Immunomodulation Type 1 Diabetes

FDA/NIH Symposium

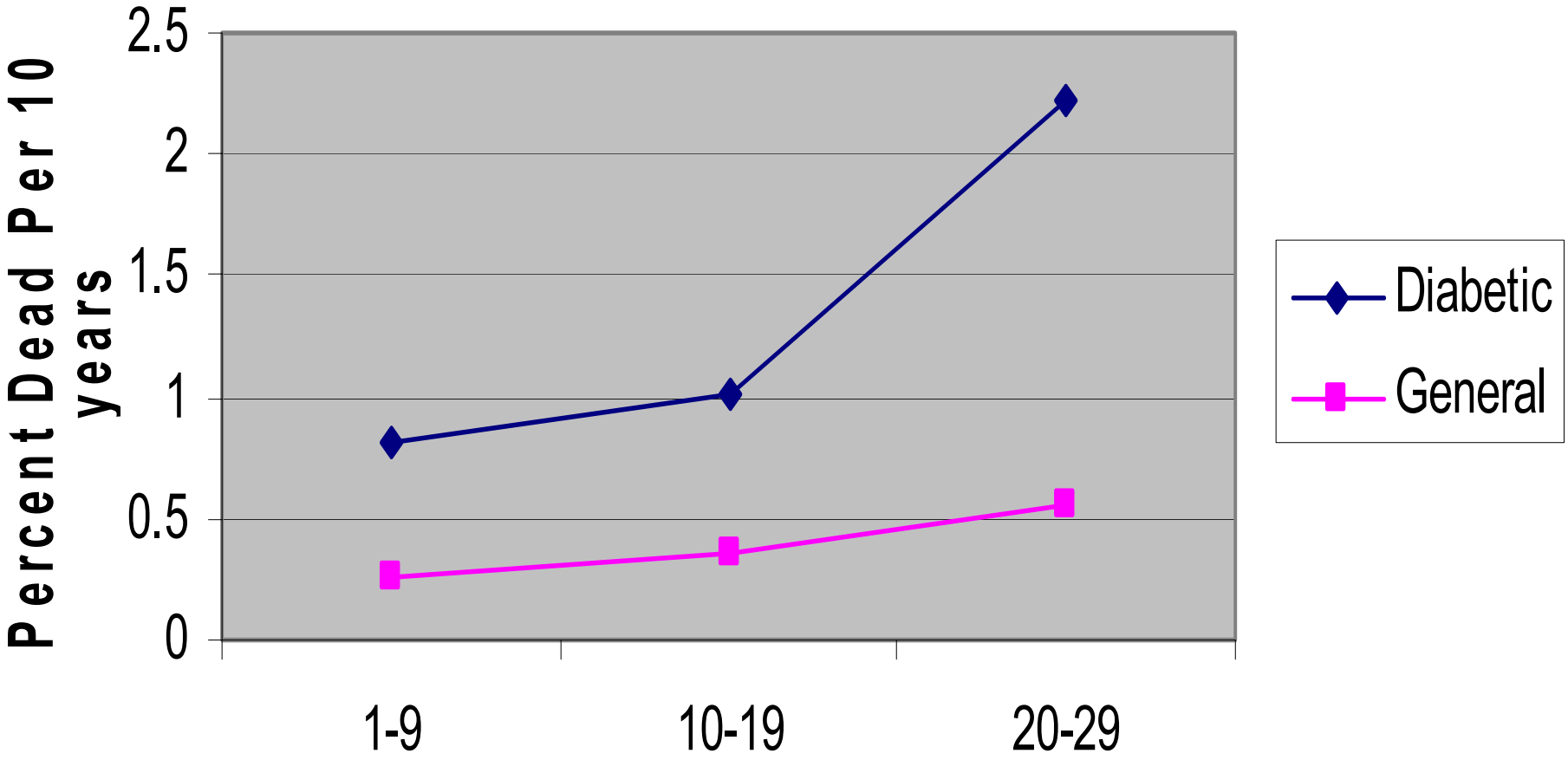
5/13/04

www.barbaradaviscenter.org

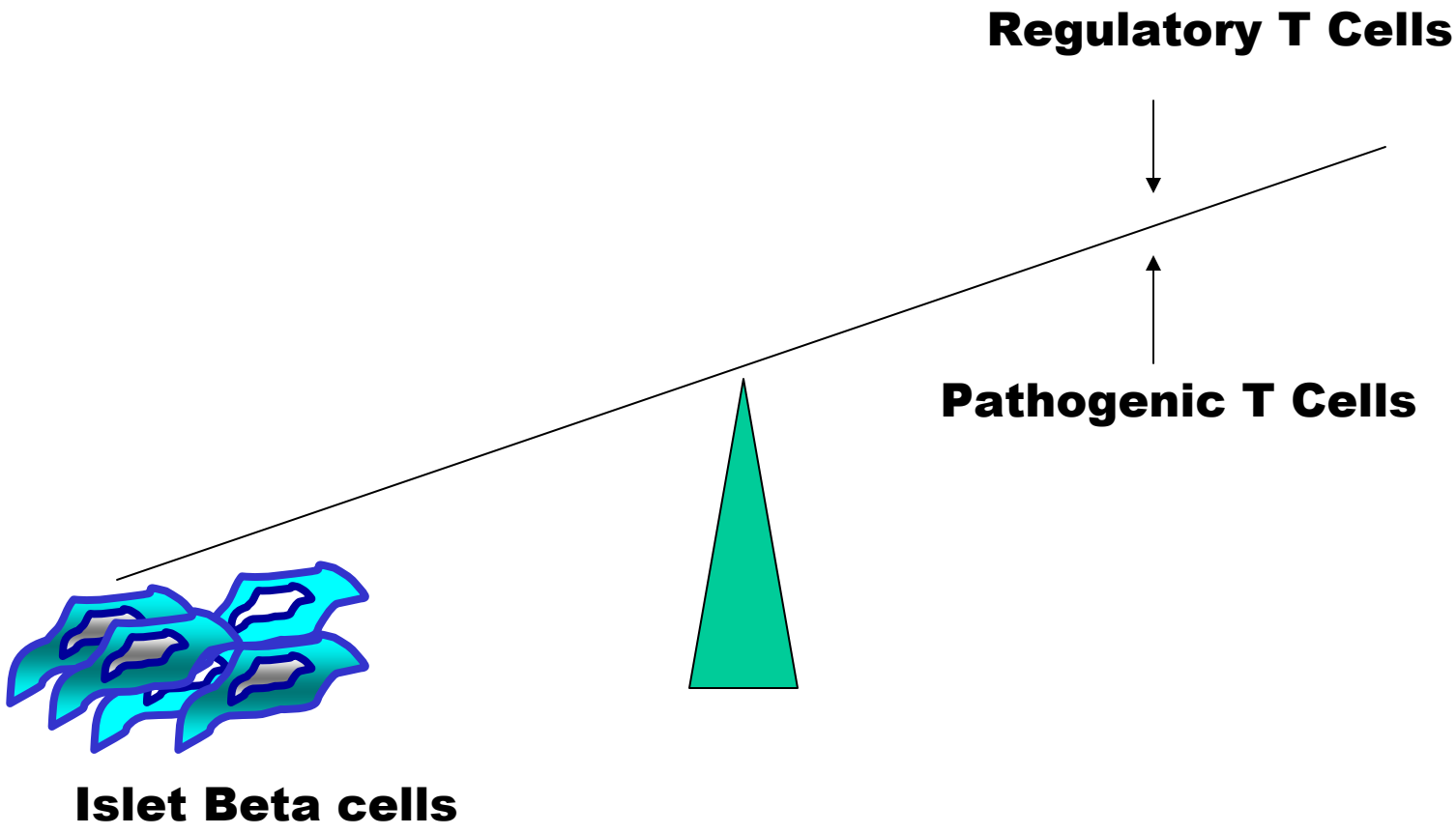
Immunology of Diabetes Book with Teaching Slides

BDA Cohort Study 1972-1993 All Cause Mortality

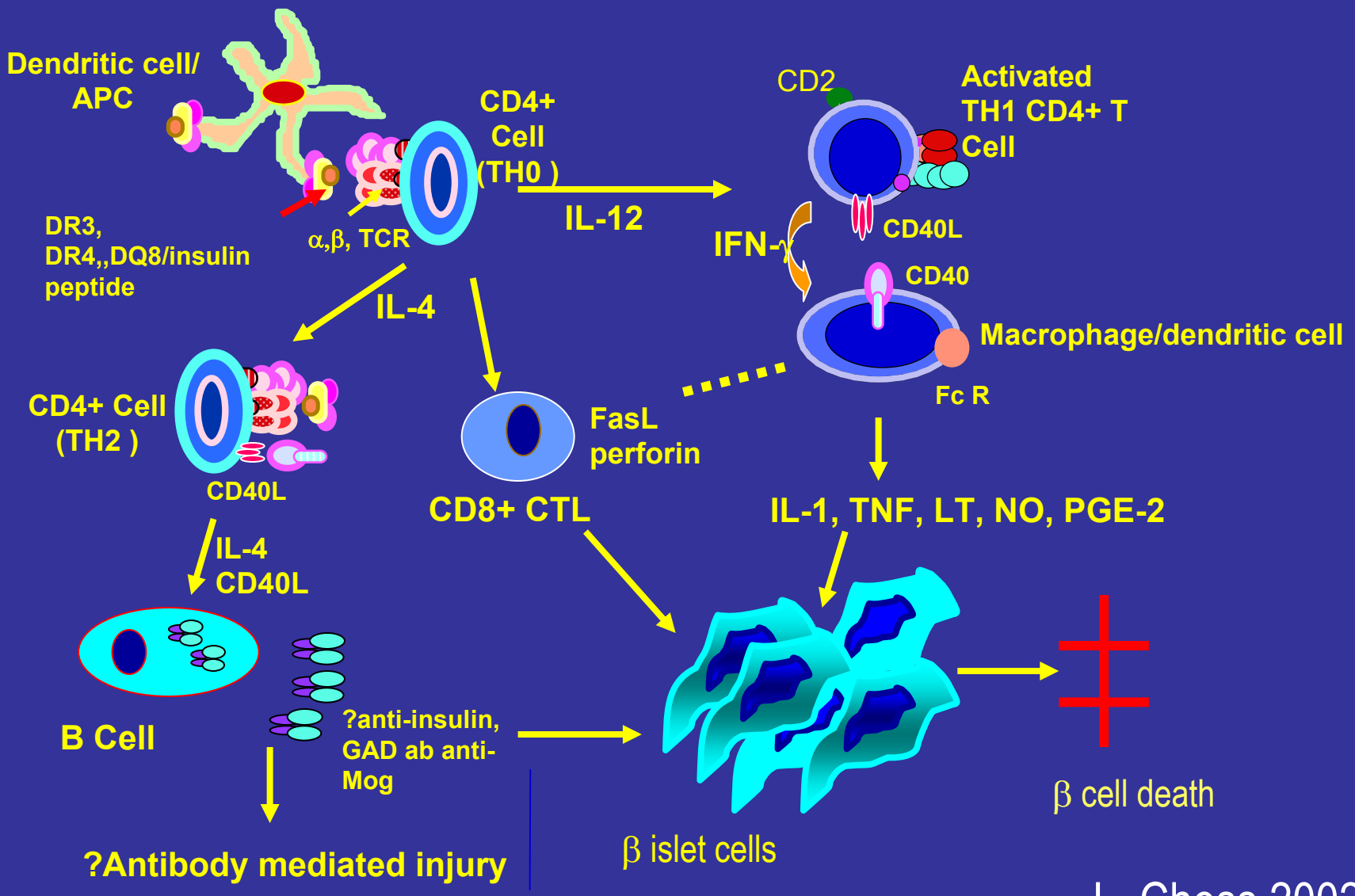
Extra 2.9% Dead by Age 30



Laing et al Diabetic Medicine 16, 459-465, 1999


Regulatory T Cells
Pathogenic T Cells
Islet Beta cells

Immunopathophysiology of Diabetes

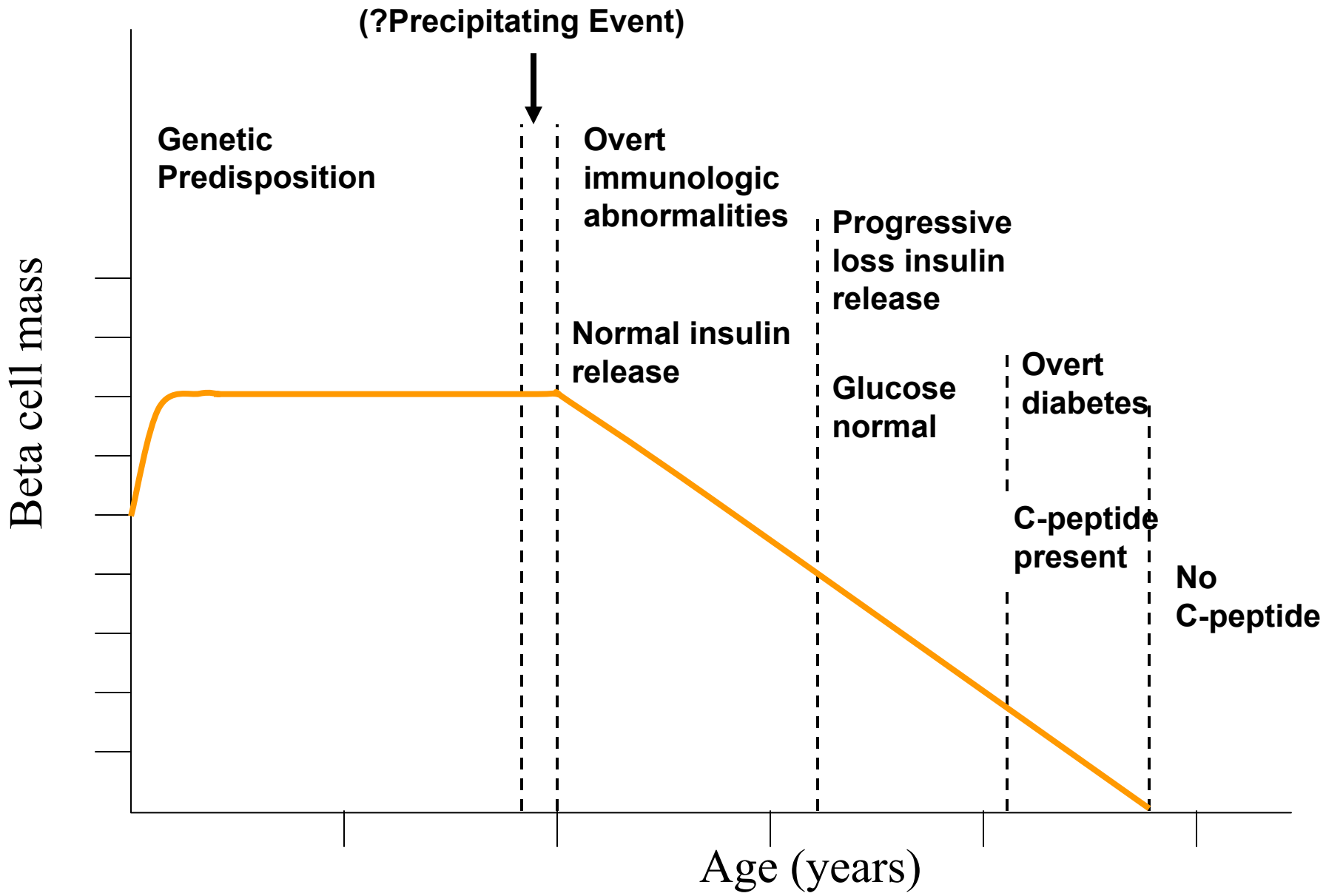


L. Chess 2002

General Paradigm

- Identify Genetic Susceptibility
- Detect Initial Autoantibodies
- Monitor Metabolic Decompensation
- Treat Overt Disease Prior to Morbidity/Mortality
- Basic/Clinical Research to Allow Prevention

“Stages” in Development of Type1 Diabetes



Stages Type IA Diabetes

- I Genetic Susceptibility
- II Triggering
- III Active Autoimmunity
- IV Progressive Metabolic Abnormalities
- V Overt Diabetes
- VI Insulin Dependence

J. Noble

TERMINOLOGY

Allele: DRB1*0401 (DR4)

Haplotype: DRB1*0401 (DR4) — DQB1*0302 (DQ8)

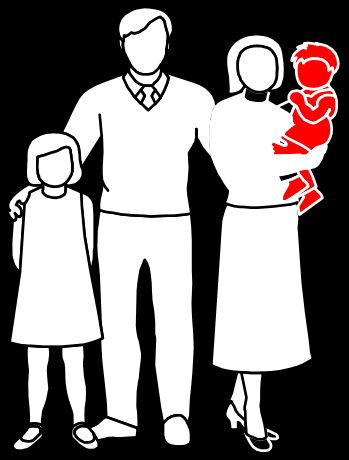
Genotype

DRB1*0401 (DR4) — DQB1*0302 (DQ8)

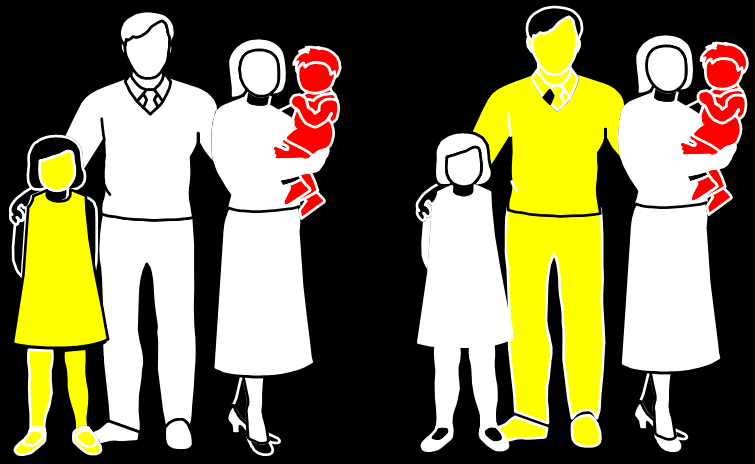
DRB1*0301 (DR3) — DQB1*02(DQ2) (DQ2)

Diabetes Autoimmunity Study in the Young

General population cohort



Sibling/offspring cohort



screened = 21,713

enrolled	=	293	high risk	72
		429	moderate risk	220
		347	average - low risk	401
		1,069	All	693
relatives		1,491		1,007

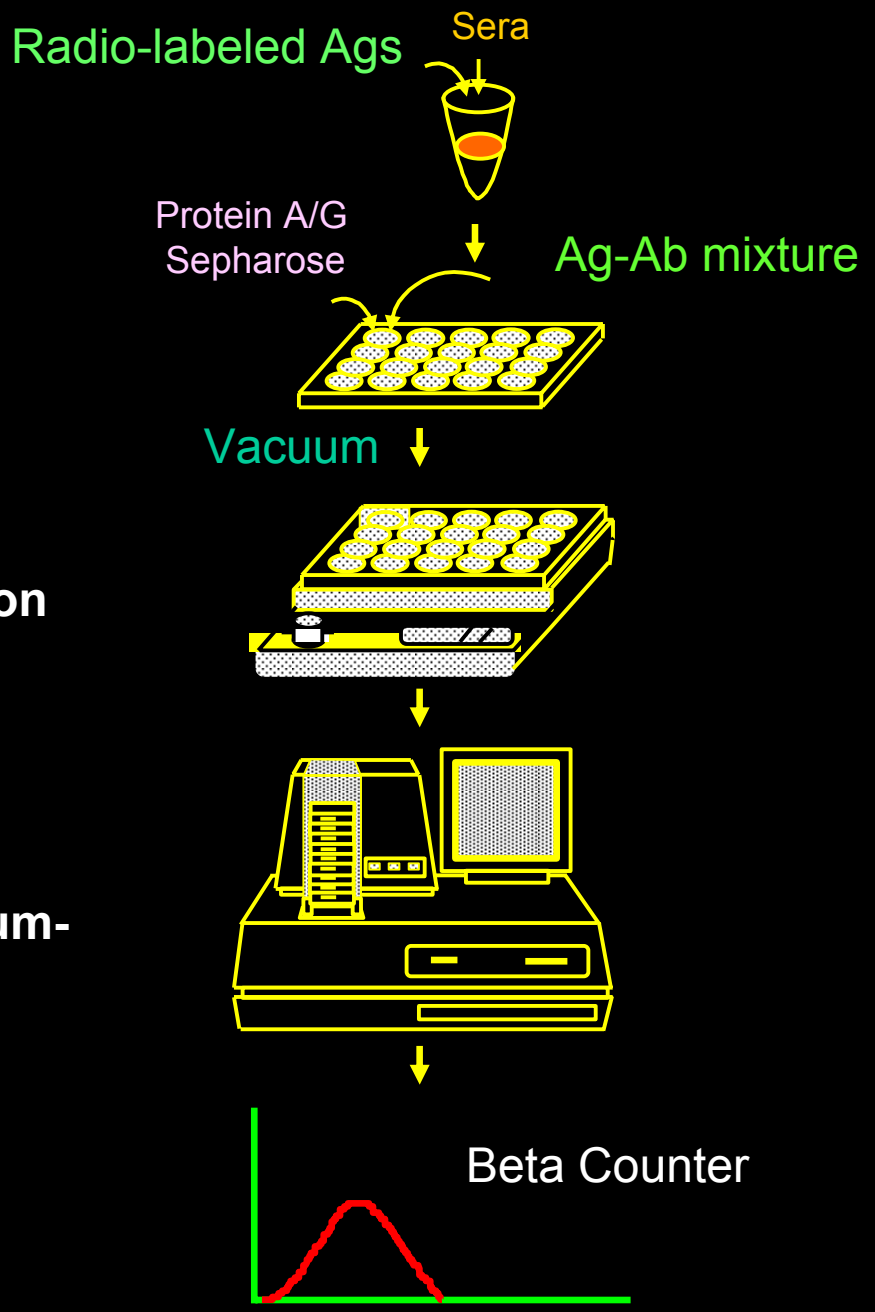
HLA-defined IDDM risk groups Denver population, n=9,338

IDDM risk by age 20	HLA-DR	DQB1	Frequency %
High 1:15	**3/4**	**0201/0302**	**2.4**
Moderate	4/x	0302/	12.7
1:60-1:200	4/4	0302/	3.0
	3/3	0201/0201	1.4
Average 1:300	3/x	0201/	12.5
	3/4	0201/not 0302	1.0
Lower than 1:300	4/x, 4/4	/not 0302	6.6
	others		60.4

DAISY 7/96

High Throughput Autoantibody Radio-Assay

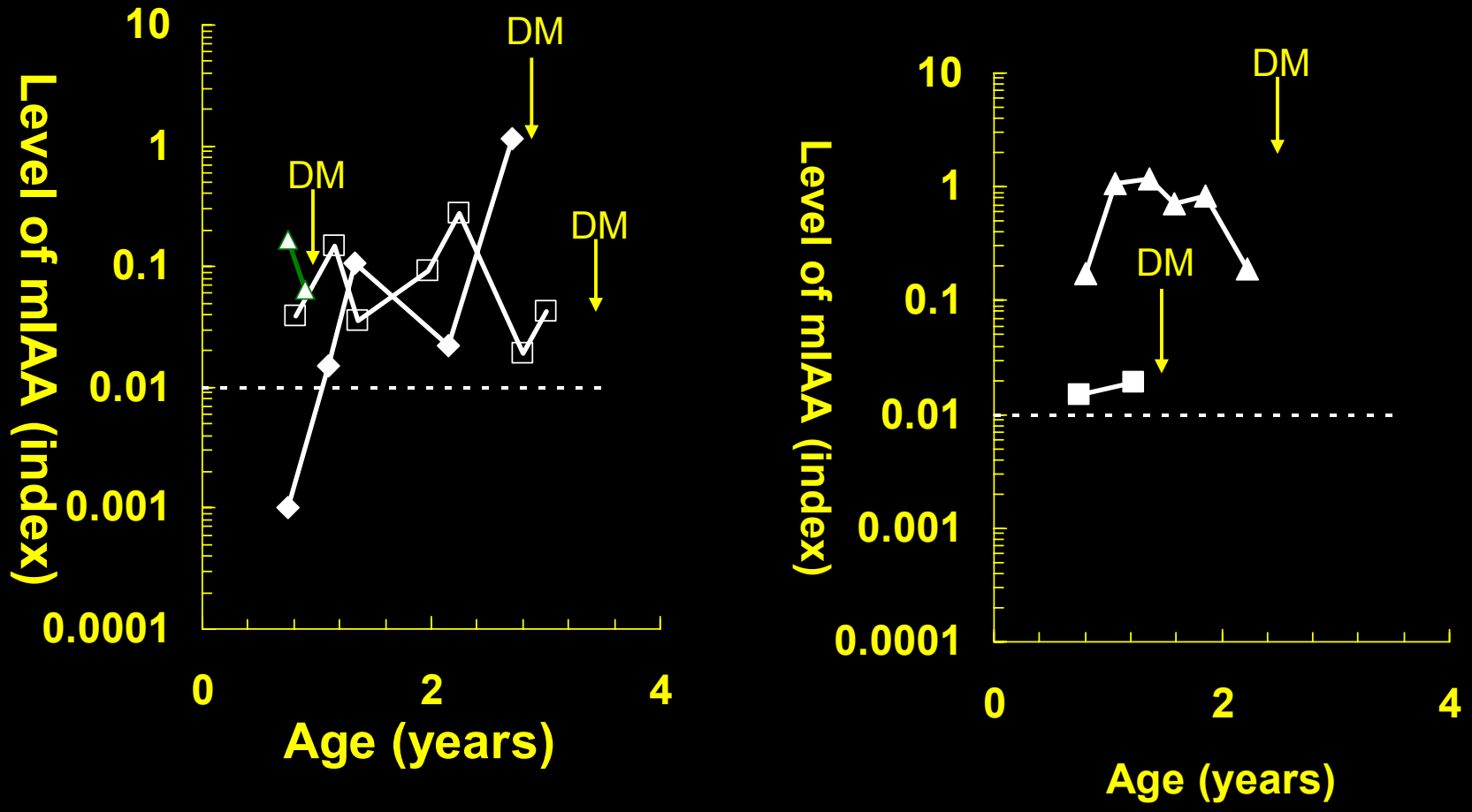
1. mix labeled Ag and sera
2. Incubate overnight at 4 C
3. Add Protein A/G-Sepharose to reaction mix in a 96-well filtration plate
4. Incubate for 45 min at 4 C
5. Wash each well using the vacuum-operated 96-well plate washer
6. Count radioactivity with 96-well plate beta counter



Autoantibodies

- Insulin
- Glutamic Acid Decarboxylase
- ICA512 (IA-2)

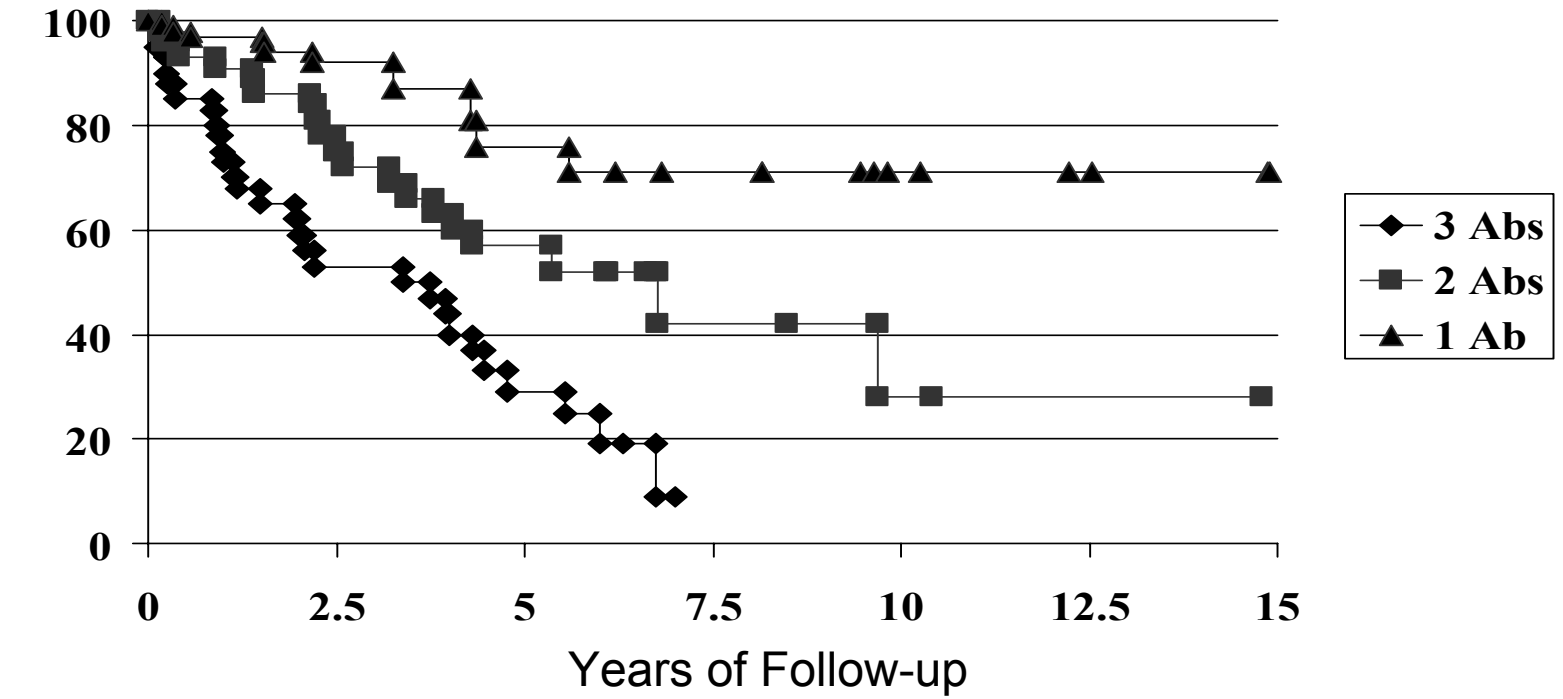
The Levels of mIAA in Prediabetic Children



Yu et al. PNAS: 97:1701-1706, 2,000

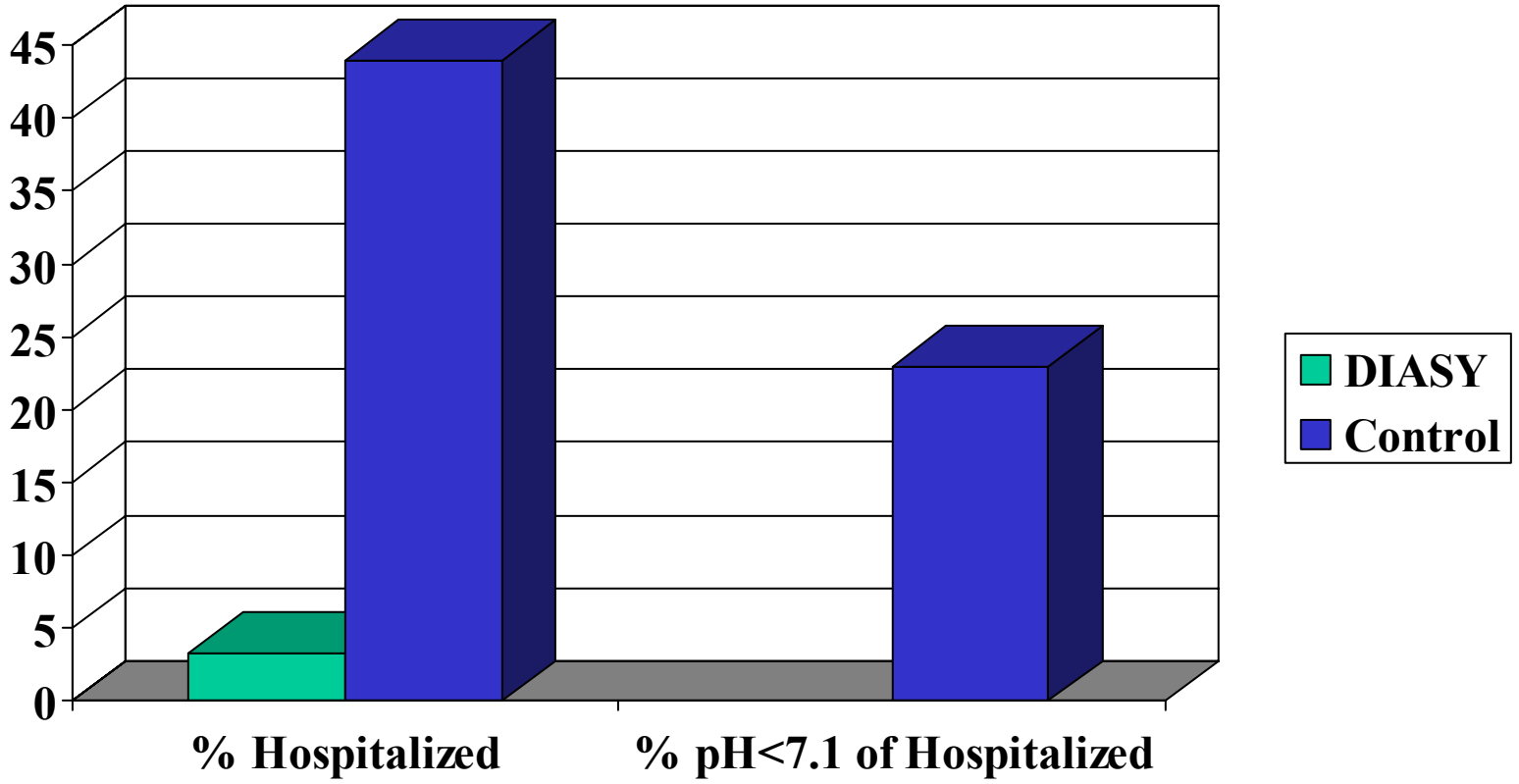
BDC

Progression to Diabetes vs Number of Autoantibodies (GAD, ICA512, Insulin)



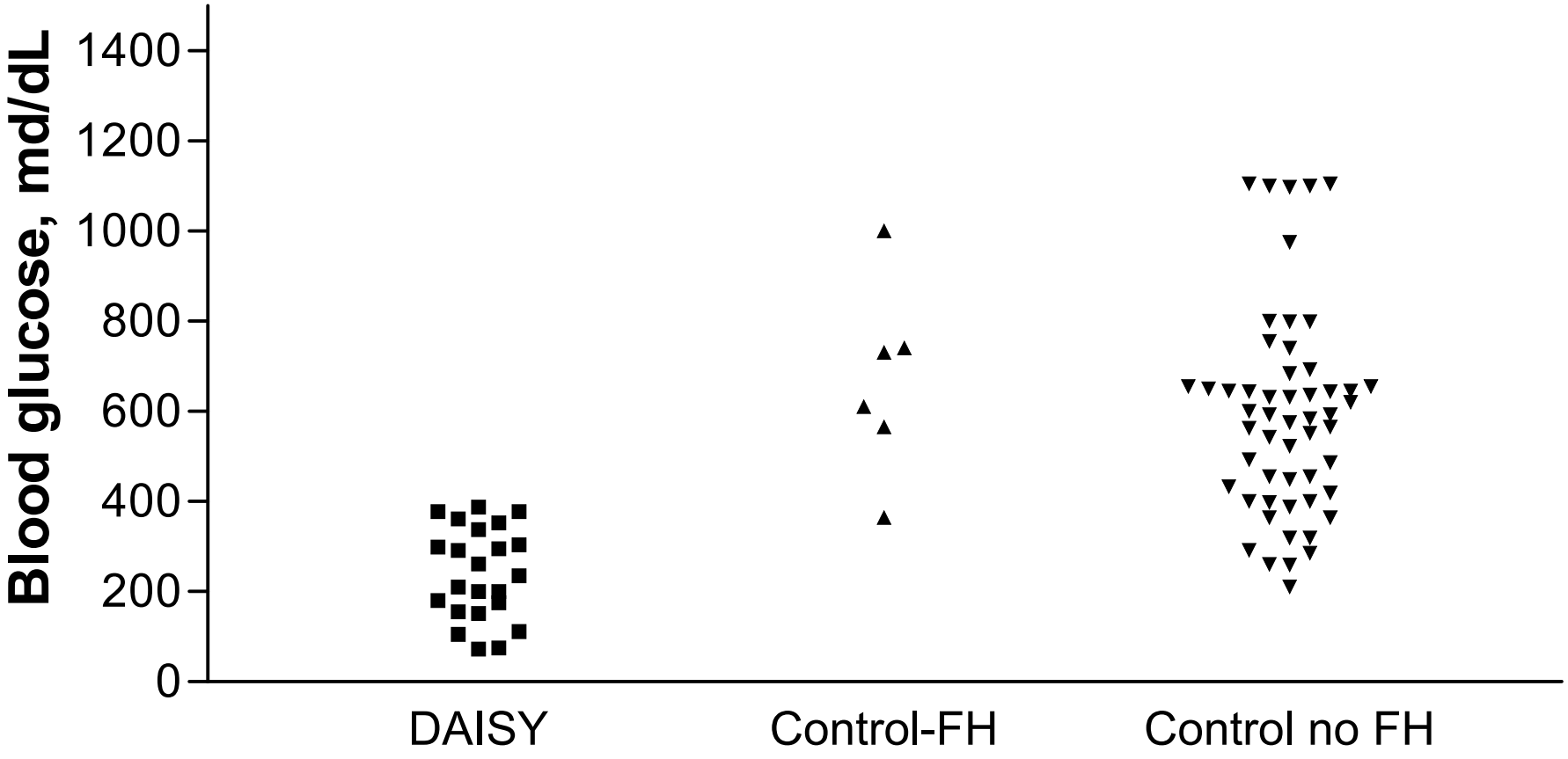
3 Ab	n = 41	17	8	1		
2 Abs	n = 44	27	15	4	2	1
1 Abs	n = 93	23	14	10	6	4

DAISY Study Prevents Ketoacidosis
Barker et al



Mean Glucose 630
Range: 259-1,105

Blood glucose values in Control vs. Daisy children

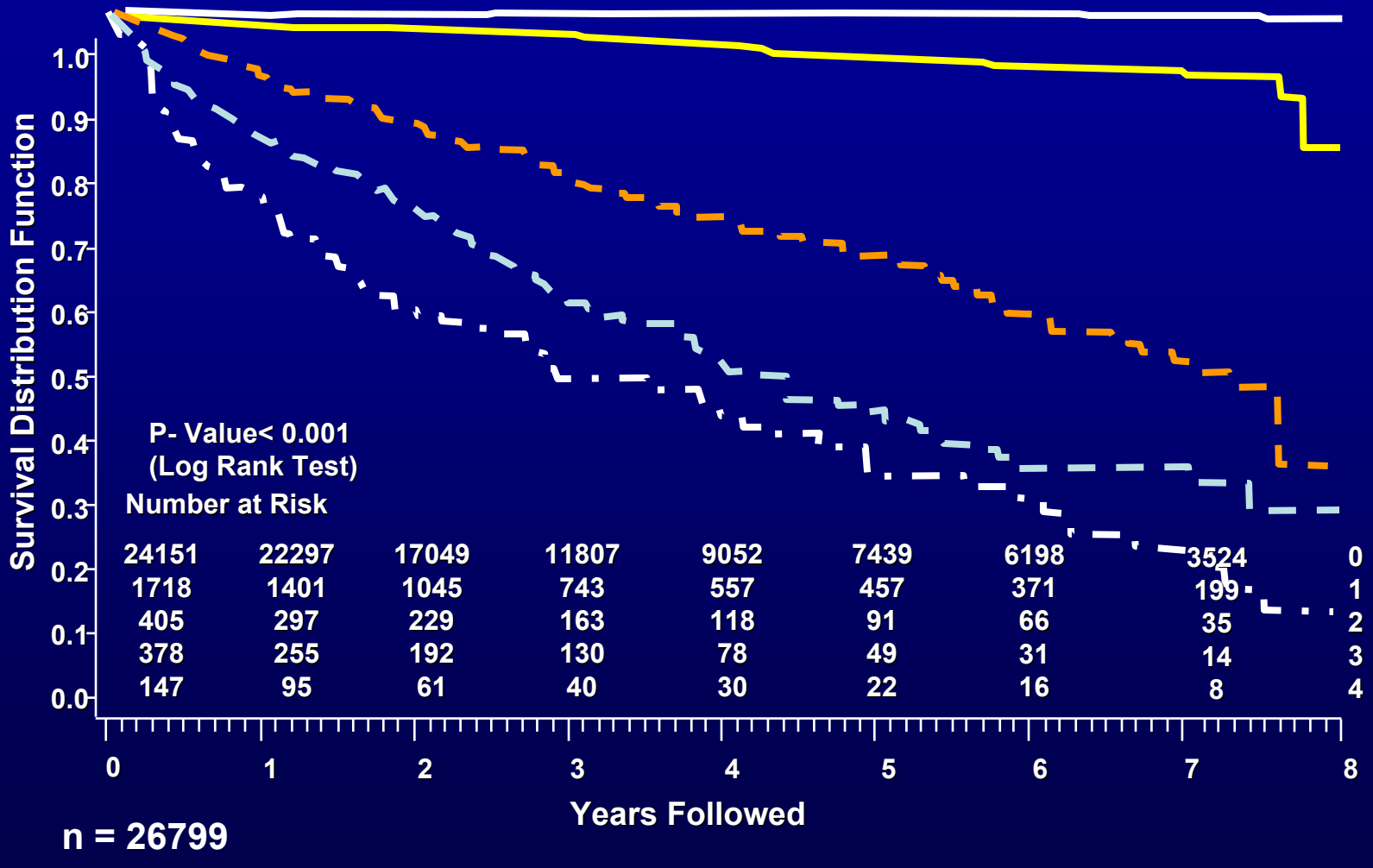


DPT-1 SCREENING

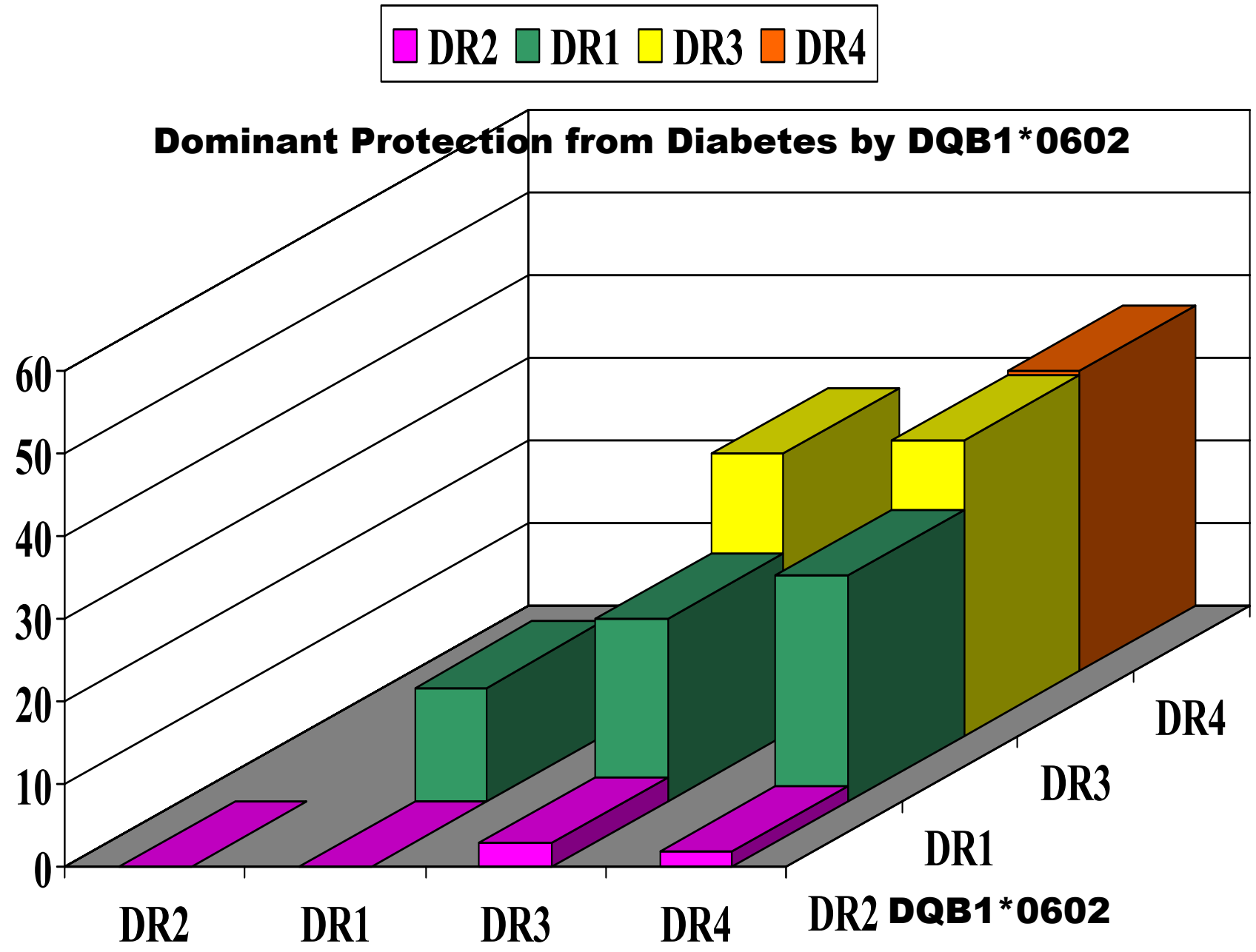
Initial Screening

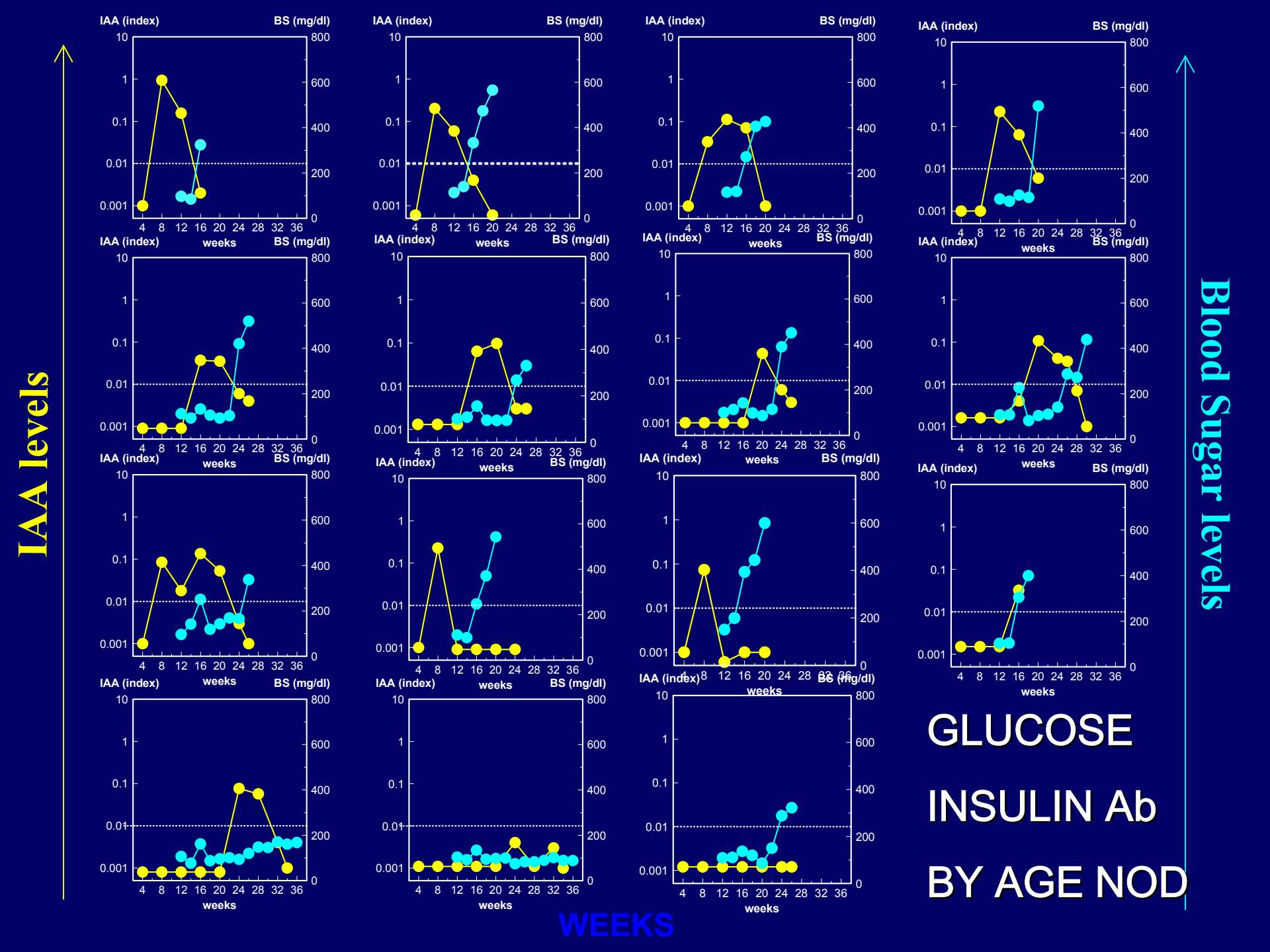
- 97,273 ICA
- 90,000 GAD, ICA512
- 67,637 GAD, ICA512, mIAA

DPT-1 – Time to Diabetes By Number of Antibodies

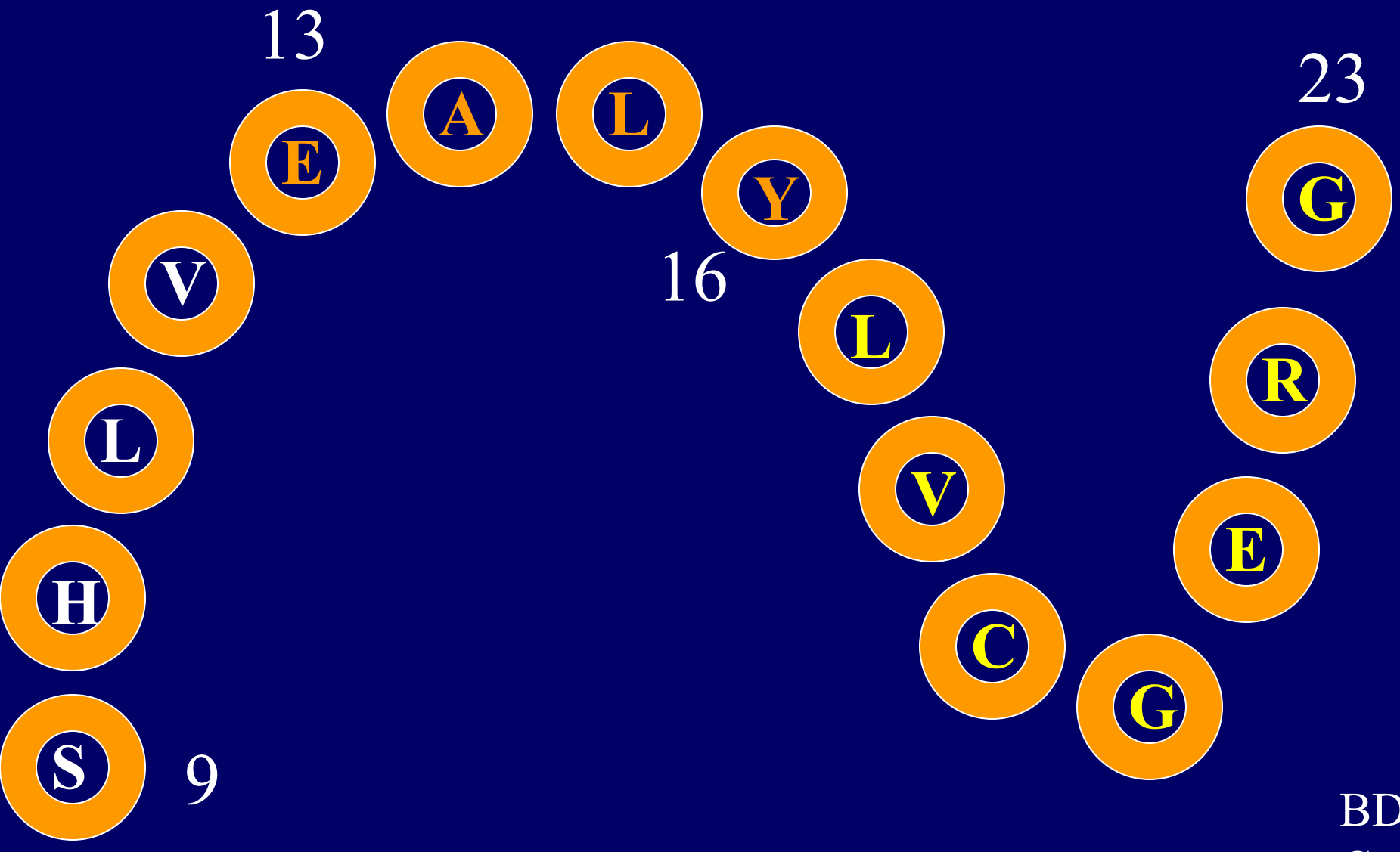


Diabetes Prevention Trial – Type 1


DR2
DR1
DR3
DR4
Dominant Protection from Diabetes by DQB1*0602
60
50
40
30
20
10
0
DR2
DR1
DR3
DR4
DR2
DR1
DR3
DR4
DQB1*0602

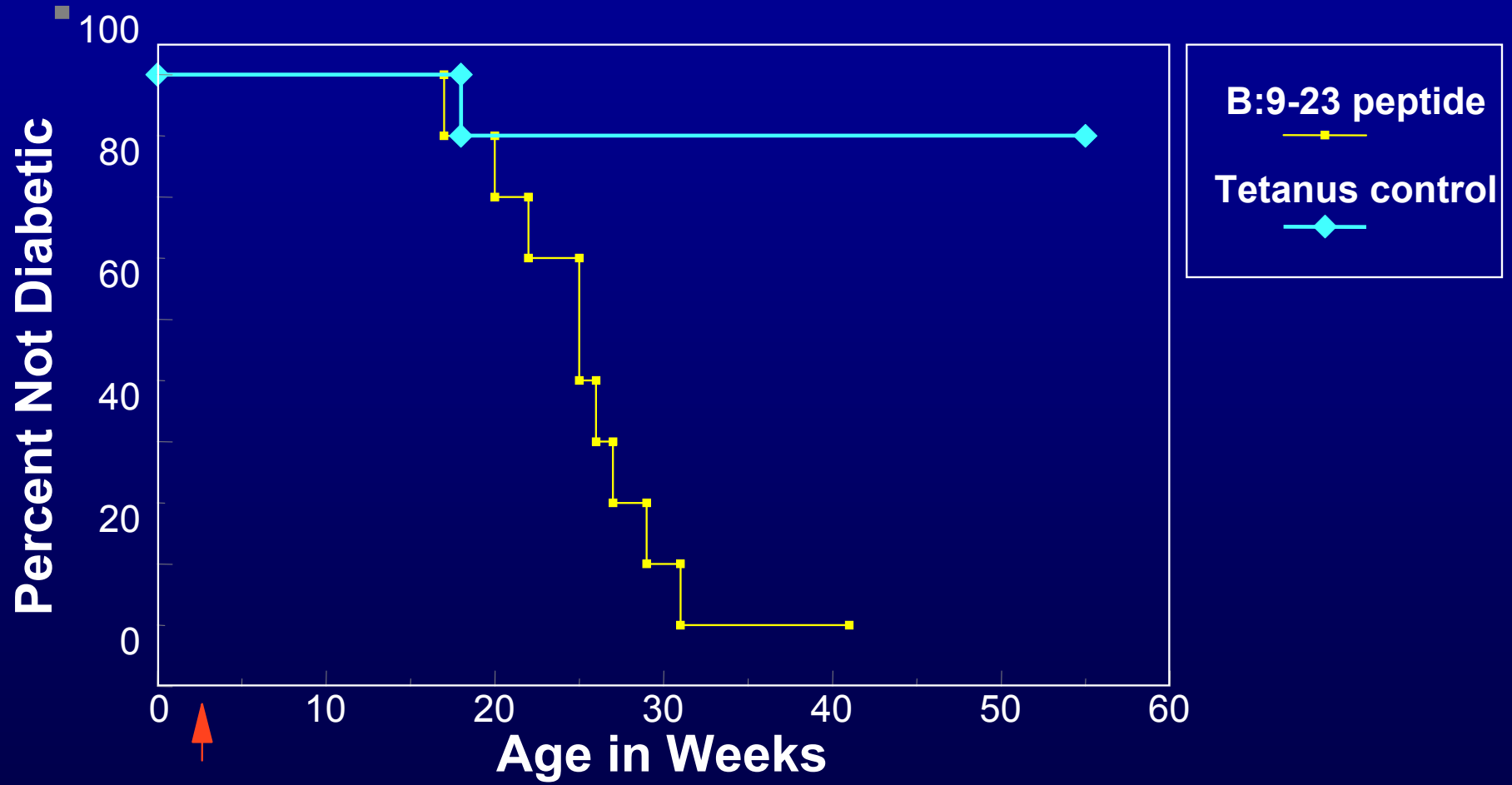

IAA levels
Blood Sugar levels
IAA (index)
BS (mg/dl)
weeks
GLUCOSE
INSULIN Ab
BY AGE NOD
WEEKS

“Pathogenic” Peptide: Insulin B:9-23



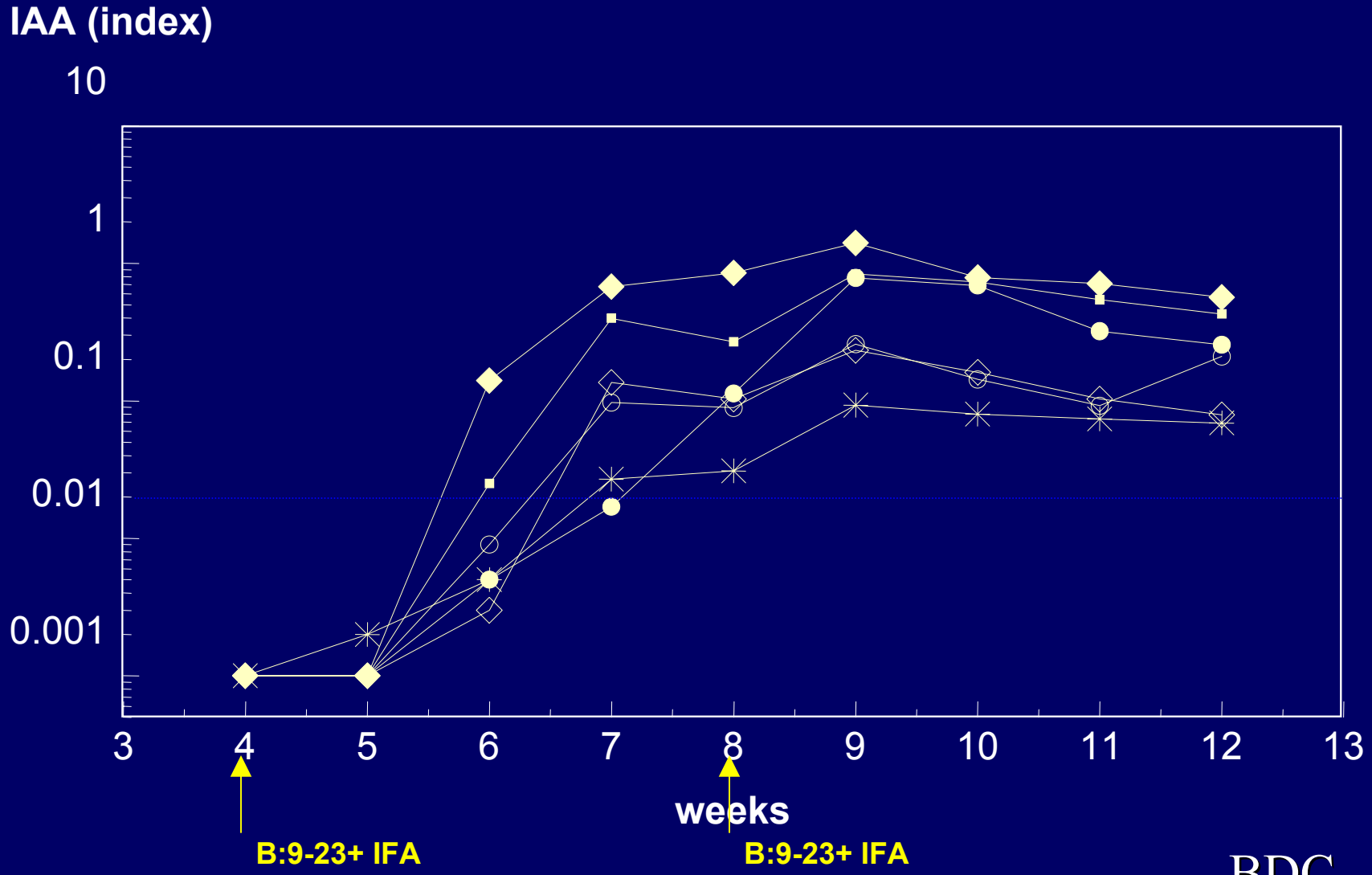
BD

Prevention of Diabetes with B:9-23 Peptide "Immunization"



D.Daniel ,D.Wegmann . PNAS,1996

Rapid induction of IAA by Insulin B:9-23 peptide Imunization in Normal BALB/c mice



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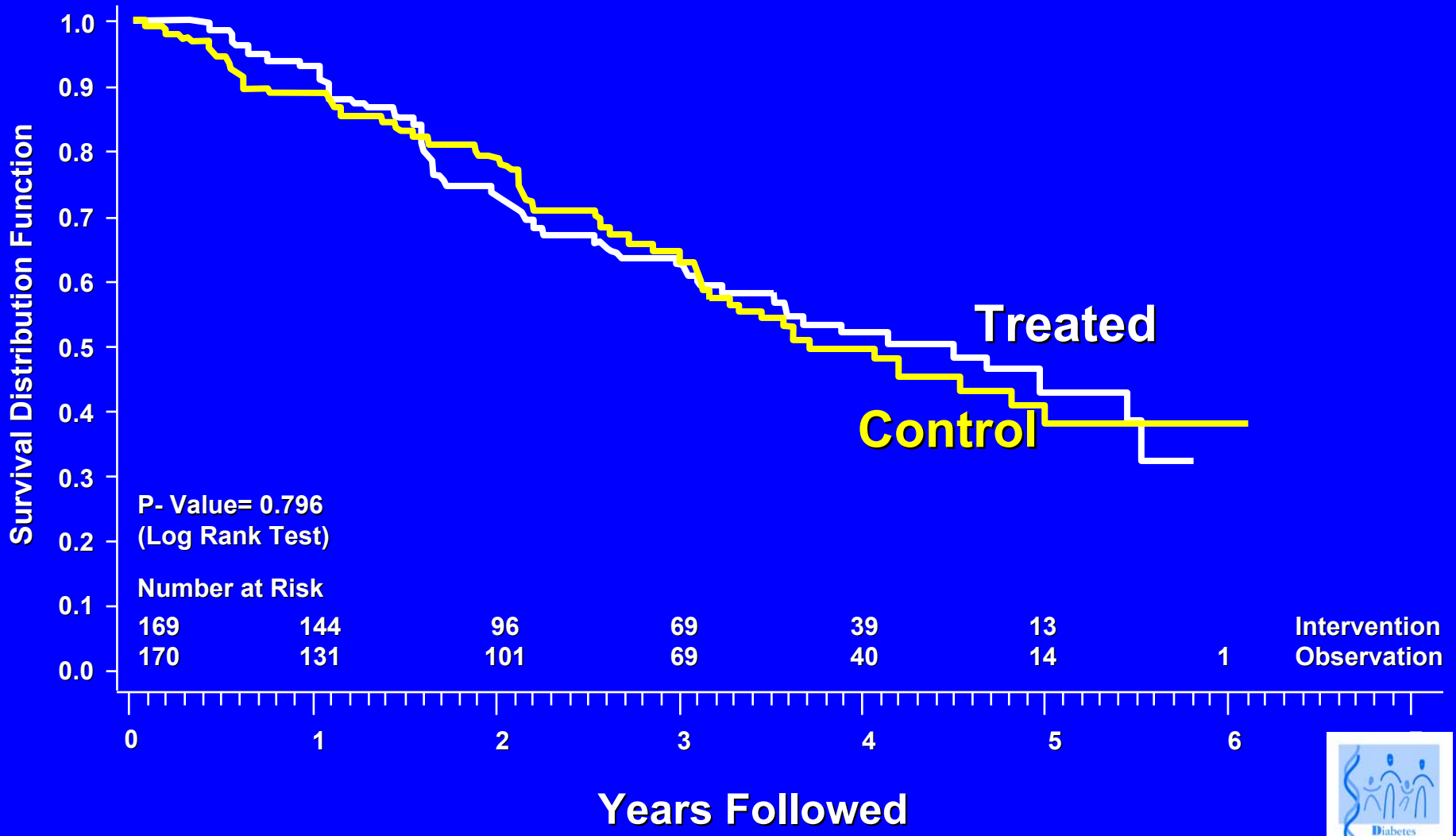
We can now predict type 1 diabetes.

We cannot now prevent type 1 diabetes.

DPT-1 Parenteral Study – Time to Diabetes By Treatment



New Engl J Med 2002; 346:1679

What are we missing?

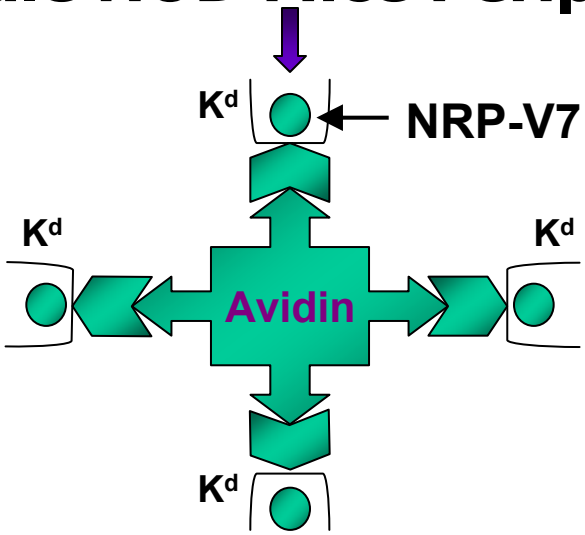
Assay for Pathogenic T cells.

? TETRAMER

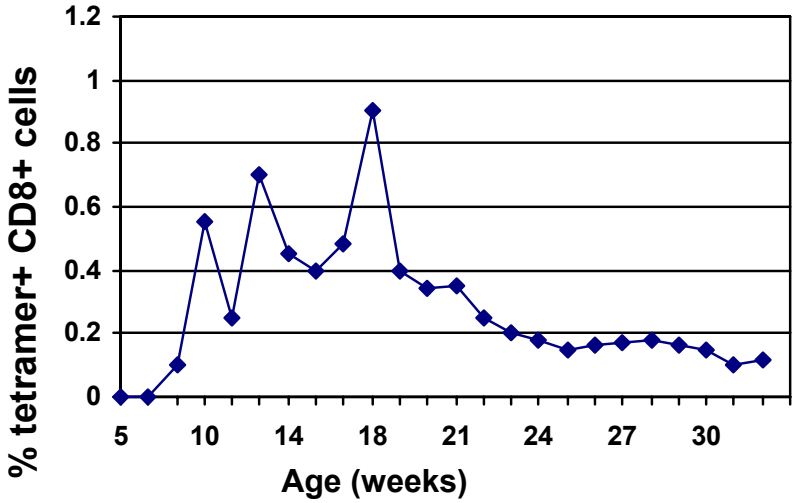
? ELISPOT

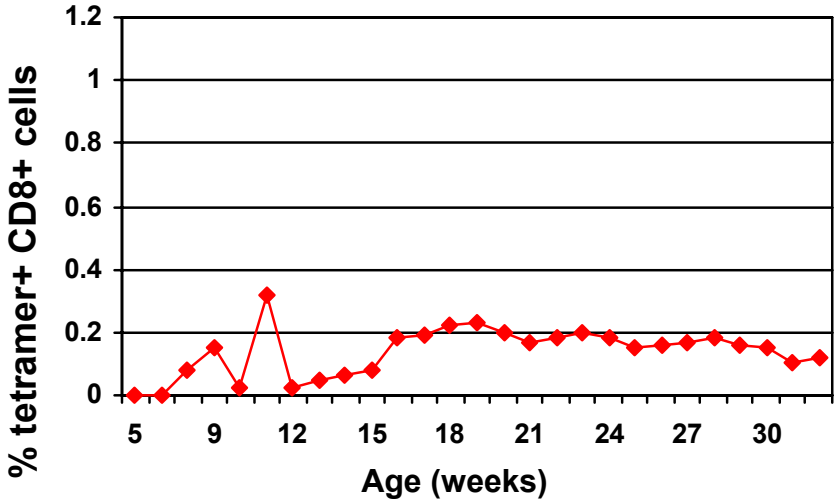
Female NOD Mice Peripheral Blood

Tetramer Analysis



IGRP-2nd Beta Cell Specific Ag





Diabetes

No Diabetes

Trudeau,Santamaria,Tan: JCI 2003

IDS Guidelines for Intervention Trials

Greenbaum and Harrison:Diabetes 52:1059, 2003

- **Diagnosis ADA criteria**
- **Document: age,sex,pubertal, family history,glucose, bicarb,ketoacidosis, weight loss, symptoms,HbA1c,islet autoab, insulin Rx, HLA**
- **Phase I >=18**
- **GAD, IA-2, IAA(<2 wks), and if DM ICA C-peptide>=.2 nmol/L, early = <12 weeks from diagnosis**
- **>=2 year trials**
- **Randomize, blind, mask, safety review, tight control, and continue insulin**
- **2 hr. AUC C-Peptide with meal tolerance test, no AM insulin except pump basal, fasting glucose 4-11.1 mmol/l**
- **Measure islet autoAb other immune with HLA**

Examples Non-antigen Specific Immunotherapy Trials in Type 1 DM

- MMF and DZB – Trialnet (Gottlieb) ?
- Multidose anti-CD3 ITN X1 ?transient (Herold and Chatenoud)
- HSP 65 p277 s.c. - (Peptor) – LADA ?
- Multi-dose DZB - Henry Rodriguez, Indiana ?
- Oral hIFN-alpha - Staley Brod, Texas ?
- NIP study “fish oil” -Trialnet (Chase) ?
- Nicotinamide Endit No Effect
- Rituximab (anti-B Cell) Trialnet ?

BDC

Recent and Ongoing Antigen-specific Immunotherapy Trials in New Onset T1 DM

- DPT-1 Parenteral Insulin: No Effect
- DPT-1 Oral Insulin: No Effect/Subgroup ?
- DIPP (intranasal): ?
- Italy/France Oral Insulin: No Effect
- Joslin/ITN Ins B chain in IFA: ?
- NBI 6024-003 - Neurocrine, BDC/VMR ?
- hGAD s.c. in alum (Diamyd) ?
- Peptor Heat Shock Protein ?

Thoughts

- Prevention DM and Preservation B cells at onset Important
- Prediction high risk “easy”
  1 million in U.S. developing DM(>=2 Abs)
- Multiple Therapies animal models
- Explosion Immunotherapies man
- Matter of time immunotherapy for chronic active insulitis
- Outcome – Diabetes/ C-peptide/ continuous glucose monitoring
- International collaboration (ITN/TrialNet)