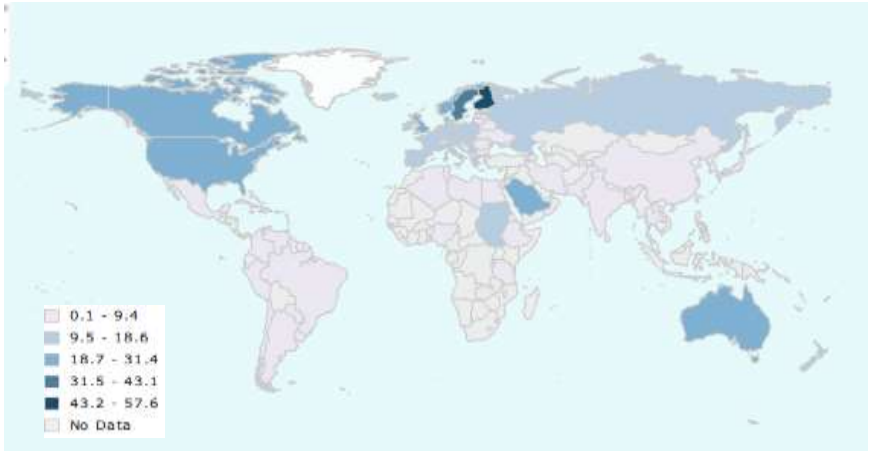
Overview of Natural History and Pathogenesis of Type 1 Diabetes

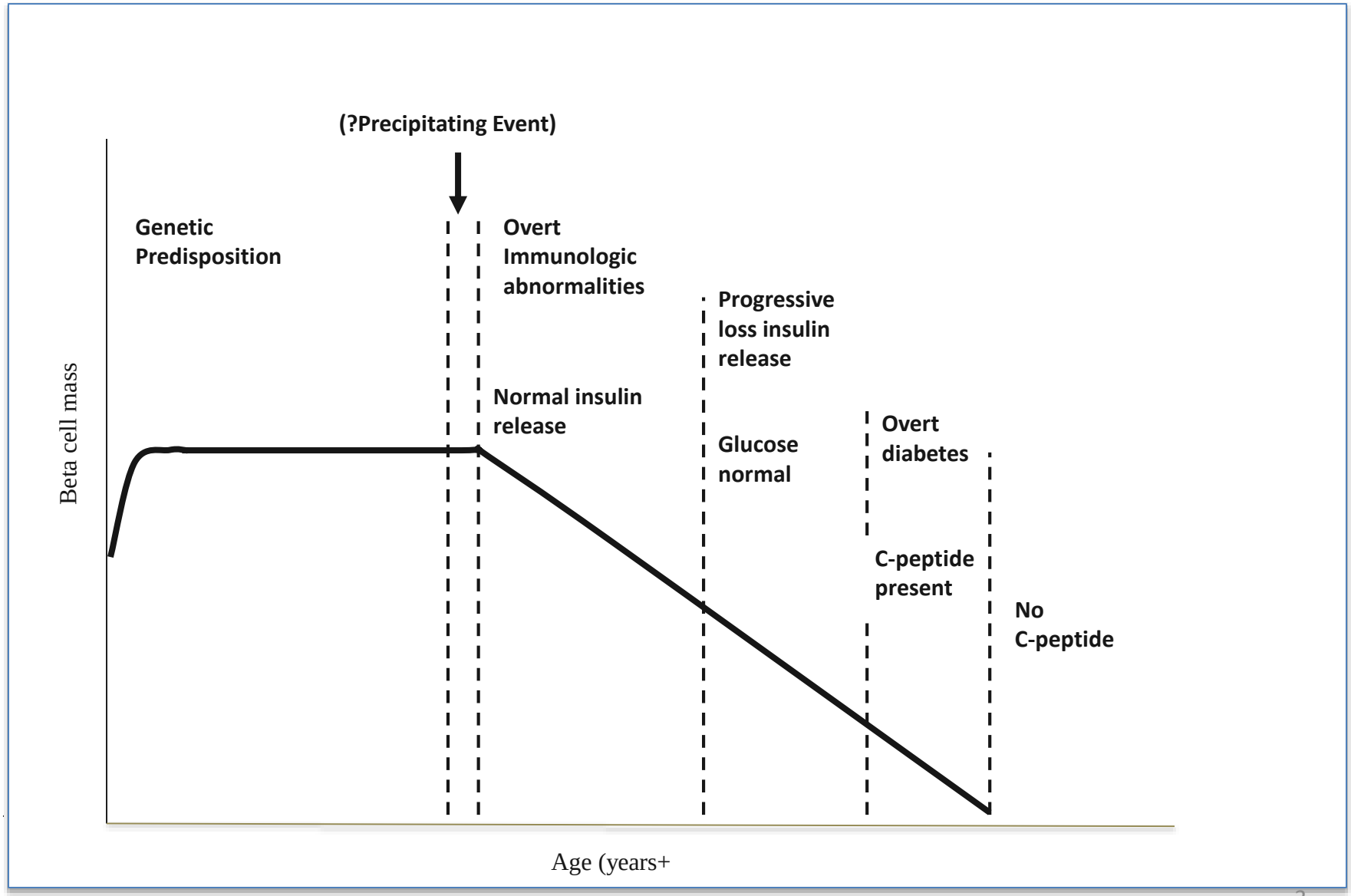
Mark Atkinson, PhD – The Departments of Pathology and Pediatrics
The University of Florida

Type 1 Diabetes Is Accelerating at a Rate that Appears Tied to the Environment (Versus Genetics)



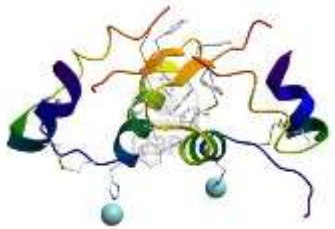
Atkinson et al, Lancet, 2014

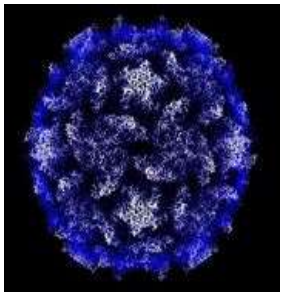
Classic Model of T1D Pathogenesis



Eisenbarth, NEJM 1986

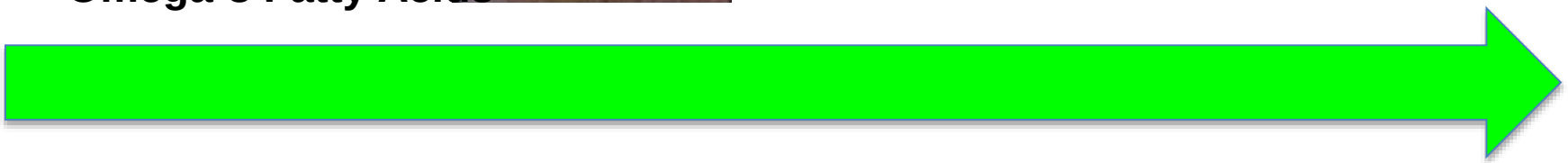
Beyond Triggering, Environment Likely Contributes throughout Natural History of T1D





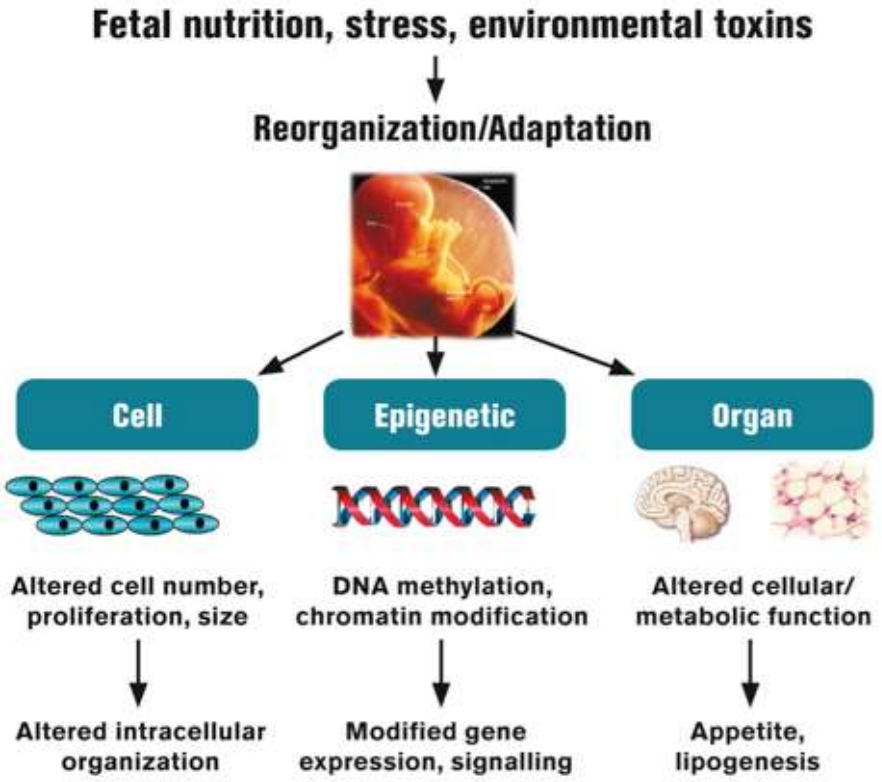
Microbiome

Omega-3 Fatty Acids

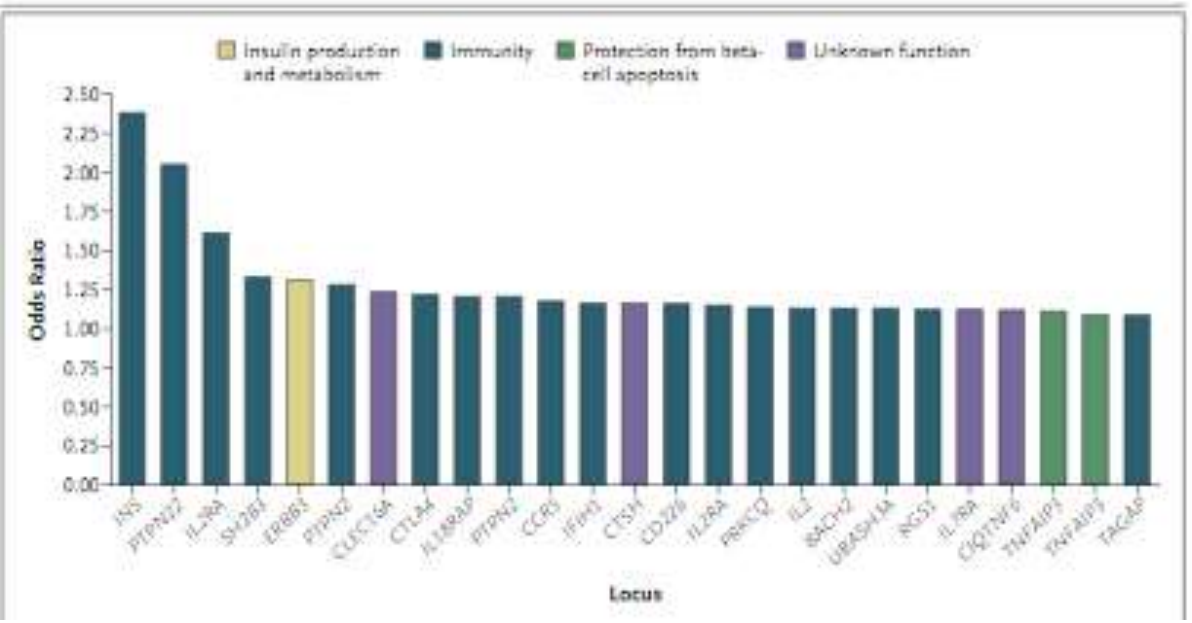


Precipitating Events Might Begin In-Utero

- Born to diabetic fathers vs. mothers
- Diabetic mother diagnosed less than 8 years of age vs later age
- First born
- Increased maternal enterovirus infections
- ABO incompatibility
- Increasing maternal age at delivery
- Season of delivery
- Early cessation of breast feeding



Genetic Linkage to T1D



Concannon P , Rich S, Nepom GT
N Engl J Med 2009;360:1646-1654

The NEW ENGLAND JOURNAL of MEDICINE

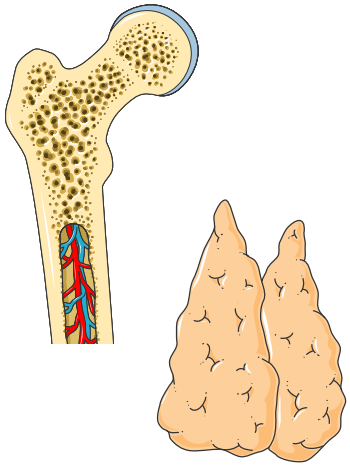
The Evolution of Type 1 Diabetes Genetics

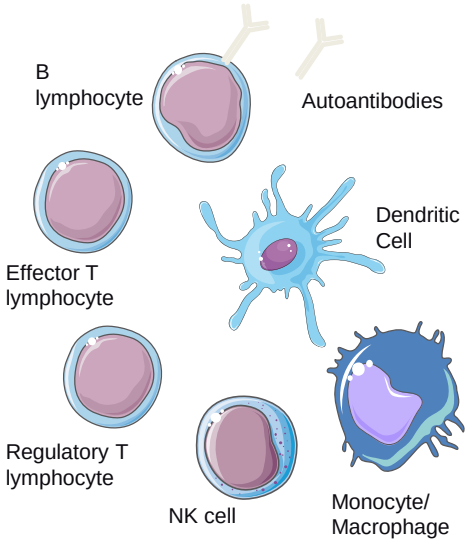
1980's to Present – Biomarkers that Define Risk for Type 1 Diabetes

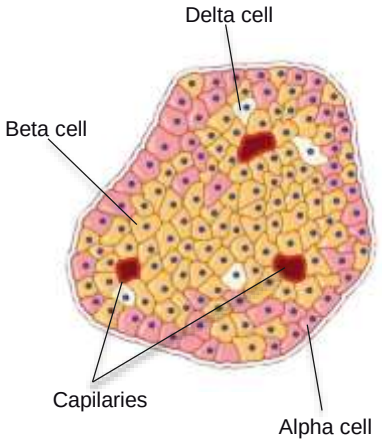
Note: Too many;
Too little OR;
Notions of GWAS
"Bust"

Future – Genotype/Phenotype Studies in Type 1 Diabetes

Genetic Linkage to T1D Abnormalities







Compartment #1
Bone Marrow / Thymus Contributions

- Defective thymic selection (positive/negative)
- Potential for self-antigens presented in incorrect register of MHC binding
- Influence of *Aire* and *VNTR* expression in thymus
- Mobilopathy
- Intrinsic defects in lymphocyte precursors
- Inherited genetic susceptibility
- "Niche" for persistent autoreactive lymphocytes

Compartment #2
Immune Contributions

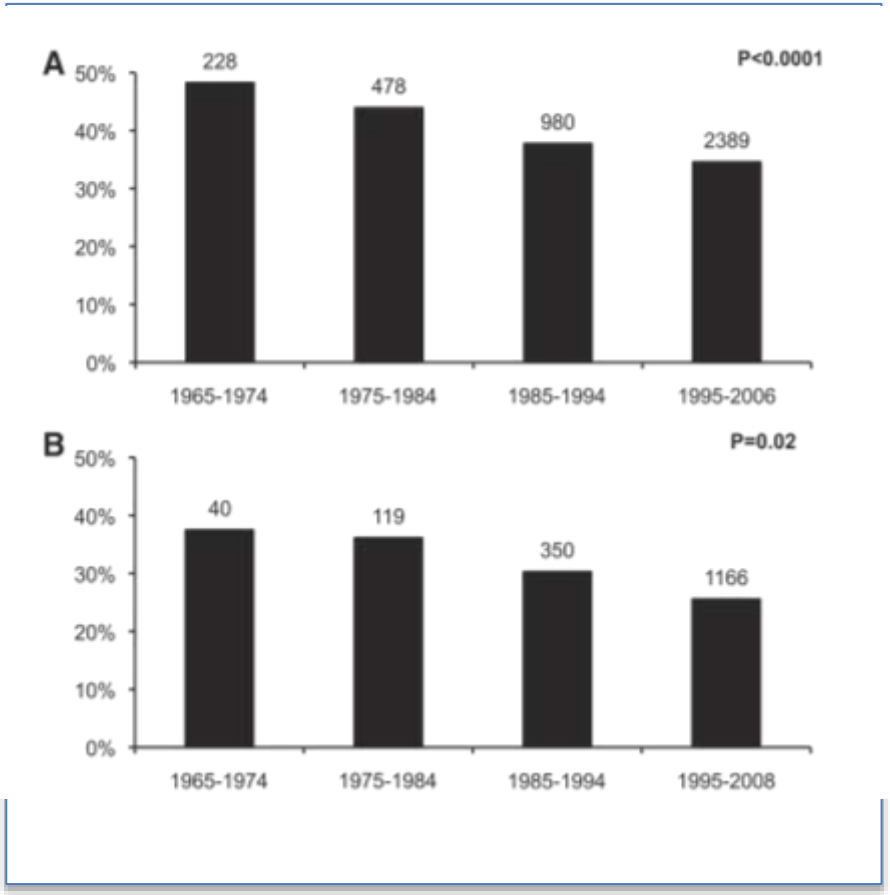
- Defective immune regulation (e.g., Teff resistance to Treg, Treg abnormalities, etc.)
- Chronic APC activation
- Autoantibody production
- Self-antigens with low affinity epitopes recognized by low avidity autoreative TCRs
- Failure to resolve autoreactive immune memory
- Abnormal cytokine production/ regulation
- Cellular trafficking/adhesion defects

Compartment #3
Beta Cell Contributions

- Expression of Class I MHC
- Production of cytokines and chemokines
- Free radical sensitivity
- Sensitivity to stress protein response
- Potential to present high quantities of self-antigen via Class II MHC
- Susceptibility to viral tropism/ inability to resolve inflammation
- Limited replication potential
- Rate of immune destruction influenced by metabolic activity

Atkinson, Eisenbarth, Michaels 2014 Lancet

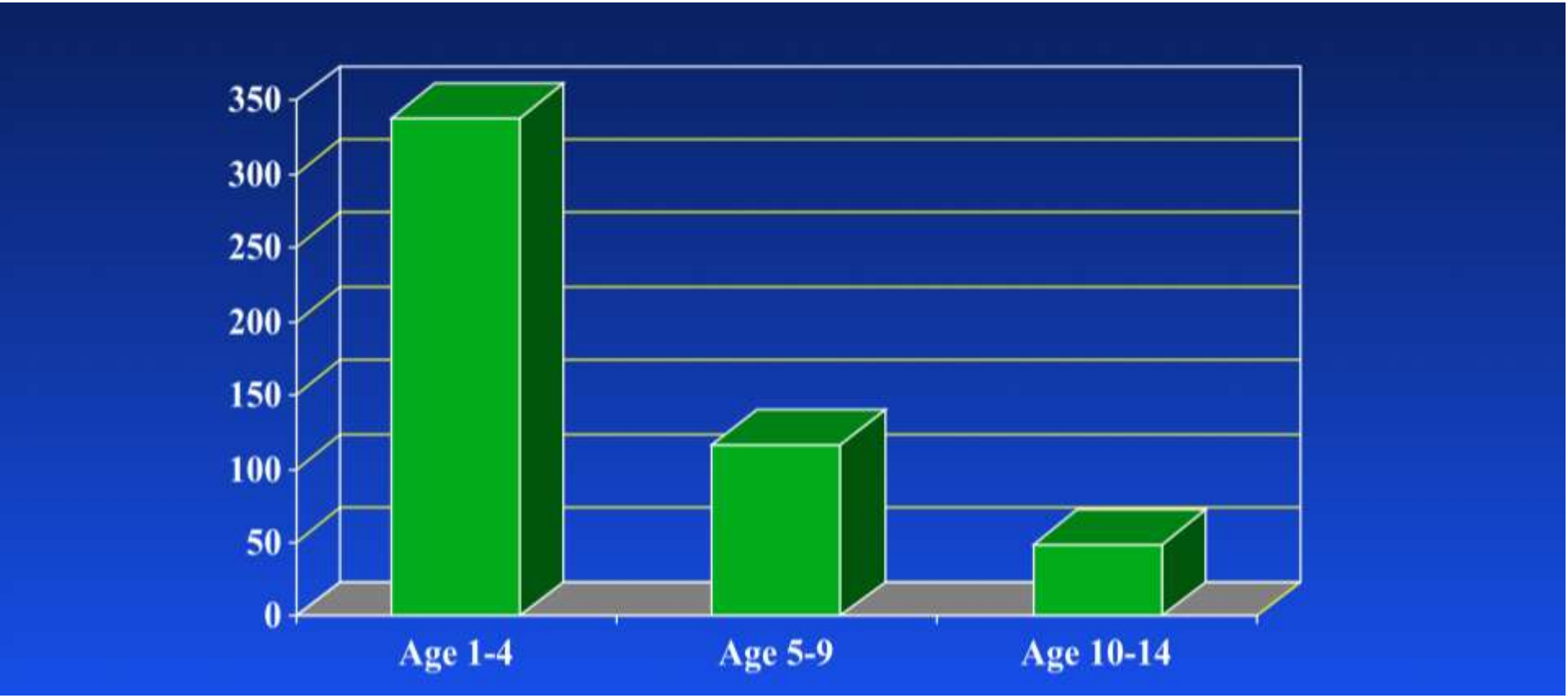
Type 1 Diabetes Is Increasing in Populations That Do Not Carry Classic High Risk Genes



Steck, Diabetes, 2011

While Type 1 Diabetes is Increasing, Most of the Increase is in the Very Young…Maybe

Finland T1D Incidence 1965-1996 (32 years)
Relative Percent Increase



While Type 1 Diabetes is Increasing, Most of the Increase is in the Very Young…Maybe

Table 1. Prevalence of Type 1 Diabetes by Demographic Characteristics

	2001 Population			2009 Population				
	No. of Youth			No. of Youth				
	Cases With Diabetes	General Population	Prevalence per 1000 (95% CI)	Cases With Diabetes	General Population	Prevalence per 1000 (95% CI)	Difference in Prevalence (95% CI)	*P* Value
Total[a]	4958	3 345 783	1.48 (1.44 to 1.52)	6666	3 458 974	1.93 (1.88 to 1.97)	0.45 (0.41 to 0.48)	<.001
Sex								
Females	2420	1 635 589	1.48 (1.42 to 1.54)	3263	1 692 112	1.93 (1.86 to 2.00)	0.45 (0.40 to 0.49)	<.001
Males	2538	1 710 194	1.48 (1.43 to 1.54)	3403	1 766 862	1.93 (1.86 to 1.99)	0.44 (0.40 to 0.49)	<.001
[illegible]								
0-≤4	217	787 251	0.28 (0.24 to 0.31)	241	832 791	0.29 (0.26 to 0.33)	0.01 (−0.01 to 0.04)	.30
5-≤9	977	832 686	1.17 (1.10 to 1.25)	1143	844 923	1.35 (1.28 to 1.43)	0.18 (0.13 to 0.23)	<.001
10-≤14	1727	885 604	1.95 (1.86 to 2.04)	2335	867 403	2.69 (2.59 to 2.80)	0.74 (0.67 to 0.81)	<.001
15-≤19	2037	840 242	2.42 (2.32 to 2.53)	2947	913 857	3.22 (3.11 to 3.34)	0.80 (0.72 to 0.88)	<.001
[illegible]ity								
White	3718	1 996 971	1.86 (1.80 to 1.92)	4804	1 885 451	2.55 (2.48 to 2.62)	0.69 (0.64 to 0.73)	<.001
Black	471	365 146	1.29 (1.18 to 1.41)	621	383 198	1.62 (1.50 to 1.75)	0.33 (0.25 to 0.42)	<.001
Hispanic	625	647 656	0.96 (0.89 to 1.04)	1042	809 267	1.29 (1.21 to 1.37)	0.32 (0.27 to 0.38)	<.001
Asian Pacific Islander	107	212 708	0.50 (0.42 to 0.61)	156	260 846	0.60 (0.51 to 0.70)	0.09 (0.03 to 0.16)	.006
American Indian	37	123 303	0.30 (0.22 to 0.42)	42	120 212	0.35 (0.26 to 0.47)	0.05 (−0.03 to 0.12)	.19

[a] Differences in the number of youth reported with type 1 diabetes in 2001[15] and in this report are due to exclusion of 1 prior study site in both years (Hawaii) and continued data cleaning.

[b] Age on December 23, 2001, and December 31, 2009.

Dabelea, JAMA, 2014

An nPOD Organized Event

"Insulitis Through the Last Century"

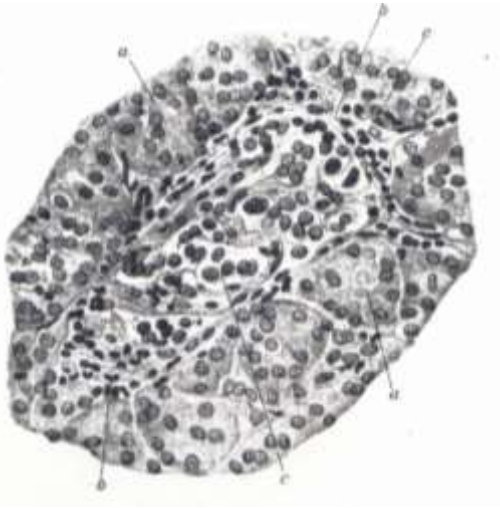
Exeter "Insulitis" Workshop
November 6-7, 2013

Martha Campbell-Thompson
University of Florida, Gainesville

Lessons Learned - Exeter

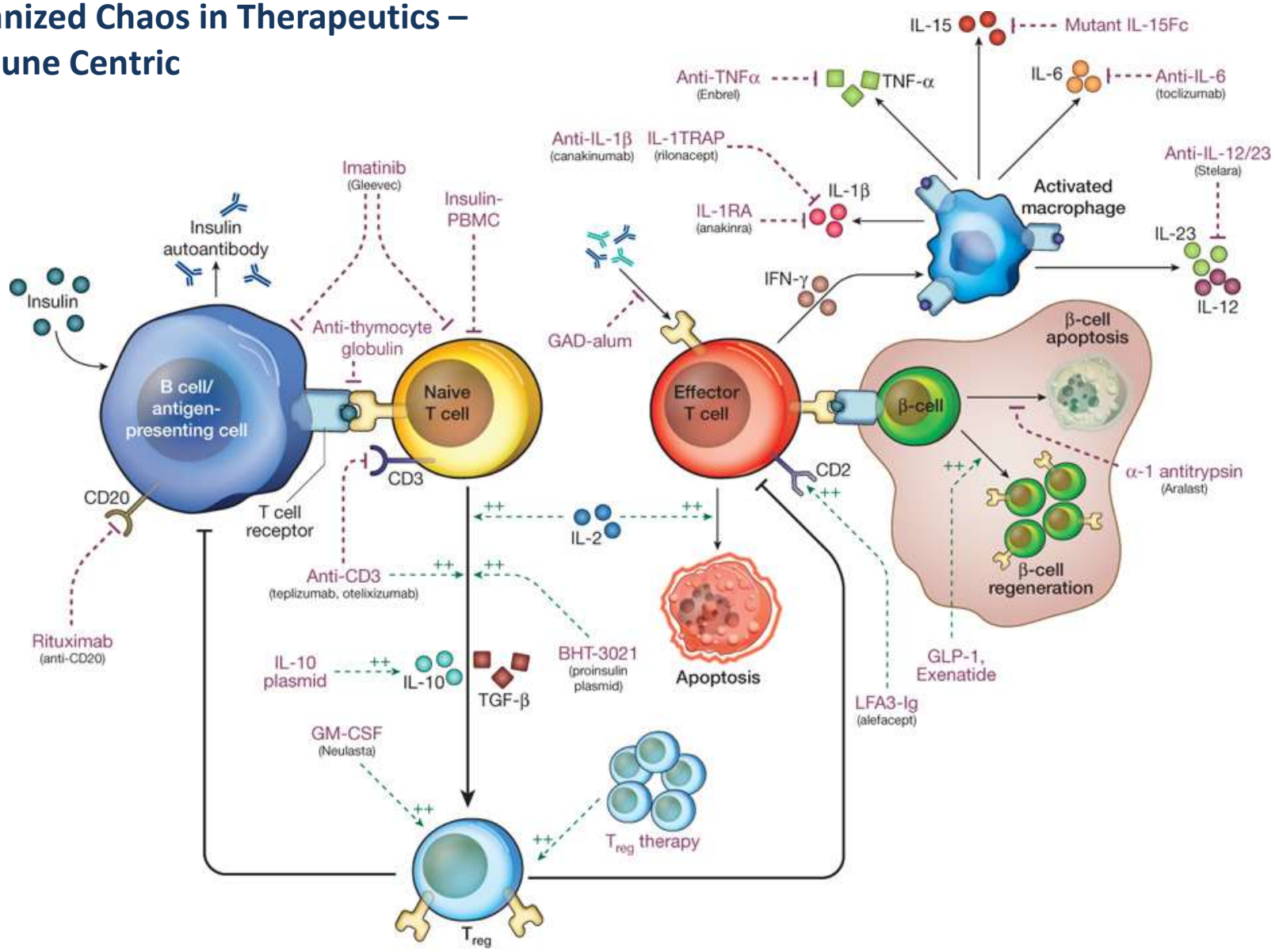
New and/or affirmed

- Consistency of insulitis through last 100 years
- Variations of T1D (versus normals) in islet size
- Insulitis intensity as function of age (breakpoint age ~15-20 years)
- Lobular distribution of insulin pos. versus psuedoatrohic islets
- Adaptation of insulitis definition (preclinical – potentially 3 WBC in 3 islets)

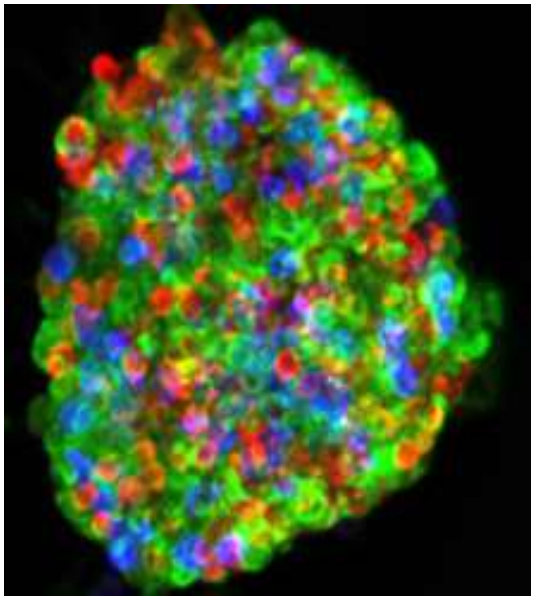


Weichselbaum, 1910

Organized Chaos in Therapeutics – Immune Centric

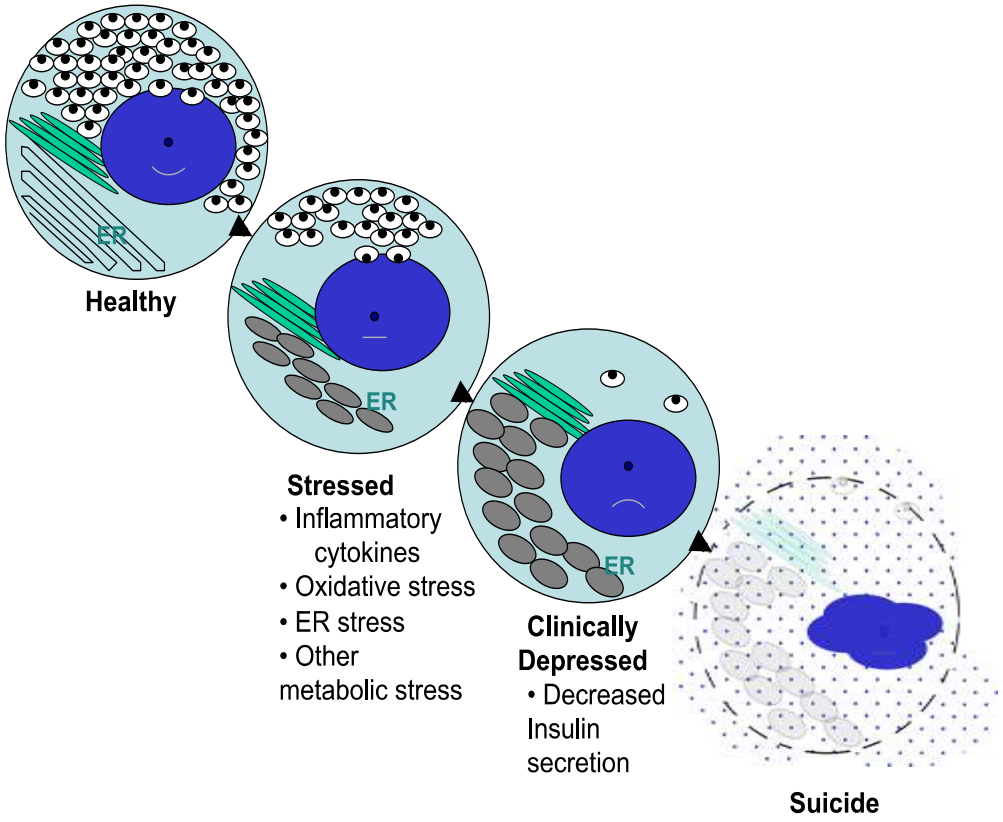


Beta Cell Destruction may be Homicide, Suicide, or Failed Mechanisms of Self-Protection



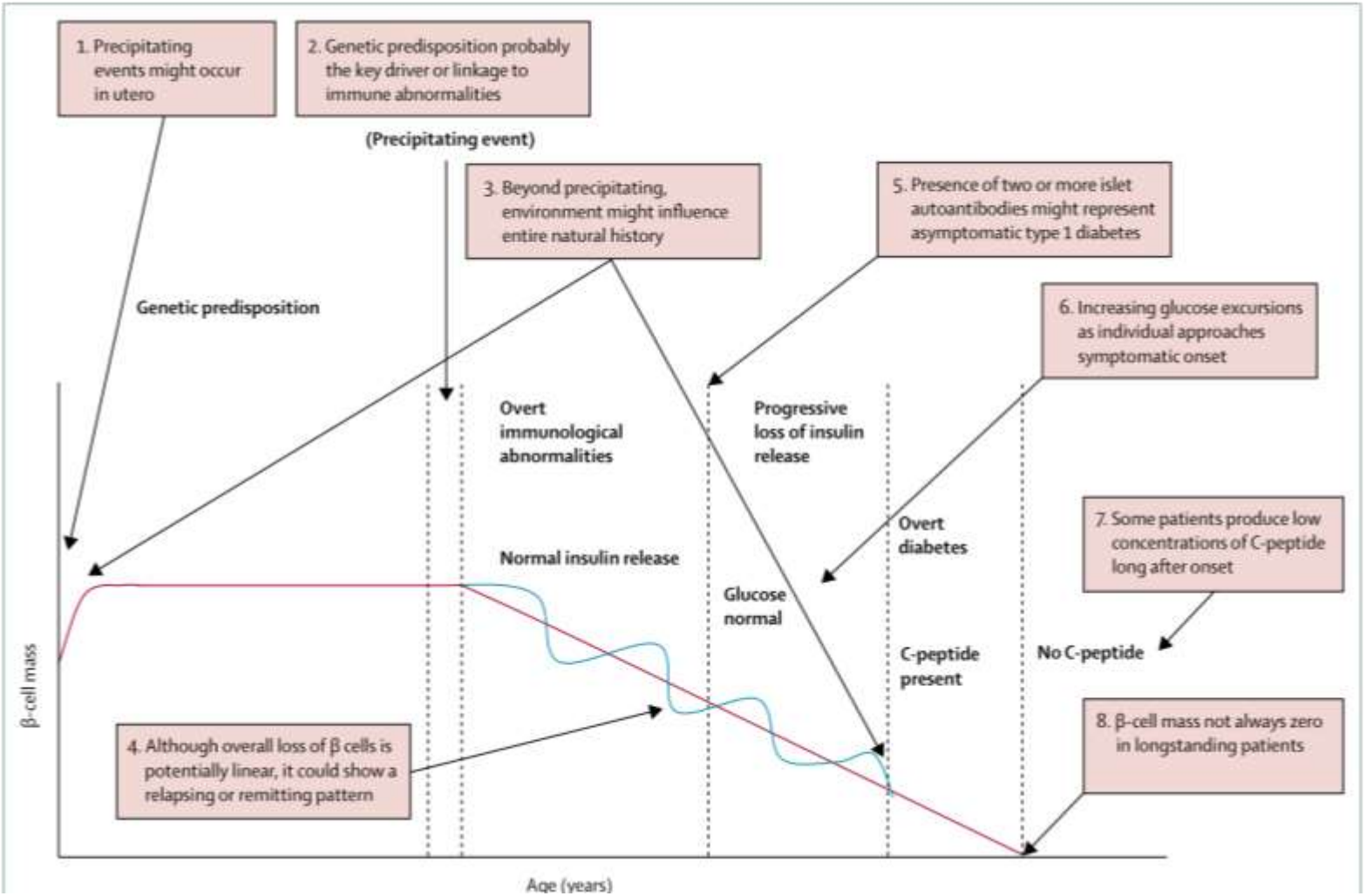
- *Glut 2 Receptor*
- *Empty Beta cells*
- *mRNA abberancies*
- *ER Stress*
- *UPR*

Disease Progression →



Courtesy, Al Powers: Atkinson, M. et al Diabetes, 2012 – Brehm Coalition

Current Model for the Pathogenesis and Natural History of Type 1 Diabetes



Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

Thank You!