic factors and consequances in different stage of disease



Pathogenic factors in different stage of disease



Diagnosis and prognosis

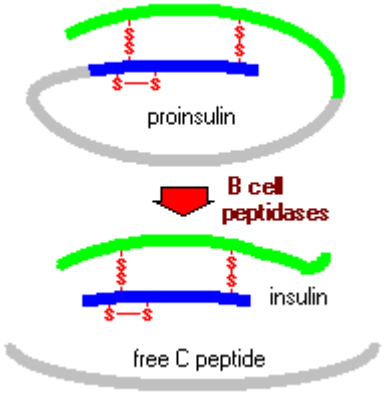


New therapeutic options

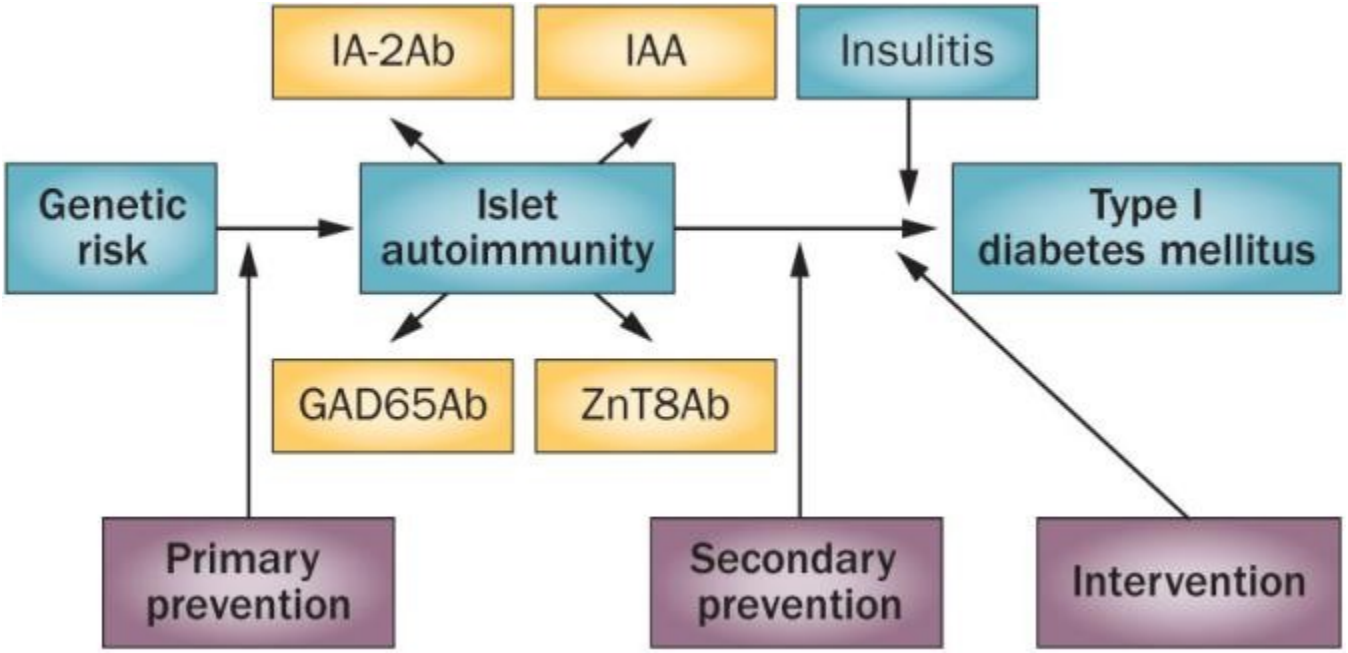
- induce immunological tolerance to islet auto-Ag
- prevent and halt the progression of the β cells destruction

- **Primary prevention** (subjects with genetic predispositions)
- **Secondary prevention** (subjects with the presence of Ab)
- **Trial interventions** (patients with the newly diagnosed T1DM)

- Problem with the evaluation and measurement of the success
  - Autoantibodies
  - C-peptid (residual imsulin)

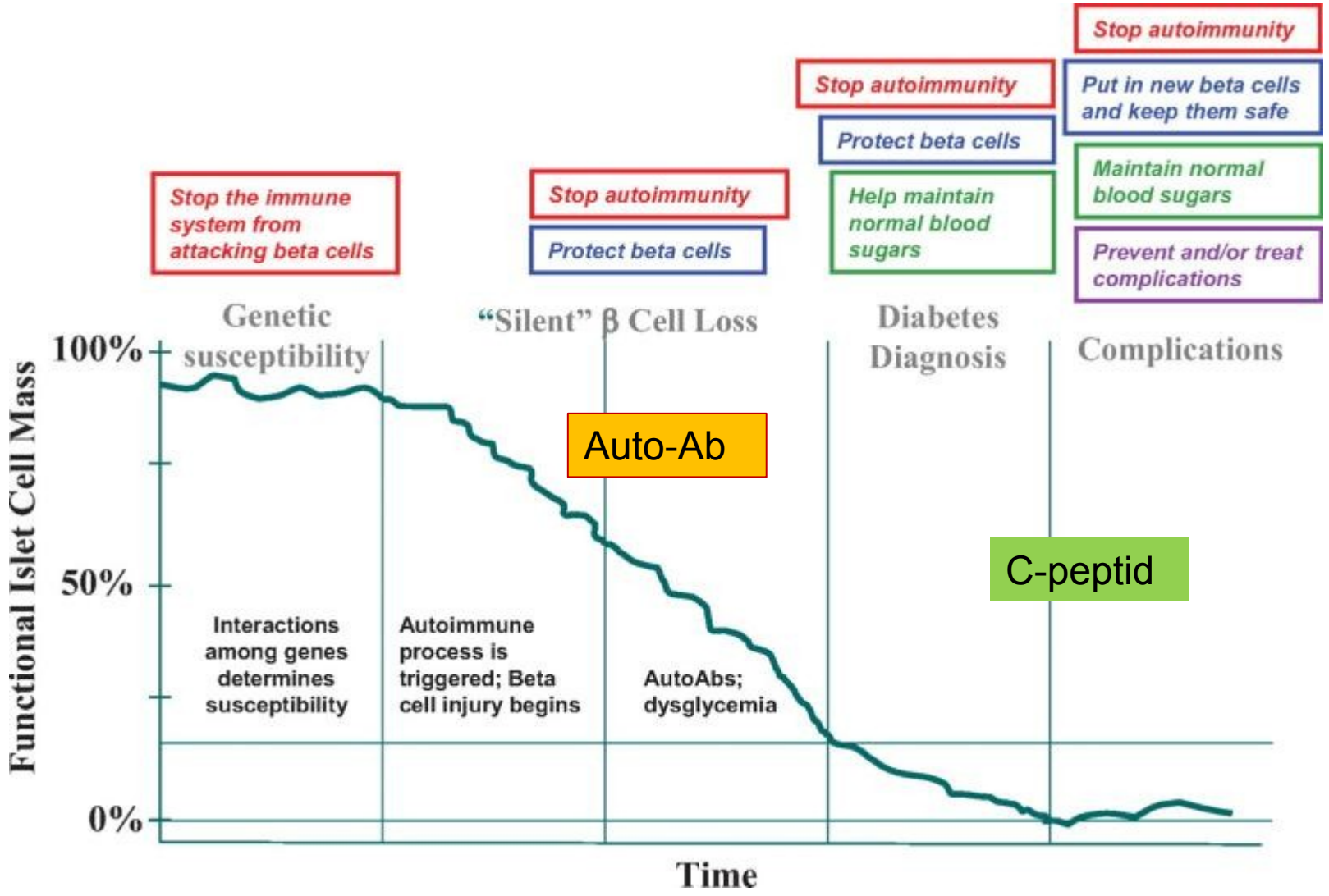


Strategy of new pathogenic mechanisms and terapy

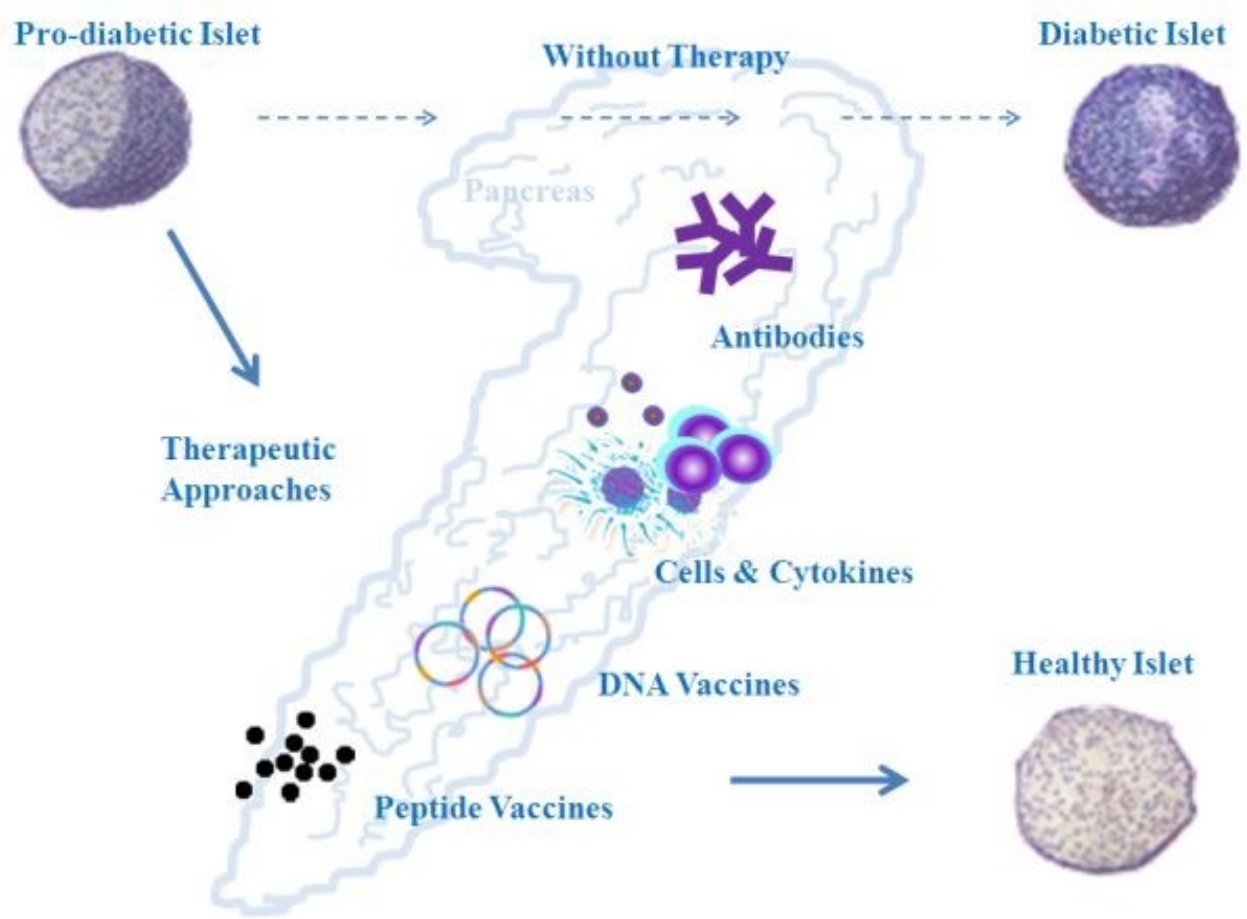


Lernmark, Å. & Larsson, H. E. (2013) Immune therapy in type 1 diabetes mellitus *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2012.237

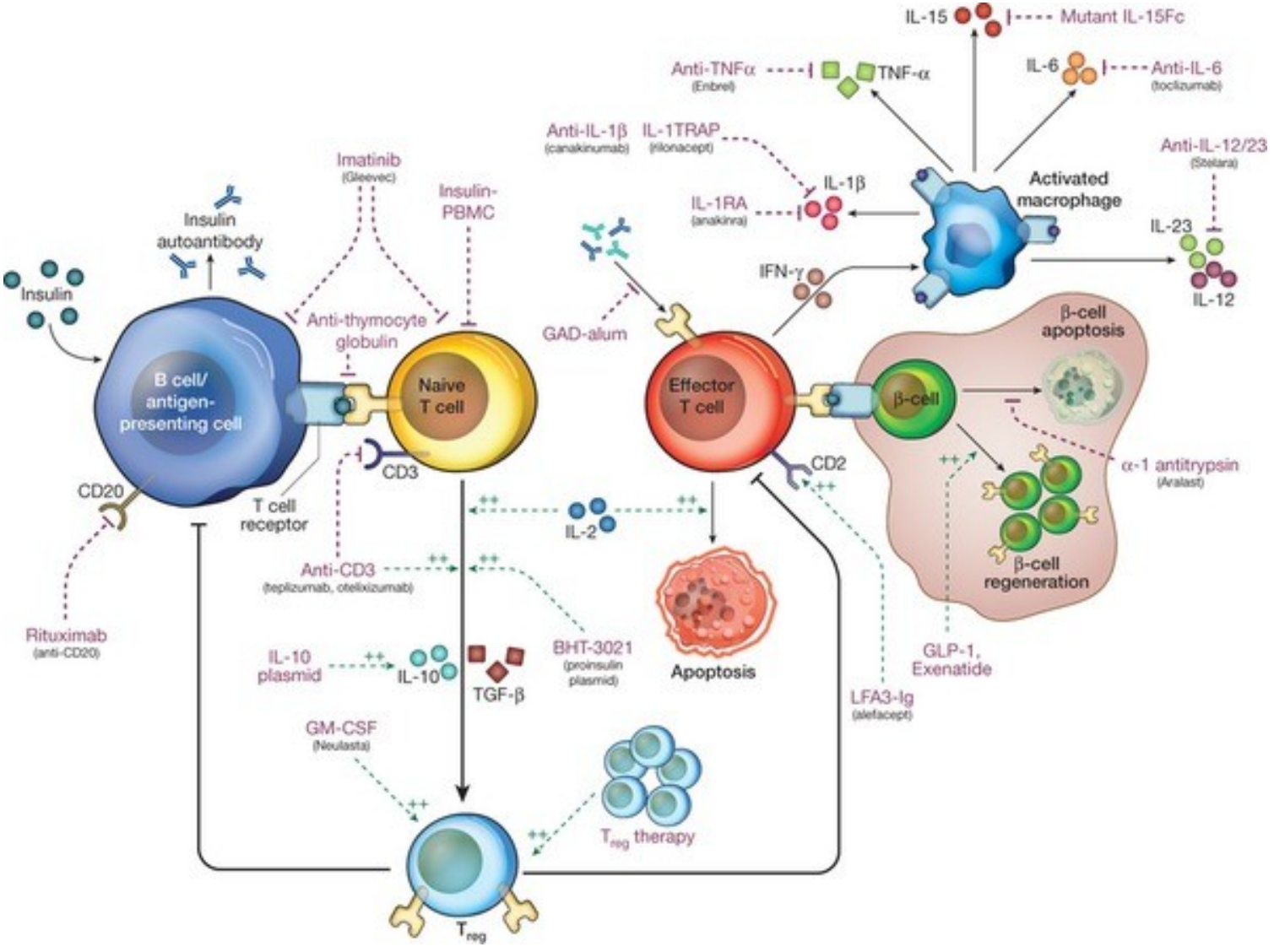
Preventing studies according to progression of disease



Therapeutic options



Immunomodulation



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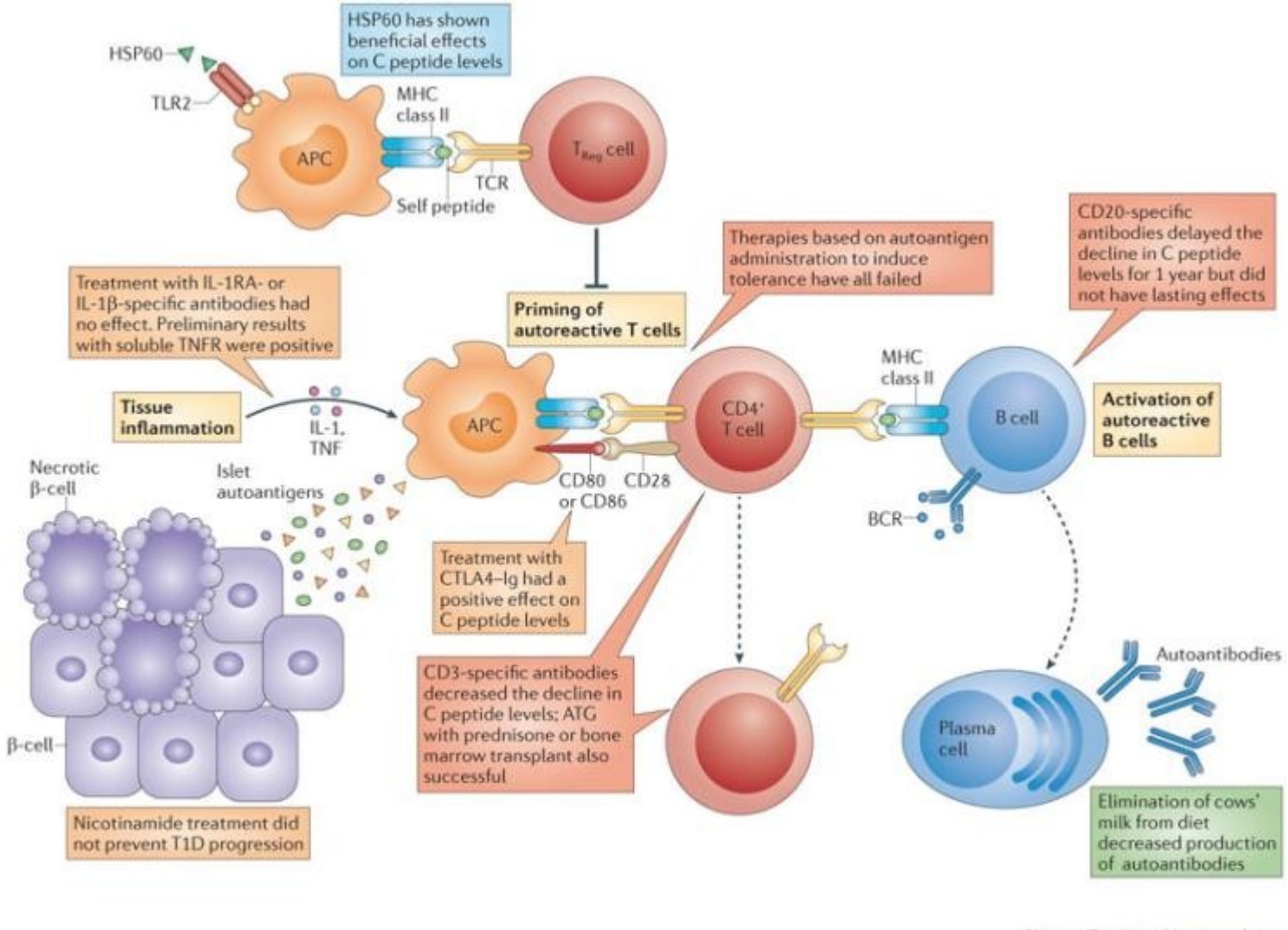

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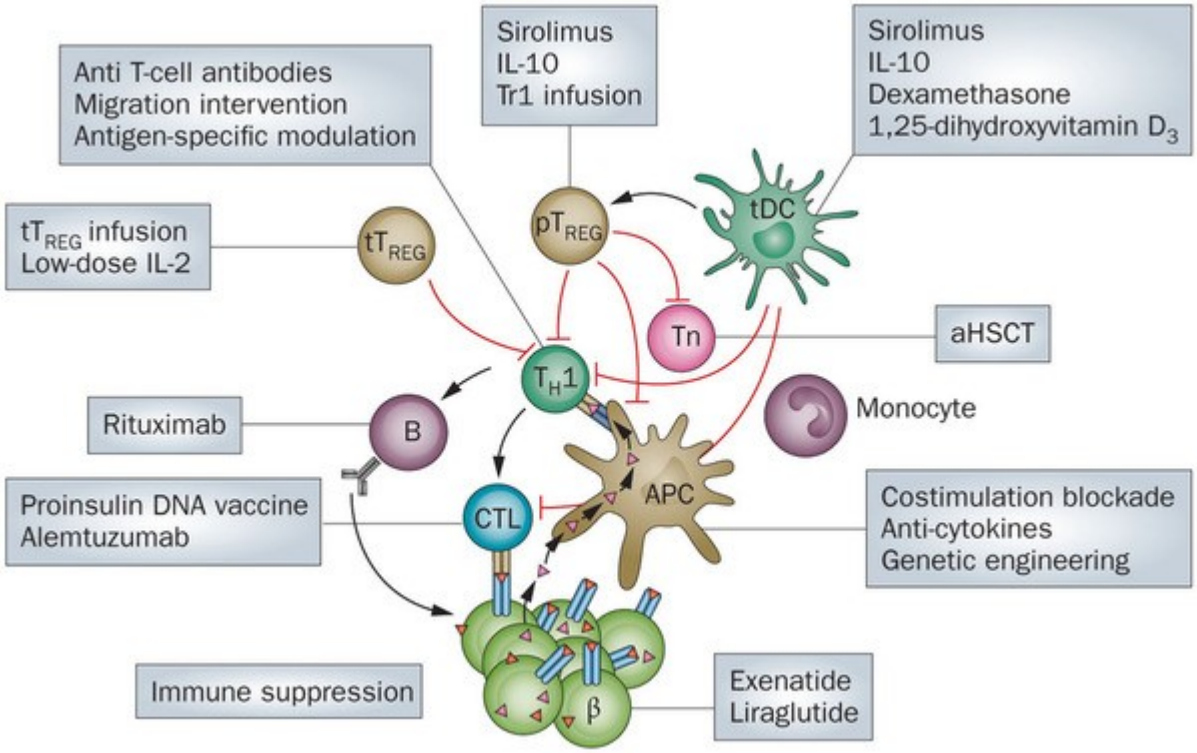
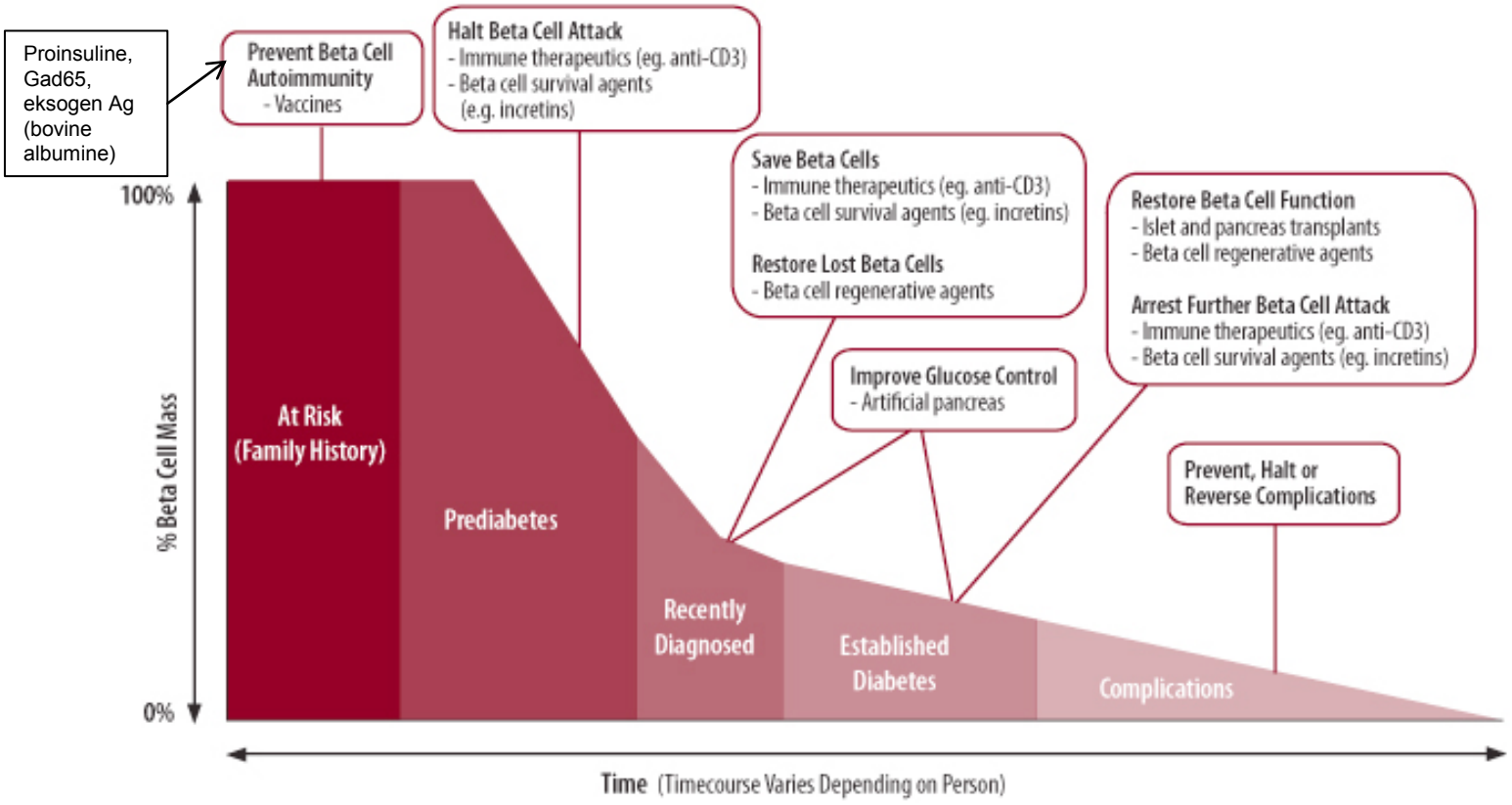
Targets of new immunomodulation therapy



Therapeutic options

how to "cure" at different stages of the disease.



Cure-targeted strategies and therapies for type 1 diabetes broken down by stage of disease. (Adapted from JDRF).

Transplantation options and future direction

- Pancreas transplant
  - Dual organ transplant with kidney
  - 3 year survival is 90%
  - Long term immunosuppresion
- Islet Cell transplant
  - Portal injection
  - 11.000 islet equivalents/kg body weight
  - Difficulties in recovering islet tisue from donor pancreas
- Xenogenic islet cells (humanized pig islet cells)
- Pancreatic duct cells (expansion and transdifferentiation)
- Fetal pancreatic stem cells and b cell precursors
- Embrionic stem cells
- Engineering other cells to produce insulin (duodenal K cells, hepatocytes)

Are we on the right way ?

Still not have the whole picture