AUTOIMMUNITY AND BIOMARKERS

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Labs of Mark Anderson and Jeff Bluestone

University of California, San Francisco

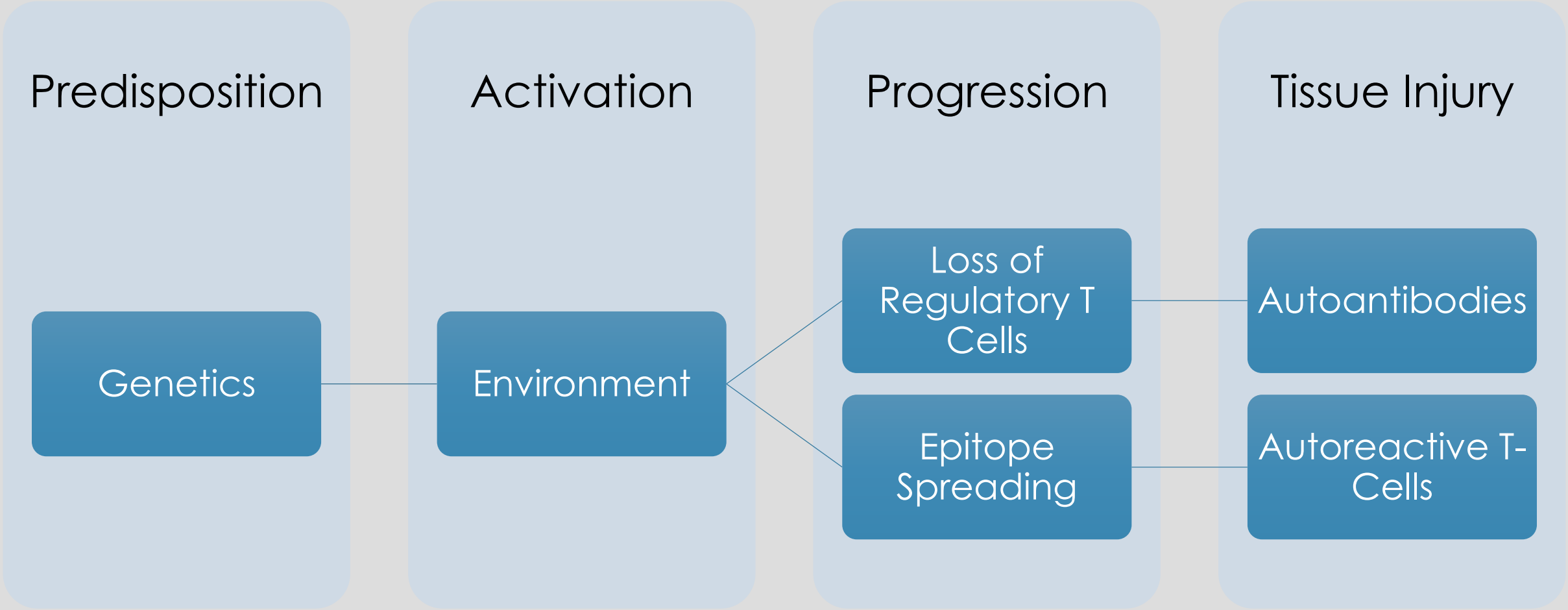
SITC: Immuno-Oncology Biomarkers: State of the Art

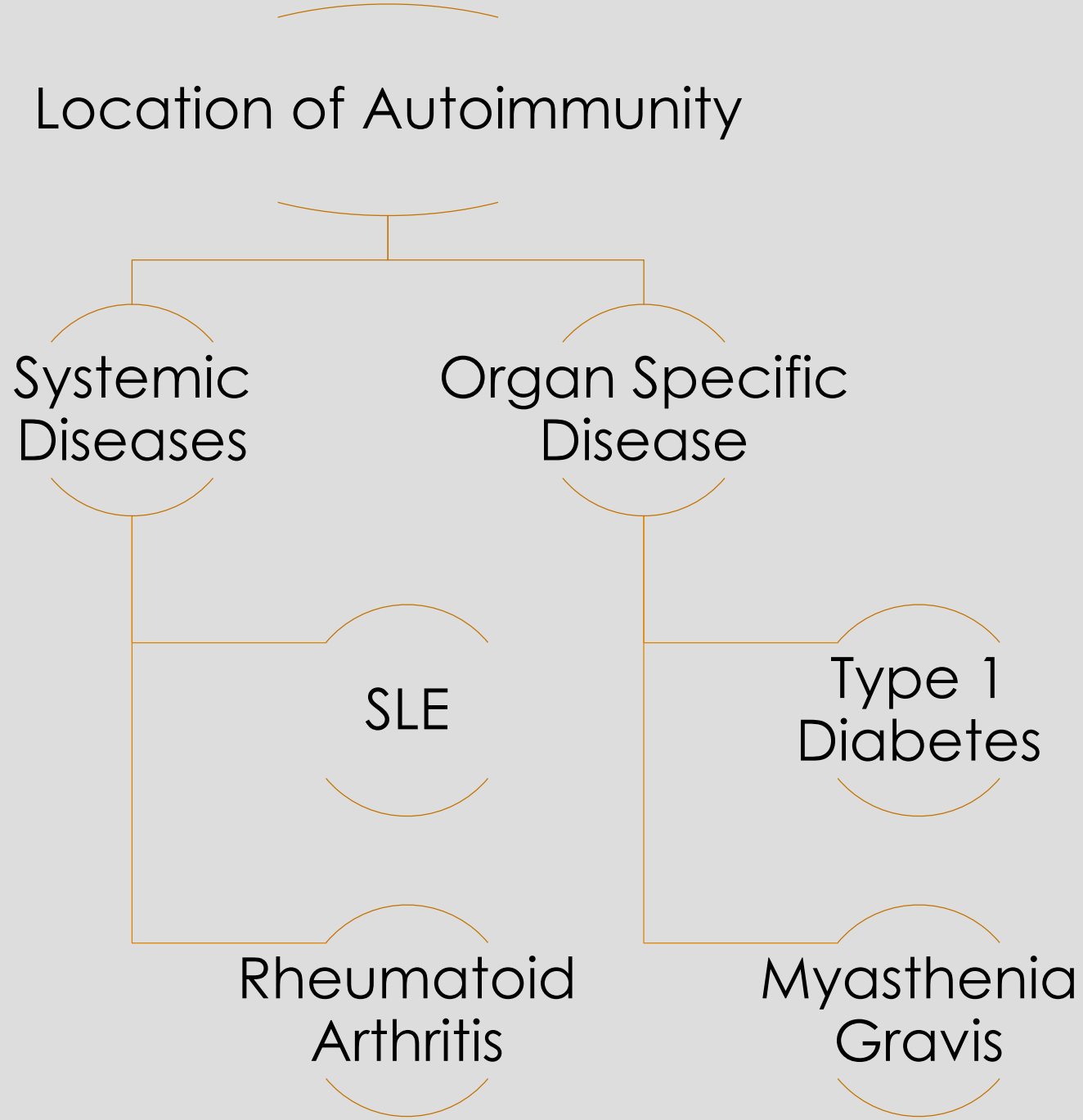
May 17, 2018

OUTLINE

- Biomarkers of autoimmunity in conventional autoimmune disease
- Findings in immune related adverse events
- Need for novel biomarker discovery

AUTOIMMUNE DISEASE PATHOGENESIS




Location of Autoimmunity
Systemic Diseases
Organ Specific Disease
SLE
Type 1 Diabetes
Rheumatoid Arthritis
Myasthenia Gravis

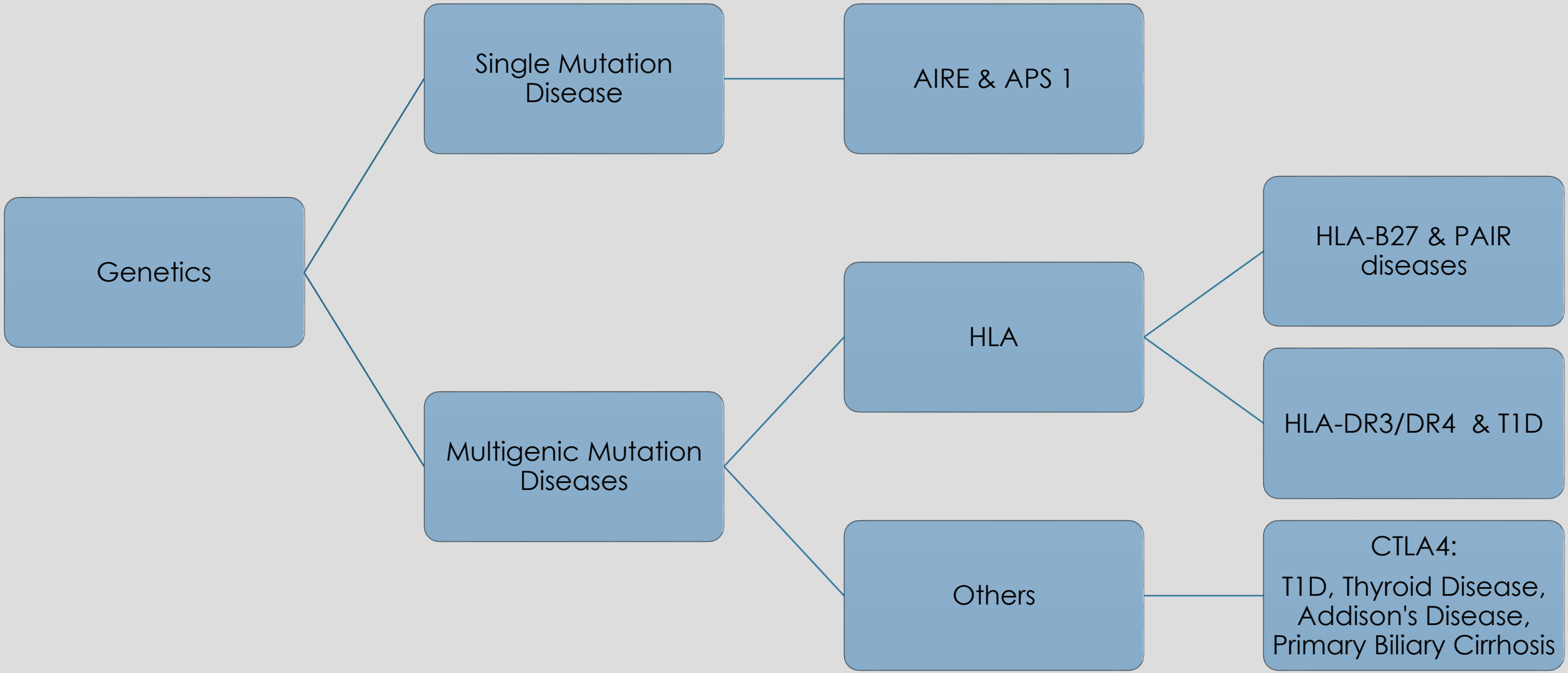
Mechanism of Autoimmune Pathogenesis

General alteration in the selection, regulation, or death of T cells or B cells

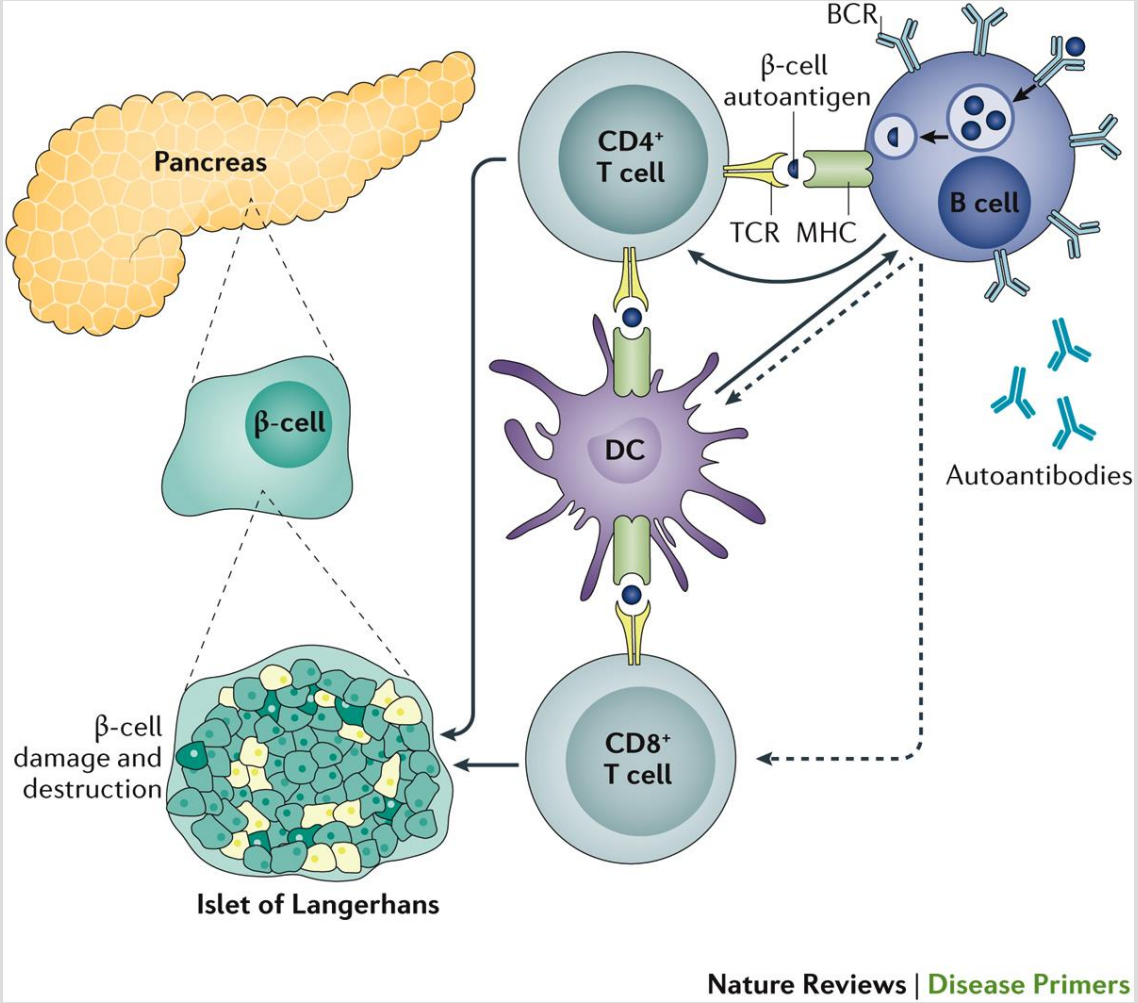
Aberrant response to a particular antigen, self or foreign

Davidson and Diamond, NEJM 20

BIOMARKERS FOR AUTOIMMUNE DISEASE (RISK)



Autoreactive T cells in Conventional Autoimmunity



Katsarou, A. *et al.* (2017) Type 1 diabetes mellitus *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2017.16

AUTOANTIBODIES IN CONVENTIONAL AUTOIMMUNE DISEASE

PATHOGENIC:

DISEASE CAUSING AUTOANTIBODIES

- SLE
- Graves Disease

NON-PATHOGENIC:

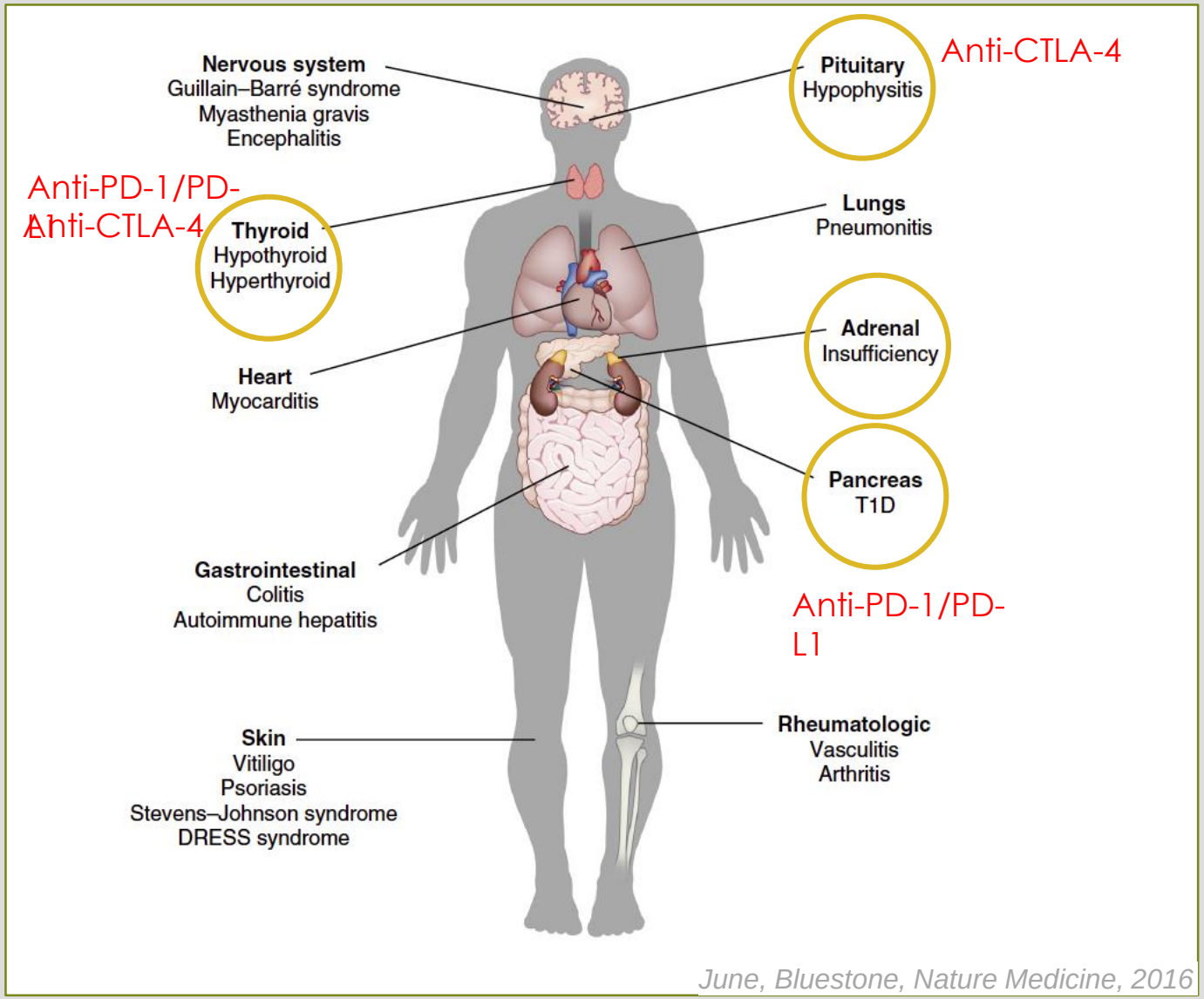
DISEASE IDENTIFYING AUTOANTIBODIES

- T1D
- Thyroglobulin Antibody in Thyroid Disease

DETOUR

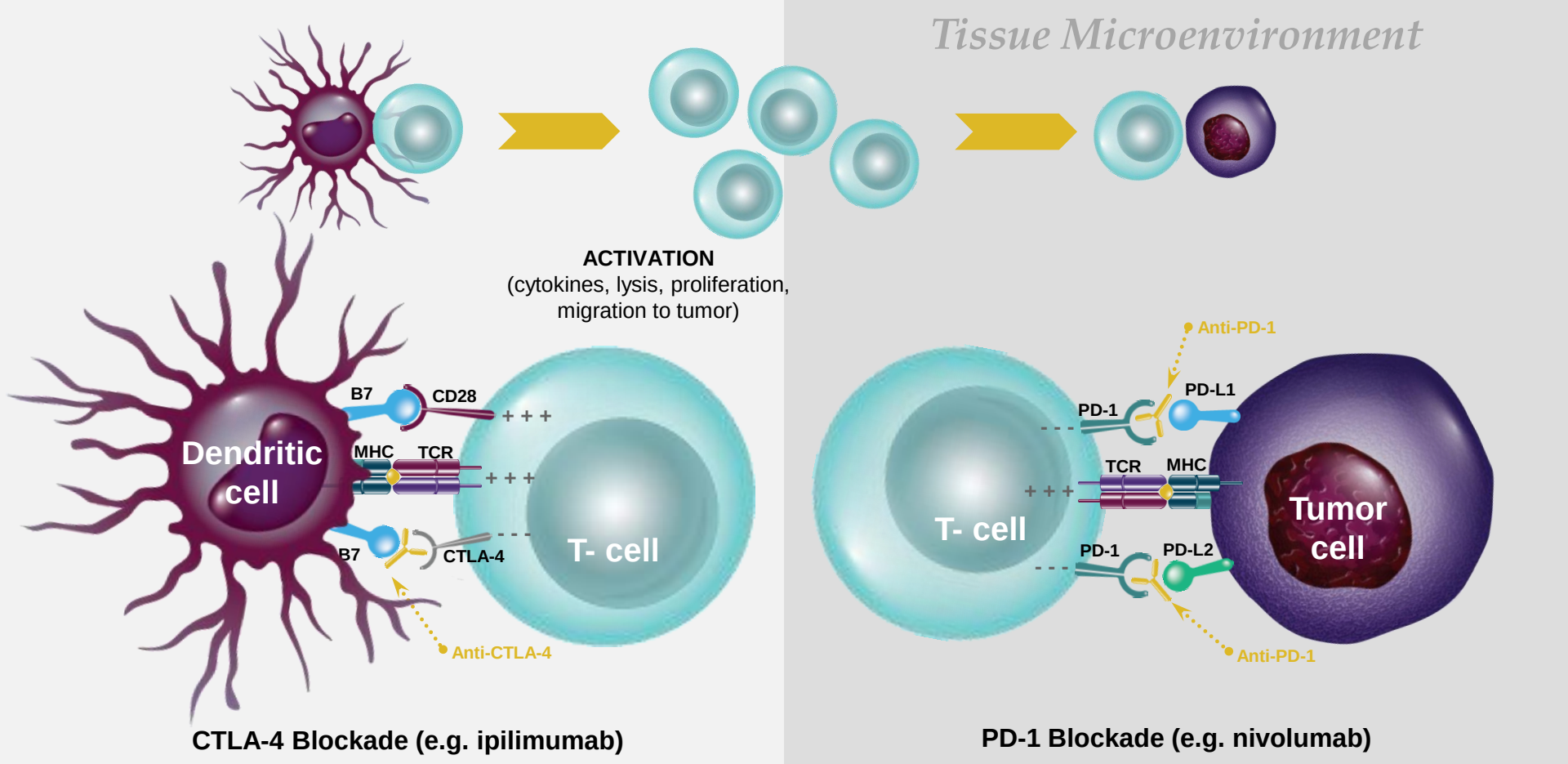
IMMUNE-RELATED ADVERSE EVENTS

DIFFERENT DRUGS INDUCE DIFFERENT DISEASES IN DIFFERENT PATIENTS?



Slide thanks to Jeff Bluestone &

THE CTLA-4 AND PD-1 CHECKPOINT CAN ACT AT DIFFERENT POINTS AND AT DIFFERENT SITES IN IMMUNITY



Dominated in CD4 compartment

Dominated in CD8 compartment

Slide thanks to Jeff Bluestone &

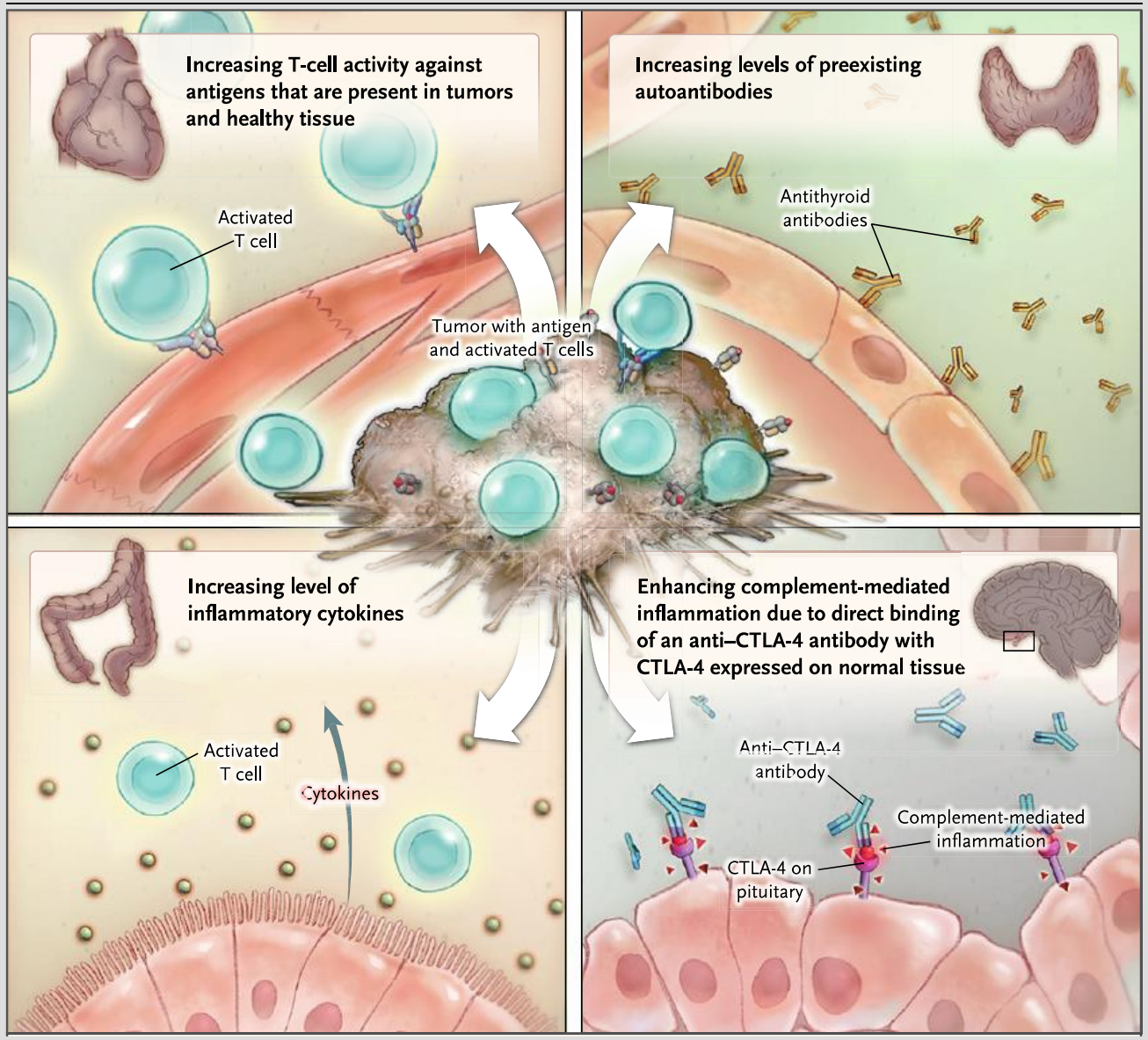
BIOMARKERS PREDICTING IRAE: AN ACTIVE AREA OF RESEARCH

- Potential Risk Factors:
  - family history of autoimmune diseases/ genetic risk of autoimmunity
  - immune checkpoint inhibitor itself
  - tumor infiltration and location
  - previous viral infections
  - concomitant use of medicines with known autoimmune toxicities

- Hints:
  - Eosinophil count (Schindler et al, 2014)
  - Circulating IL-17 levels might be associated with gastrointestinal toxicity (Tarhini et al, 2015)
  - Diversification of the T-cell repertoire (Oh et al, 2017)

Reviewed in:
Topalian et al, Nature Reviews Cancer 20
Hopkins et al, British Journal of Cancer 20
Michot et al, European Journal of Cance

DIFFERENT IRAE – DIFFERENT MECHANISMS?



Postow et al, NEJM 201

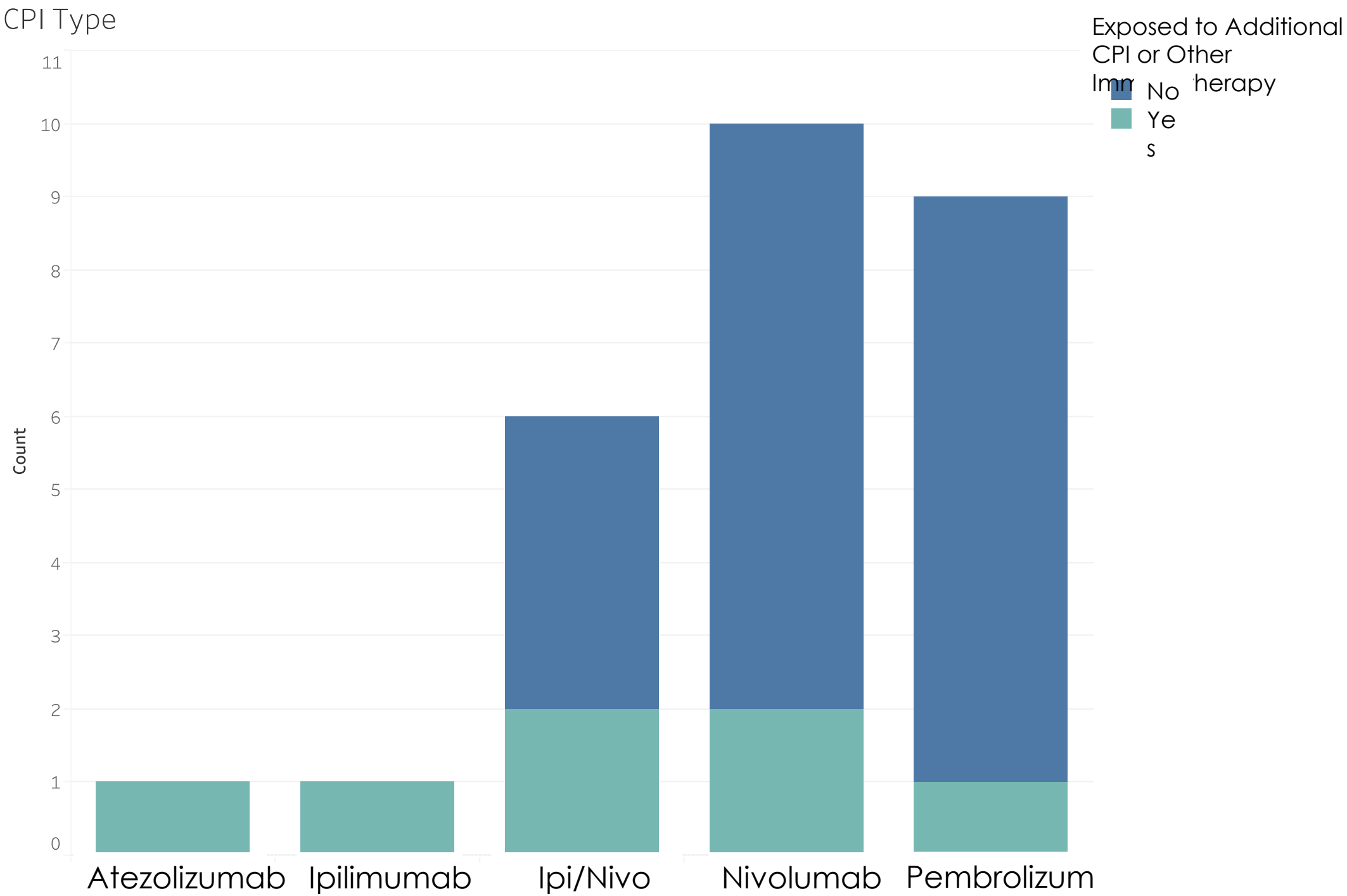
A CASE STUDY: IMMUNE CHECKPOINT INHIBITOR INDUCED DIABETES MELLITUS IN A YALE-UCSF COHORT

- New onset hyperglycemia requiring exogenous insulin treatment
- Evidence of insulin deficiency through either presentation in DKA or absent c-peptide
- Continued to require insulin for more than 1 month

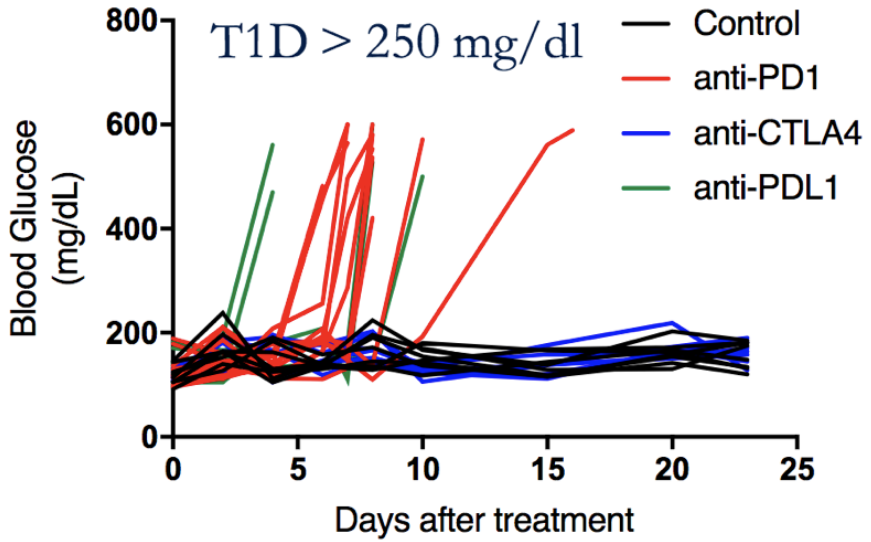
27 Patients

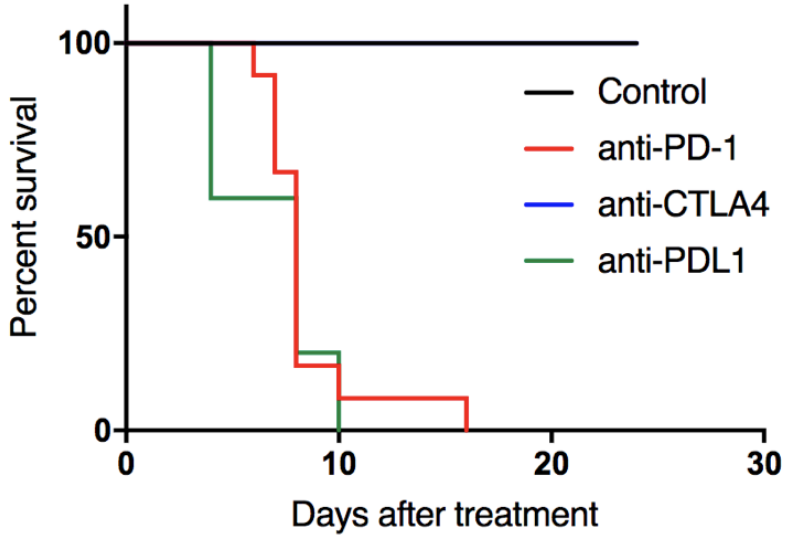
0.9% incidence in all immune checkpoint inhibi

Stamatouli, Herold (Yale)
Quandt, Anderson, Bluestone (UCSF)
unpublished data

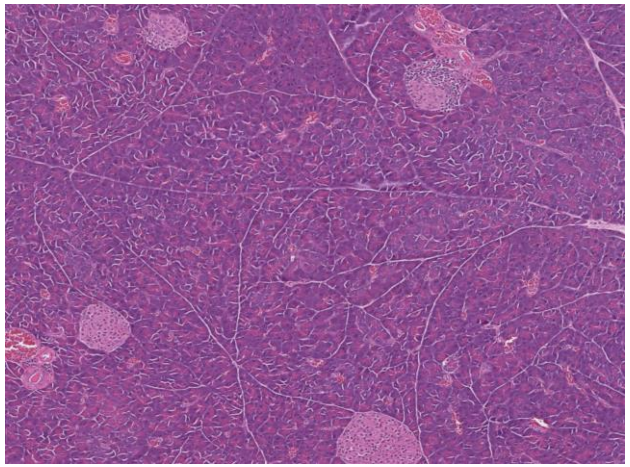

CPI Type
Exposed to Additional CPI or Other Immunotherapy
No
Yes
Count
11
10
9
8
7
6
5
4
3
2
1
0
Atezolizumab
Ipilimumab
Ipi/Nivo
Nivolumab
Pembrolizum

PD-1, BUT NOT CTLA-4, BLOCKADE INDUCES RAPID T1D

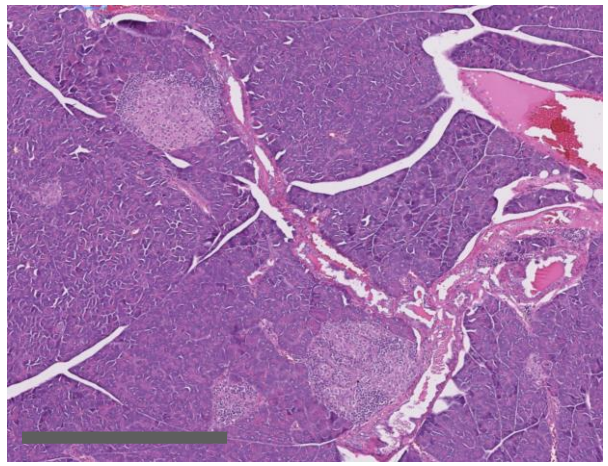




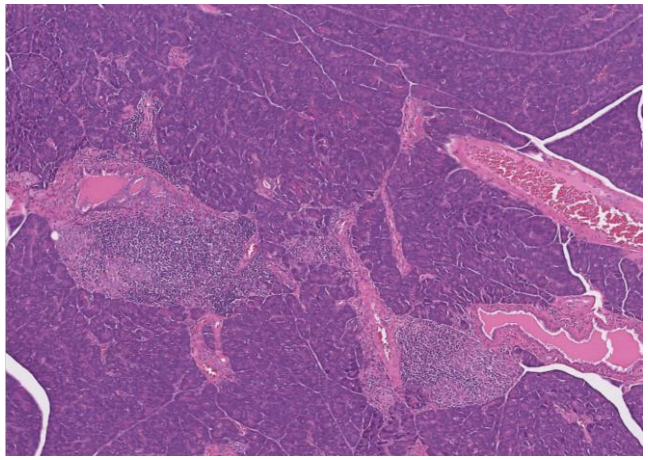
control



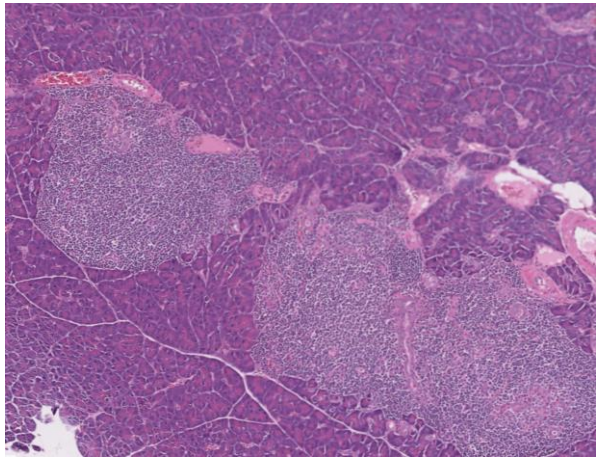
anti-CTLA-4



anti-PD1

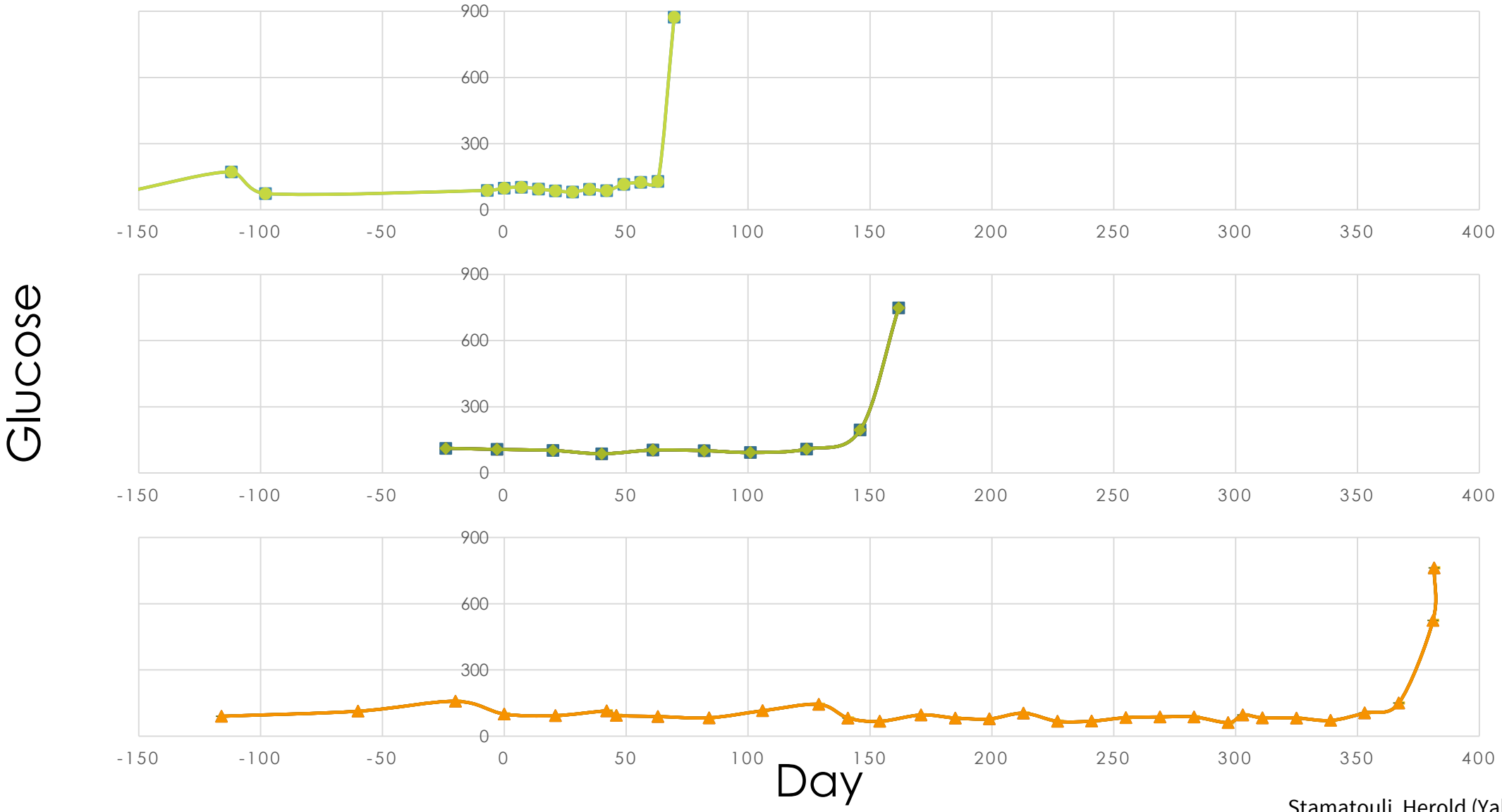


anti-PDL1



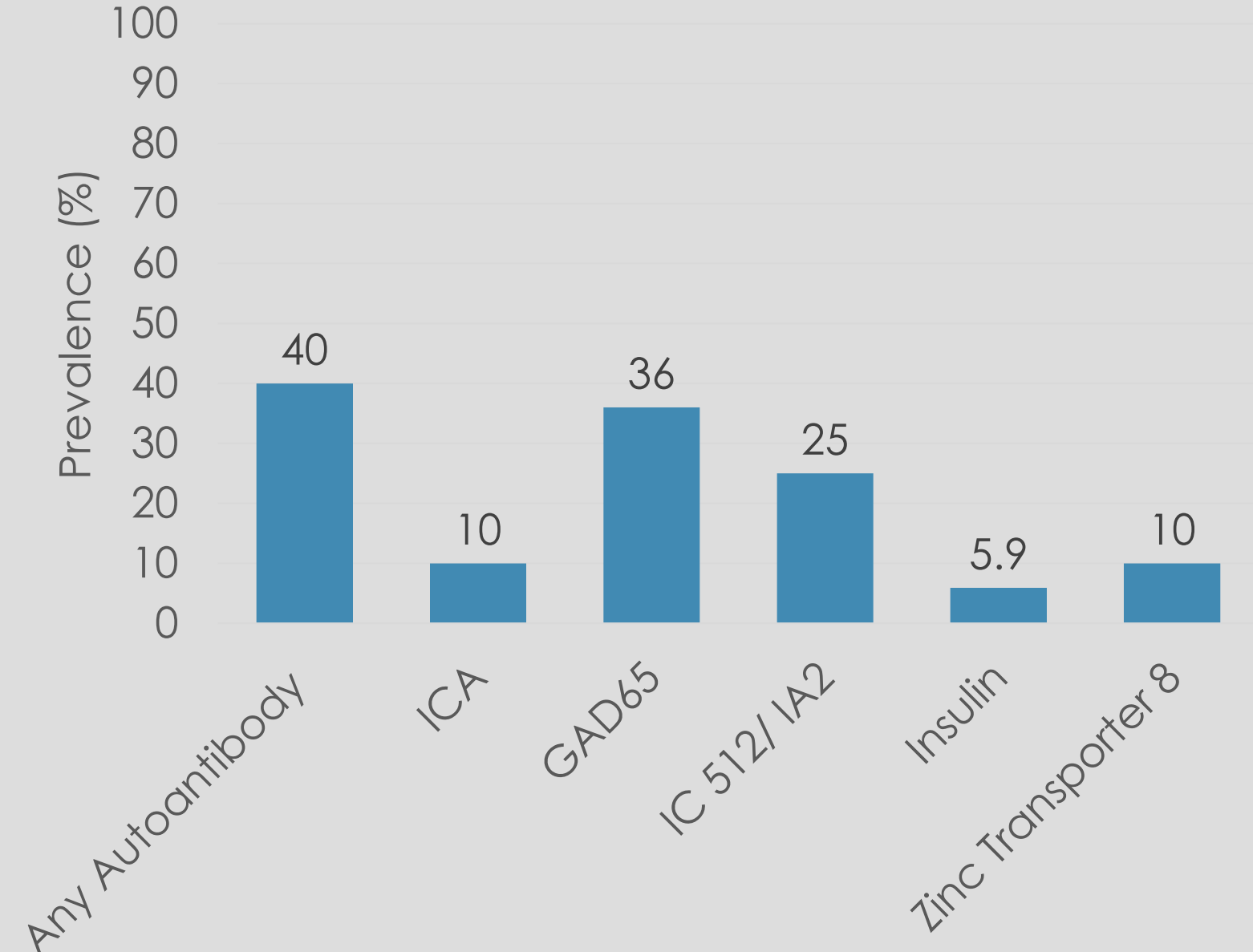
Young, Bluestone, unpublished, 2018

Progression of Hyperglycemia

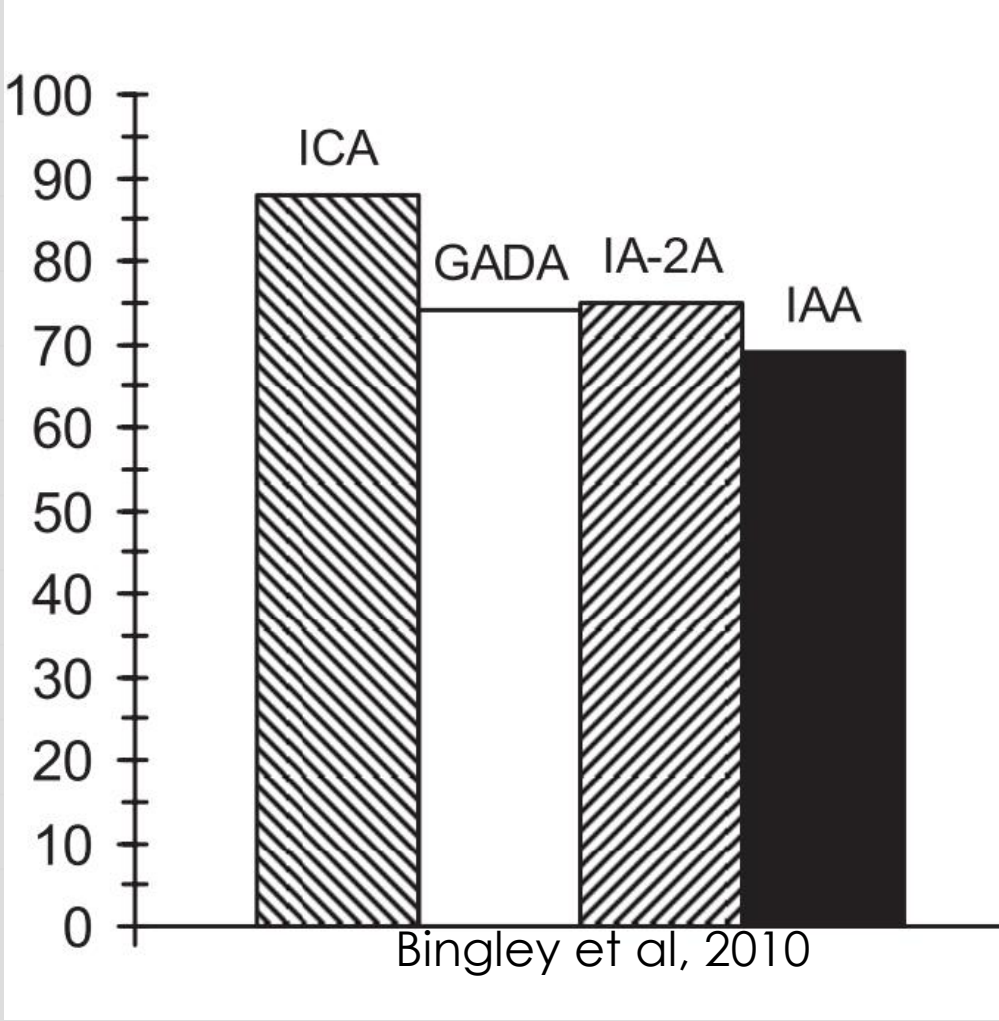


Stamatouli, Herold (Yale)
Quandt, Anderson, Bluestone (UCSF)
unpublished data

Autoantibody Positivity at Time of CPI DM Diagnosis



Autoantibody Positivity at Time of T1DM Diagnosis



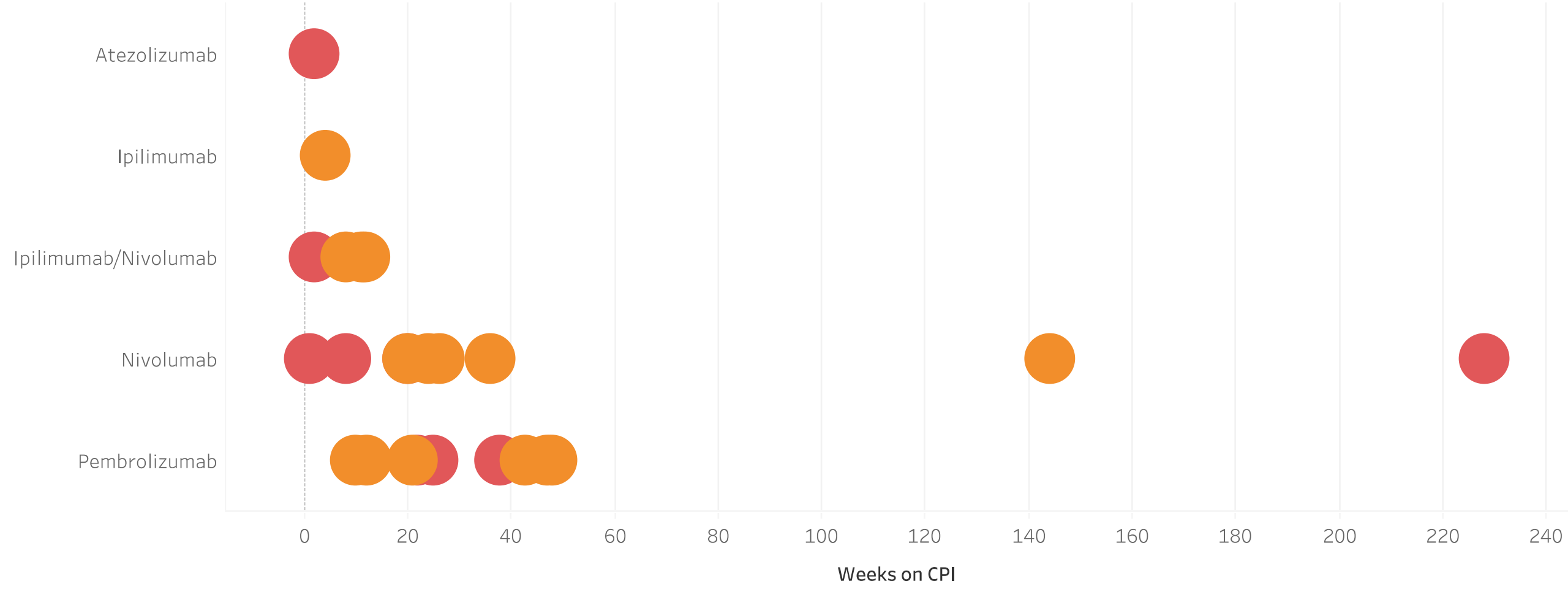
If four markers are measured—GADA, IA-2A, IAA, and ICA or ZnT8A—only 2–4% of patients are autoantibody negative at the time

Pre and Post Treatment T1D Autoantibodies in Patients with CPI Diabetes

Patient	Abs before tx			Abs after tx			
	GAD	IA-2	ZnT8	GAD	IA-2	ZnT8	Insulin
1	NEG	NEG	NEG	NEG	NEG		NEG
2	POS	POS	POS	POS	NEG		NEG
3	NEG	NEG	NEG	POS	POS	NEG	POS

Stamatouli, Herold (Yale)
Quandt, Anderson, Bluestone (UCSF)
unpublished data

Autoantibody Positivity and Timing of DM Onset

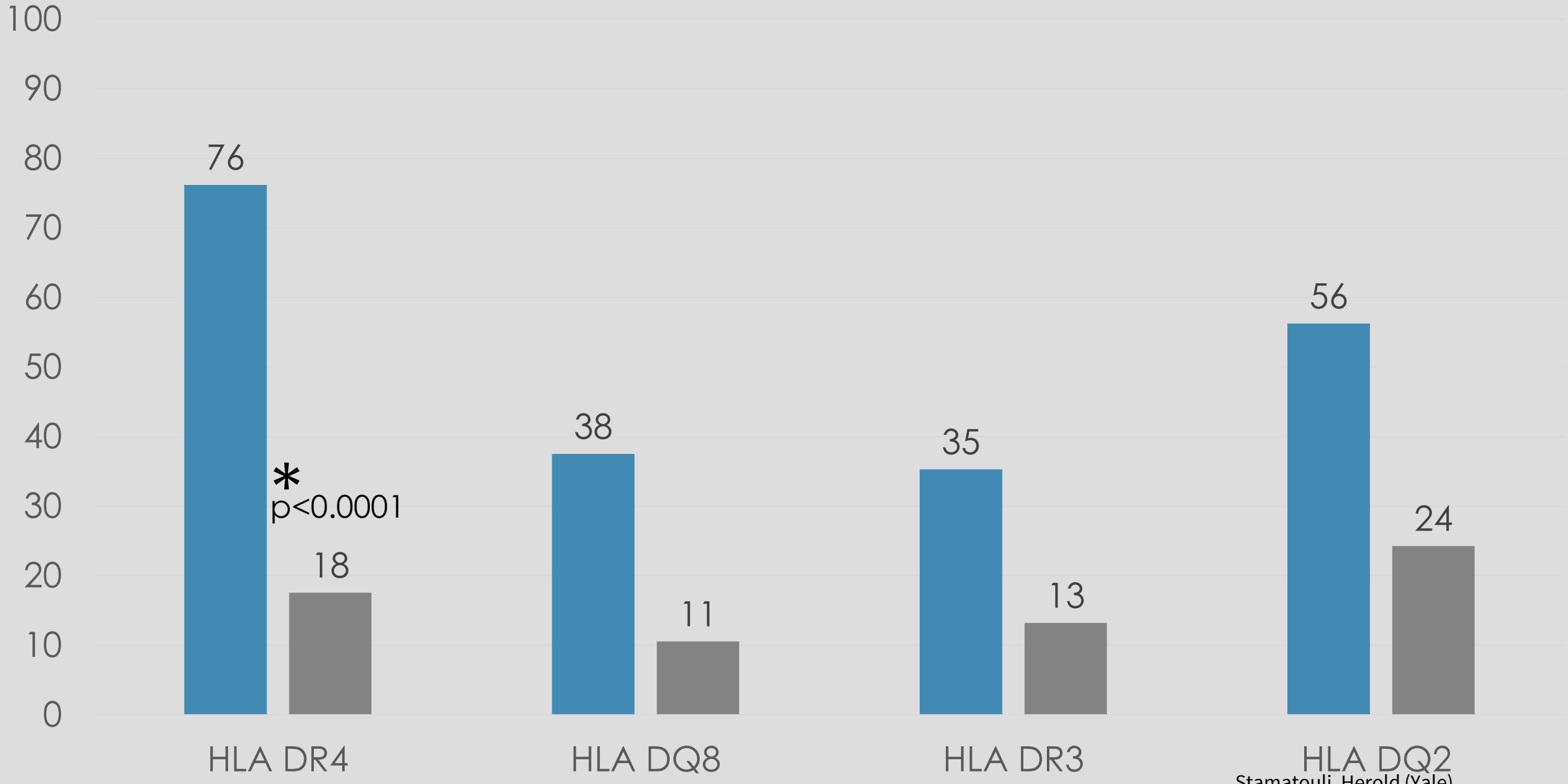


Any Ab
- No Ab
- At Least 1 Ab Positive

Significantly faster time to onset in Ab+ individuals:
Wilcoxon Rank Sum Test, median cycles 2.5 for those with any positive autoantibody and 13 for those with negative autoantibodies, p= 0.024

Stamatouli, Herold (Yale)
Quandt, Anderson, Bluestone (UCSF)
unpublished data

HLA Allele Frequencies



Stamatouli, Herold (Yale)
Quandt, Anderson, Bluestone (UCSF)
unpublished data

KEY FINDINGS

- 100% of subjects were recently exposed to PD-1 or PD-L1 inhibitors; only 1 developed CPI-DM while on ipi monotherapy (having recently gotten combination therapy)
- Over 95% of subjects had no significant hyperglycemia until within 14 days of CPI-DM diagnosis.
- 40% of patients had at least one positive T1D autoantibody at the time of diagnosis
- 76% were positive for HLA-DR4, whereas only 35% were positive for other major risk allele, HLA-DR3

Stamatouli, Herold (Yale)
Quandt, Anderson, Bluestone (UCSF)
unpublished data

ANOTHER IRAE AND ITS CONVENTIONAL DISEASE CORRELATE: INFLAMMATORY ARTHRITIS

MONOTHERAPY: PD-1/PD-L1

- Small joints are affected
- Arthritis is the only irAE

COMBINATION THERAPY: CTLA-4 + PD-1/ PD-L1

- Large joints, especially in the lower extremity
- Often have colitis

- HLA B27 Negative
- RF and antiCCP antibodies were largely negative
  - In 50 patients, 2 had positive antibodies
- More often persists even after CPI cessation

Dr. Clifton Bingham, Johns Hopkins Univ
Cancer, Autoimmunity and Immunolog
March 22, 2018

BIOMARKER DISCOVERY

- Clinical Considerations:
  - Timing of biomarker
  - irAE as a biomarker of treatment benefit

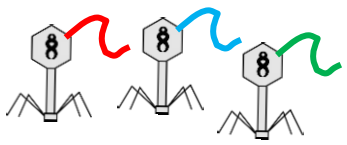
- Interrogation of T-cell Repertoire for Antigen Discovery
  - Understanding the changes in the T-Cell Repertoire (David Oh with PI Larry Fong)
  - Deep sequencing (10x)

- Antigen and Antibody Discovery
  - Phage Display Assays and Proteome Array (Sara Vazquez with PI Joe DeRisi)

PHAGE DISPLAY ASSAYS

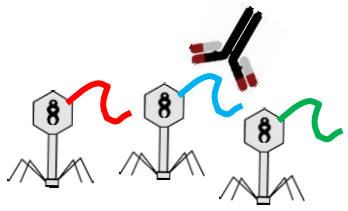
Here: positive control anti-GFAP antibody

Serum

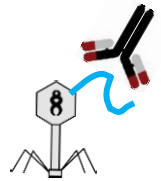


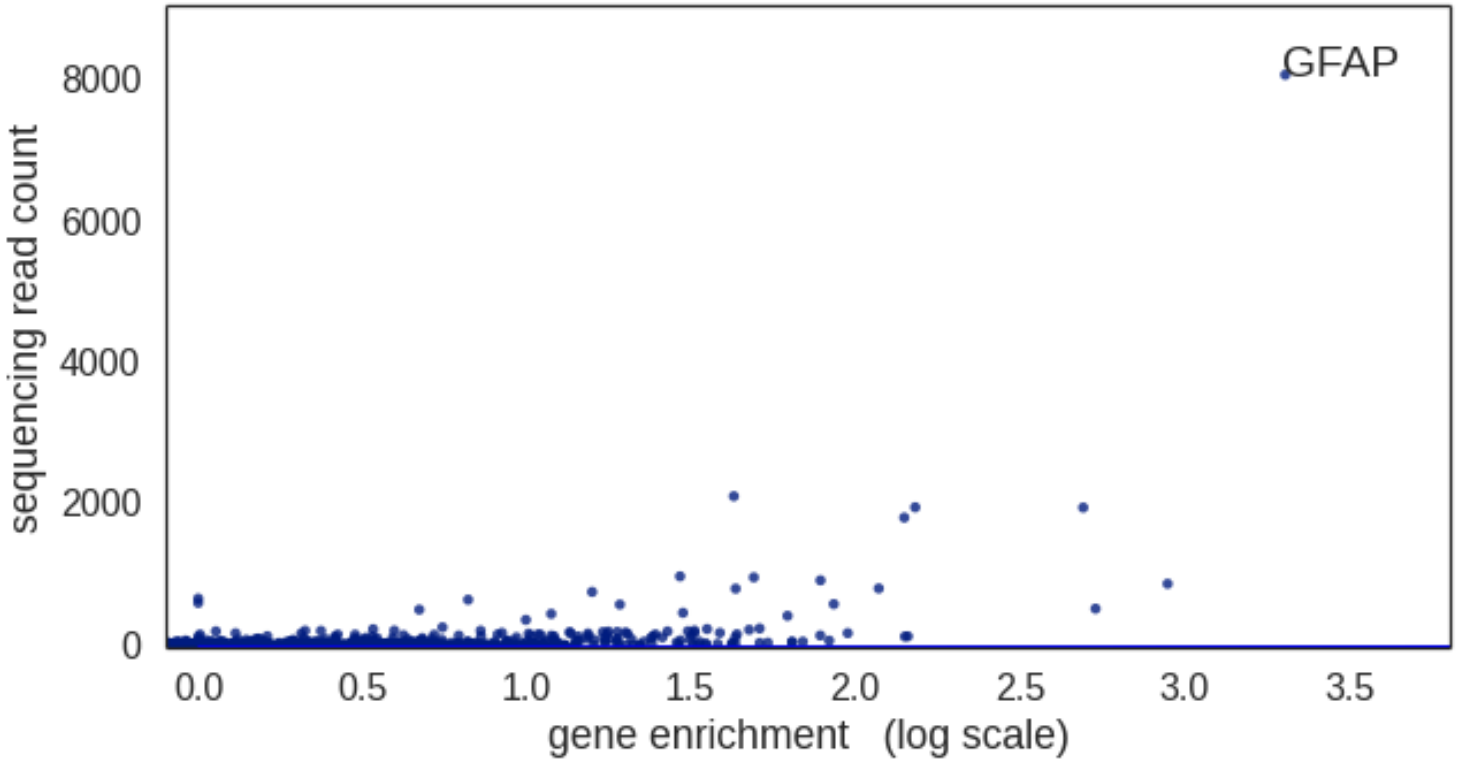
Phage library
Represents full human proteome

Binding



→ Immunoprecipitation & DNA sequencing





Slide thanks to Sara Vazq

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Umesh Masharani

Heidemarie MacMaster

Marisela Tan

Hansen Ho

Other Collaborators

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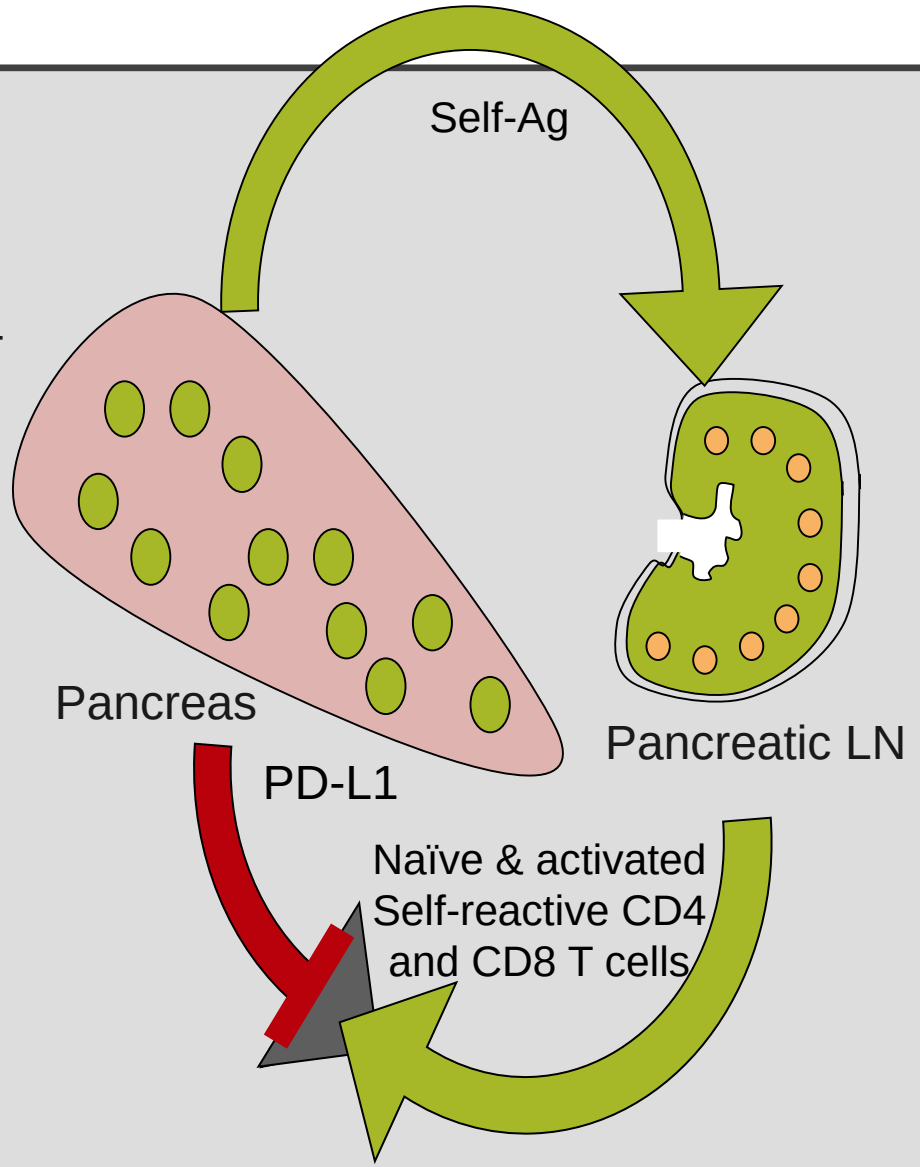
Joe DeRisi's Lab, UCSF

TISSUE EXPRESSION OF PD-L1 PROMOTES SELF TOLERANCE

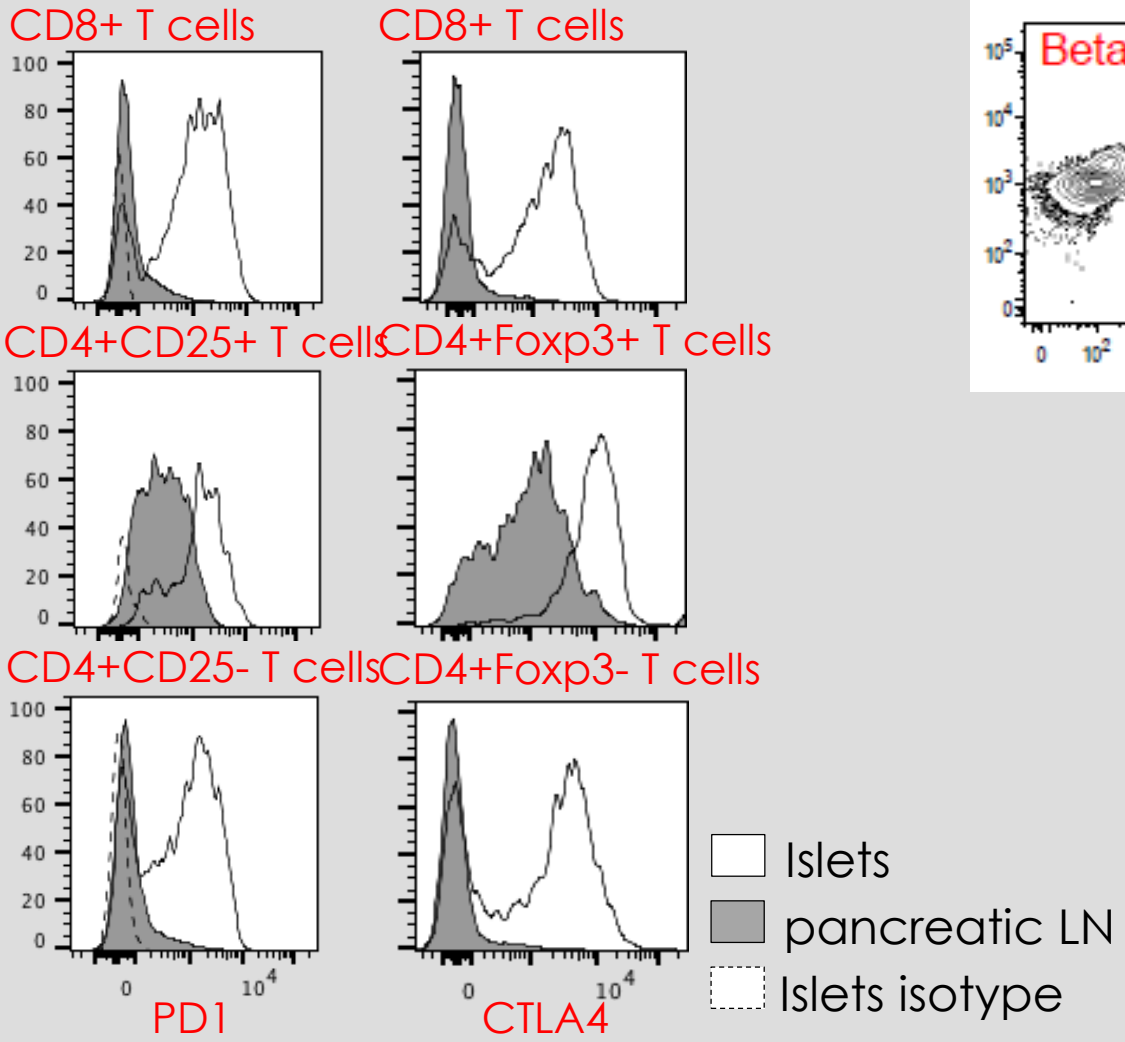
•PD-1:PD-L1 pathway regulates limits activation of self reactive & pathogenic effector CD4 and CD8 T cells

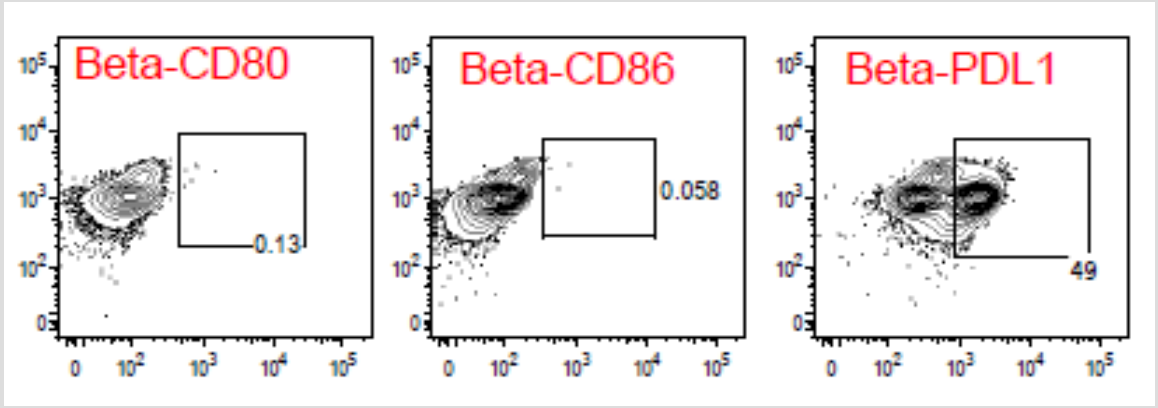
•PD-L1 on non-hematopoietic cells inhibits self-reactive T cells & shields target organ from immune-mediated tissue damage

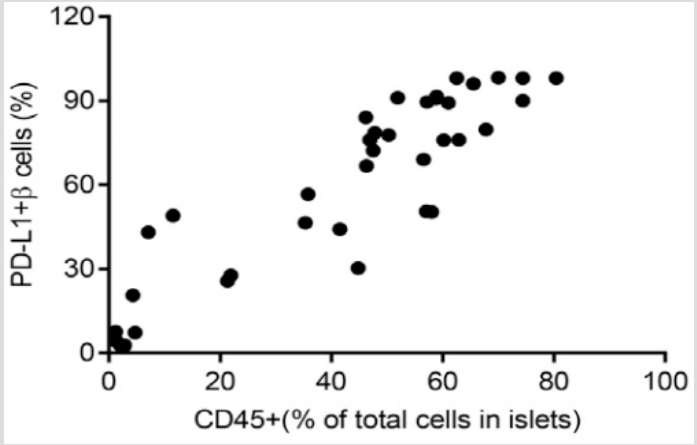
•PD-L1 acts as a tissue-specific negative regulator of pathogenic T cell responses



THE PD1-PDL1 AXIS IS CRITICAL FOR LIMITING AUTOREACTIVE T CELL DAMAGE OF BETA-CELLS

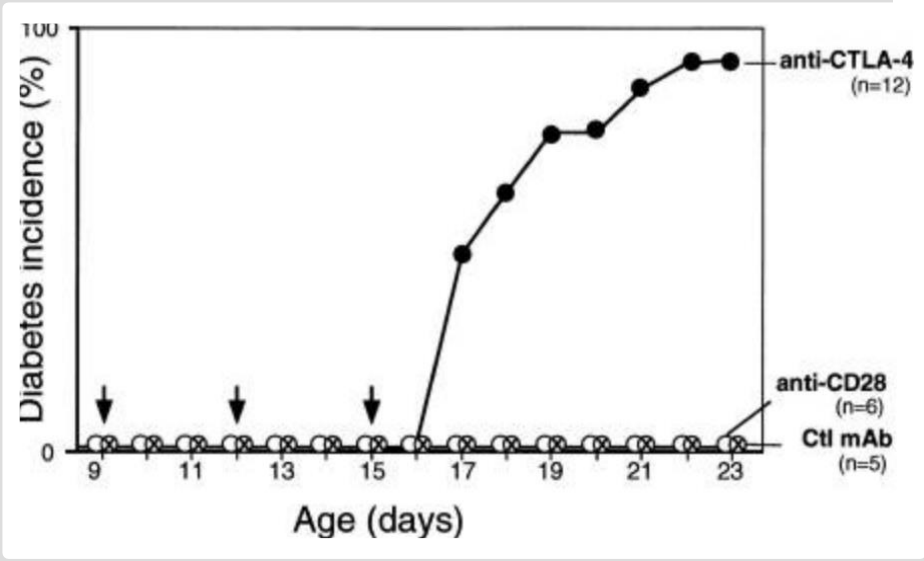




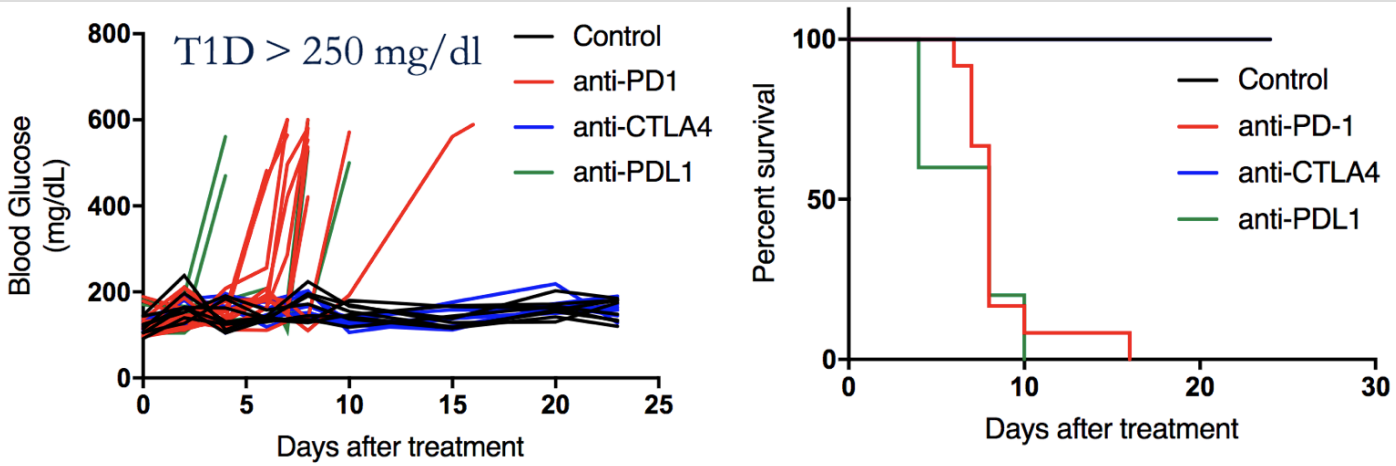


Rui et al. Cell Metabolism, 2017; Kevan Herc

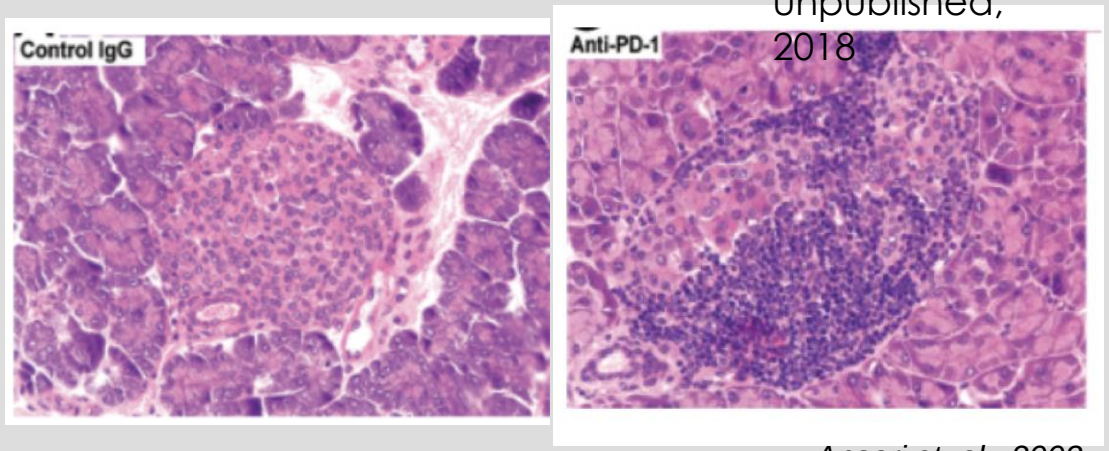
RELATIVE ROLE OF CTLA-4 VERSUS PD-1 DEPENDS ON THE AGE OF THE MICE



BDC2.5/NOD mice were injected at 9, 12, and 15 d of age

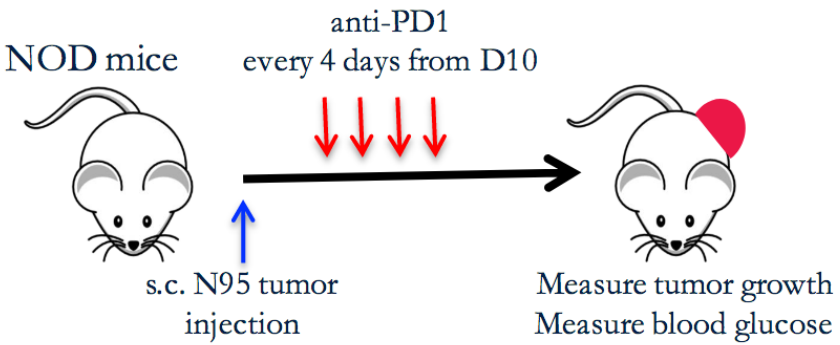


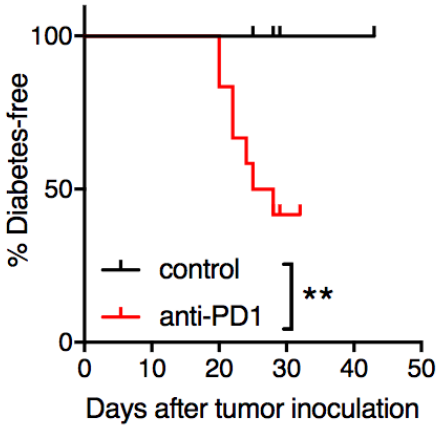
Young, Bluestone, unpublished, 2018

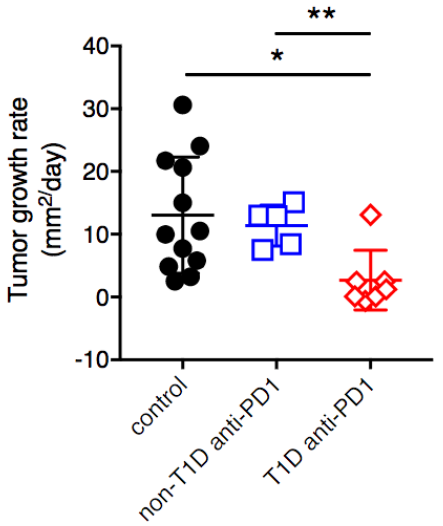


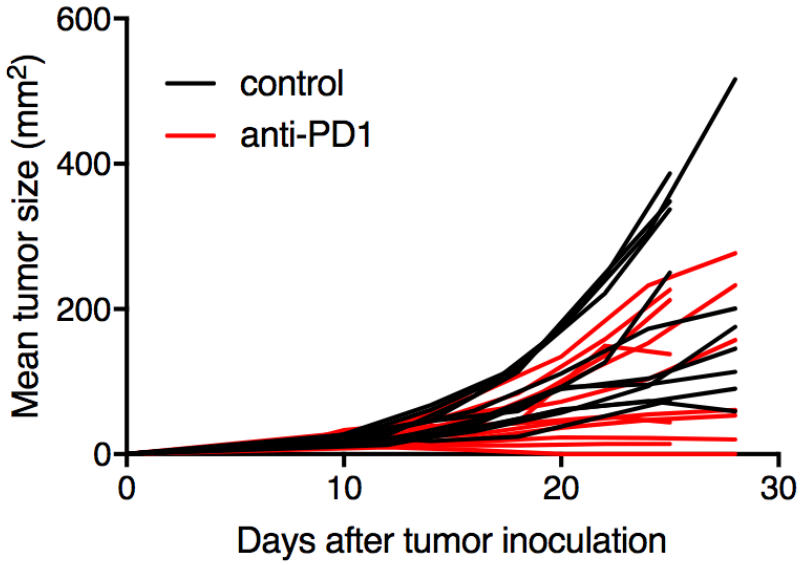
Ansari et. al. 2003

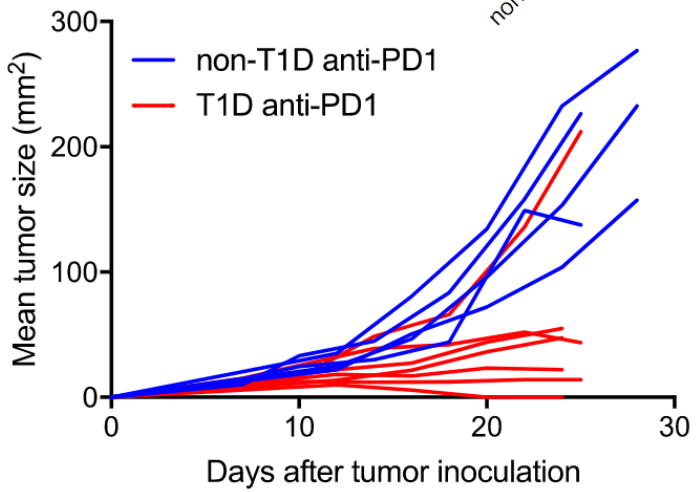
Anti-PD1-induced T1D mice display improved anti-tumor immune responses





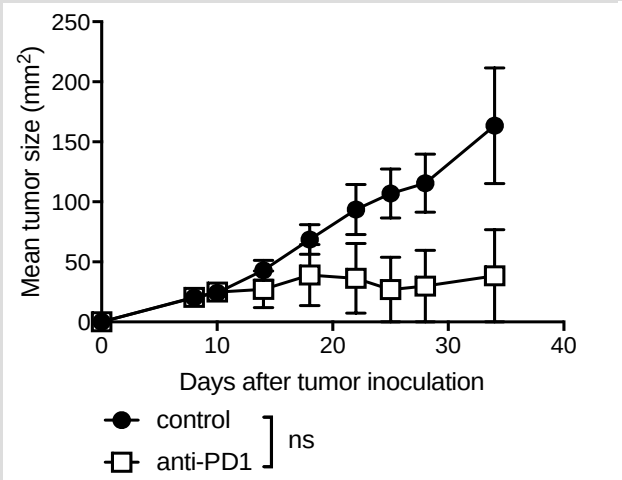


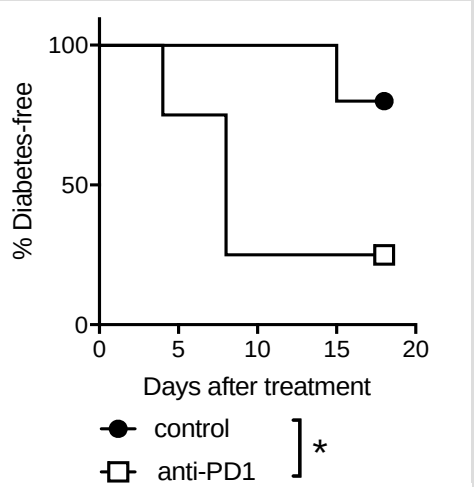




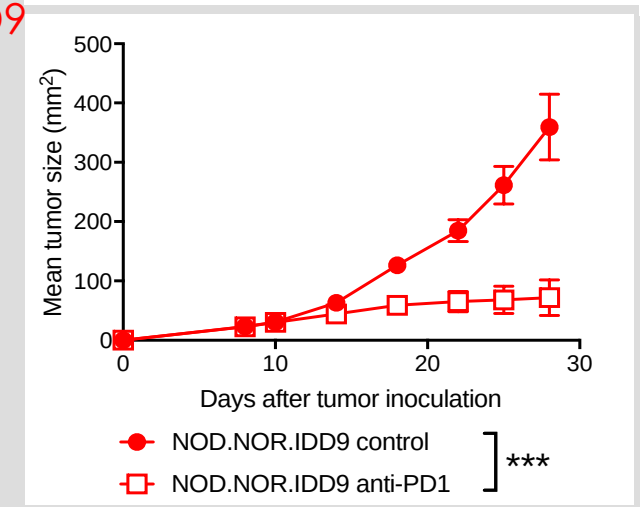
IDD9 CONGENIC MICE DISPLAY RESISTANCE TO ANTI-PD1 T1D AND ROBUST TUMOR CONTROL

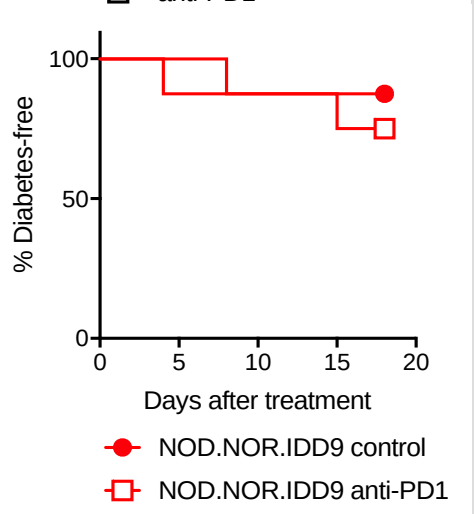
NOD



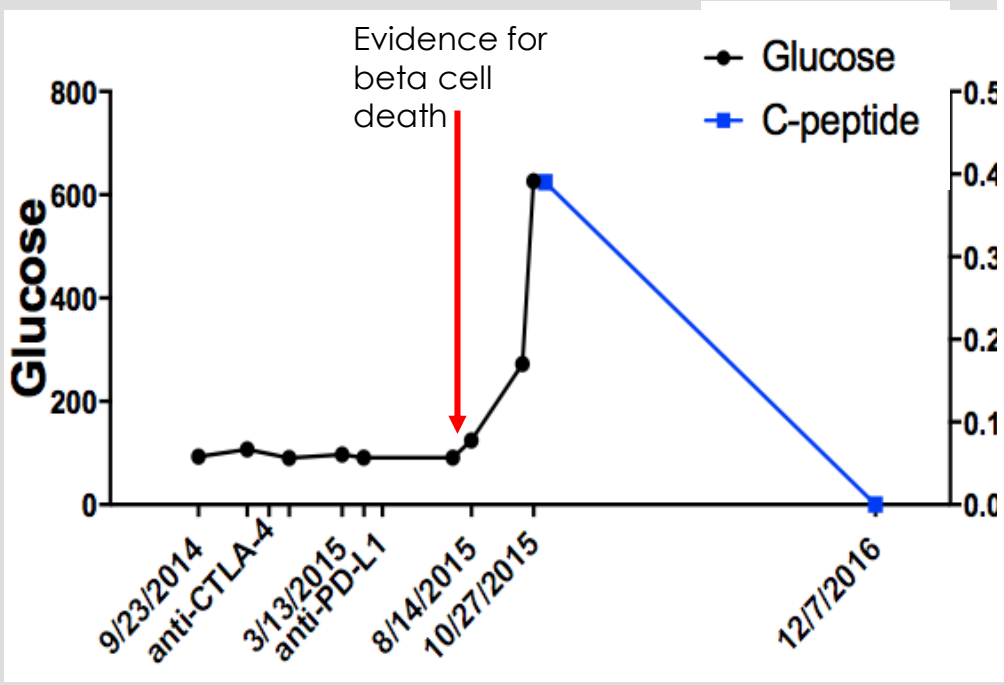


NOD.NOR.IDD9

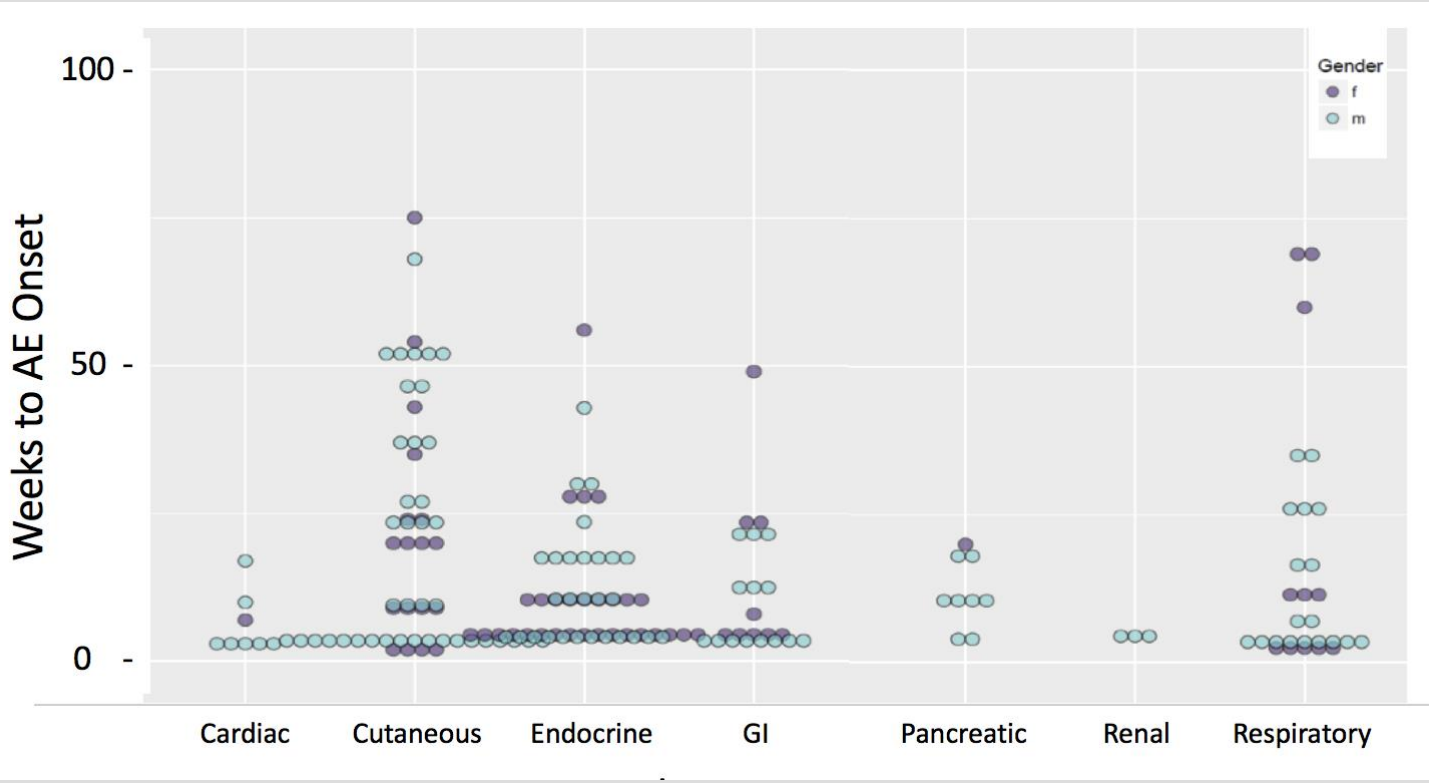




TIMING – ARE WE BREAKING IMMUNE TOLERANCE AND ENGAGING NEW CELLS IN IMMUNITY?

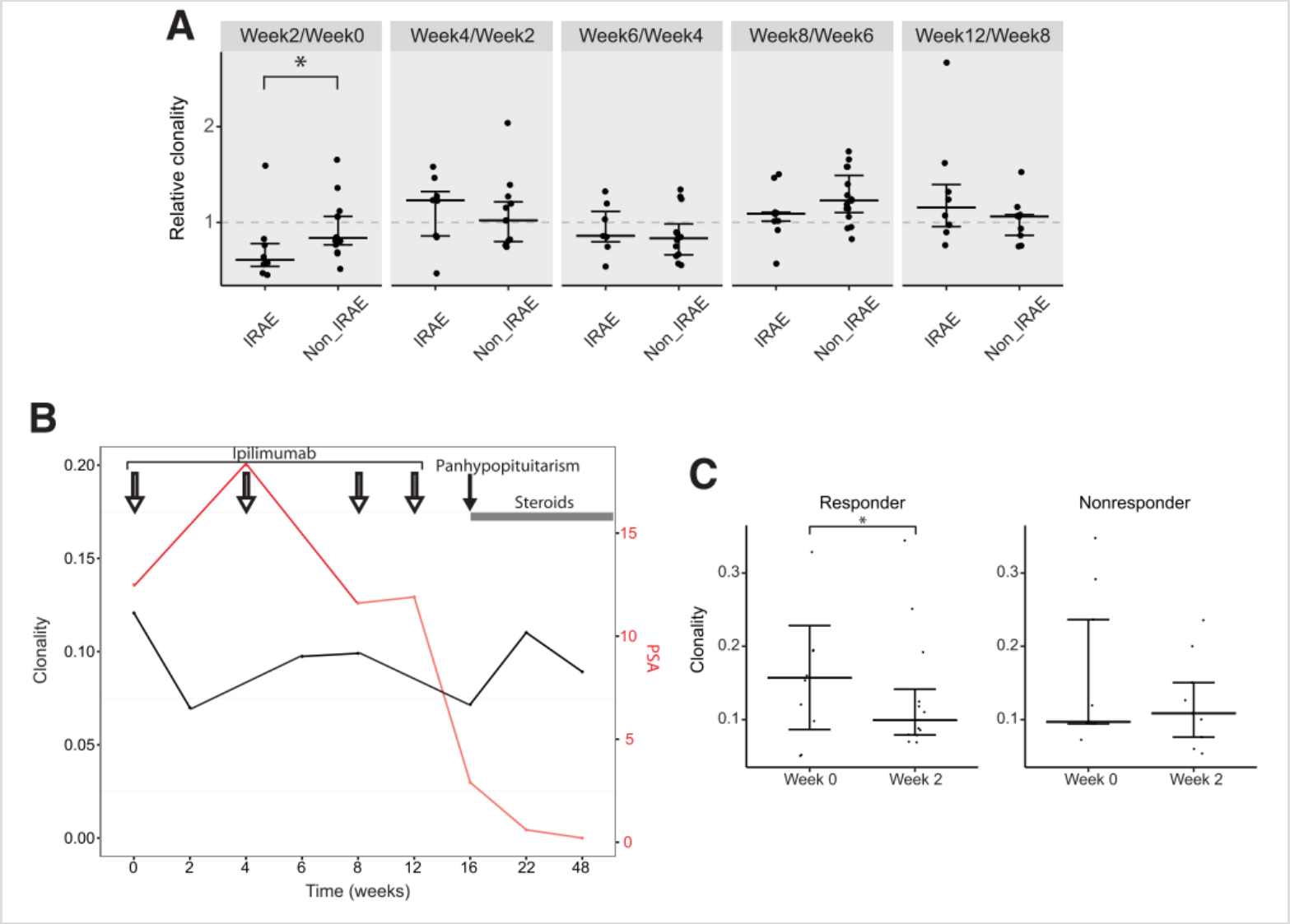


Herold and colleagues, unpublished



(Analysis by Nick Bayless, data originally from Hofmo and Zimmer et al, Eur J Cancer 2016)

T CELL REPERTOIRE AND IRAES



** A decrease in clonality connotes an increase in the number of unique clones, i.e. an increase in diversificat

Oh et al, 201