Forte associazioni tra HLA e rischio di sviluppare diabete di tipo 1: perché ce ne dimentichiamo negli studi di meccanismi immunologici?

Georgia Fousteri, PhD

10-6-2016

Summer School AIBT, Pesaro, IT

SAN RAFFAELE DIABETES RESEARCH INSTITUTE

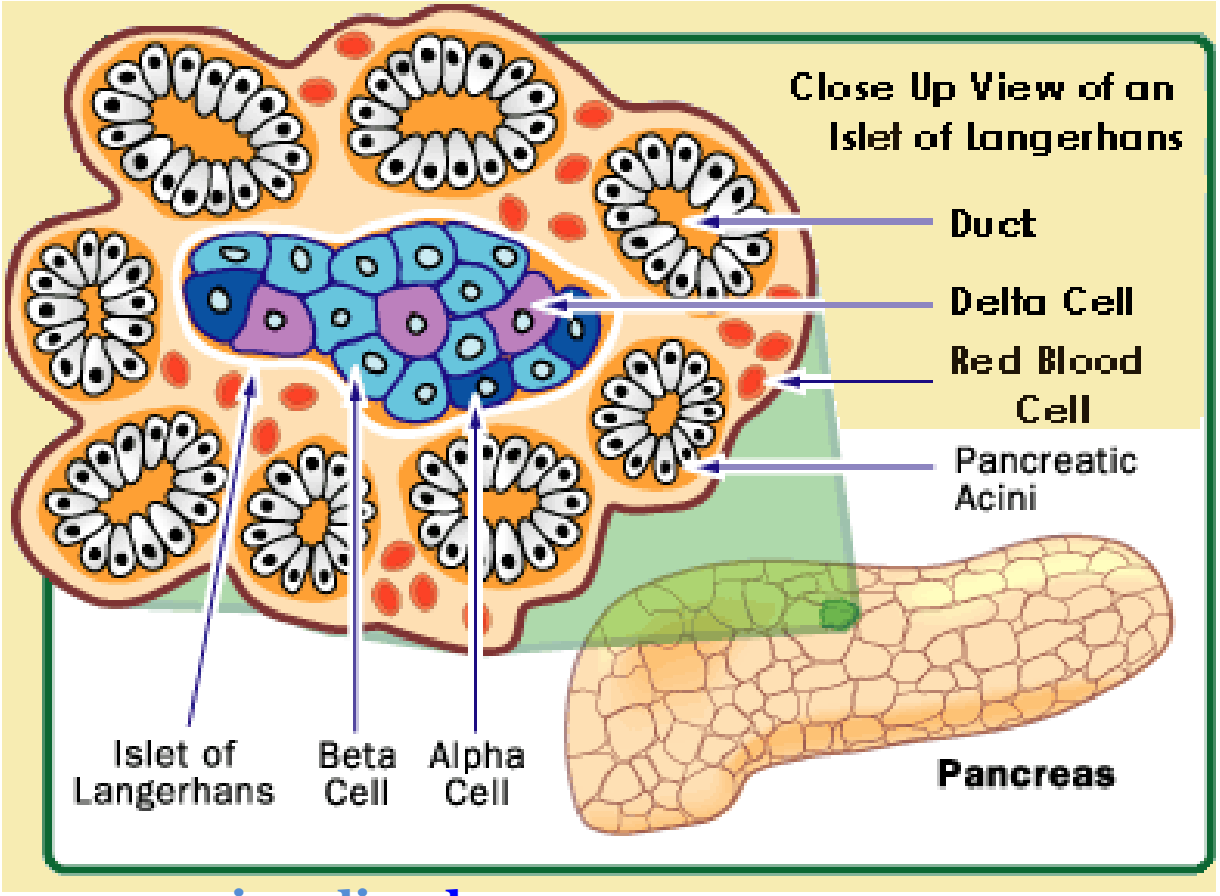
Division of Immunology, Transplantation and Infectious Diseases

DIABETES RESEARCH INSTITUTE

Talk outline

- What is T1D?
- Which factors contribute to T1D pathogenesis and how?
- Which HLA associate with T1D risk?
- Which other genetic factors associate with T1D?
- How can we predict T1D?
- How are subjects stratified according to their risk for developing T1D?
- Why genetics are not taken so much into consideration in immunological studies?

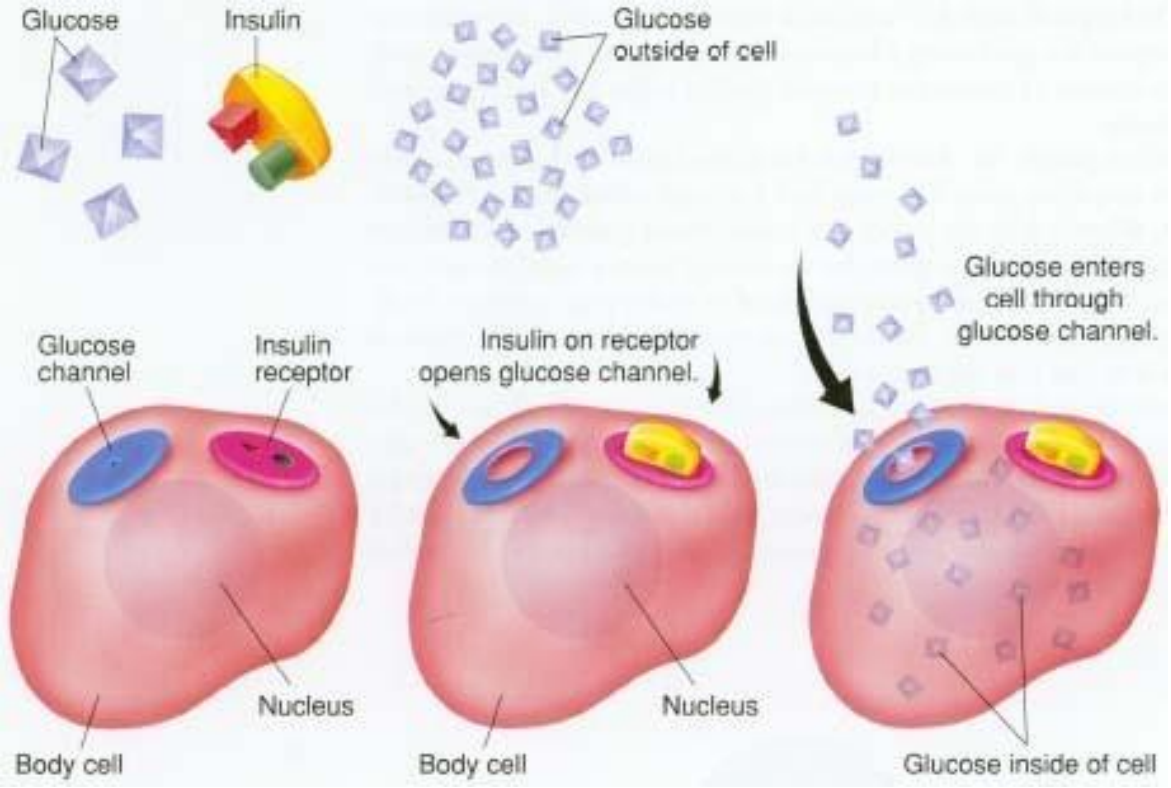
The Pancreas



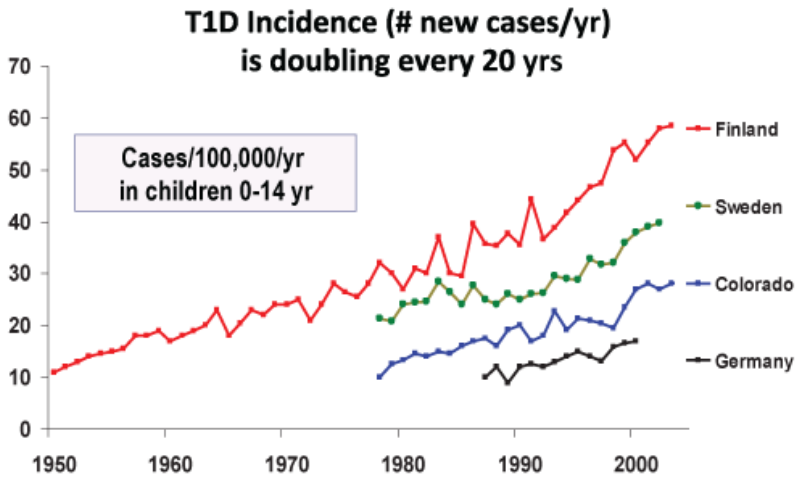
insulin glucagon

What is Insulin? What does it do?

Hormone, causes body cells to take up glucose from the blood.

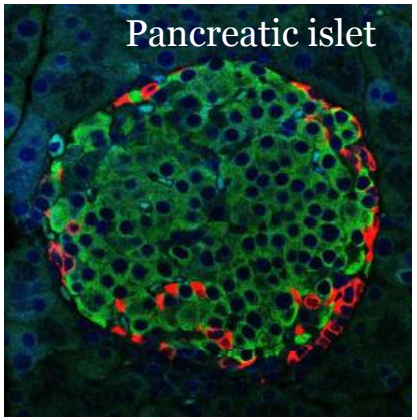


Type 1 Diabetes "old view"

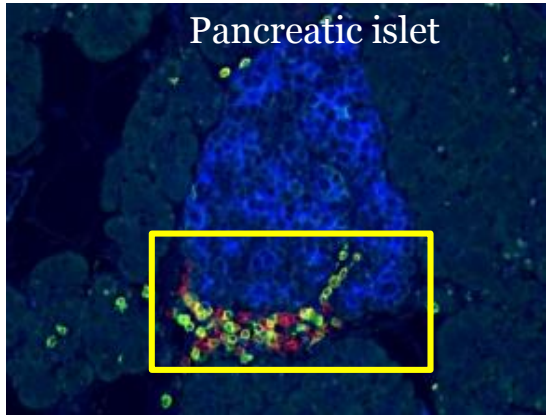


Ann NY Acad Sci 2008

Normal



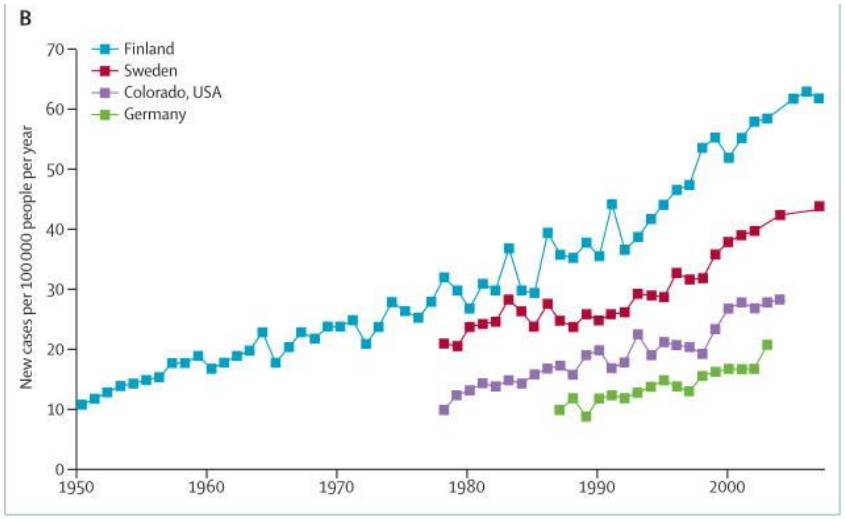
T1DM



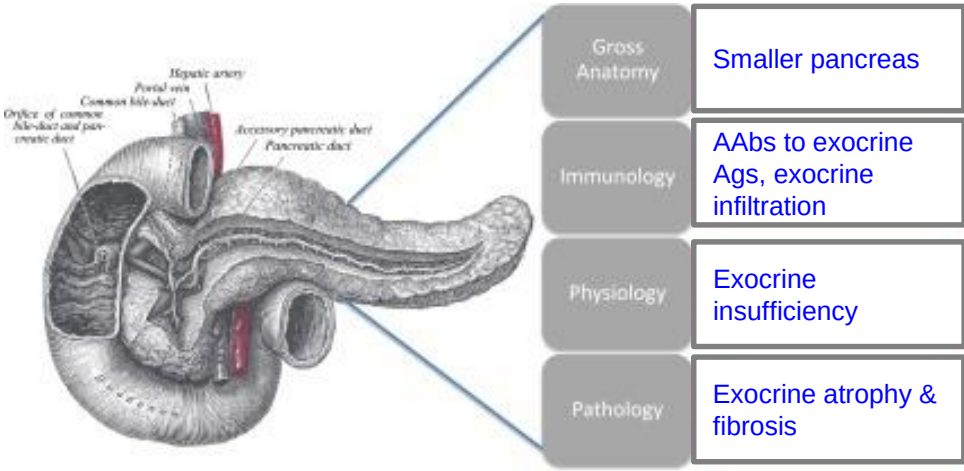
Rate constrantly increases

Autoimmune disease affecting insulin-producing beta cells

Type 1 Diabetes "updated view"



Atkinson, Lancet, 2015



Atkinson, Diabetes, 2014

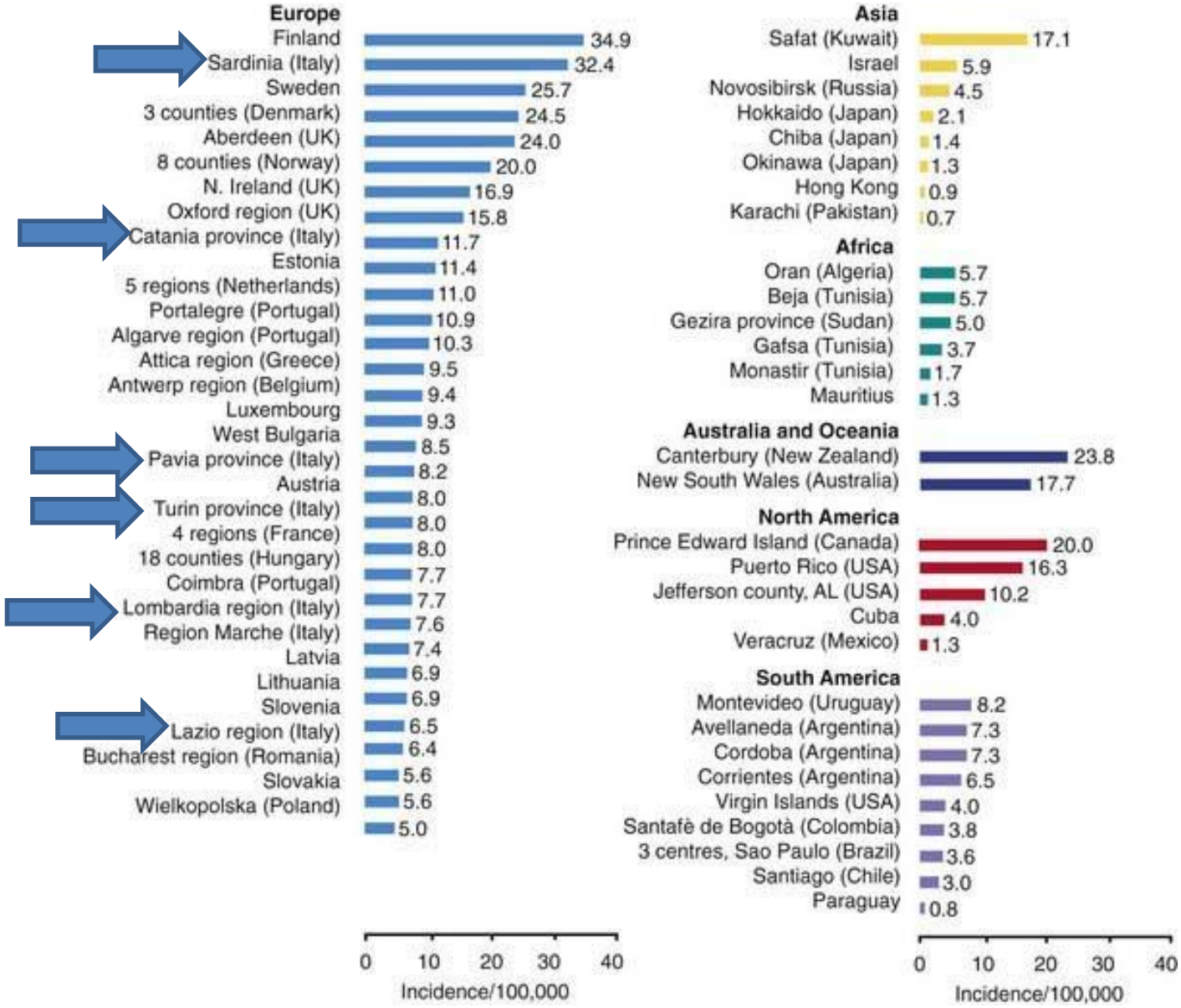
Rate increases mostly in children, has reached a plateu in certain countries

Not a beta-cell specific disease, but a pancreas disease

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

nPOD Network for Pancreatic Organ Donors with Diabetes

Prevalence of Type 1 diabetes in the world



Symptoms, Diagnosis & Treatment

- Polyuria
- Polydipsia
- Polyphagia
- Glycosuria
- Lipidemia: *Lack of insulin starves body of glucose, body begins metabolizing fatty acids as energy source.*
- Diabetic ketoacidoses: *ketones build up in blood, dropping Ph*
- Ketouria: *Ketones in urine*

.....Secondary complications
-Macular degeneration
-Kidney failure...

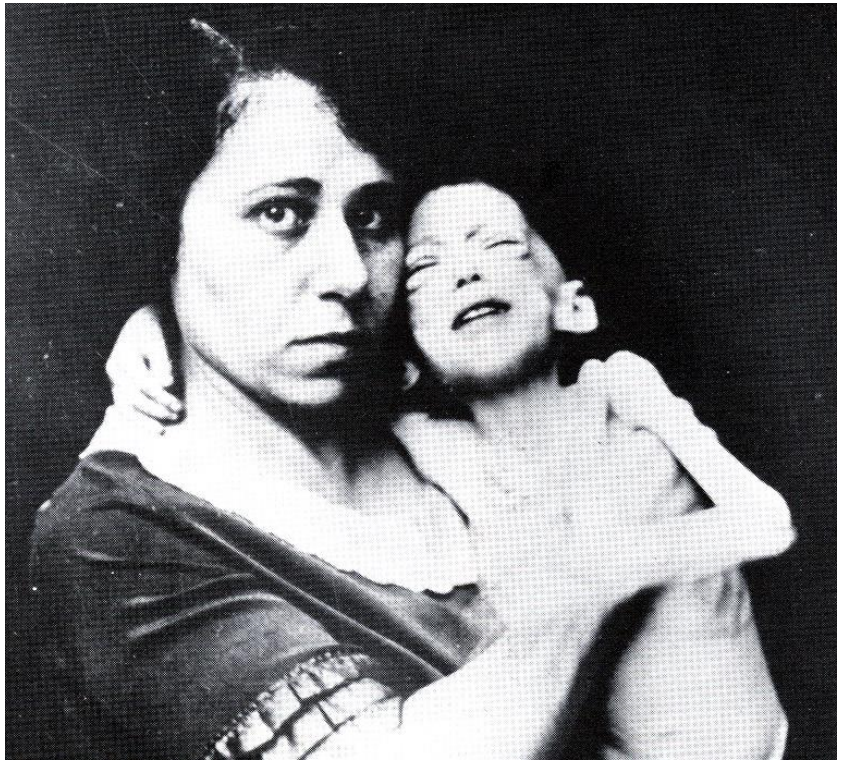
- Fasting plasma glucose levels.
- Detection of antibodies against islet antigens (insulin, beta cells, etc.) in the serum.

→Detects autoimmunity before diabetes is clinical

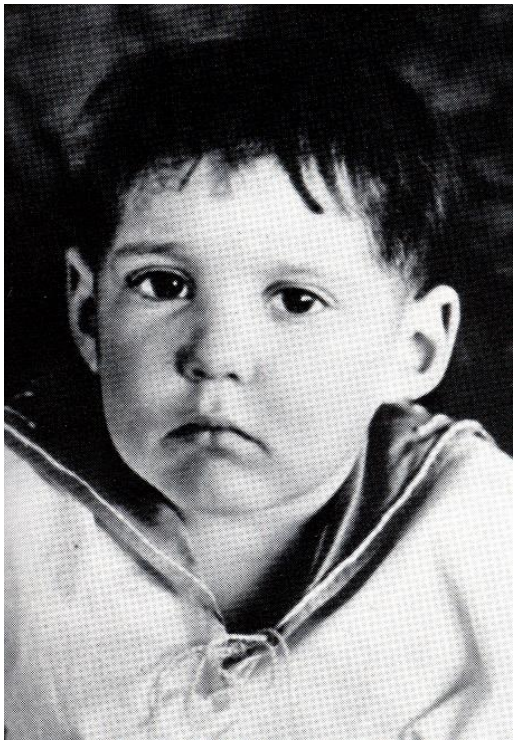
- HbA1c levels

Insulin replacement

Almost 100 years since the discovery of insulin



1922



1923

Banting and Best

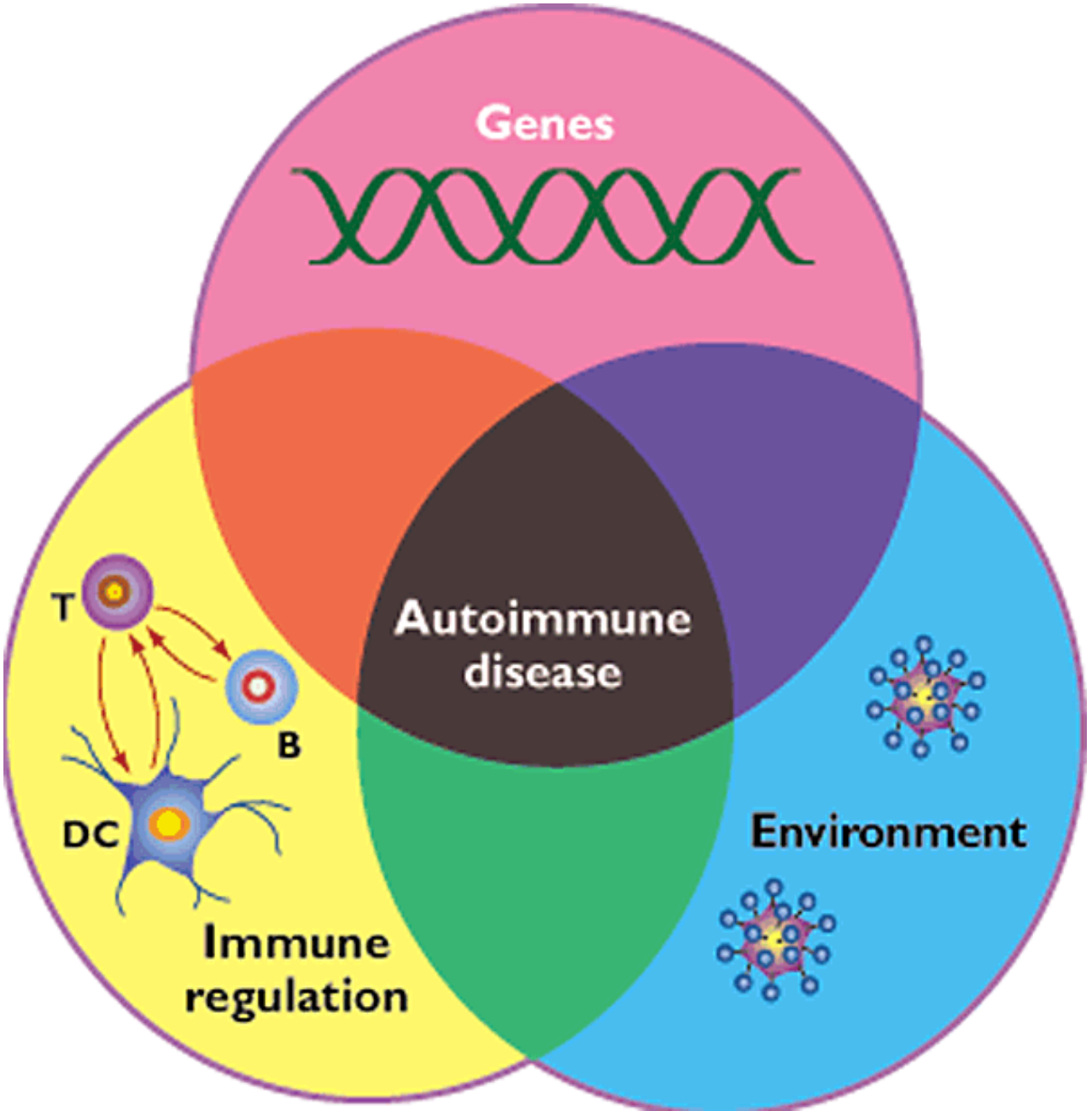
1923 Nobel Prize for discovery of insulin

but.. Insulin therapy treats the symptom and not the disease

Type 1 diabetes is currently non-preventable or curable in humans

How are we going to prevent or cure the Type 1 diabetes?

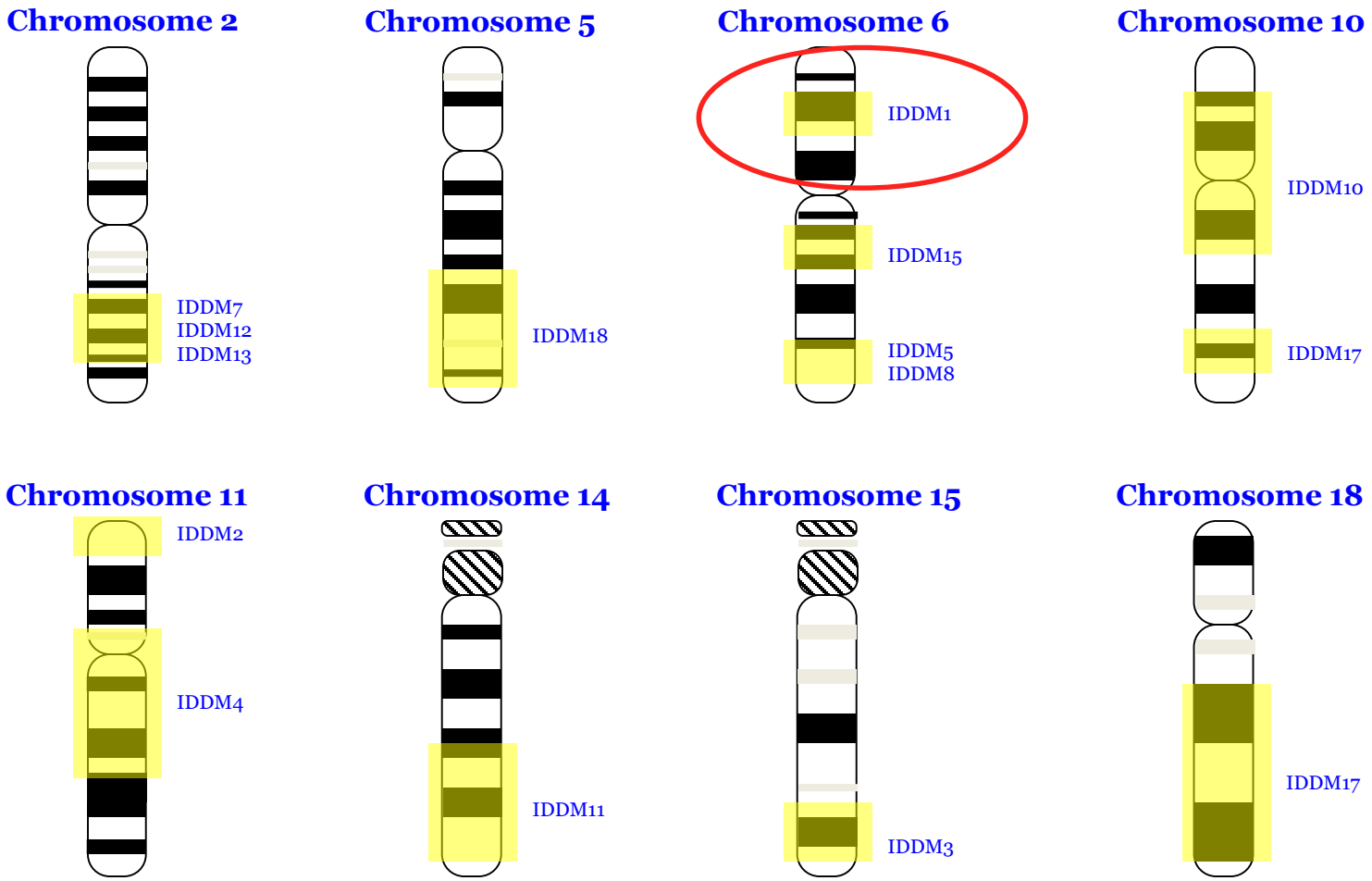
Type 1 diabetes is a multifactorial disease



Joerg Ermann &
C. Garrison Fathman
Nature Immunology
2, 759 - 761 (2001)

Type 1 diabetes susceptibility loci

18 regions of the genome have been linked with influencing type 1 diabetes risk.



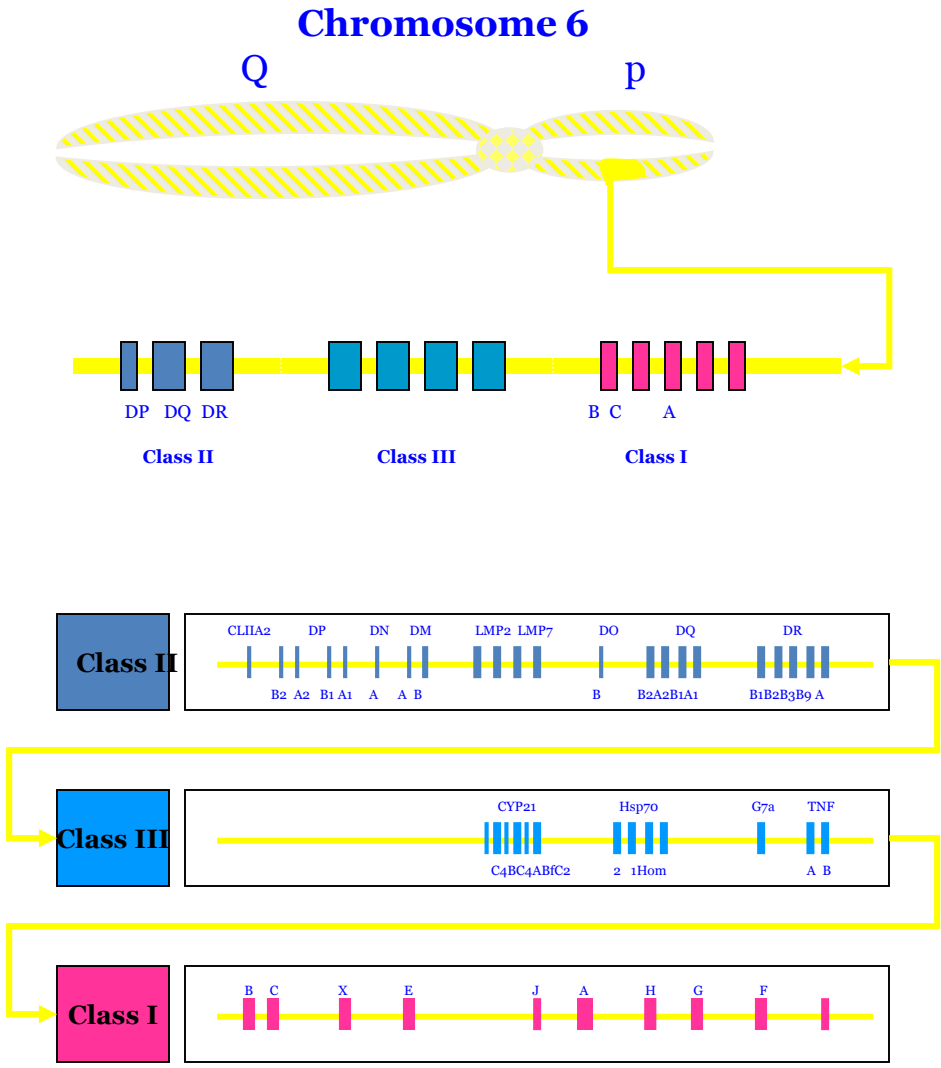
IDDM 1

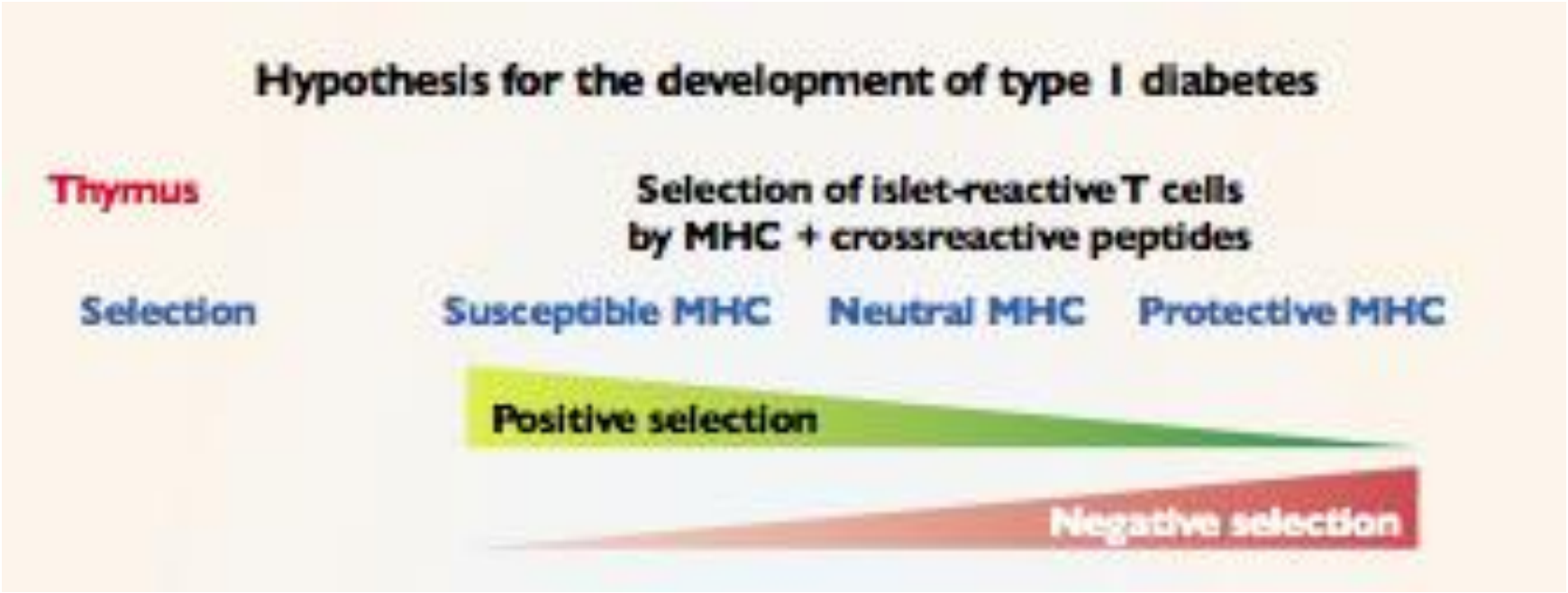
HLA alleles documented in the 1970s.

Locus contains many diabetes susceptibility genes.

predisposing: HLA DR3-DQ2, DR4-DQ8

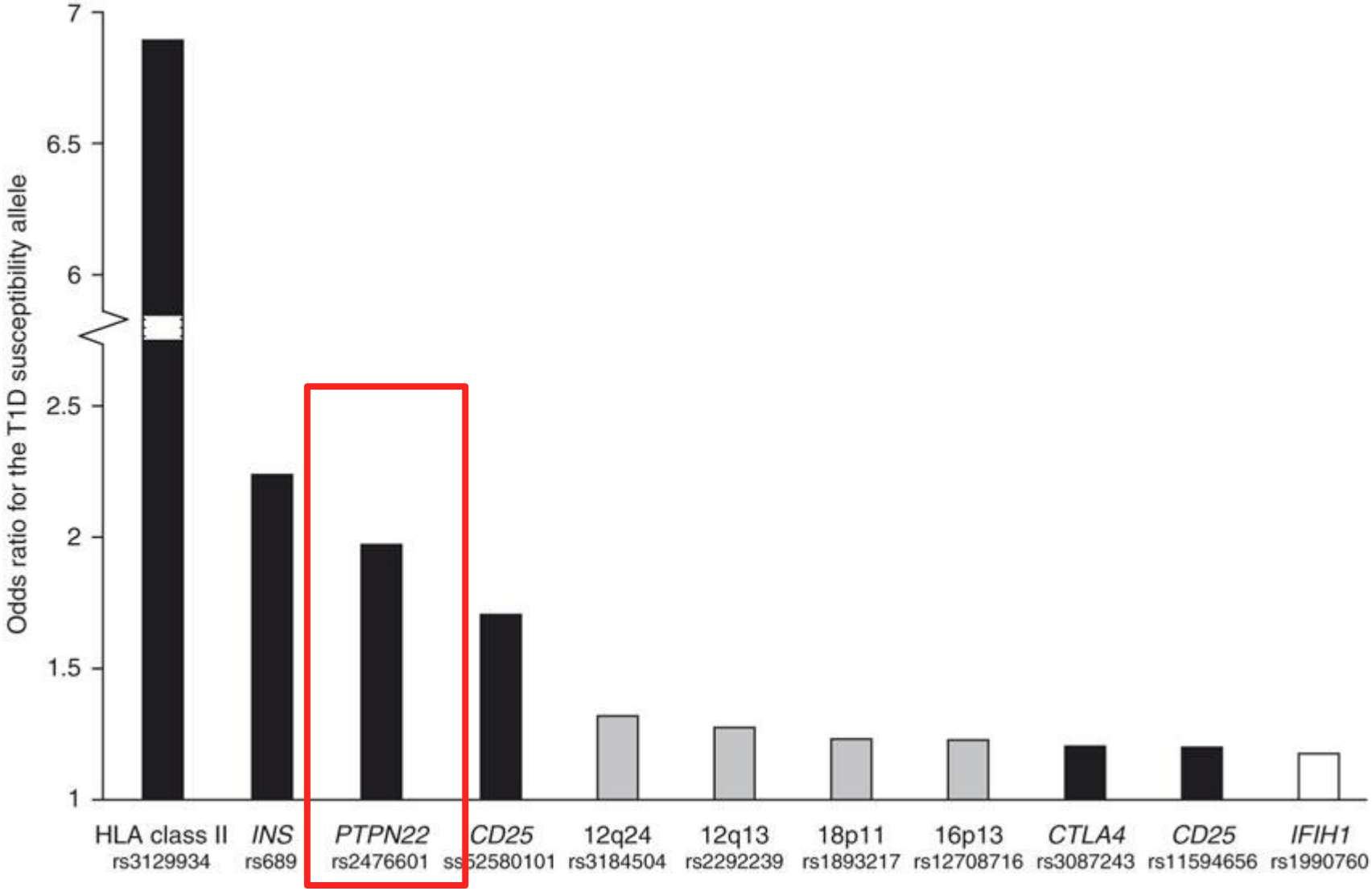
protective: HLA DR2-DQ6





KAI W. WUCHERPFENNIG1 AND GEORGE S. EISENBARTH.:Type 1 Diabetes

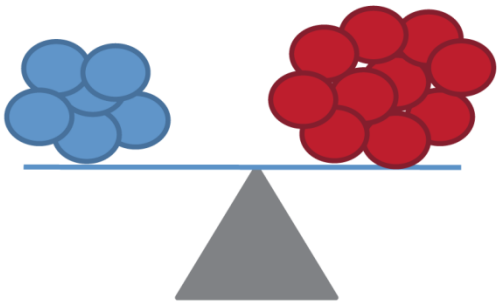
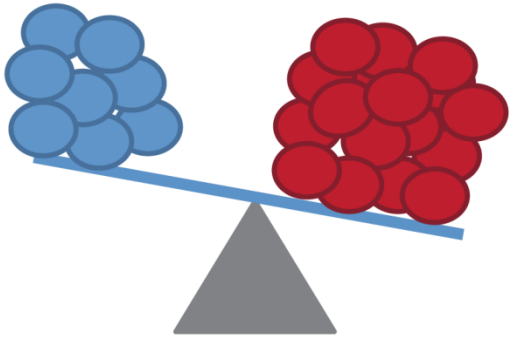
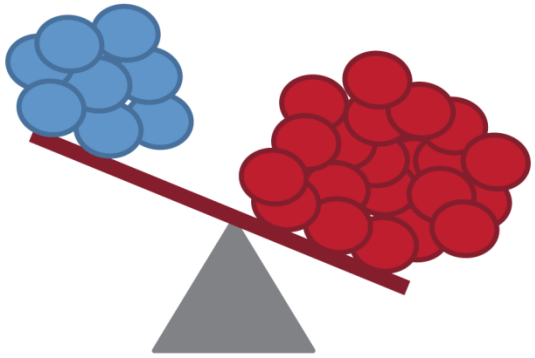
Other genetic factors in T1D

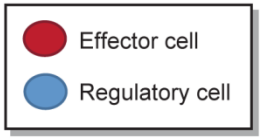


Todd JA, Nat Genetics, 2007

Hypothesis

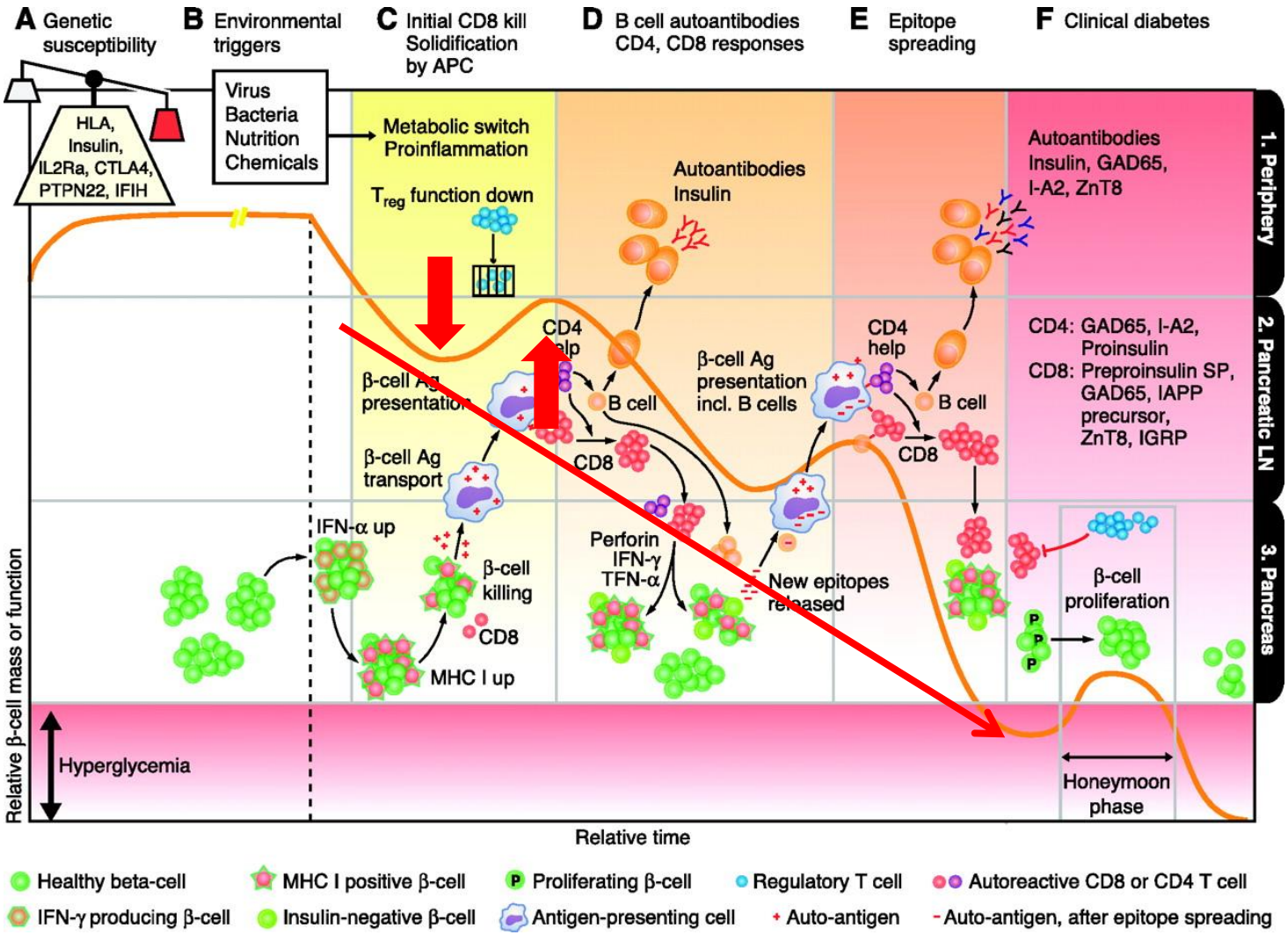
Alterations lead to disequilibrium and... → **Autoimmmunity**

Healthy	Genetic polymorphisms *At risk*	Trigger? *Disease*
		
TOLERANCE	**TOLERANCE**	**TOLERANCE**



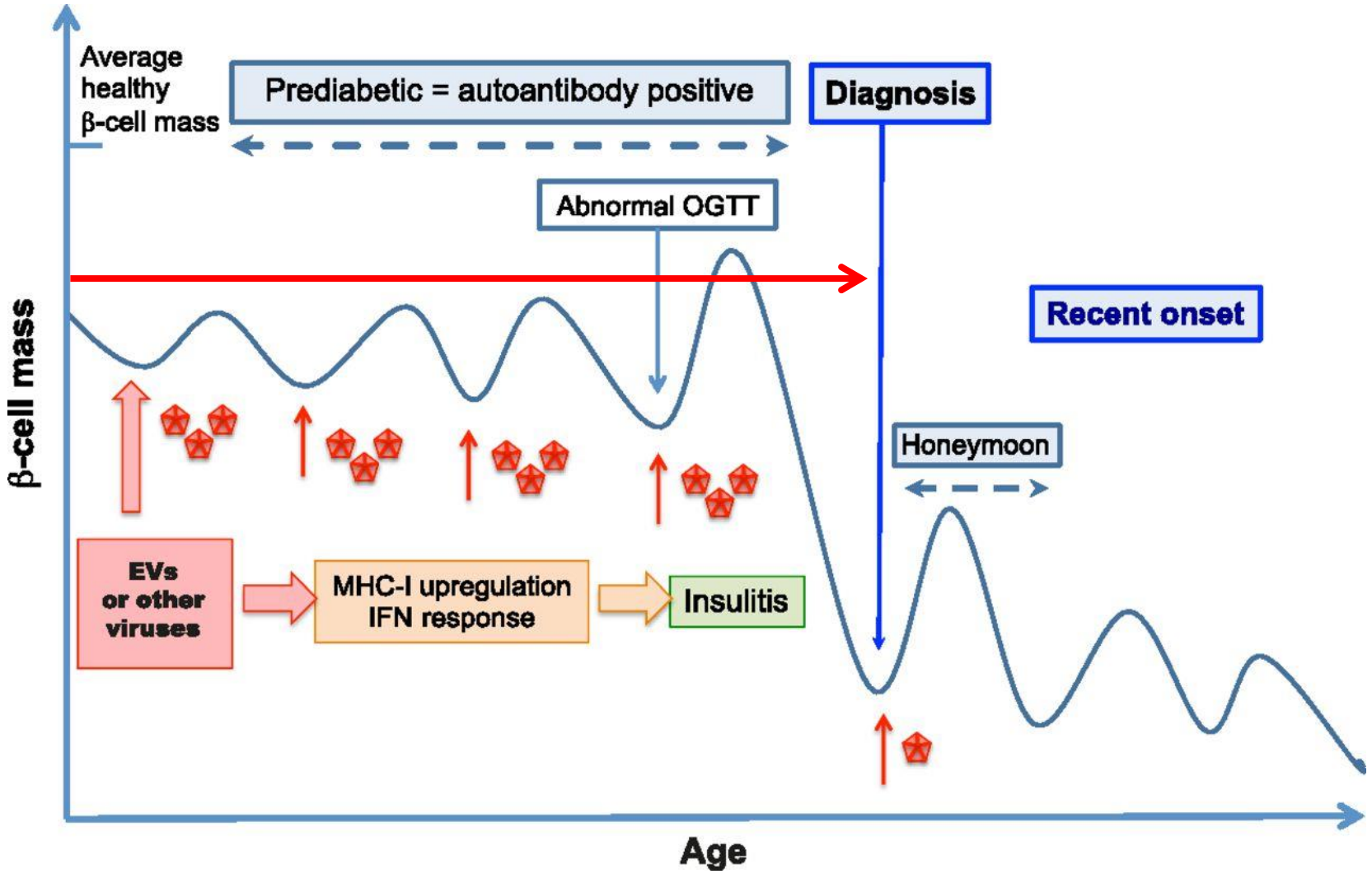
***Fousteri G** et al, Curr Diab Rev, 2016*

Beta cell loss during progression to T1D
Old view



Van Belle et al, Physiol. Rev, 2011

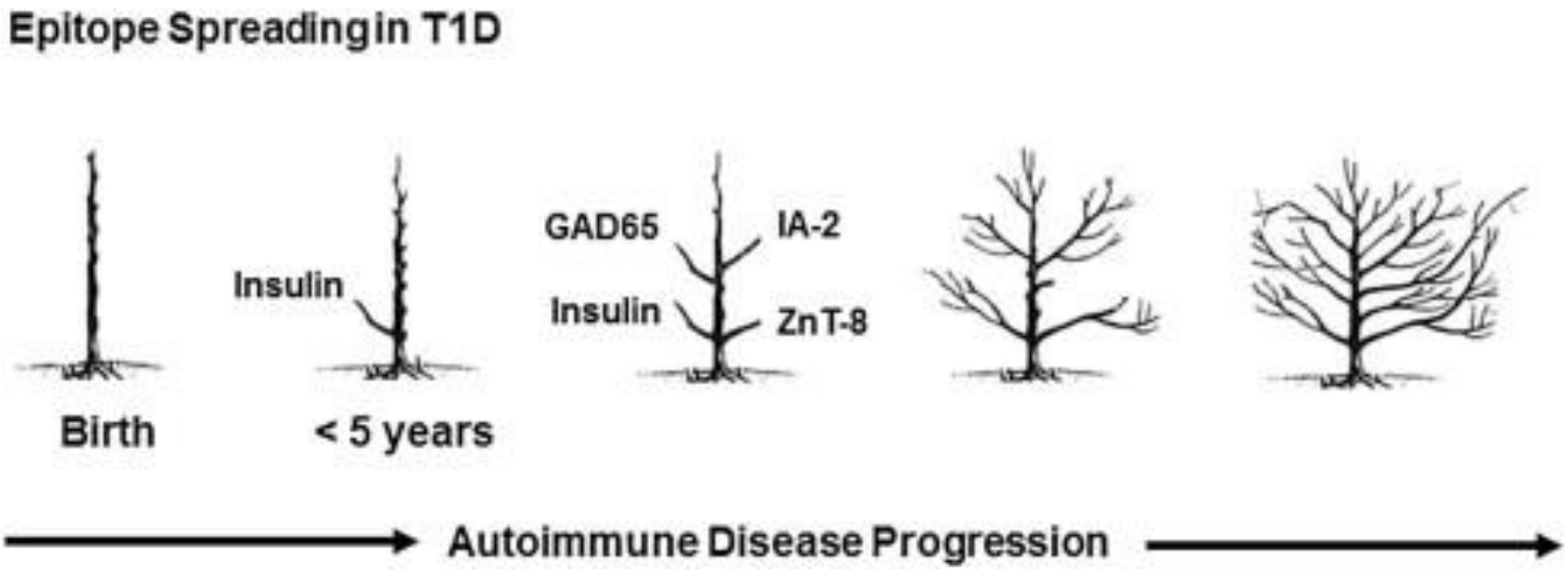
Beta cell loss during progression to T1D
Updated view



Teresa Rodriguez-Calvo, and Matthias G. von Herrath
Diabetes 2015;64:1503-1505

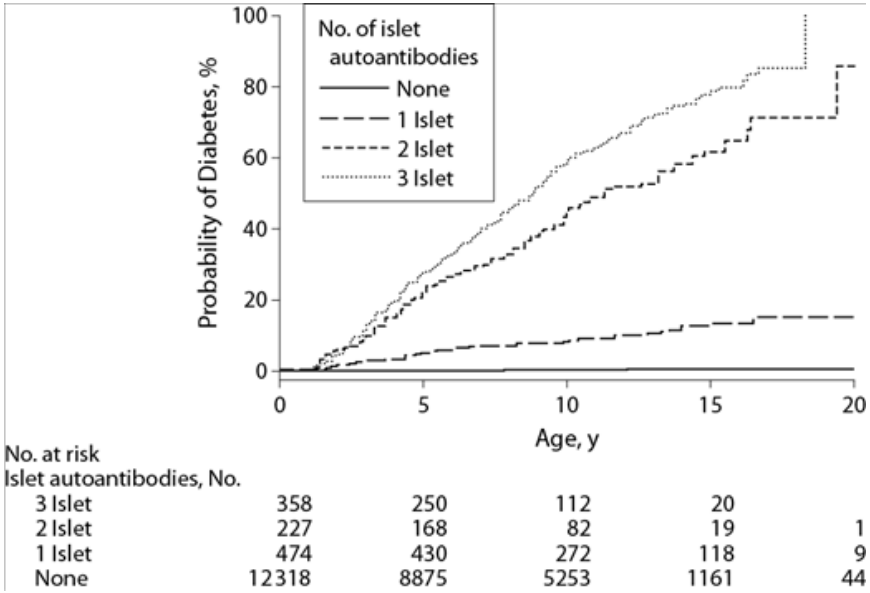
How can we predict the development of T1D?

Development of islet-specific high-affinity autoantibodies is a hallmark of progression to T1D

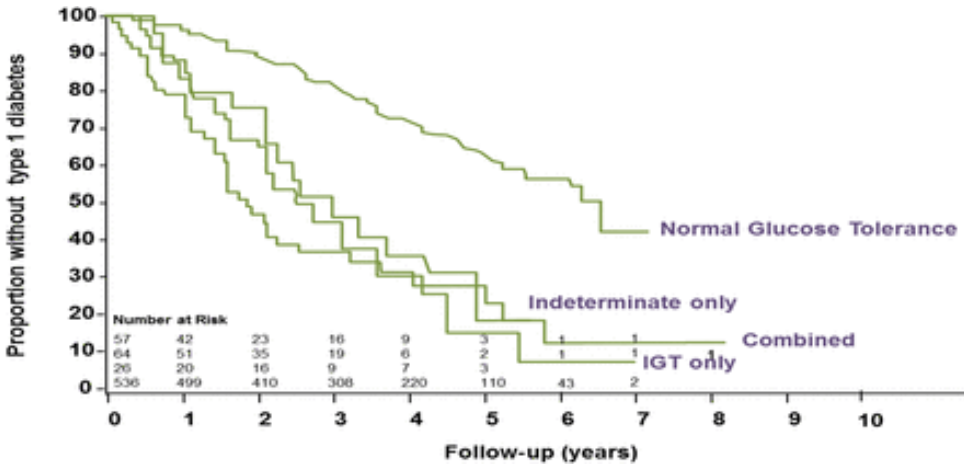


Morran M, Mol Asp Med, 2015

Islet-specific autoantibodies (Aabs) are the best predictive biomarkers for T1D



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44



70% chance to develop T1D in 10 yrs if 3 islet-specific AAbs or more

Probability of progression from dysglycemia stage 2 to T1D is >90%

Ziegler A et al, NEJM, 2013

Unpublished (Insel RA et al, Diabetes Care, 2015)

Today T1D risk scoring is calculated:

Genetic susceptibility:
HLA risk genotypes: HLA *DRB1*03* and **04* and *DQB1*0302*.
HLA protective genotypes: HLA *DQB1*0602*, **0301*, **0303*, **0603*, and **0503*.
Genetic risk score derived from HLA plus nine single nucleotide polymorphisms from *PTPN22, INS, IL2RA, ERBB3, ORMDL3, BACH2, IL27, GLIS3,* and *RNLS* genes.

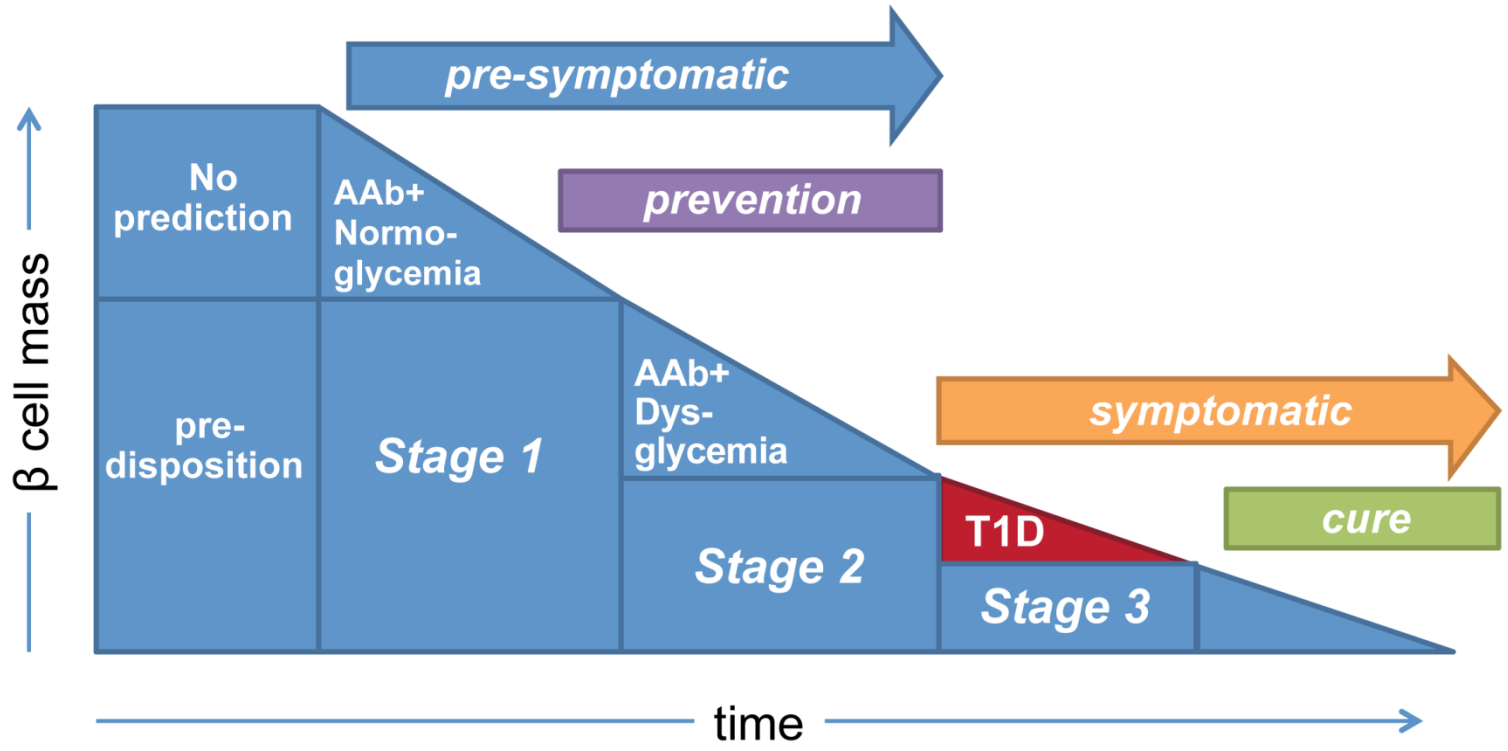
Number, type and titer of Aabs:
IAA, ICA, IA-2, ZnT8, GAD65

Family history:
Father, mother, sibling, twin, multiple affected FDRs

OGTT:
Dysglycemia or not

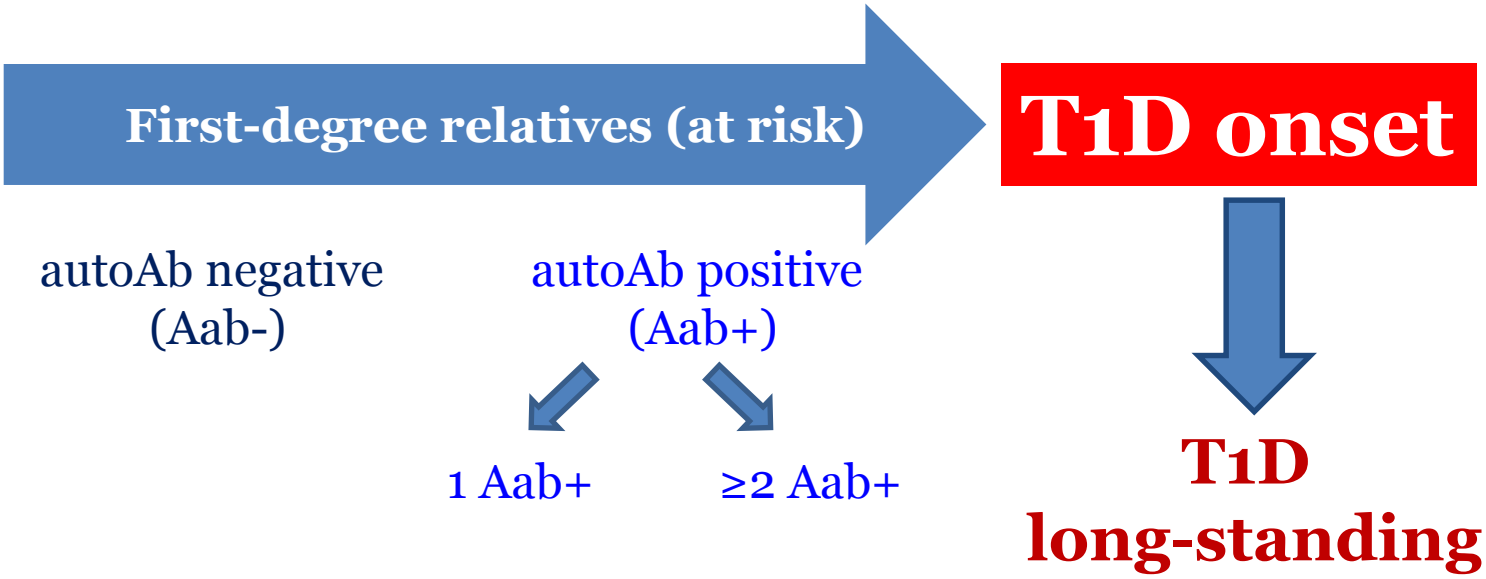
Score: .....

Staging Presymptomatic Type 1 Diabetes:
A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association



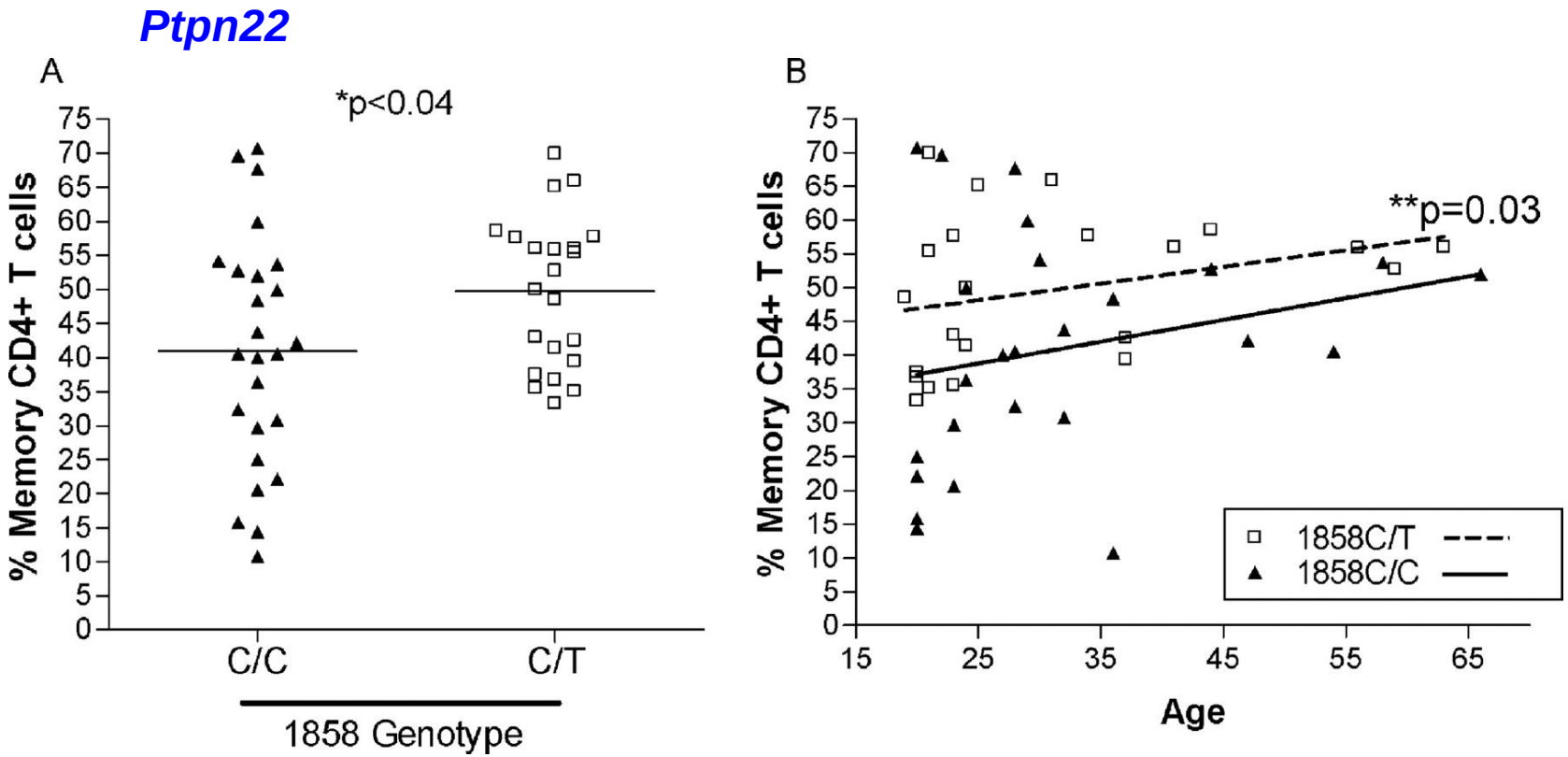
Modified Insel RA et al, Diabetes Care 2015
Fousteri G et al, Curr Diab Rev, accepted

Most immnological studies stratify the subjects:



Wihout taking into consideration the genetics…

An example of how genetics can change the results…



Mary Rieck et al. J Immunol 2007;179:4704-4710

Taking into account just one gene…

Imagine if to take into account just all genes, their polymorphisms and the different groups of donors…

Imagine the number of data produced…

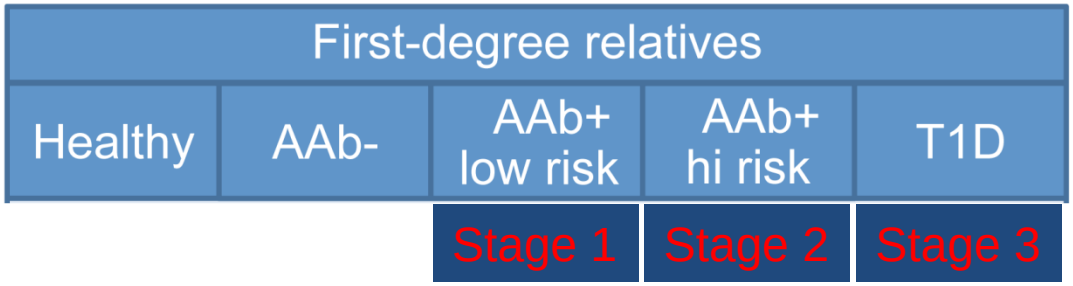
Imagine the cost of genetic analysis…

Also we don’t know how the combination of all these genes can be used as biomarker to predict risk for T1D…

Only reliable biomarker that predicts risk to T1D is:

number of AAbs and OGTT

the best stratification we can do is:



Summary

- **What is T1D? Autoimmune pancreas-specific disease**
- **Which factors contribute to T1D pathogenesis and how? Genetic and environmental**
- **Which HLA associate with T1D risk?HLA DR3-DQ2 and DR4-DQ8**
- **Which other genetic factors associate with T1D? 18 IDDM loci, *PTPN22, INS etc***
- **How can we predict T1D? islet-specific AAbs and OGTT**
- **How are subjects stratified according to their risk for developing T1D? Stage 1 (low risk), 2 (high risk) and 3 (patients)**
- **Why genetics are not taken into consideration? We still don't know how they can stratify subjects according to risk**

Acknowledgements

DEDICATED TO FINDING THE CURE

Regulation of Adaptive Immunity

Tatiana Jofra
Roberta Di Fonte
Elio Ippolito
Jolanda Gerosa
Giuseppe Galvani

Immune-mediated diseases

Manuela Battaglia
Angela Stabilini
Bechara Mfarrej

San Raffaele International Postdoctoral Programme

REPVBBLICA ITALIANA
Ministero della Salute

RIC FIN 2011-2012
GR11-127

MARIE CURIE ACTIONS

UE7RNPTPN22
276745

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

ZJDRF 10-2012-204

1-FAC-2016-144-A-N

xmille SANRAFFAELE