

nPOD Annual Meeting 1/16/12

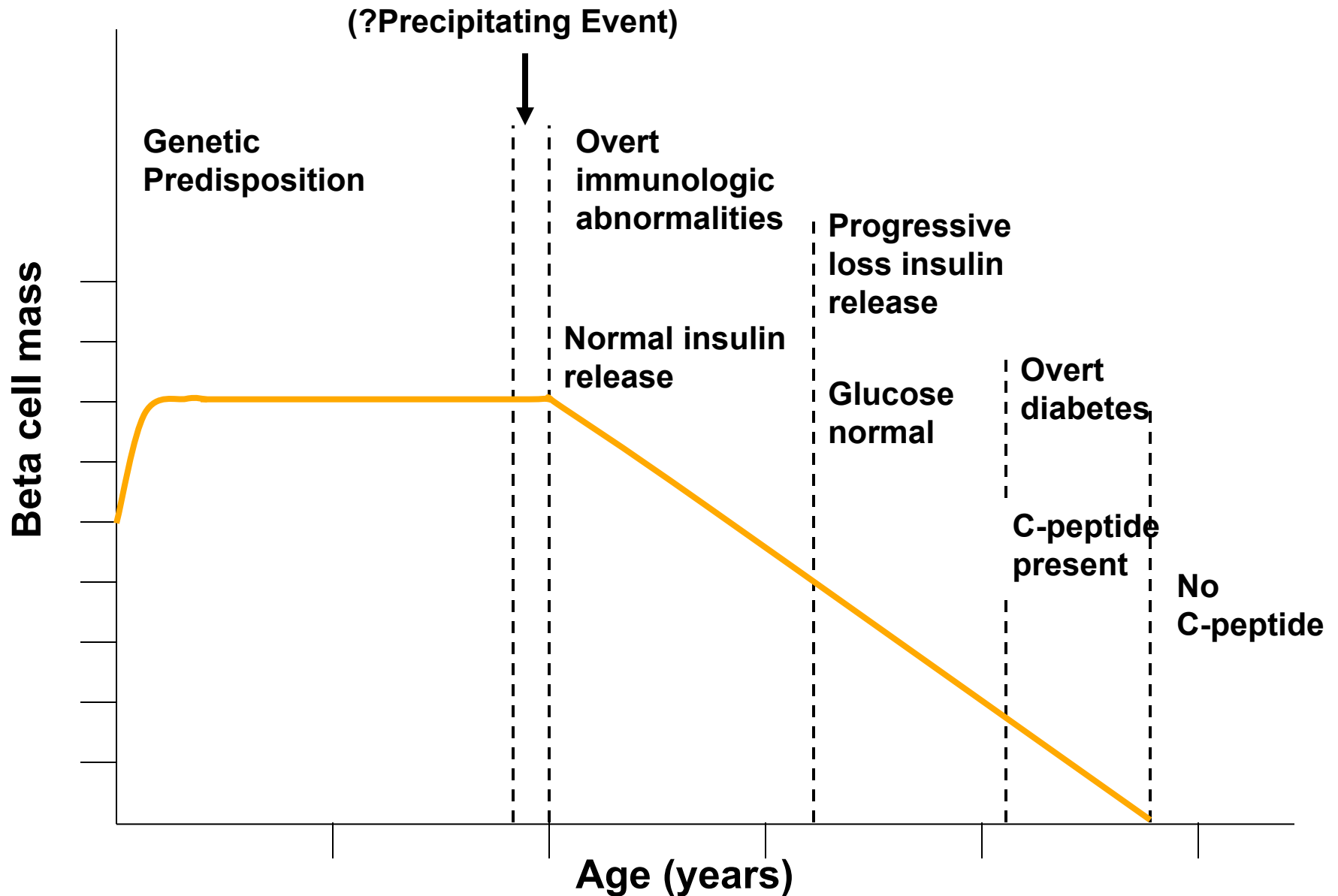
George Eisenbarth – Islet
Autoantigens, Autoreactive T
Cells and the MHC-TCR-Peptide
Molecular Complex - Therapeutic
Targets in T1D



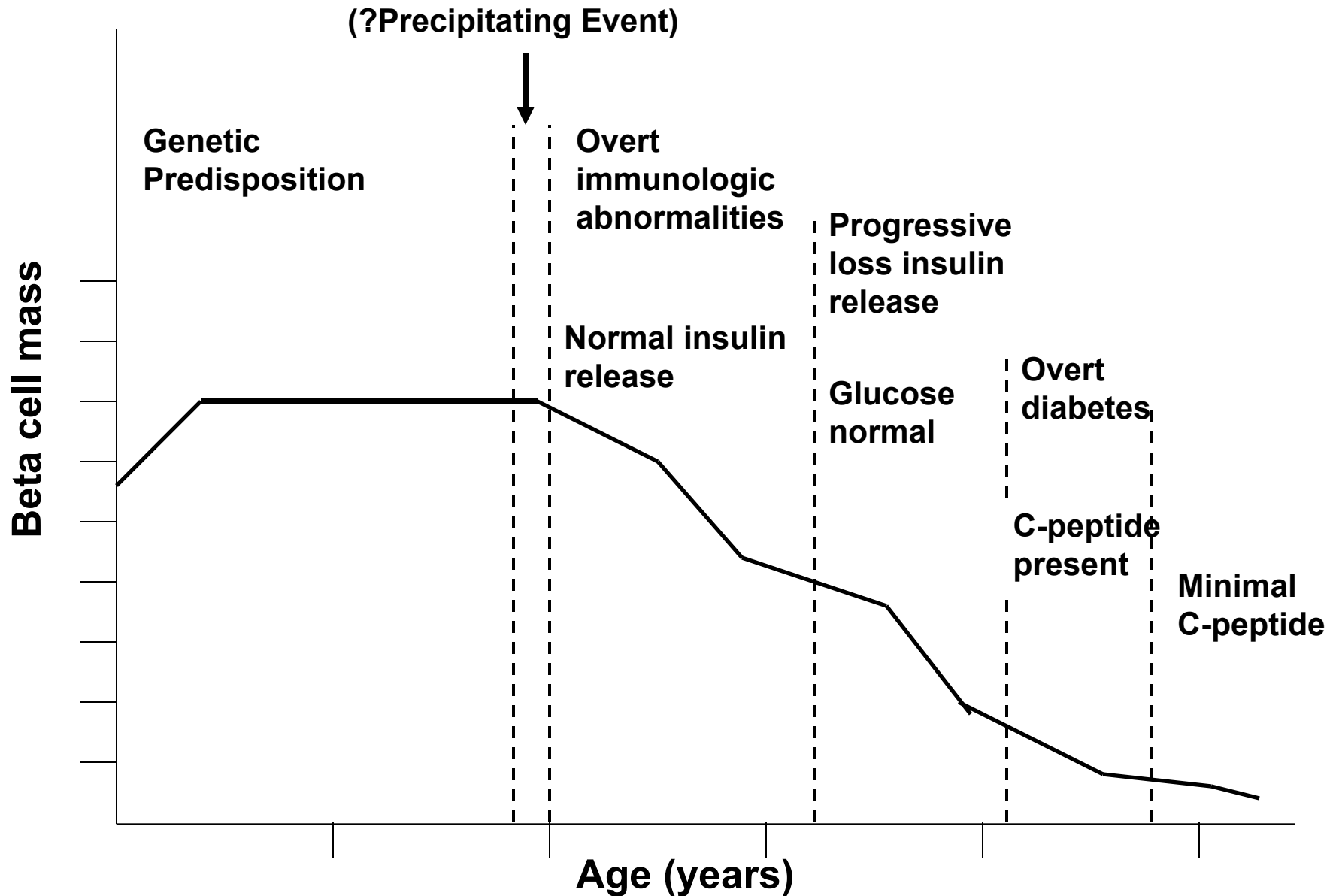
Beta Cell Destruction QUESTIONS (for nPOD)

- Heterogeneity pancreatic Pathology?
- Potential mechanisms?
- How complete Beta Cell Destruction?
- Exceptions?

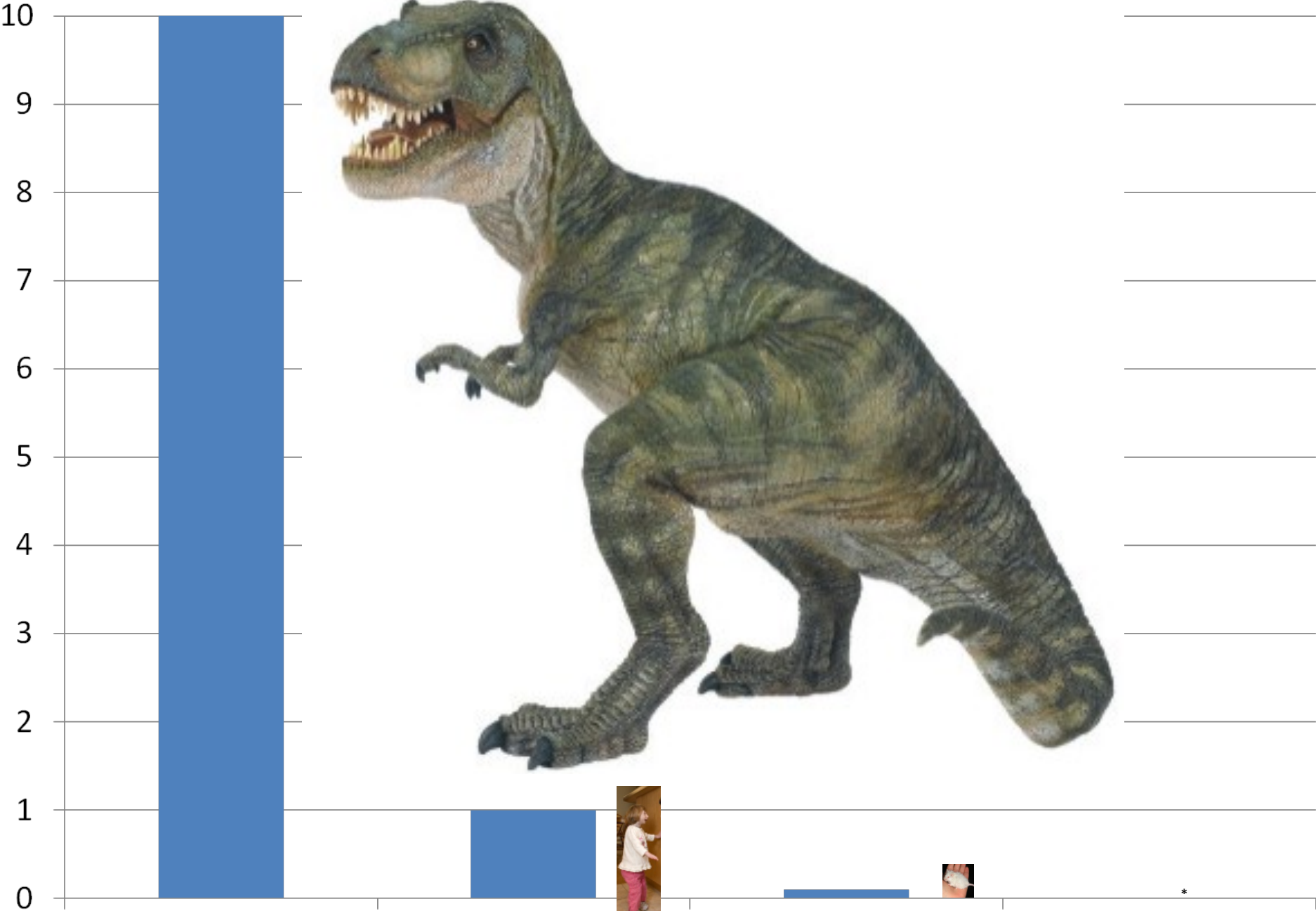
“Stages” in Development of Type 1A Diabetes



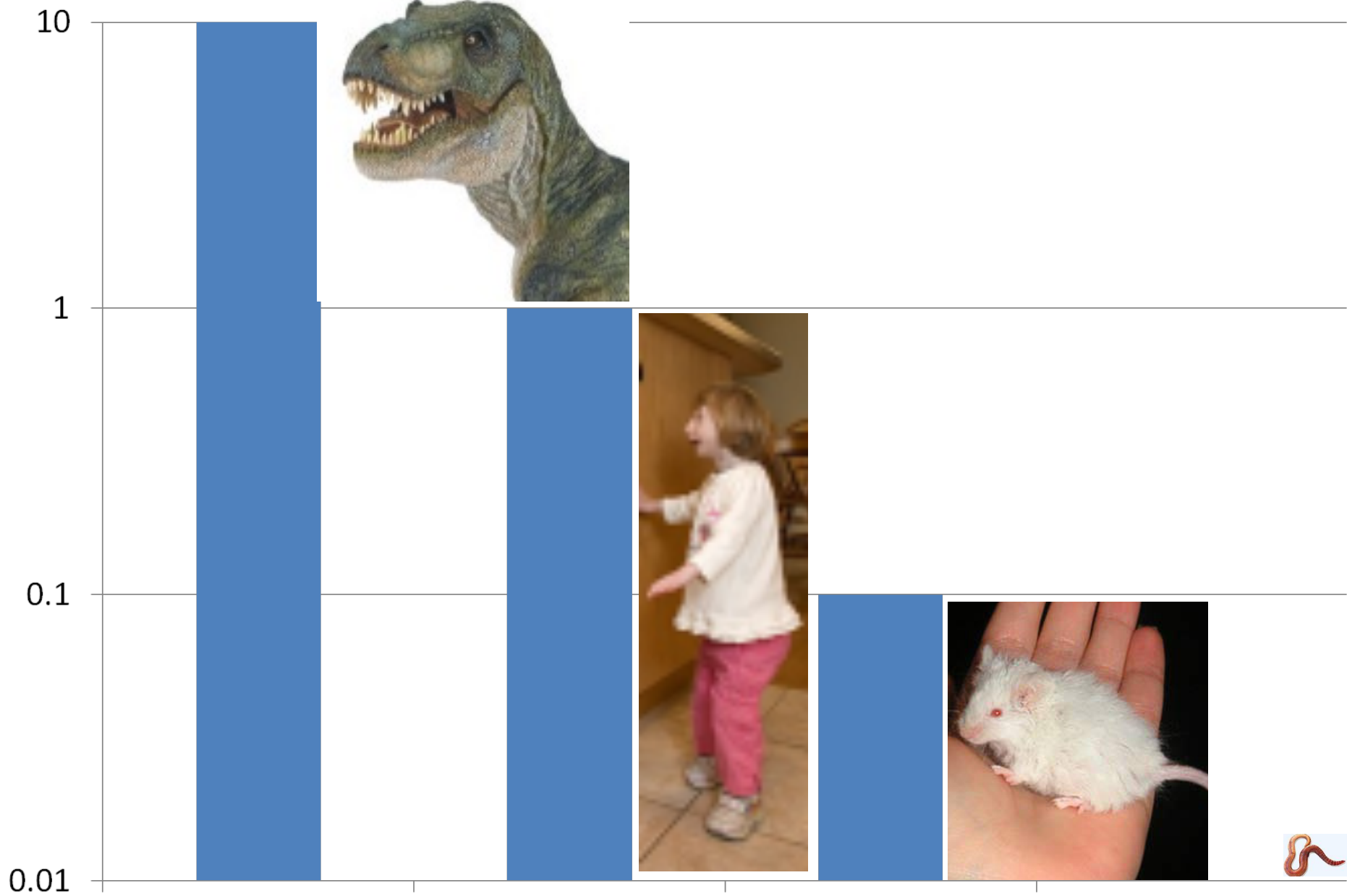
“Stages” in Development of Type 1A Diabetes



ORDERS OF MAGNITUDE: linear plot

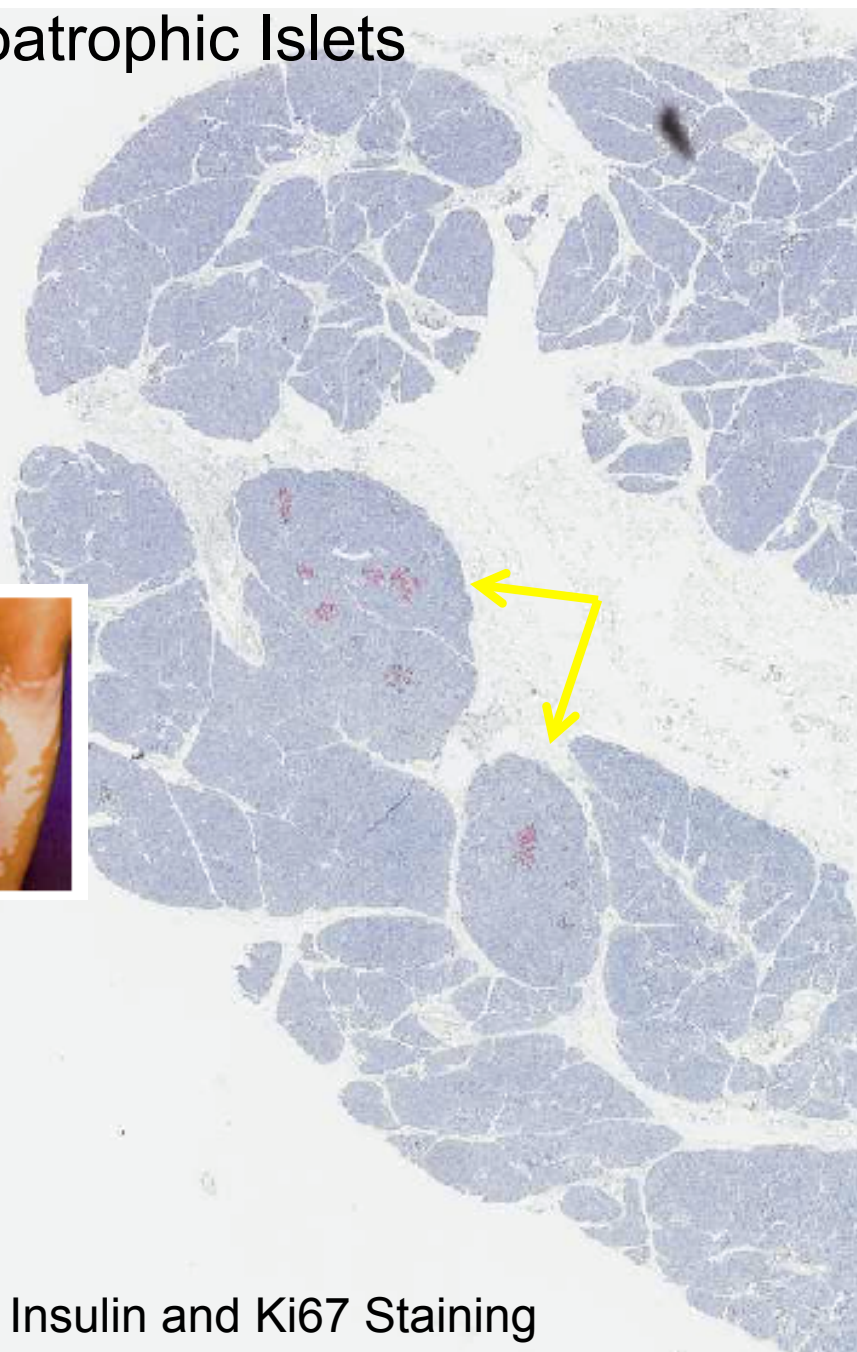
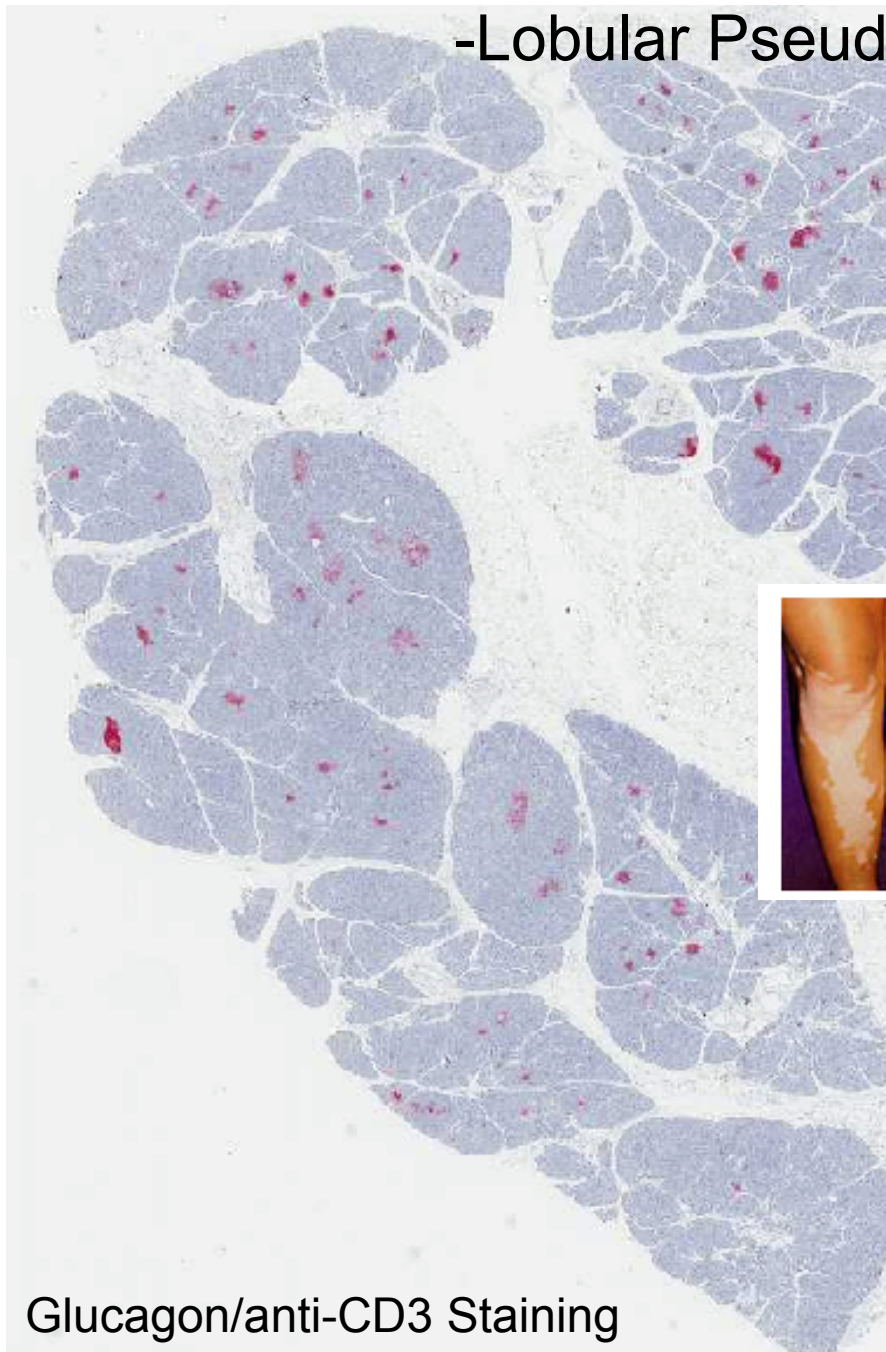


ORDERS OF MAGNITUDE: Log Plot



nPOD 6052-02 Tail: 12 yo 1 year diabetes

-Lobular Pseudoatrophic Islets



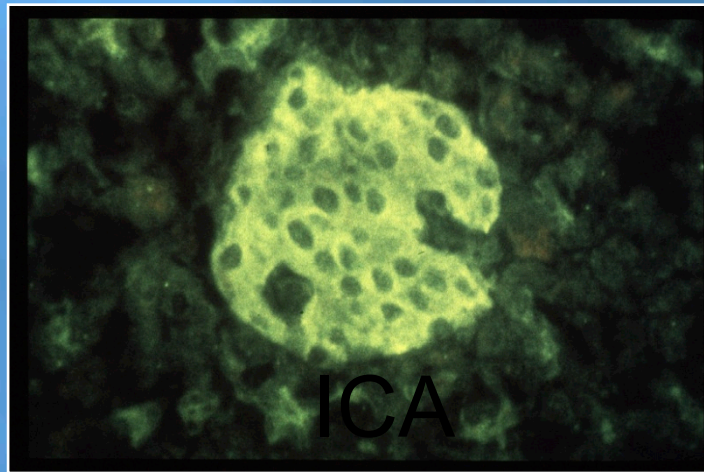
Glucagon/anti-CD3 Staining

Insulin and Ki67 Staining

TRIGGERING QUESTIONS (for nPOD)

- Is there an environmental trigger?
- Does autoantibody appearance mark triggering?
- Time lag between trigger and insulinitis?
- Time lag between insulinitis and beta cell killing?
- “Best Model”
 - ?Kilham Rat Virus (Multiple Other viruses)
 - ACTIVATION INNATE IMMUNITY BY VIRUS
 - SPECIFIC MHC AND SPECIFIC TCR (Mordes et al)
 - ANTI-INFLAMMATORY PREVENTS (Zipris et al)

Major Islet Autoantigens



Insulin autoantibodies

?

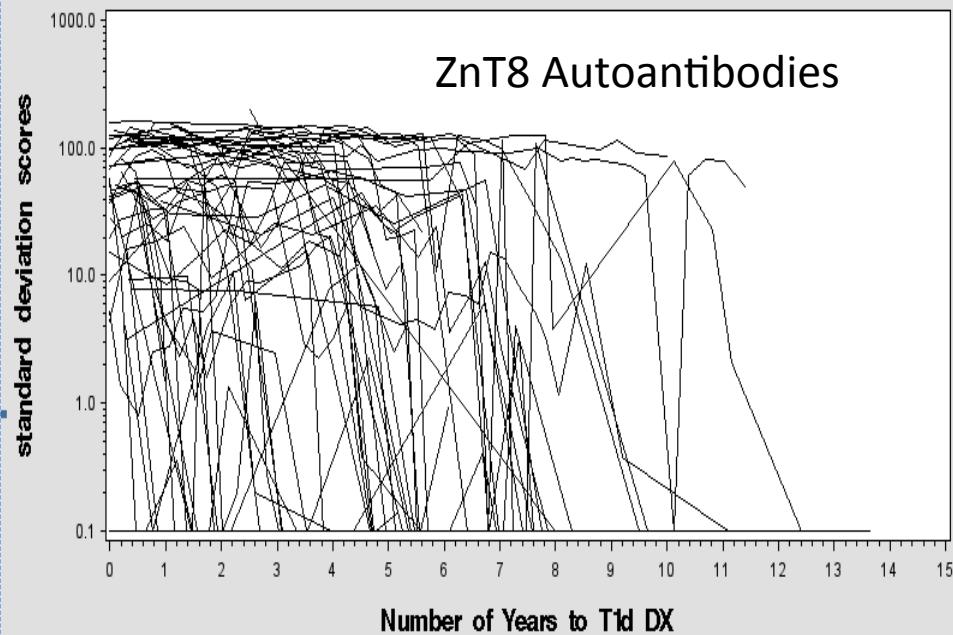
ZnT8

IA-2
(ICA512BDC)

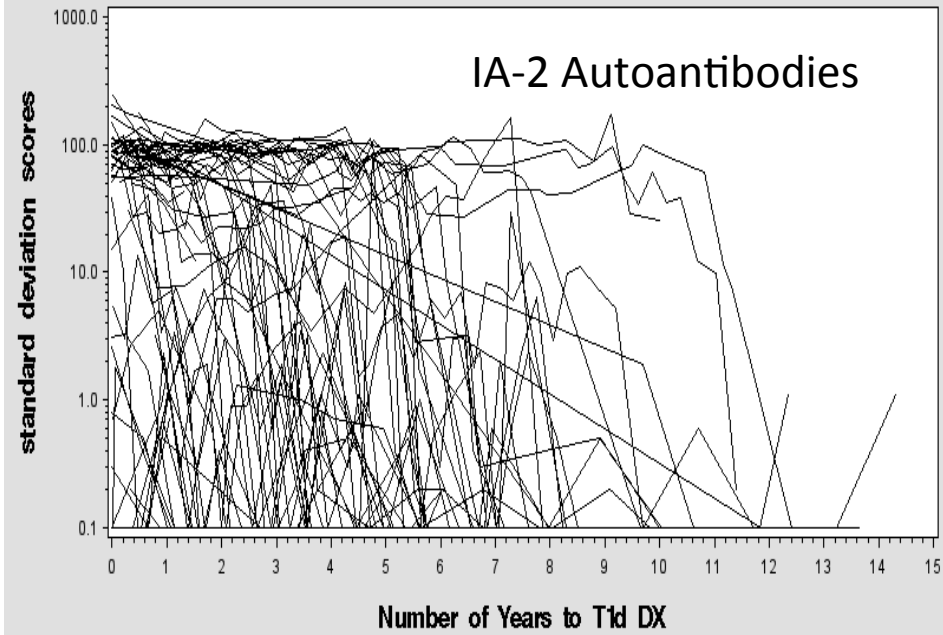
GAA
(GAD₆₅)

IAA

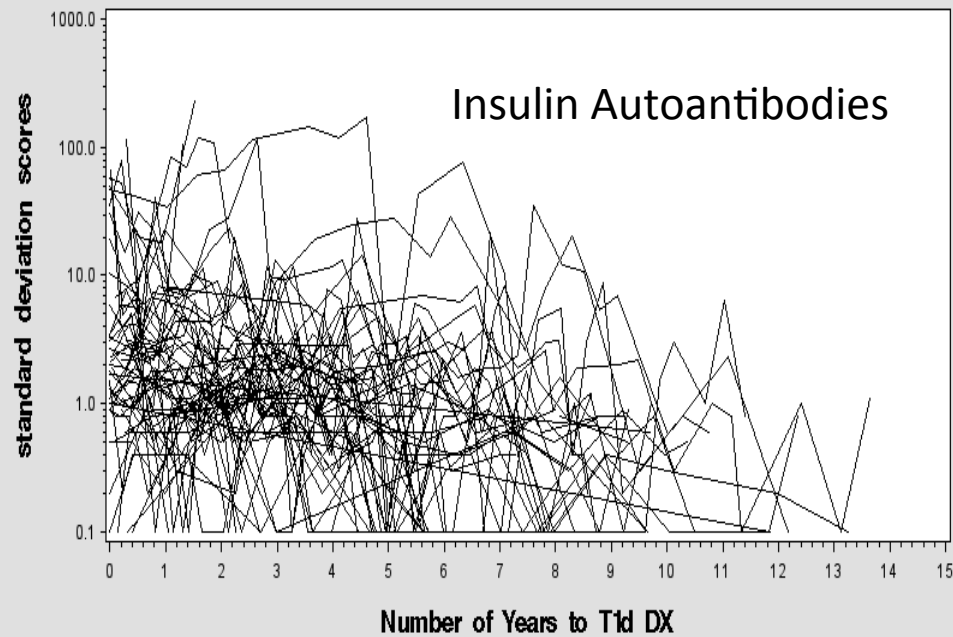
znt8_z level by Patient



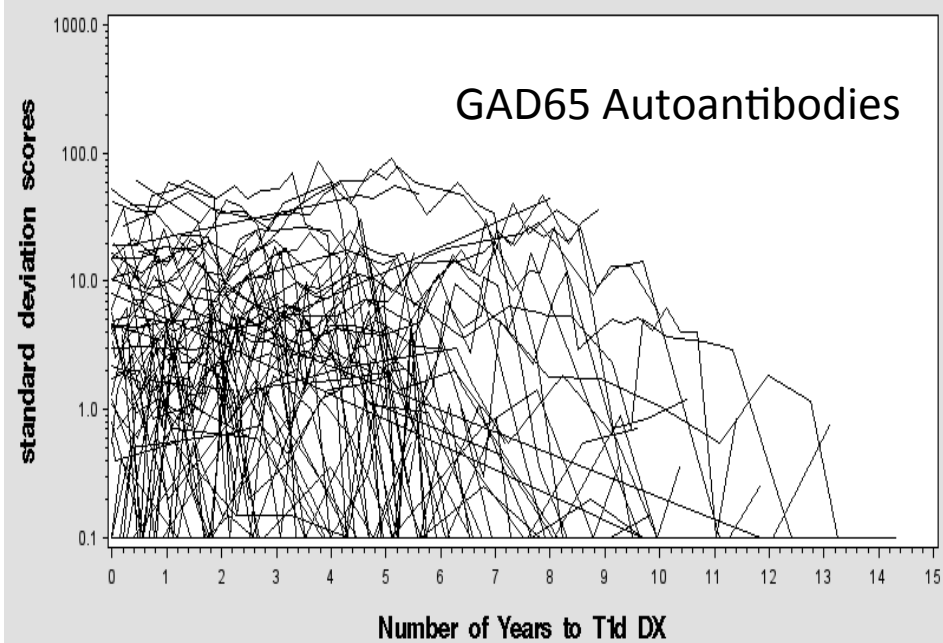
bdc512_z level by Patient



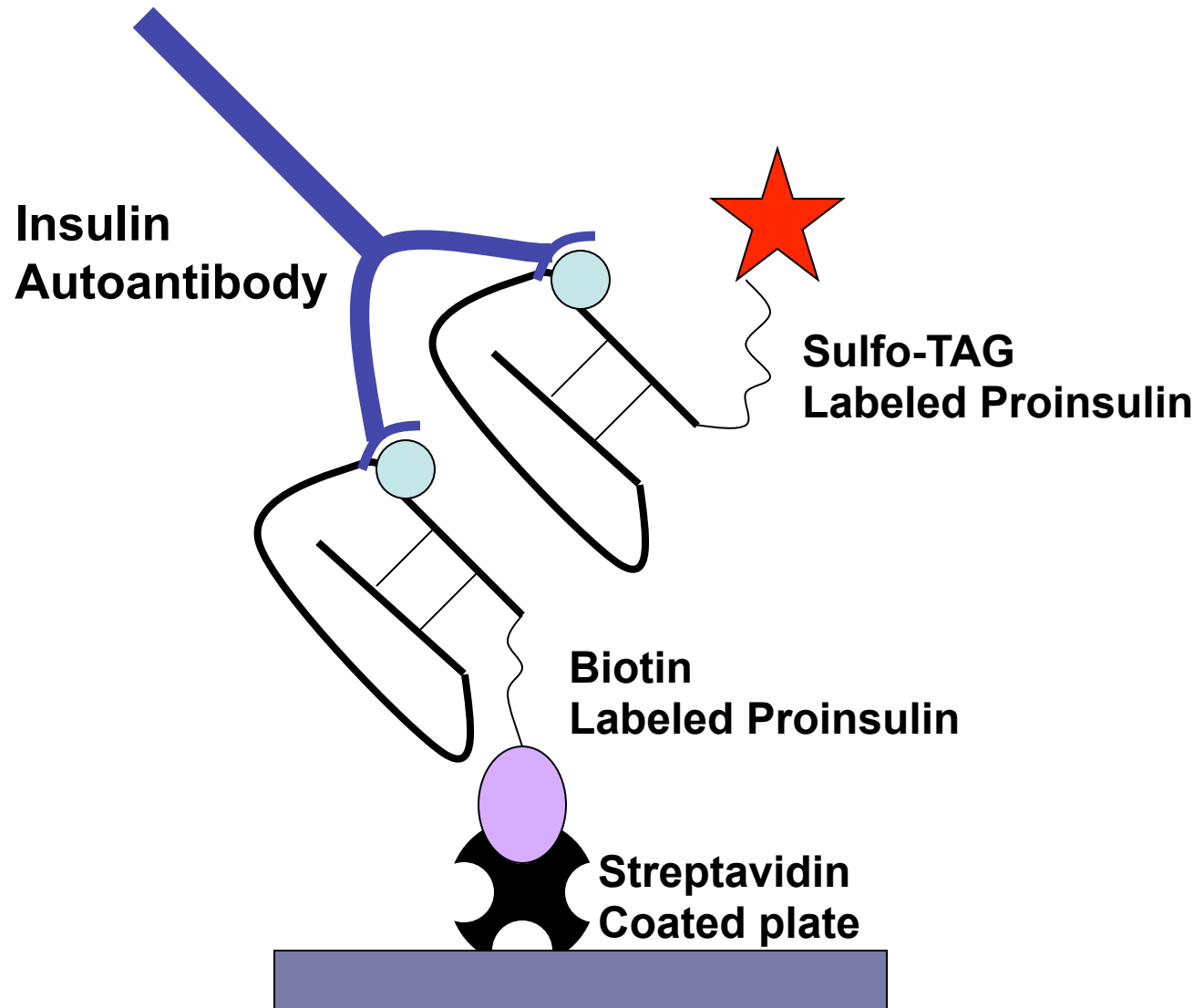
miaa_z level by Patient



gaa_z level by Patient

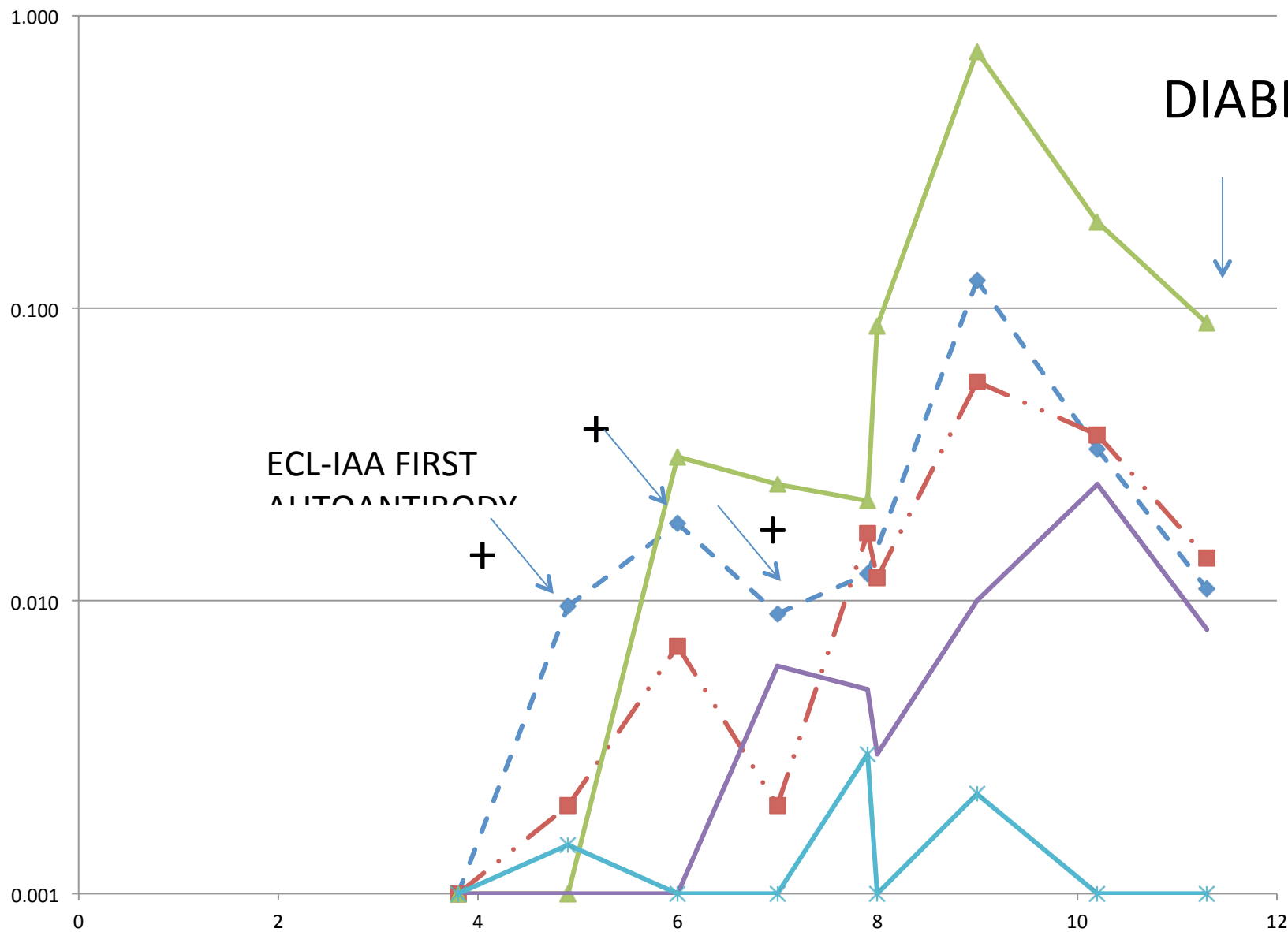


Non-Radioactive Electrochemiluminescent Insulin Autoantibody Assay



DAISY PREDIABETIC; MSD-IAA FIRST AUTOANTIBODY

INDEX



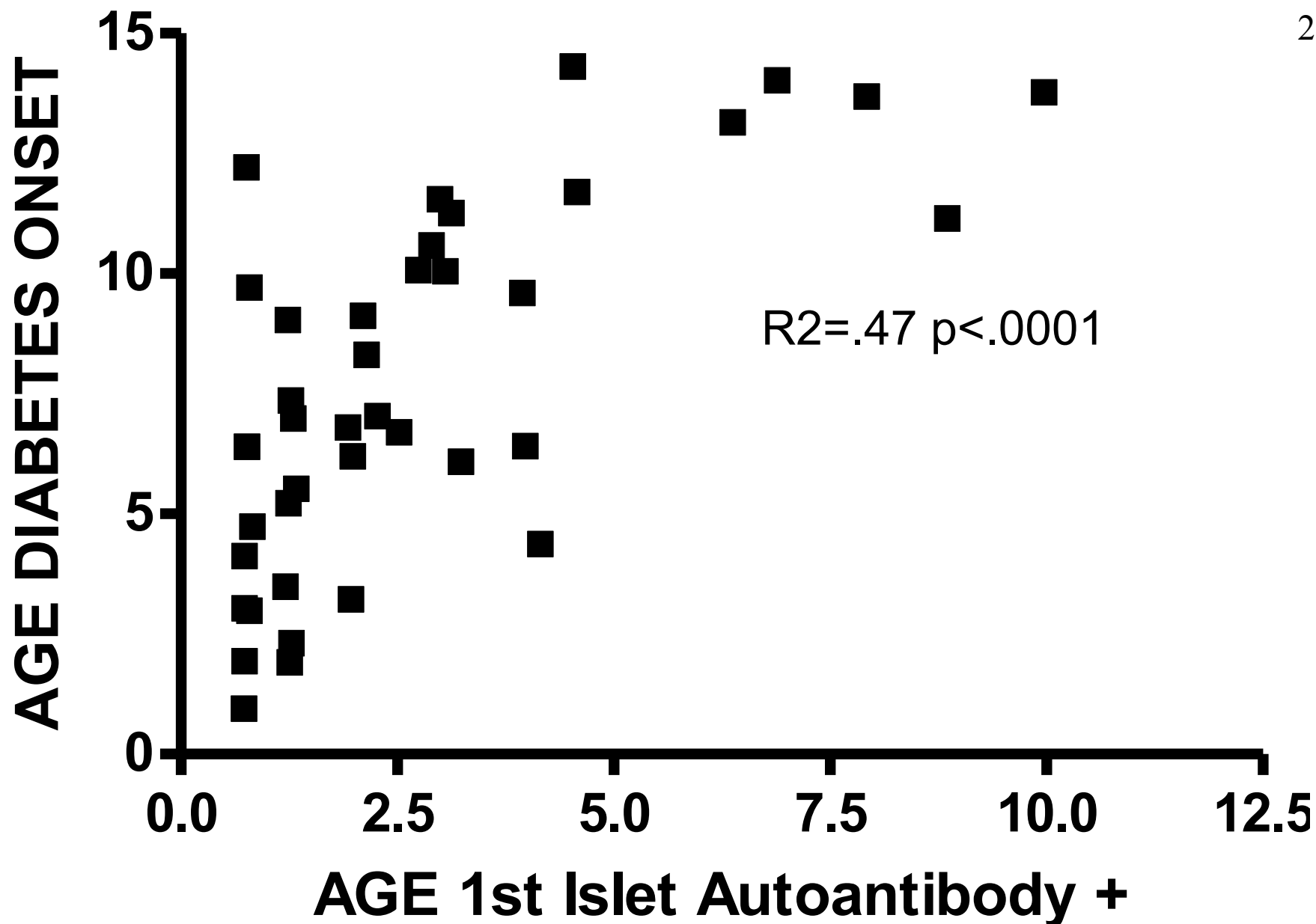
- MSD
- Miaa
- gad65
- ica512bdc
- znt8

AGE (YEARS)

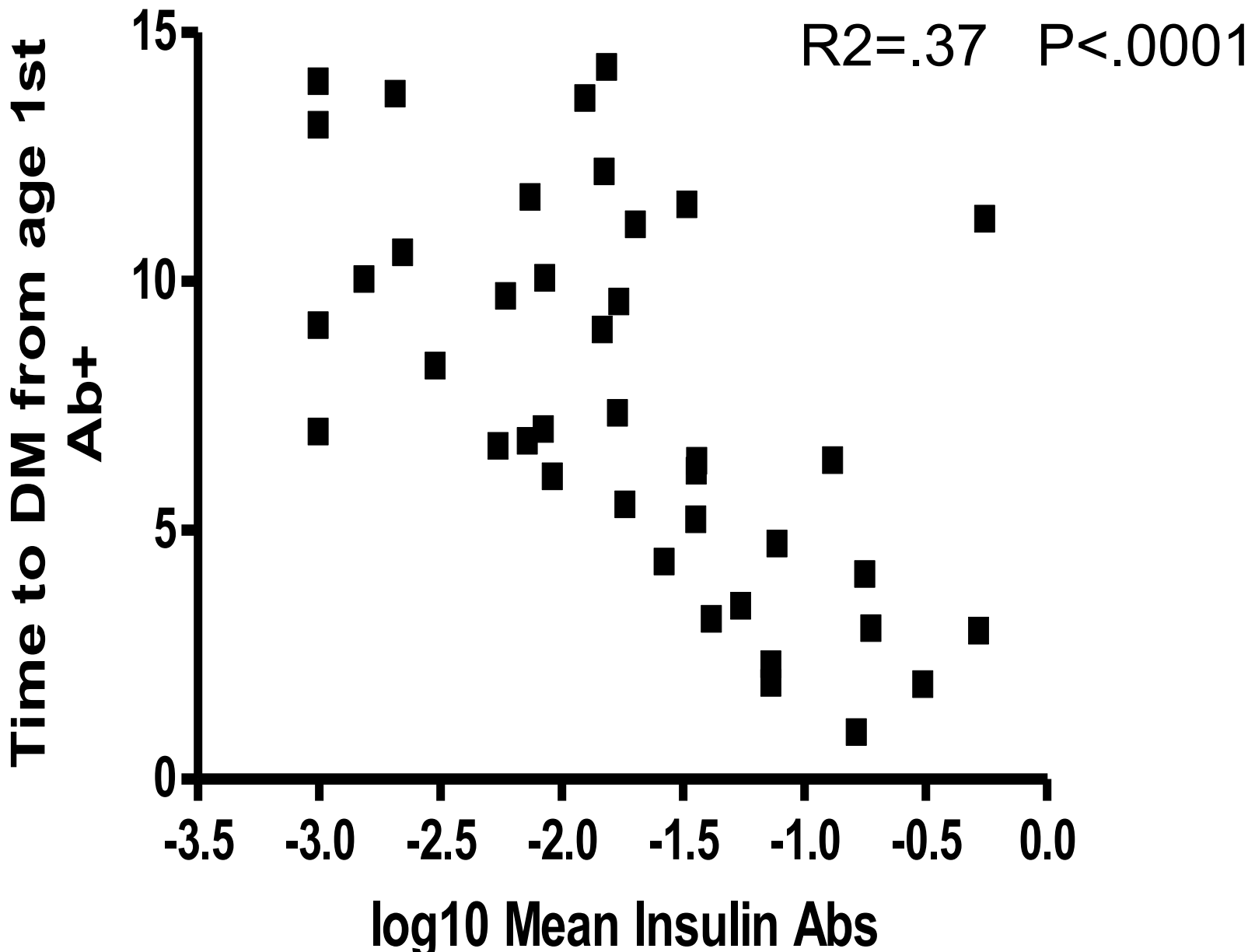
00748-0

Age 1st Islet Ab+ vs Age DM Onset

Steck et al Diabetes Care
2011

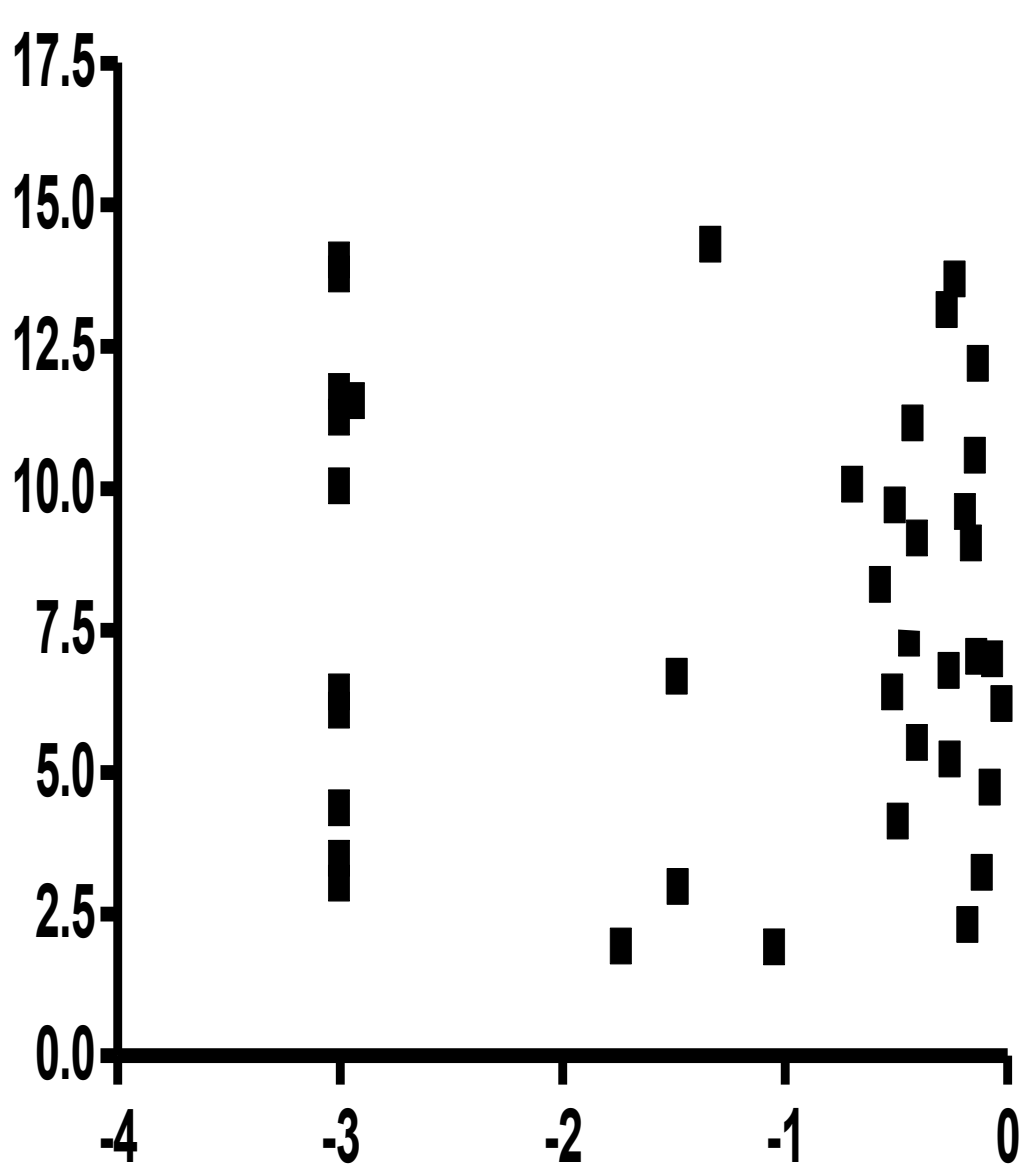
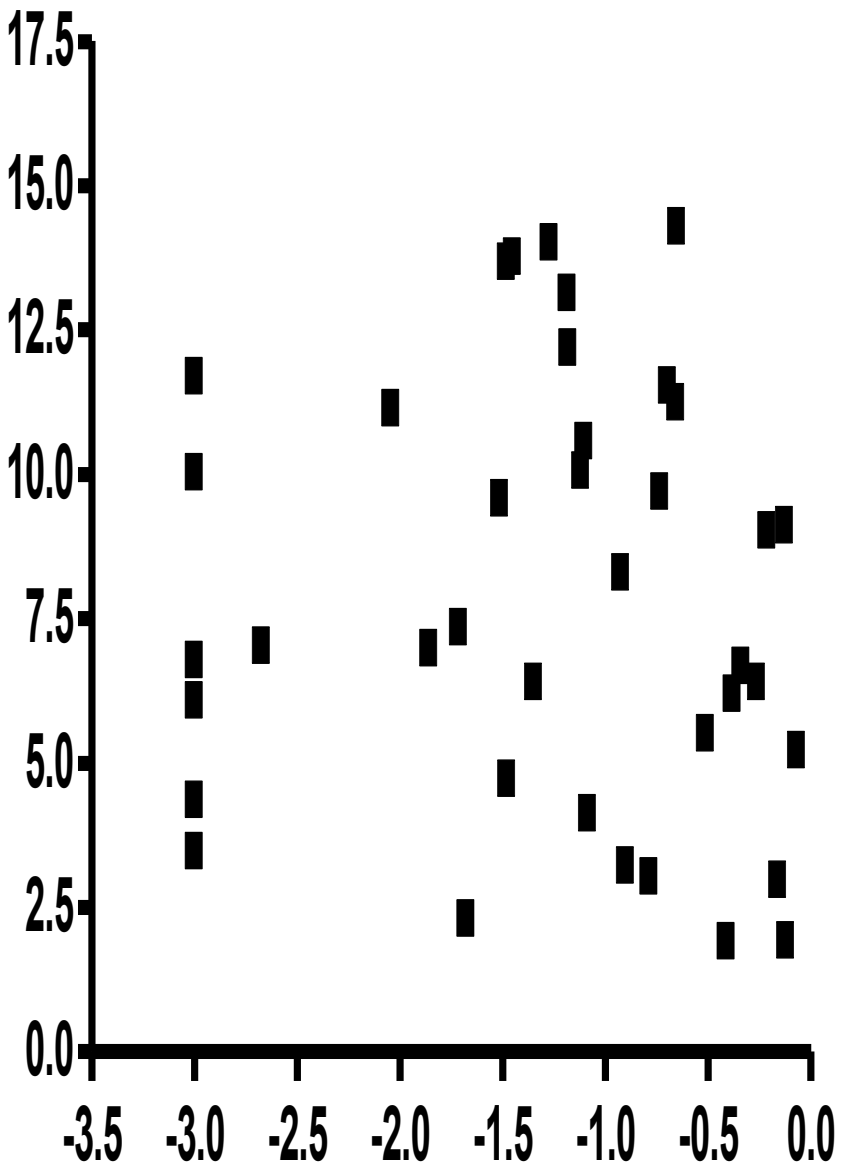


MEAN LOG IAA vs Time to DM from age Islet Ab first +



GAD65 Levels with Years to Diabetes

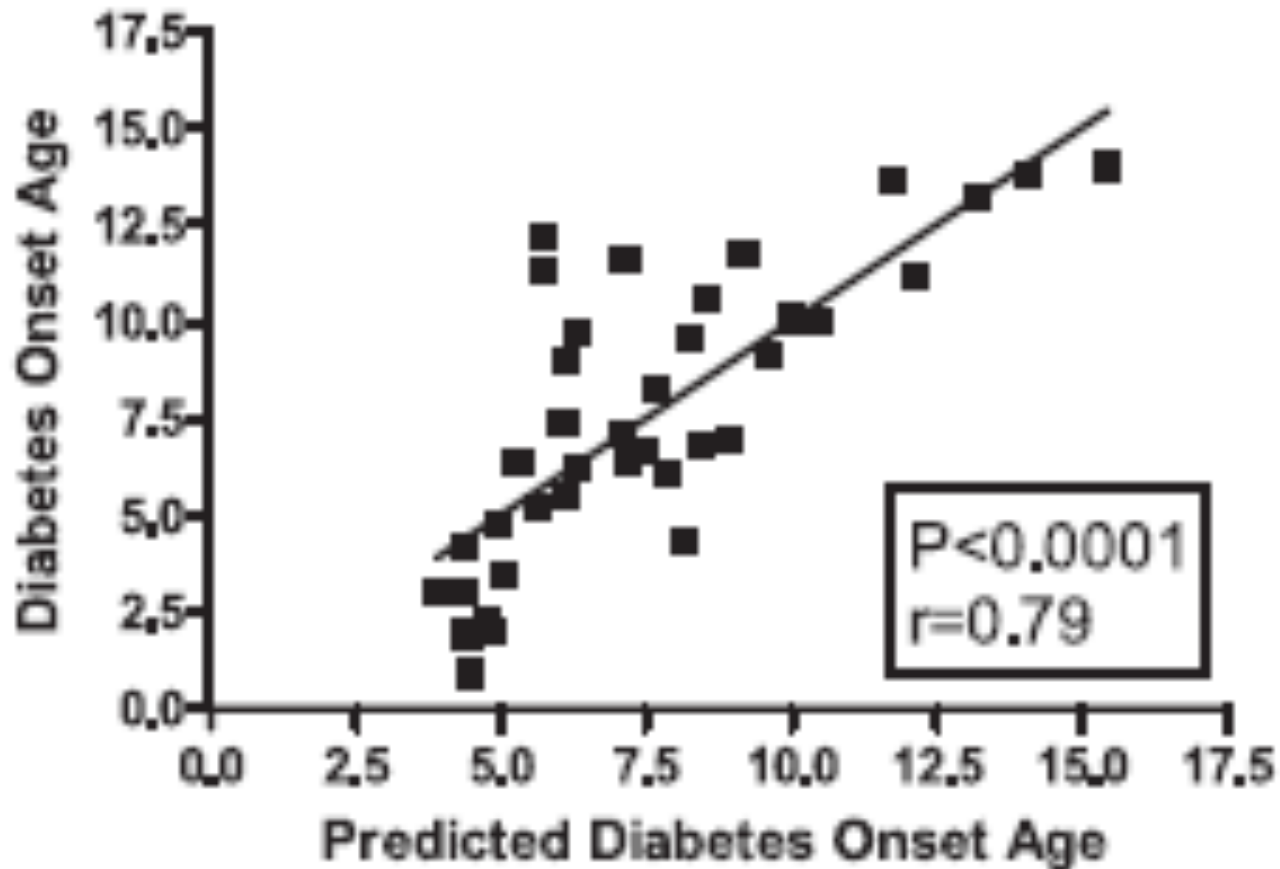
ICA512 Levels with Years to Diabetes



Mean GAD65 Levels (Log10)

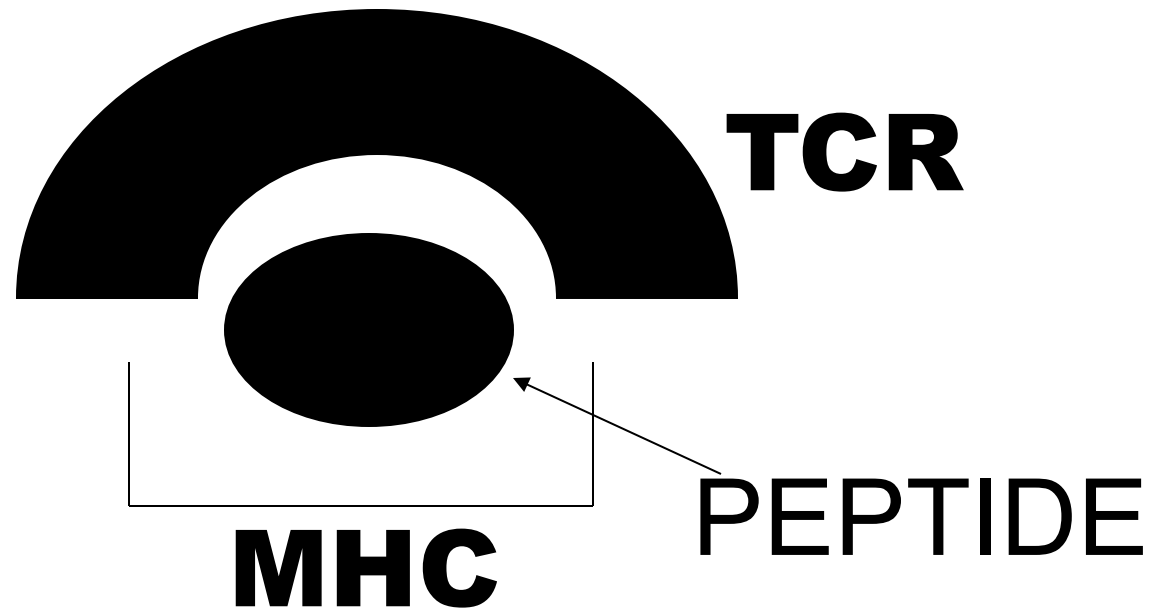
Mean ICA512 Levels (Log10)

Predicted Onset Age=
 $2.6 - 1.3 * \log(\text{mean IAA}) = 0.8 * \text{age first Ab+}$

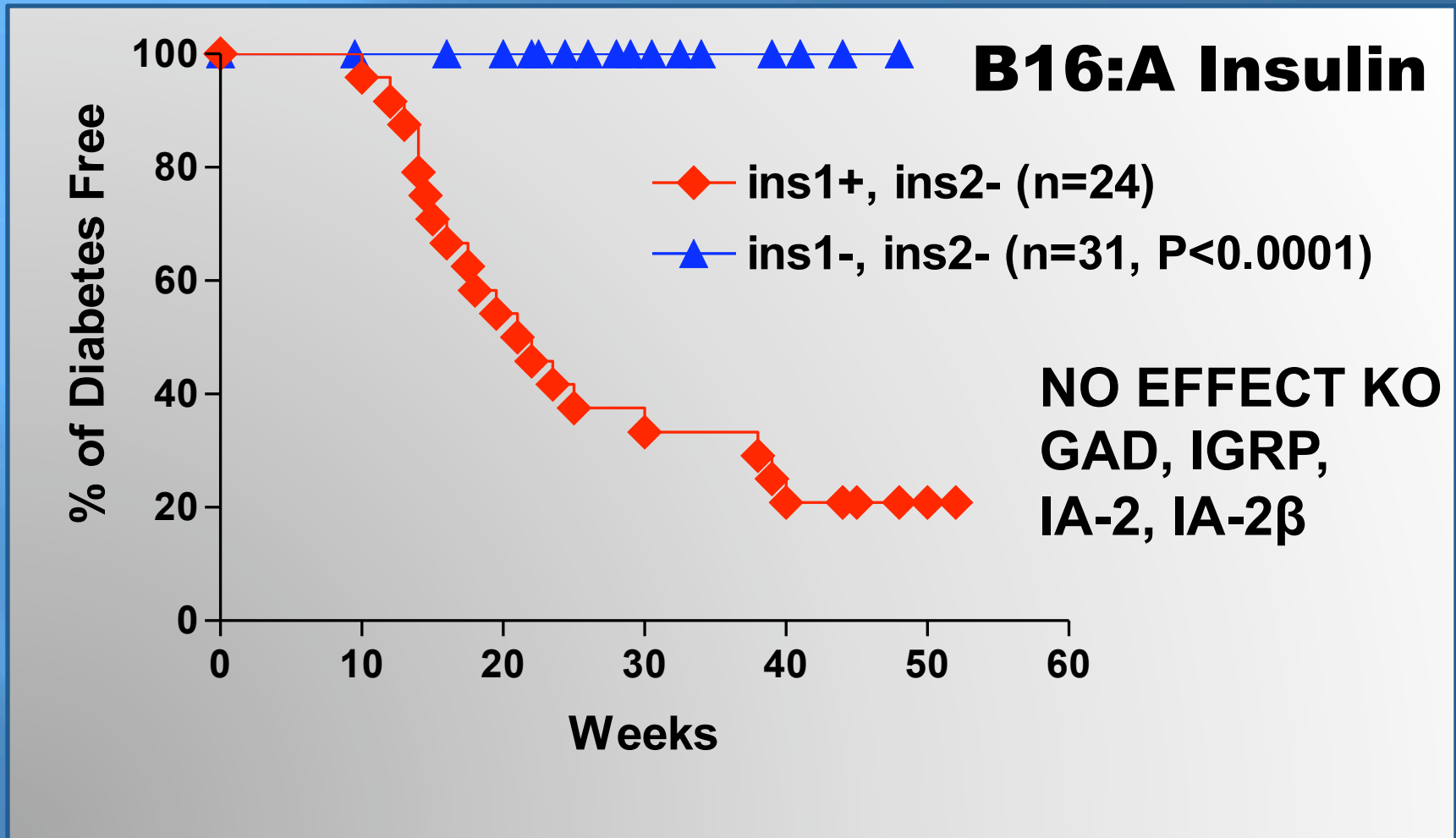


Trimolecular Recognition Complex

Fundamental Structure Diabetes Susceptibility

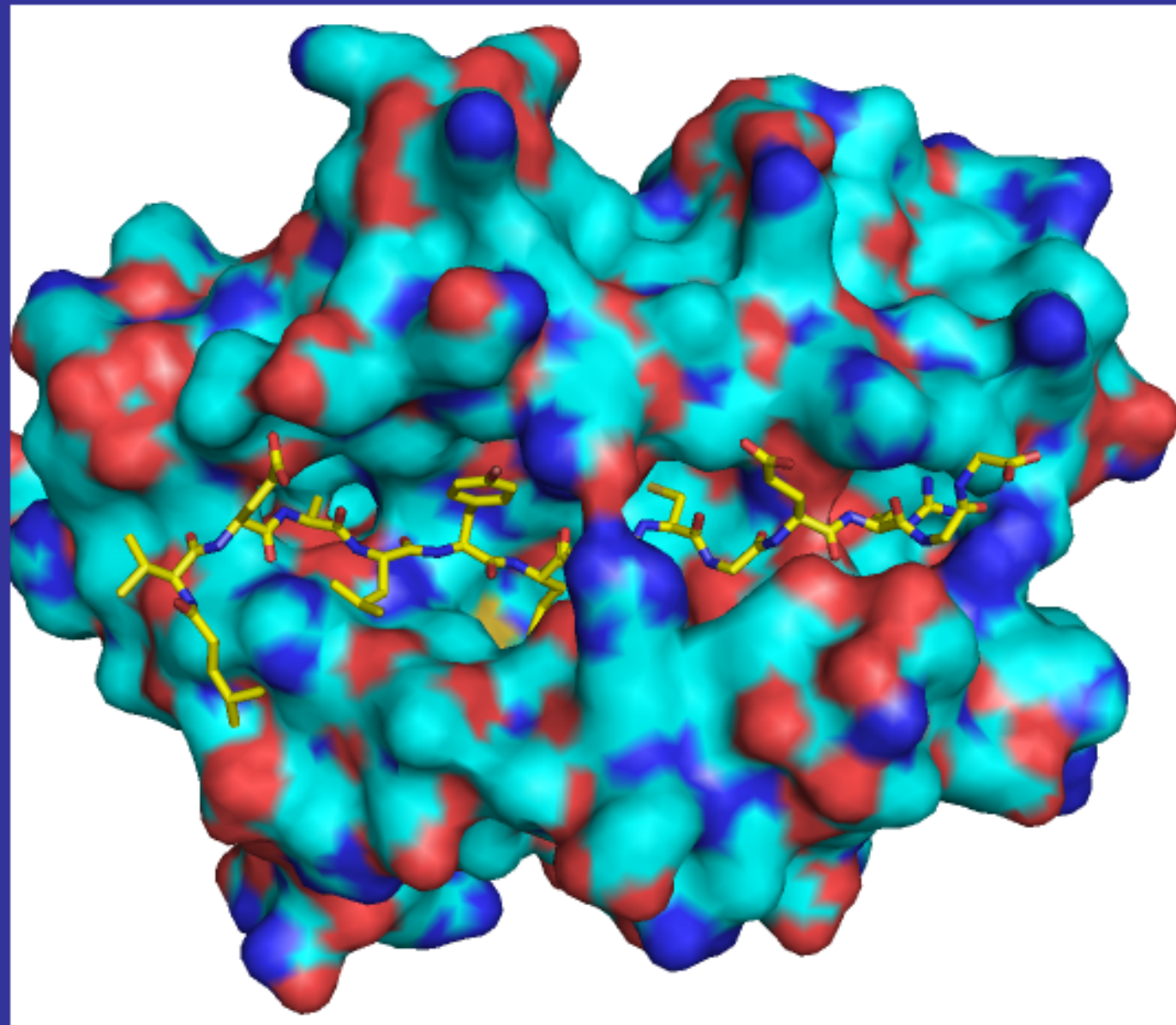


Mutating One Amino Acid of Insulin Prevents (B16:A) All NOD Diabetes

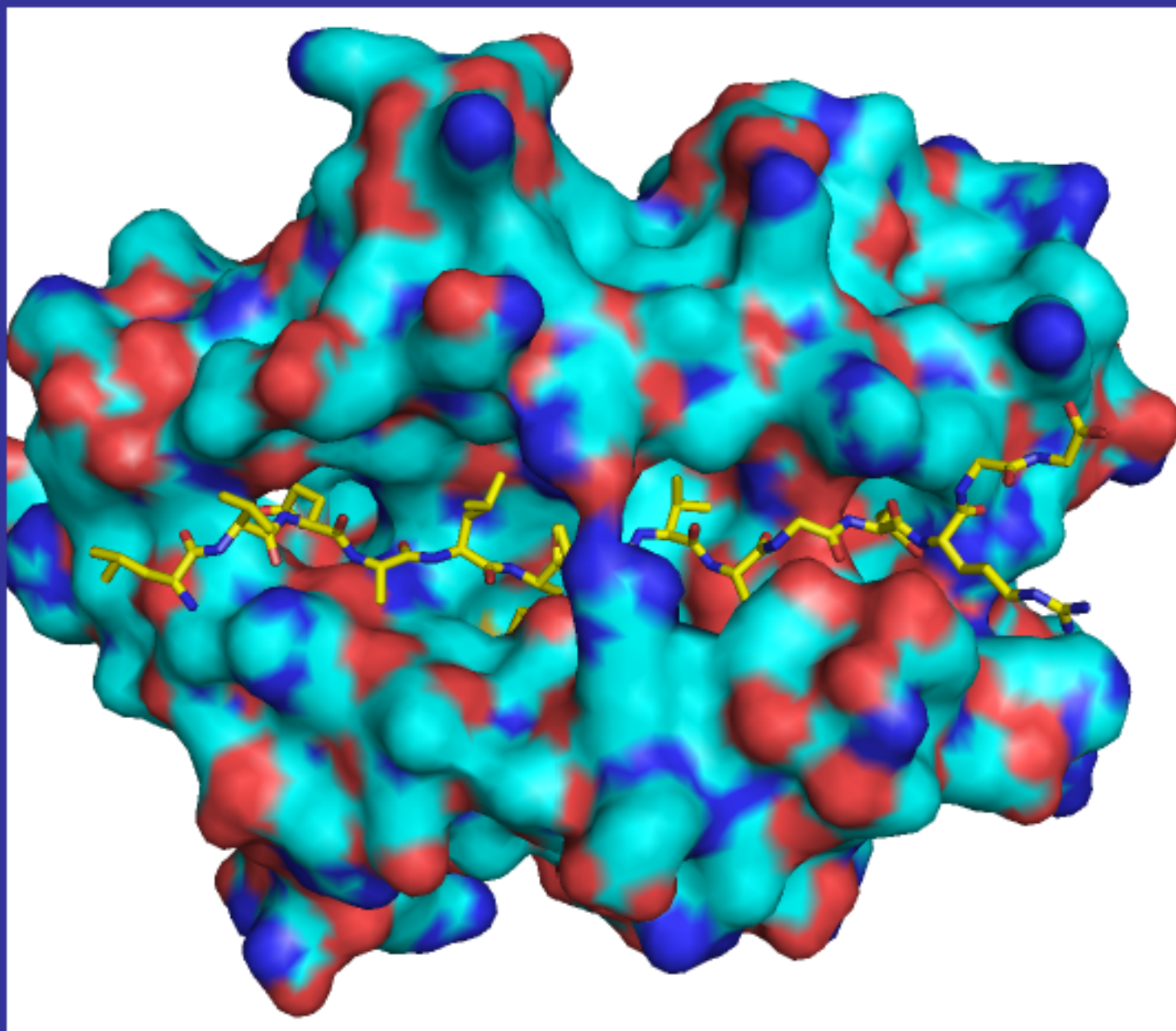


Ostrov
Model
Insulin
Peptide B:
9-23 in
Register 3
of I-A^{g7}

Register 3

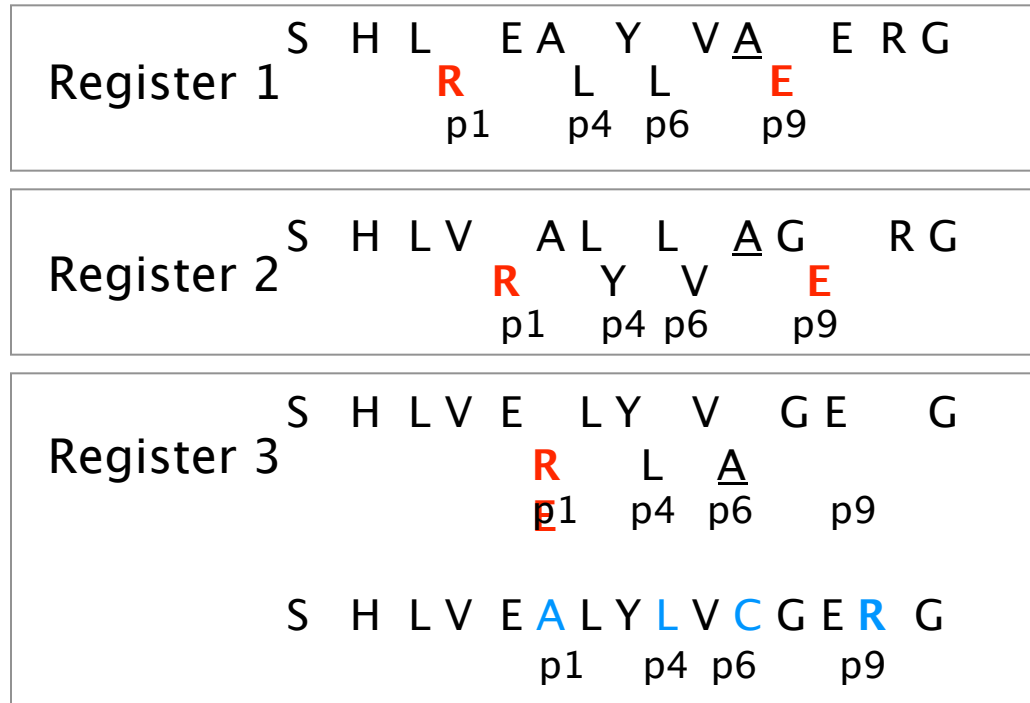


Register 2

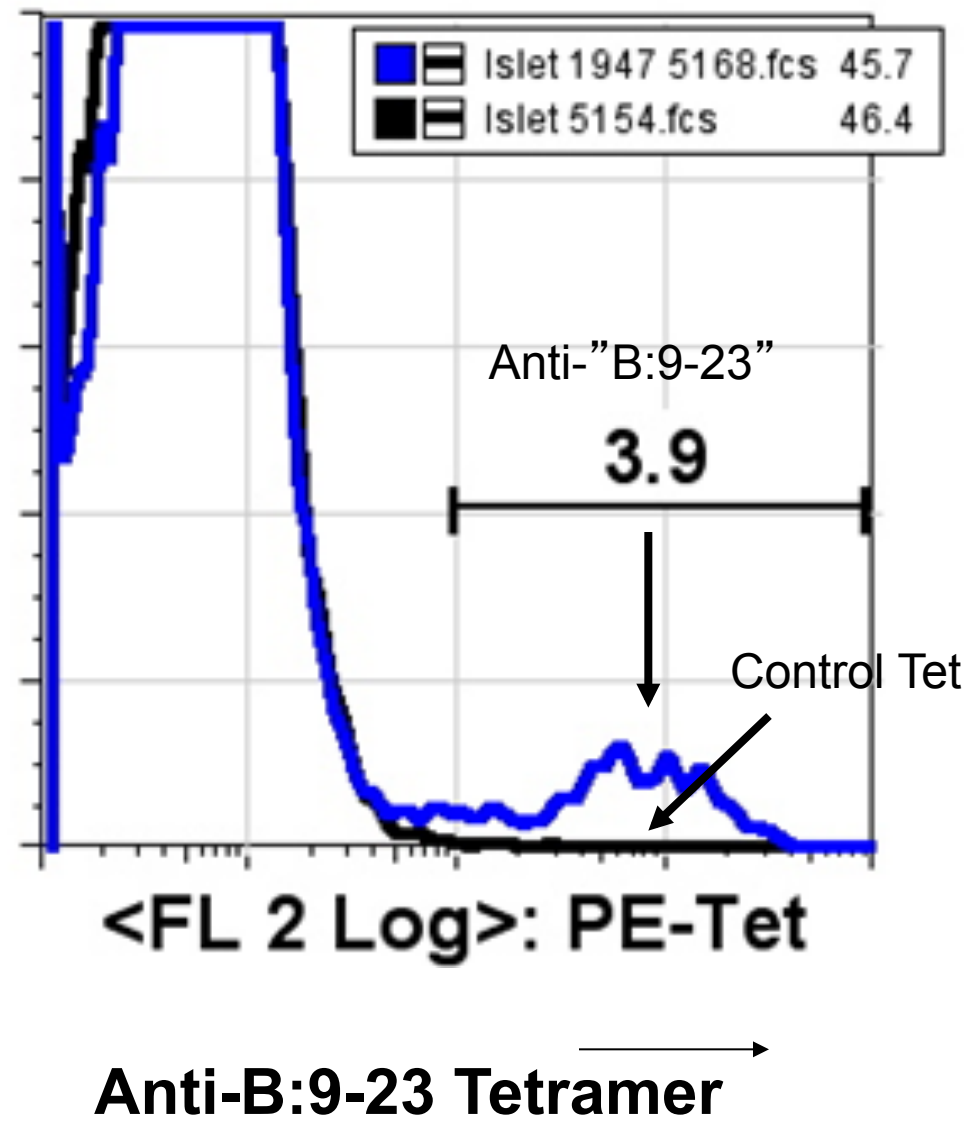
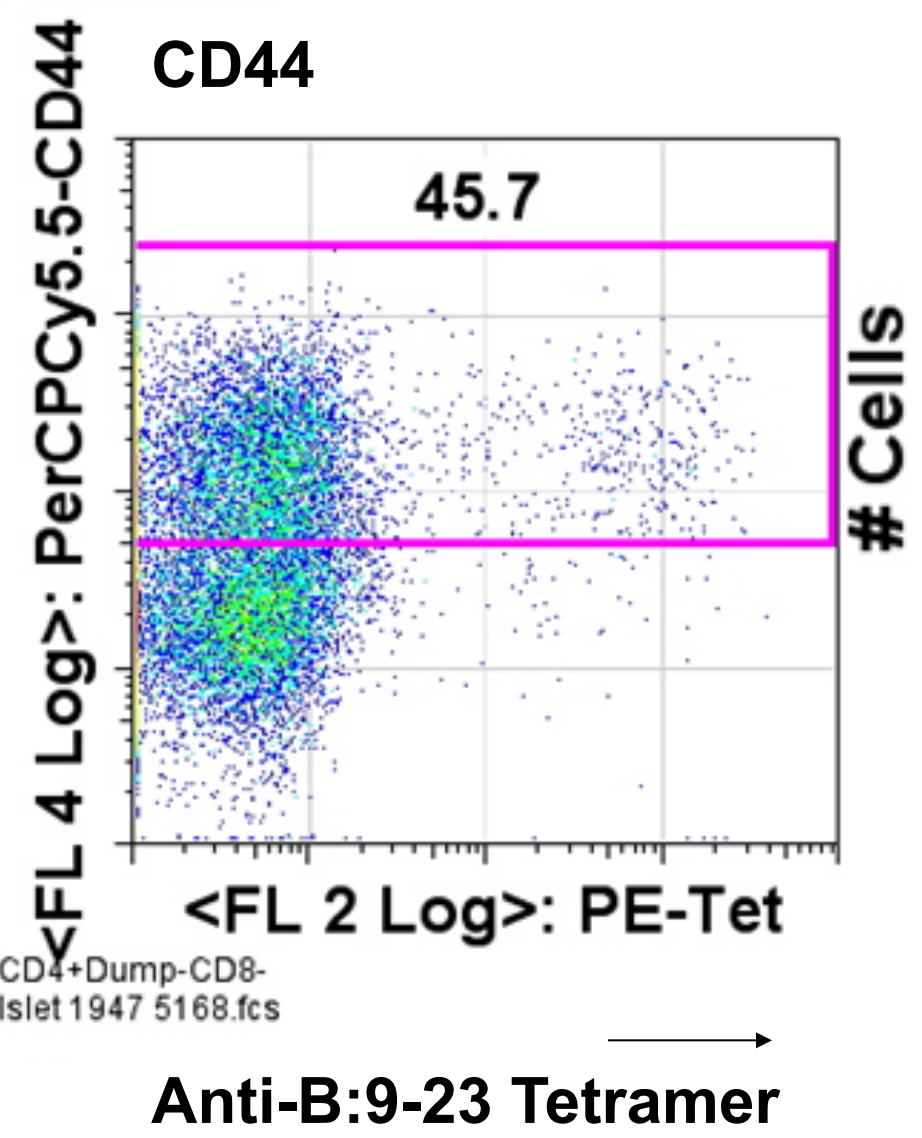


NOD mice – peptide INSULIN B:9-23 REGISTER

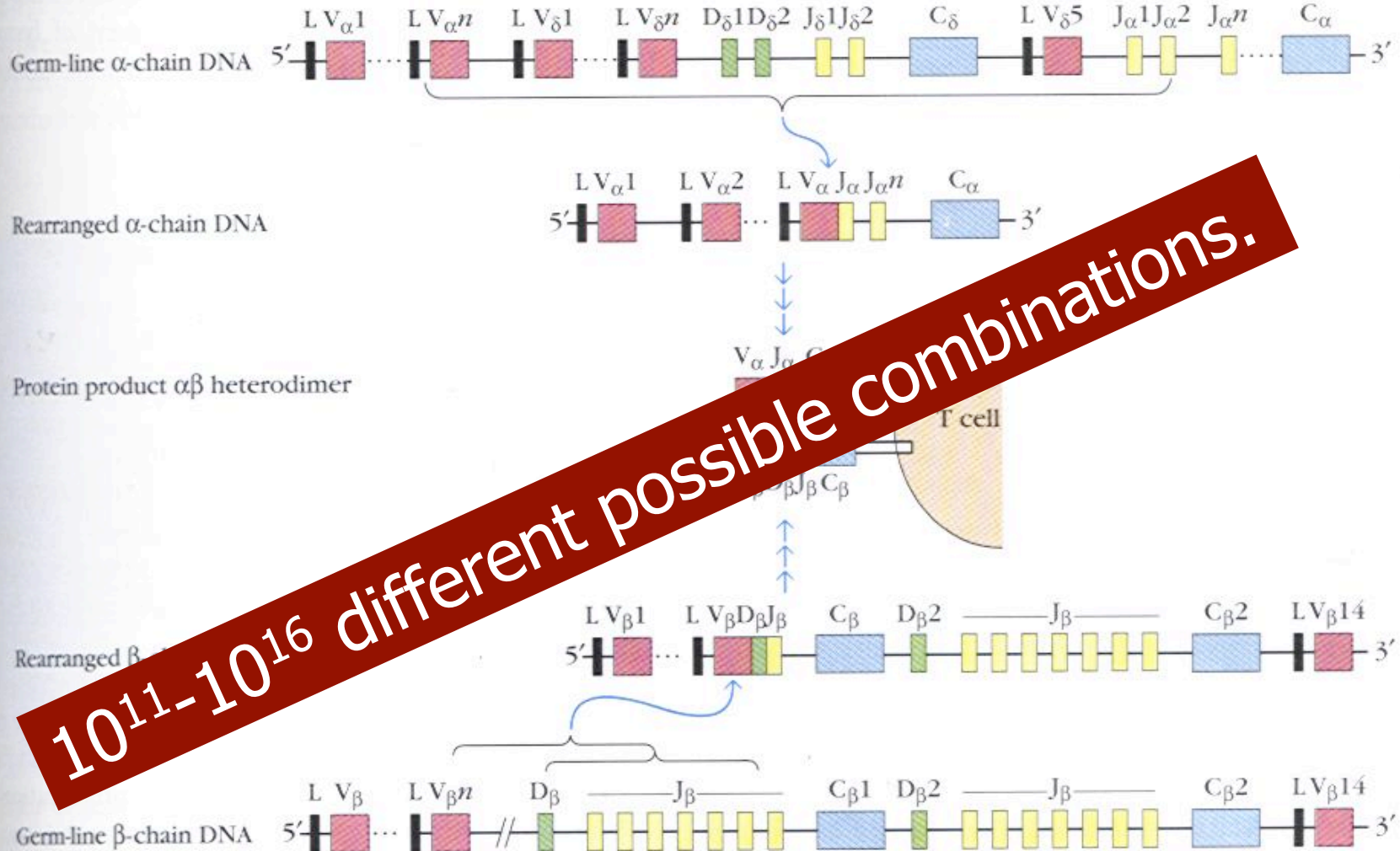
Insulin B:9-23: S H L V E A L Y L V C G E R G



Non-Expanded CD4 POSITIVE CELLS ISOLATED FROM 8 WEEK OLD NOD ISLETS (Kappler PNAS 2011)



V(D)J Rearrangement



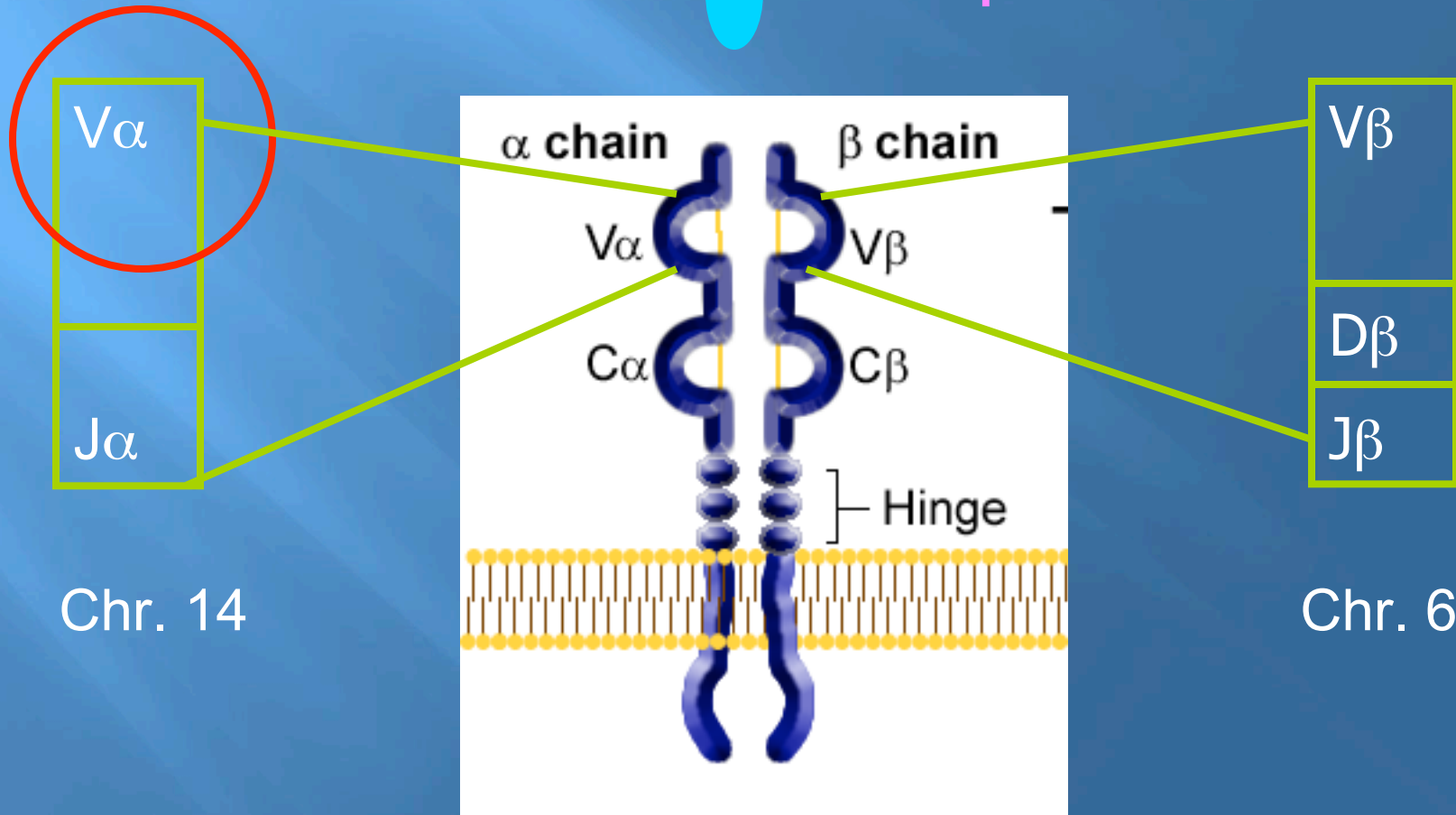
10^{11} - 10^{16} different possible combinations.

T Cell Receptor Gene Segments

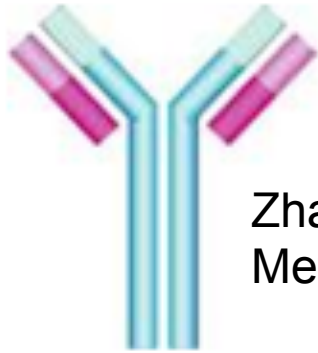
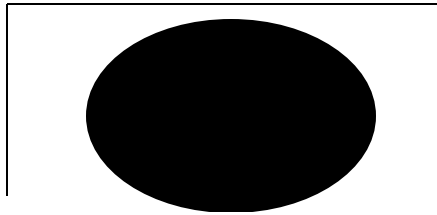
Antigen Presenting Cell

HLA Molecule

Peptide

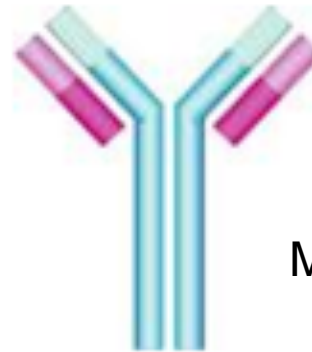
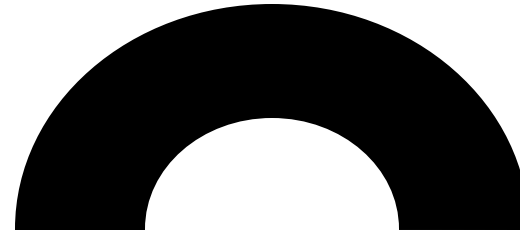


MHC

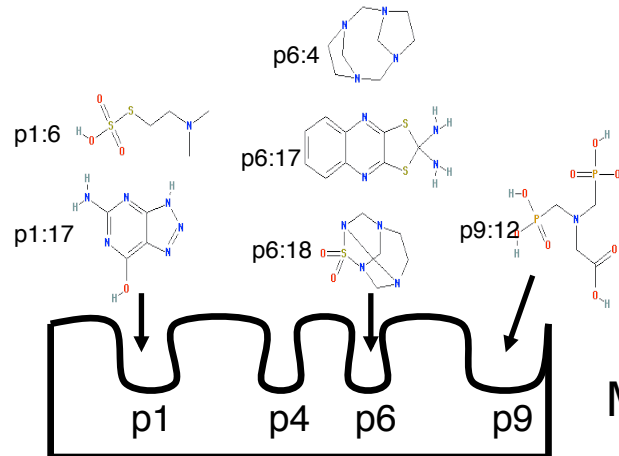


Zhang et al Diabetes
Metab Res Rev. 2011

TCR



Mordes abstract



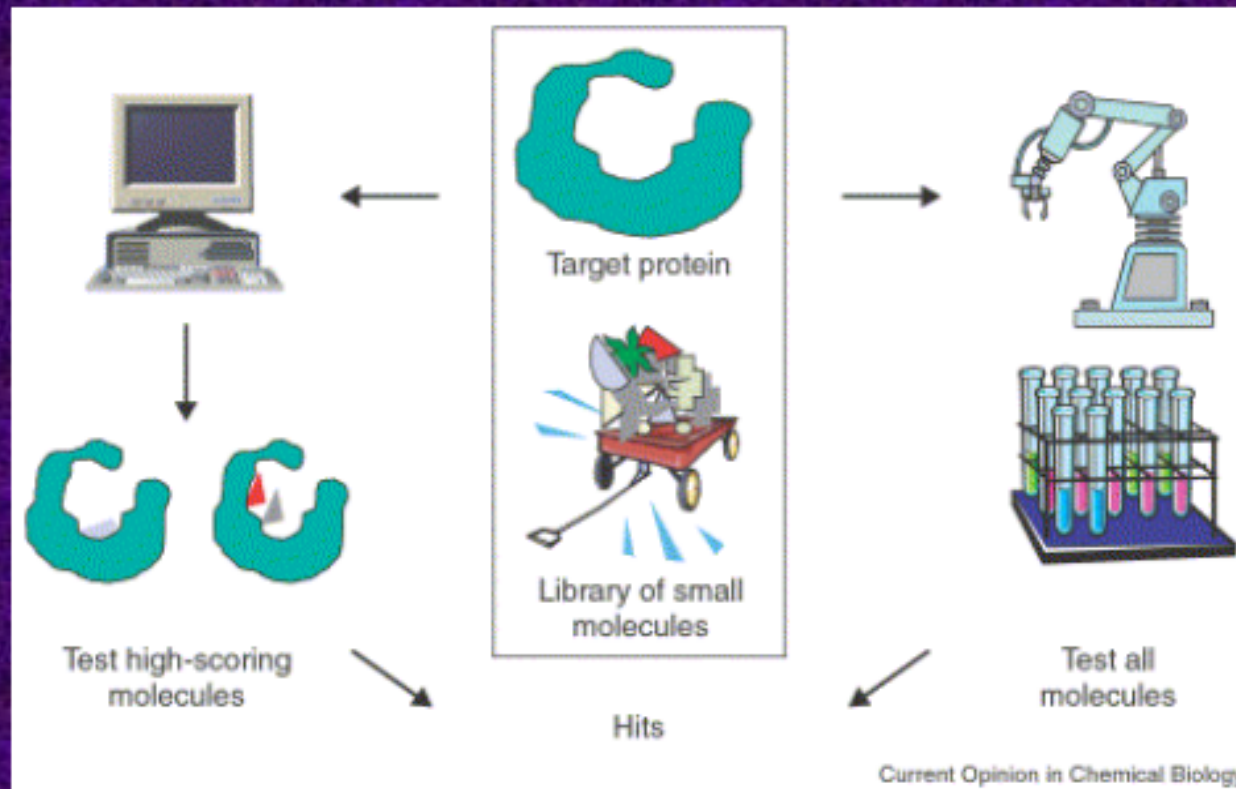
Michels et al J. Immunol 2011

MHC

Screen, *in silico*, large chemical libraries of drug-like small molecules for their abilities to interact with I-A^{g7} structural pockets by high-throughput molecular docking

Molecular Docking

High-Throughput Screening



No MHC specific compounds identified to date by conventional high throughput screening

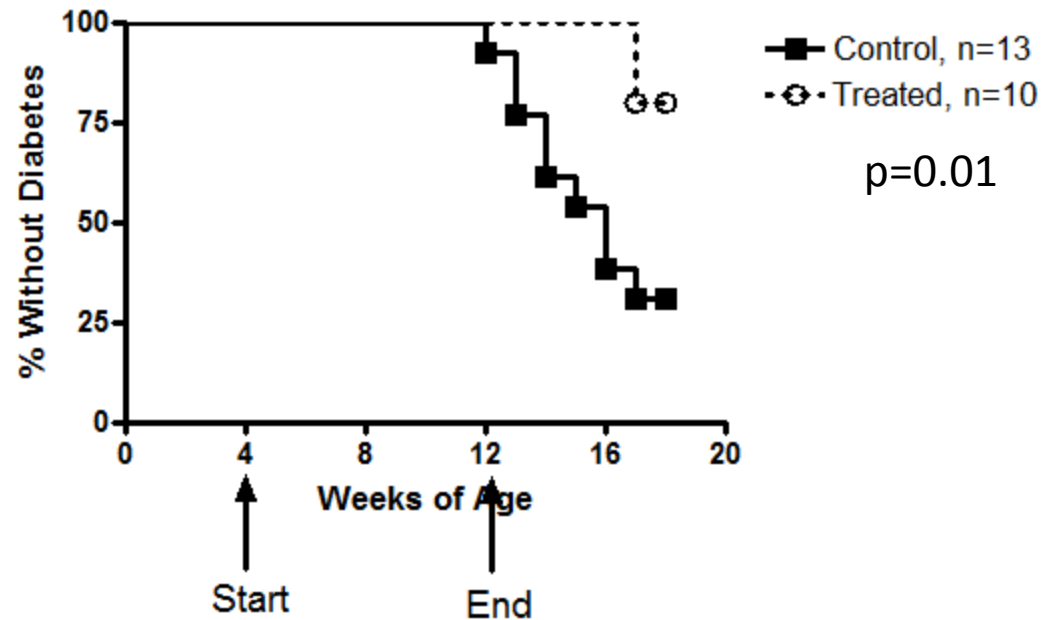
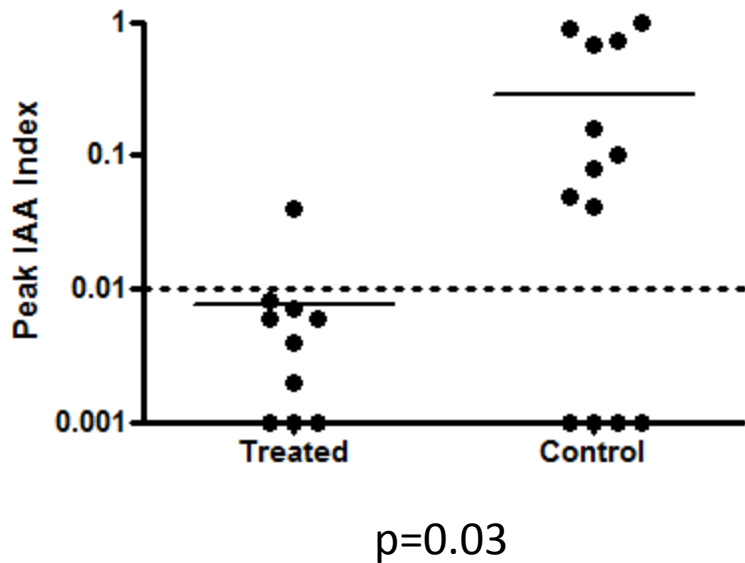
Current Opinion in Chemical Biology

Rapid and economical

Expensive, false positives

Ostrov

Early Prevention Study with Inhibitor



Michels et al Unpublished

Treatment starting at 4 weeks of age & ending at 12 weeks.
IAA measured at 4, 8, 10, & 12 weeks of age; all negative at 4 weeks prior to treatment.
Jax NOD mice.

NEEDED- Trimolecular Anatomy of Human Type 1A Diabetes

- DQ8 and DQ2 relevant human T cell receptor sequences.
- Crystal structures pathogenic trimolecular complexes.
- TCR based biomarkers.
- Optimized therapeutic monoclonals and small molecules(medicinal chemistry).

- Aaron Michels
- Li Zhang
- Maki Nakayama
- Tomasz Sosinowski
- Liping Yu
- John Kappler
- David Ostrov
- Mark Atkinson
- Marian Rewers



National Institute of Allergy and Infectious Diseases
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AND KIDNEY DISEASES

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JDRF IMPROVING
LIVES.
CURING
TYPE 1
DIABETES.

