Immunologie du diabète de type 1: outils diagnostiques

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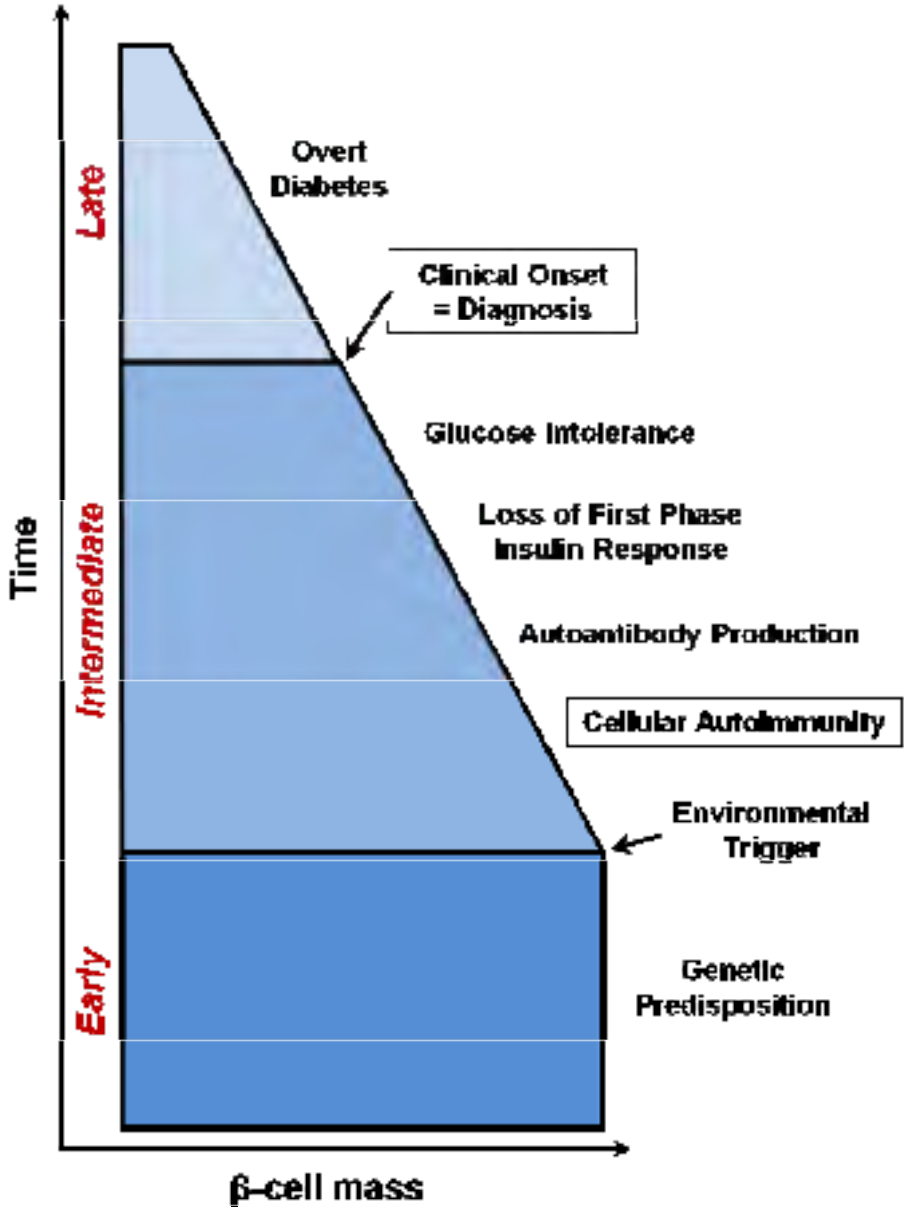
Diagnostic options in type 1 diabetes

Type 1 Diabetes: a T-cell-mediated autoimmune disease

Metabolic manifestations are only the tip of the iceberg



A period of silent

β-cell autoimmunity

precedes clinical onset

→ search for <u>autoimmune</u> markers:

*** earlier**

*** may provide mechanistic insights**

Type 1 diabetes immune markers: what for?

3 objectives:

1) Risk stratification for early diagnosis/intervention:

* Identify pre-clinical β-cell autoimmunity before extensive β-cell destruction
* Metabolic markers (i.e. reduced insulin responses) come too late

2) Etiological classification at diagnosis:

* The ‘black or white’ dichotomy T1D-T2D is rather a grayscale
* Does a given diabetes case have an autoimmune component?

3) Markers of immune tolerance restoration in intervention trials:

* Early surrogate immune markers of clinical efficacy

Type 1 diabetes immune markers: which ones?

1) Islet autoantibody markers

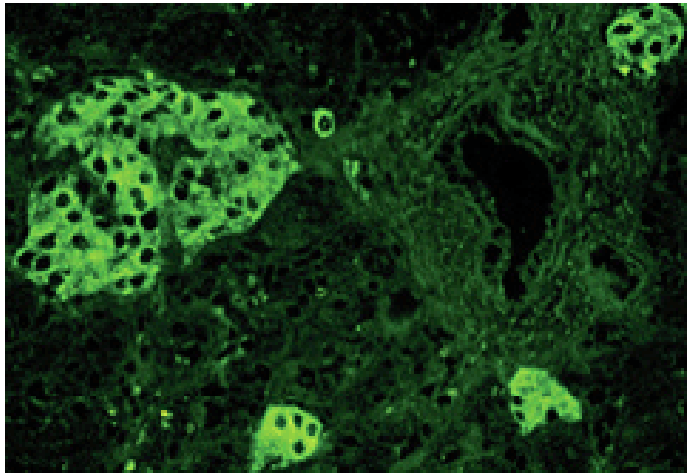
2) Genetic markers

3) T-cell markers

4) Islet imaging markers

1) Islet autoantibody markers

The origins



- Sera from T1D patients capable of recognizing pancreatic islets
- Discovery of ICA (Islet Cell Antibodies)
- Subsequent definition of their molecular specificity

→ Today:

immunoassays for anti-GAD, anti-IA-2, anti-insulin (IAA), anti-ZnT8

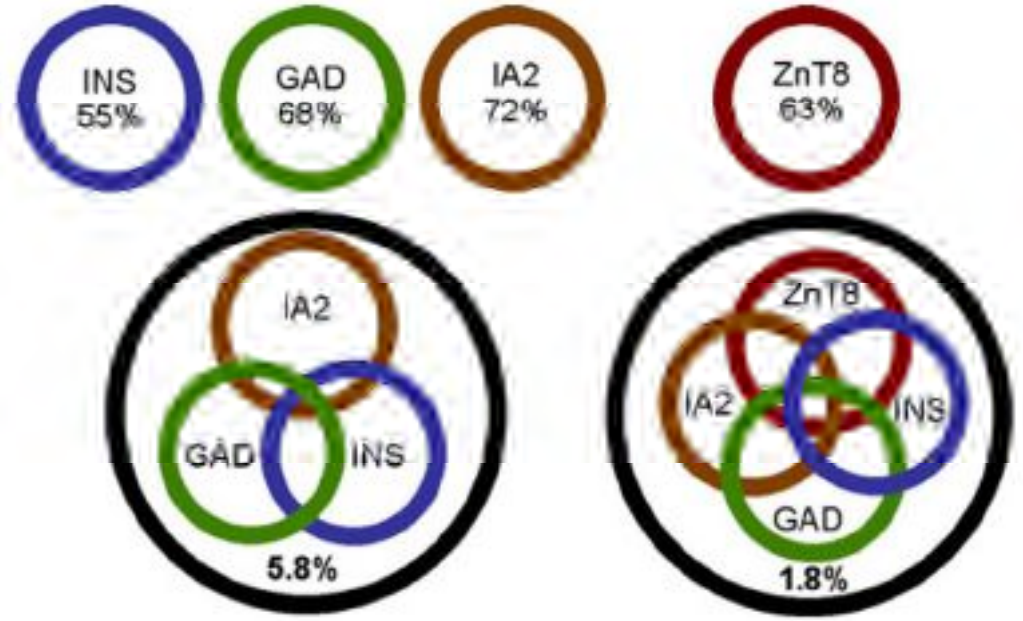
Bottazzo et al., *Lancet* 2:1279 (1974)

1) Islet autoantibody markers

Significance

A combination of GAD, IA-2, IAA and ZnT8 identify:

1) 95-98% of patients at T1D onset
→ useful for etiological classification of new-onset diabetes cases (T1D or diabetes with an autoimmune component, e.g. LADA)



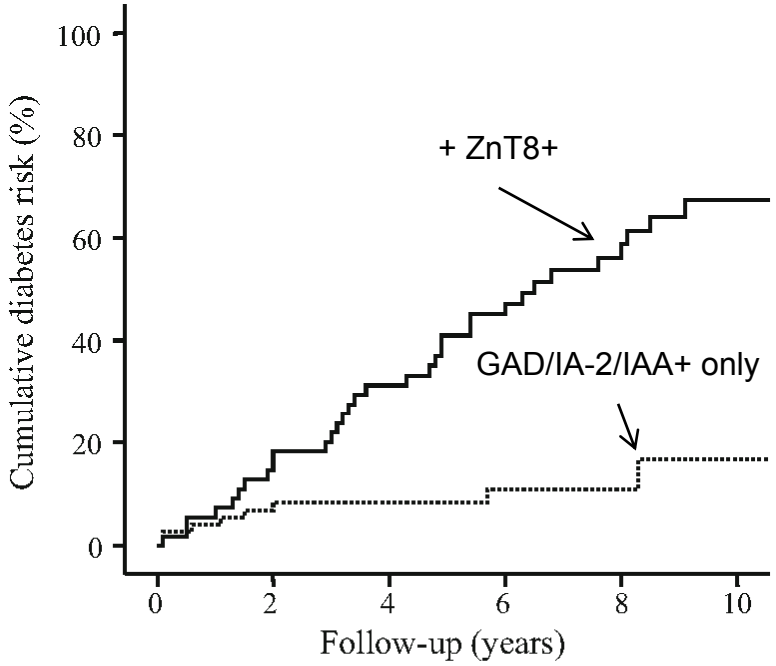
1) Islet autoantibody markers

Significance

A combination of GAD, IA-2, IAA and ZnT8 identify:

2) 75-90% of individuals at risk of developing T1D

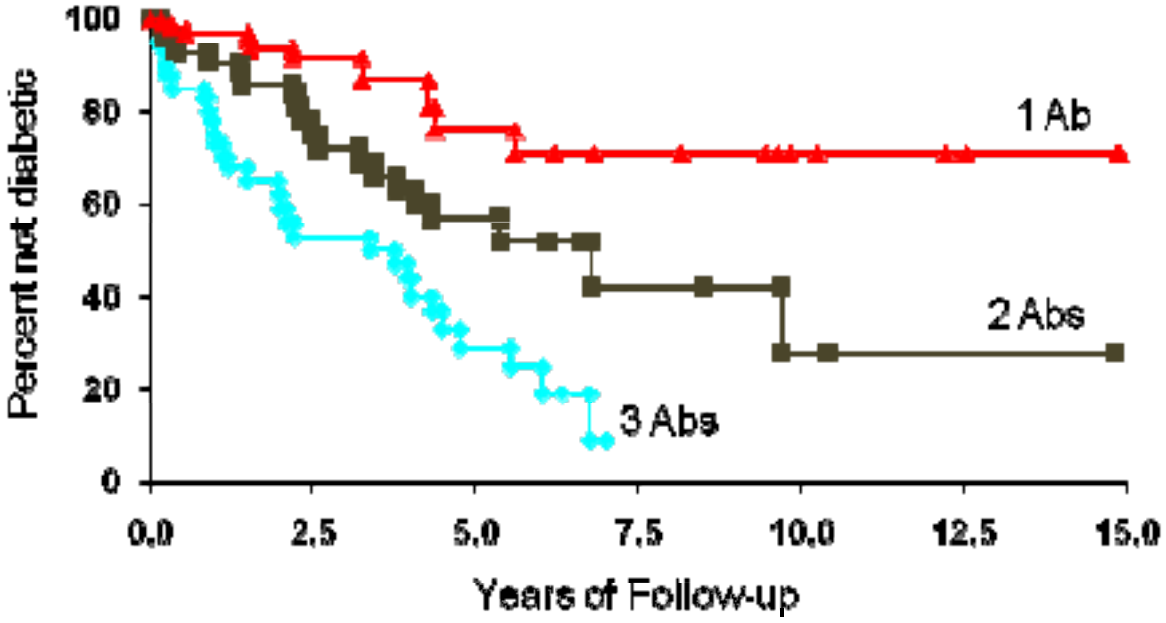
→ useful for prognostic stratification in at-risk subjects



Achenbach et al., *Diabetologia* 52:1881 (2009)

1) Islet autoantibody markers

Limitations



Verge et al., *Diabetes* 45:926 (1996)

- **They predict the "if", not the "when"**
- **Little yet significant risk in single Ab+ individuals**

→ Need very accurate predictions to enroll into immune prevention trials because:

1) T1D prognosis is benign for many years; near-normal life expectancy

2) Immune therapeutics: long-term adverse effects frequently unknown

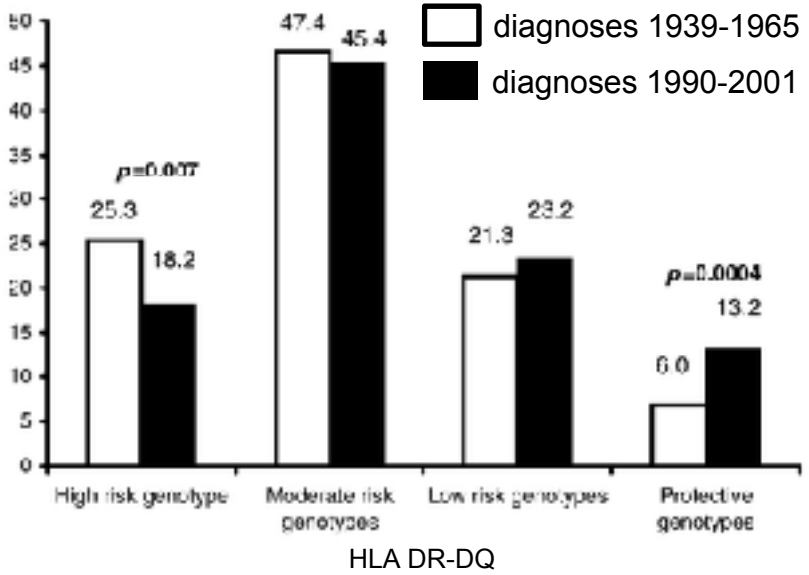
→ Acceptable to experimentally treat only if T1D will eventually develop

→ Useful to identify responders already before and/or during treatment

2) Genetic markers

HLA Class II alleles

MHC class II molecules grouped by disease association	MHC class II alleles	Disease association*
Narcolepsy		
HLA-DQ6.1	HLA-DQA1*0102/DQB1*06011	Negative
HLA-DQ6.2	HLA-DQA1*0102/DQB1*0602	Positive
Coeliac disease		
HLA-DQ2	HLA-DQA1*0501/DQB1*0201	Positive
HLA-DQ8	HLA-DQA1*0301/DQB1*0302	Positive
Type 1 diabetes		
HLA-DQ2	HLA-DQA1*0501/DQB1*0201	Positive
HLA-DR4.1	HLA-DRA1*0101/DRB1*0401	Positive
HLA-DR4.3	HLA-DRA1*0101/DRB1*0403	Negative
HLA-DR4.5	HLA-DRA1*0101/DRB1*0405	Positive
HLA-DQ6	HLA-DQA1*0102/DQB1*0602	Negative
HLA-DQ8	HLA-DQA1*0301/DQB1*0302	Positive
Rheumatoid arthritis		
HLA-DR1	HLA-DRA1*0101/DRB1*0101	Positive
HLA-DR4.1	HLA-DRA1*0101/DRB1*0401	Positive
HLA-DR4.2	HLA-DRA1*0101/DRB1*0402	Neutral or negative
Multiple sclerosis		
HLA-DR2a	HLA-DRA5*0101/DRB5*0101	Positive
HLA-DR2b	HLA-DRA1*0101/DRB1*1501	Positive
HLA-DQ6.2	HLA-DQA1*0102/DQB1*0602	Positive



HLA DR-DQ

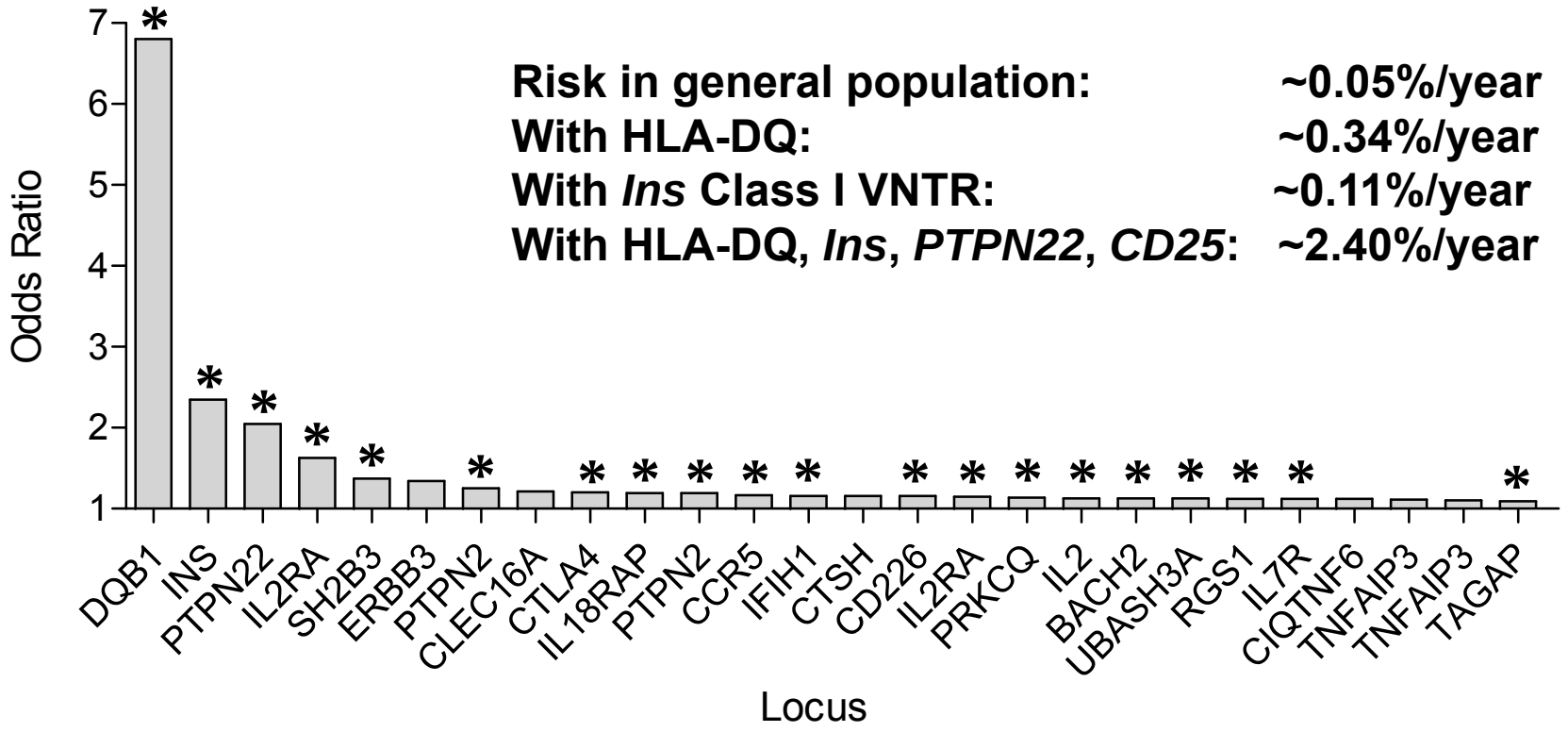
The most powerful markers of T1D genetic susceptibility

Yet, they are becoming less and less important, hinting to an increased environmental pressure

Gillespie et al., *Lancet* 364:1699 (2004)

2) Genetic (immune) markers

Beyond HLA Class II



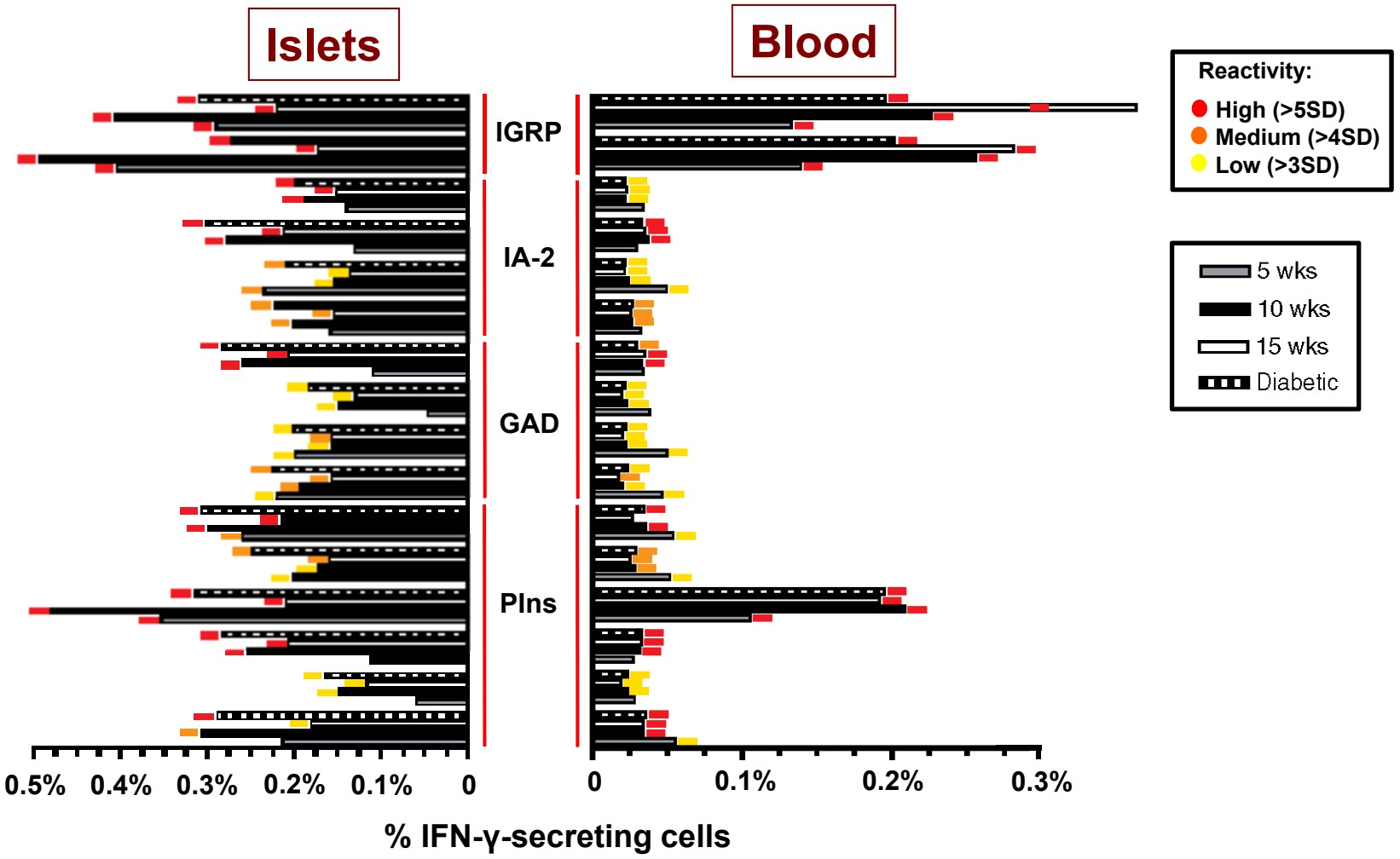
Risk in general population: ~0.05%/year
With HLA-DQ: ~0.34%/year
With *Ins* Class I VNTR: ~0.11%/year
With HLA-DQ, *Ins*, *PTPN22*, *CD25*: ~2.40%/year

- **The problem of complex polygenic disease:**
  the influence of single genetic polymorphisms is mostly limited
- **Even combining information from multiple loci gives a modest relative risk**
- **Combination with other markers**
  → useful for stratification of at-risk groups (i.e., 1st degree relatives)

3) T-cell markers

Circulating T cells mirror local islet infiltrates

Studies on humanized HLA-A2-transgenic NOD mice

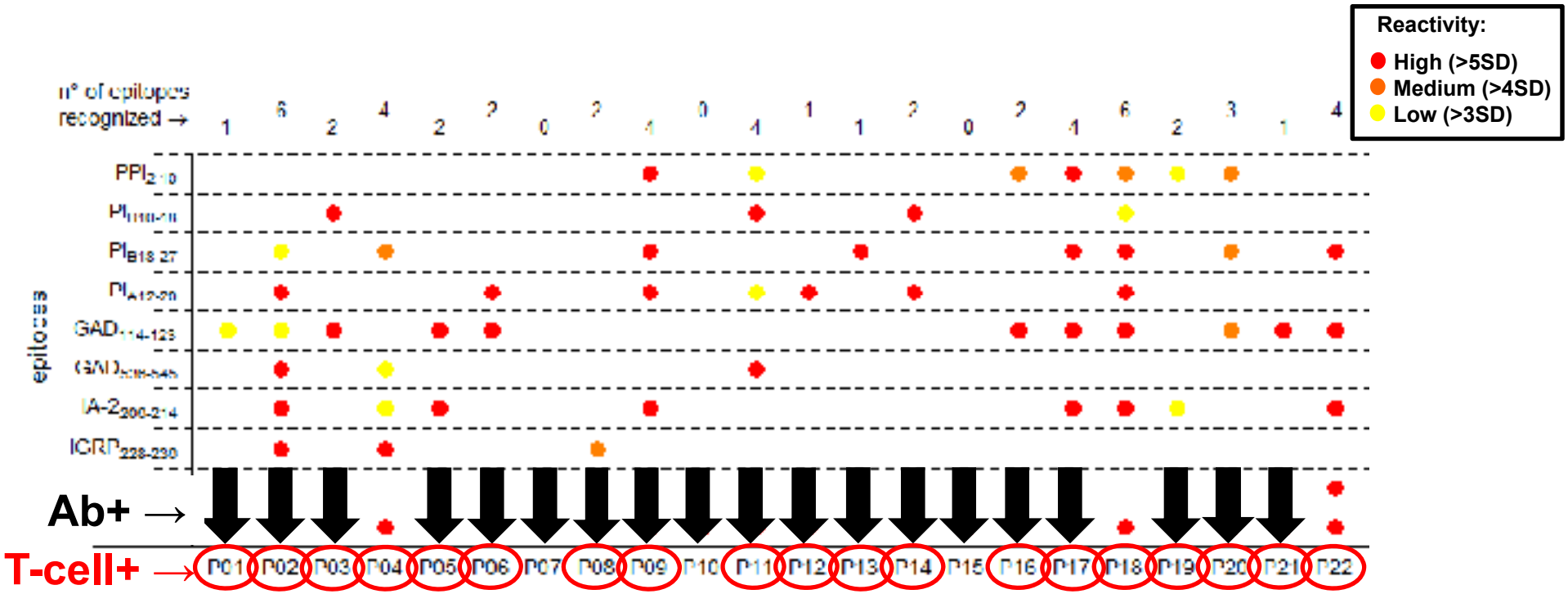


CD8+ T-cell epitope specificity and immunodominance is similar in blood and islets

Enée et al., *J.Immunol.* 180:5430 (2008)

3) T-cell markers

Combining Ab and T-cell markers yield higher diagnostic sensitivity



New-onset insulin-dependent T1D patients

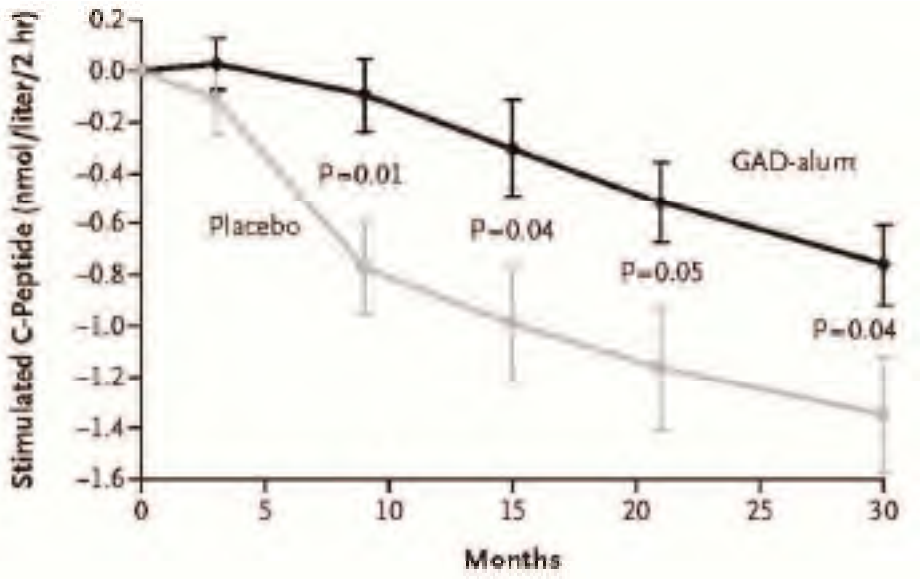
- 19 of 22 T1D patients are T-cell-positive → sensitivity = 86.4%
- 19 of 22 T1D patients are Ab-positive (GAD, IA-2, IAA, ICA) → sensitivity = 86.4%
- 22 of 22 patients were positive for EITHER T cells or Abs → sensitivity = 100%

Mallone et al., *Diabetes* 56:613 (2007)

The utility of surrogate immune biomarkers in immune intervention trials

Metabolic markers are useful, but not sufficient

Mixed meal tolerance test



Ludvigsson et al., *N.Engl.J.Med.* 359:1 (2008)

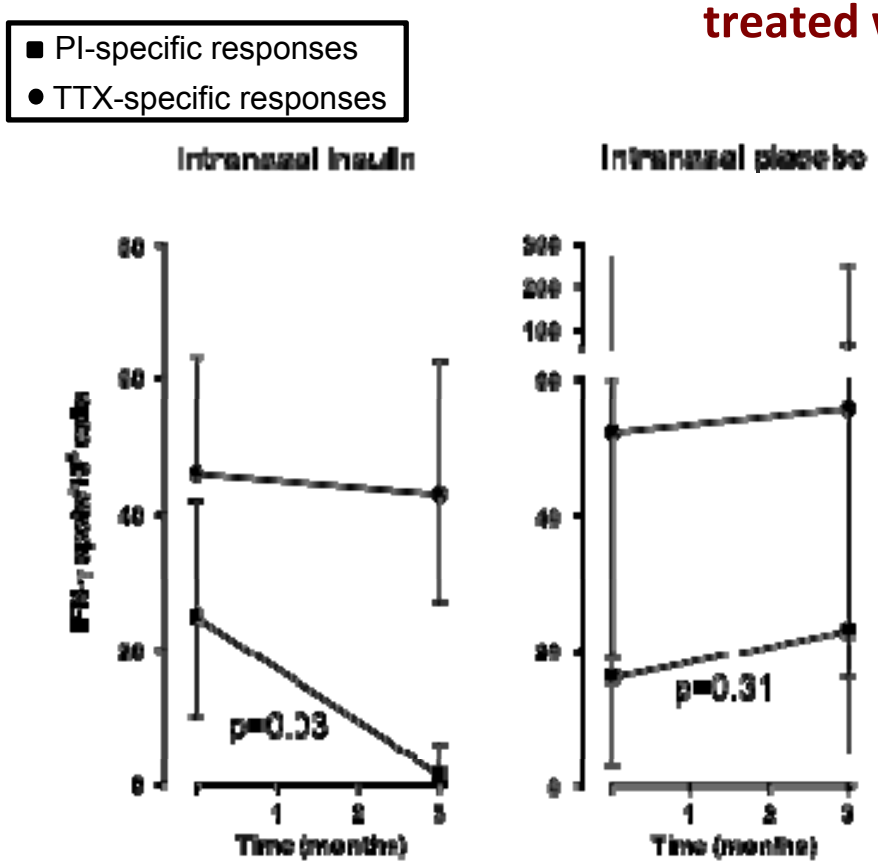
- **C-peptide secretion: measures residual insulin function, but:**
  - **1) limited change, sometimes no change (subjects are already diabetic)**
  - **2) takes years to assess (especially in prevention trials)**

→ need surrogate immune markers to see whether the immune modulation has been achieved, independent of clinical outcome

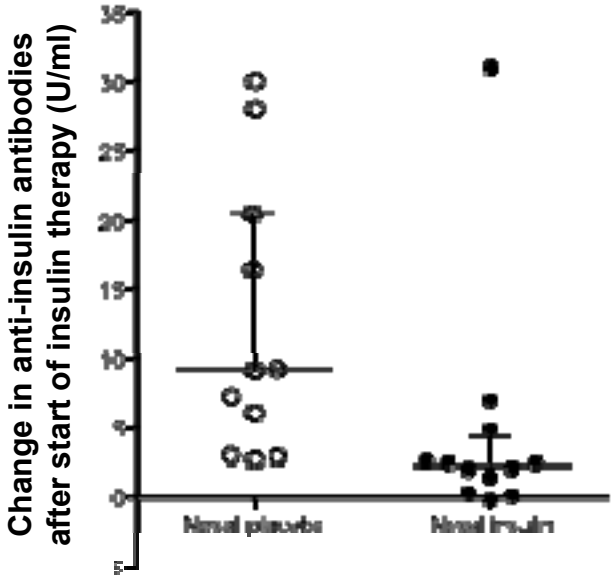
3) T-cell markers

Reveal tolerance restoration following immune intervention

Insulin-free adults with type 1 diabetes treated with nasal insulin

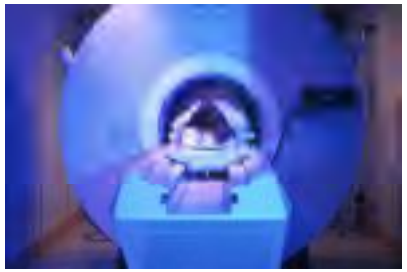


Decrease in PI-specific T-cell responses in intranasal insulin arm



Smaller rise in anti-insulin Abs upon start of s.c. insulin therapy in intranasal insulin arm

Fourlanos et al., *Diabetes*, in press

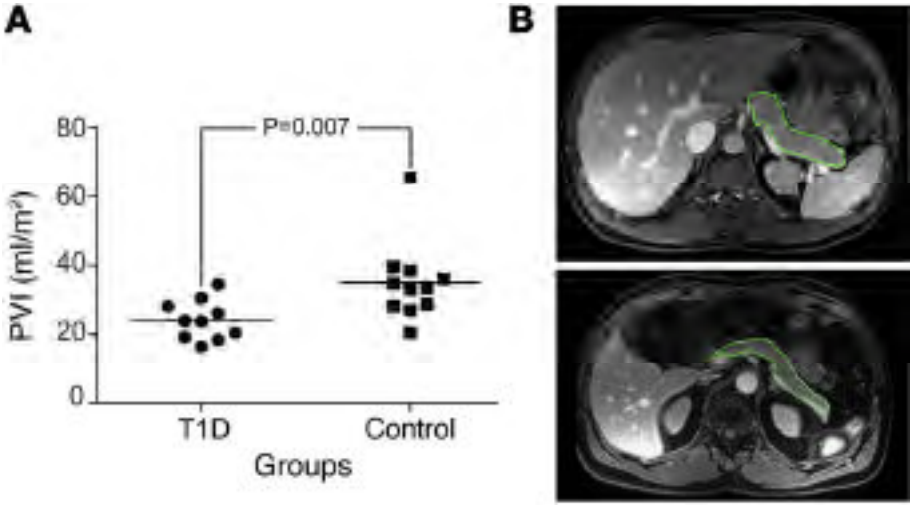


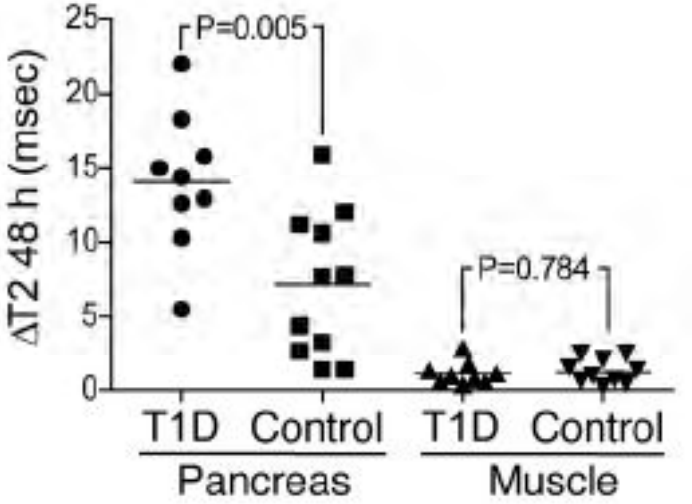
4) Islet imaging

Can we visualize islet mass and insulitis?

NMR imaging

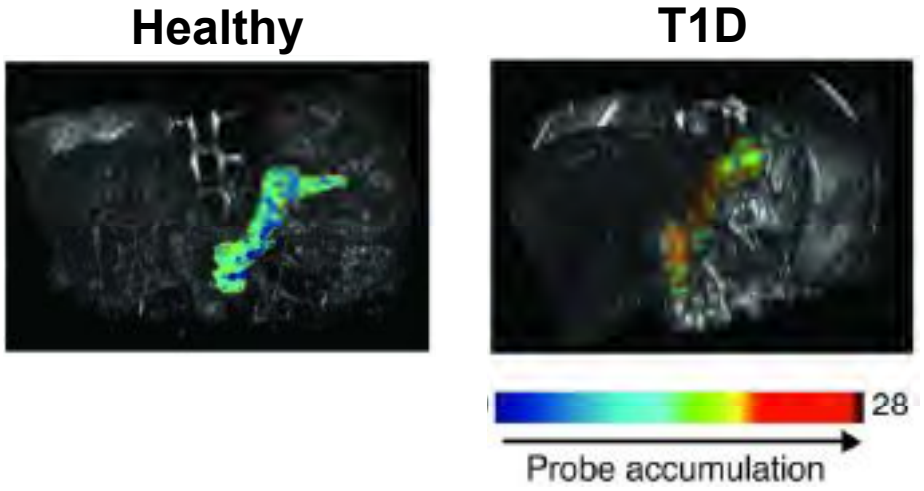
0 h: pancreatic mass





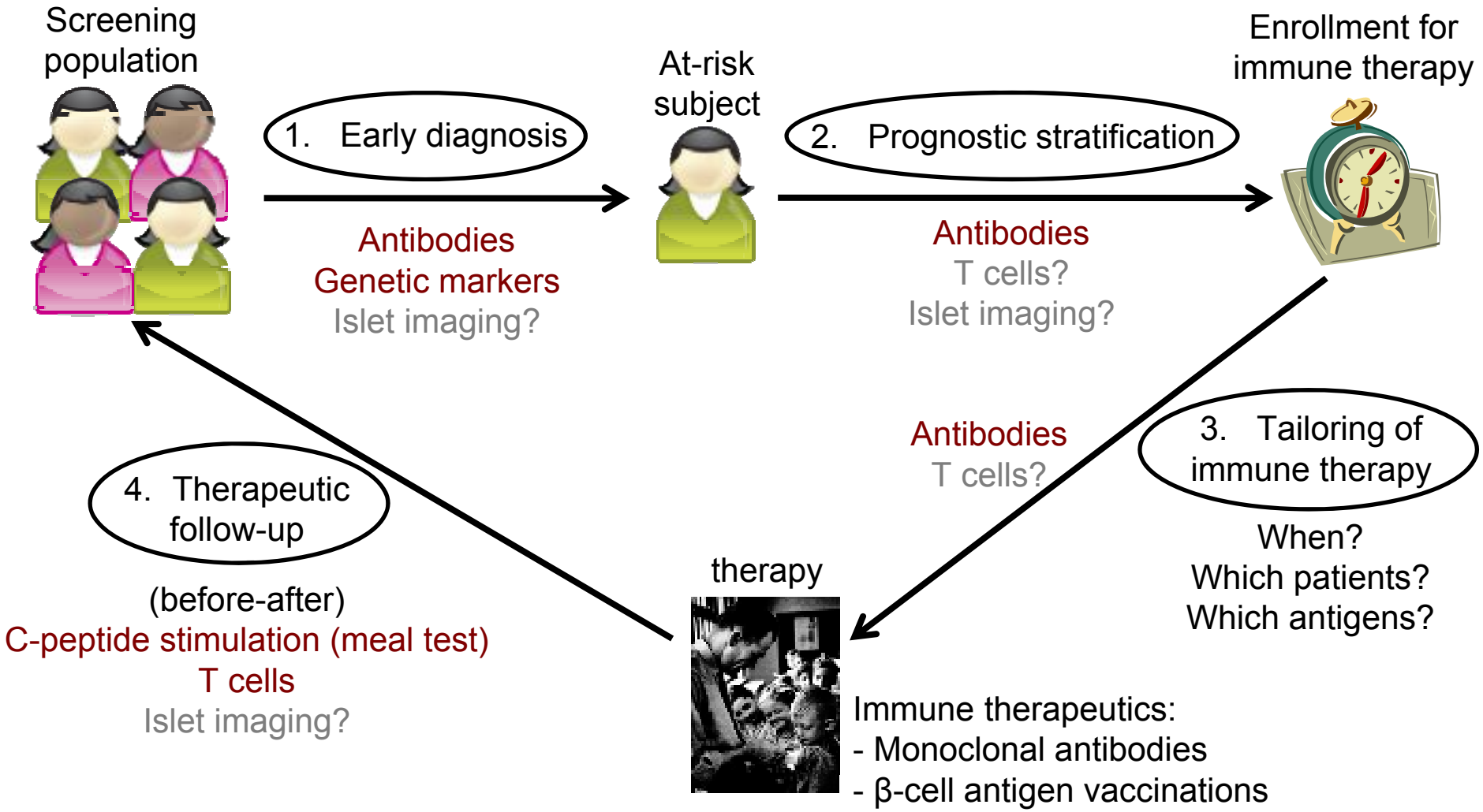
Magnetic nanoparticles: pancreatic uptake reflects inflammatory microvascular leakage and monocyte/macrophage recruitment

48 h: pancreatic infiltration



Gaglia et al., *J.Clin.Invest.* 121:442 (2011)

Biomarker-driven T1D staging and intervention



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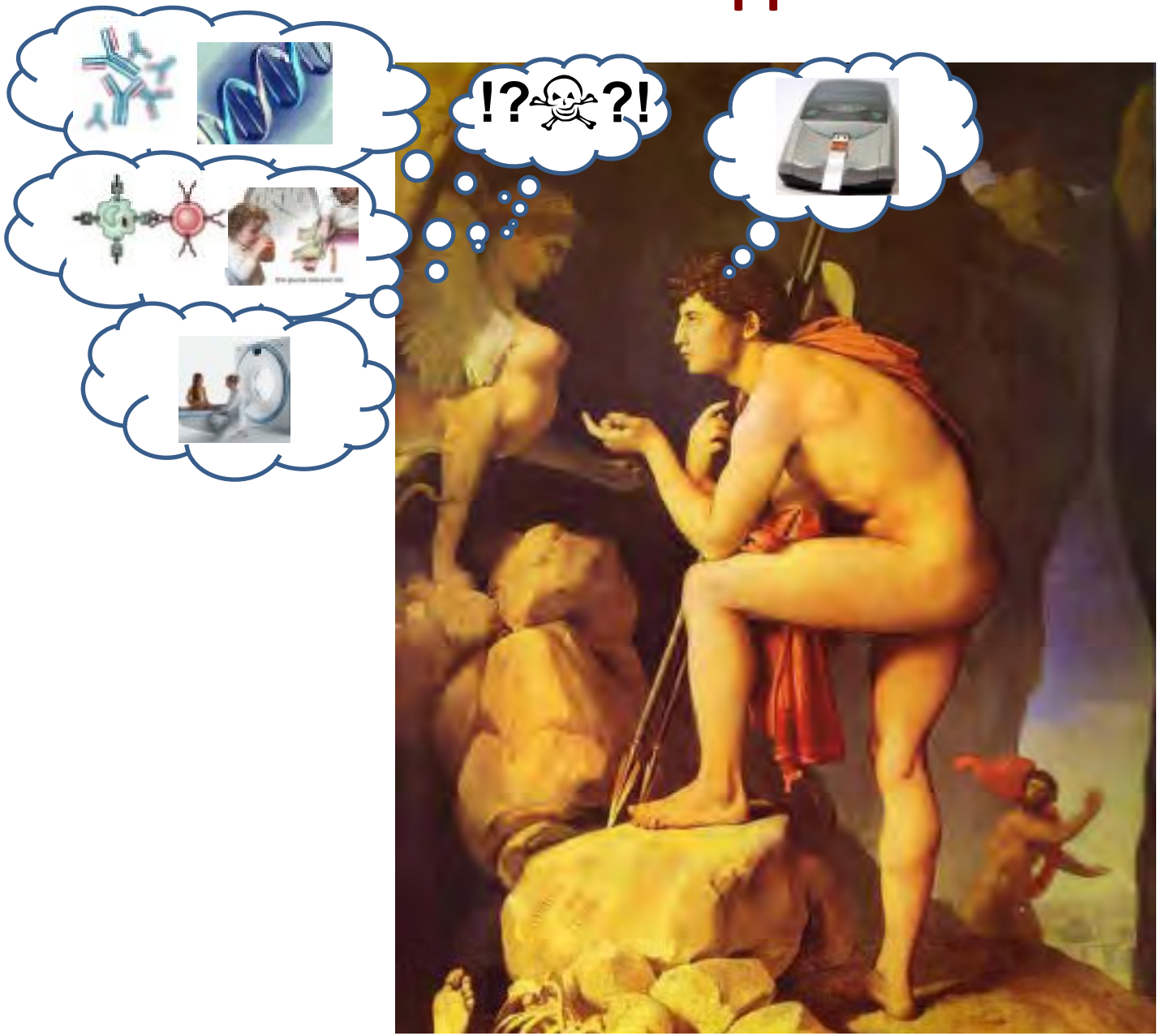
A novel biomarker-based approach to T1D management?



Ingres, “Oedipus and the Sphinx”, 1808

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