Linking APS1 to common autoimmune syndromes like type 1 diabetes

Mark Anderson MD, PhD
UCSF Diabetes Center

UCSF University of California San Francisco

IMMUNO Harnessing Immunology To Improve Human Health

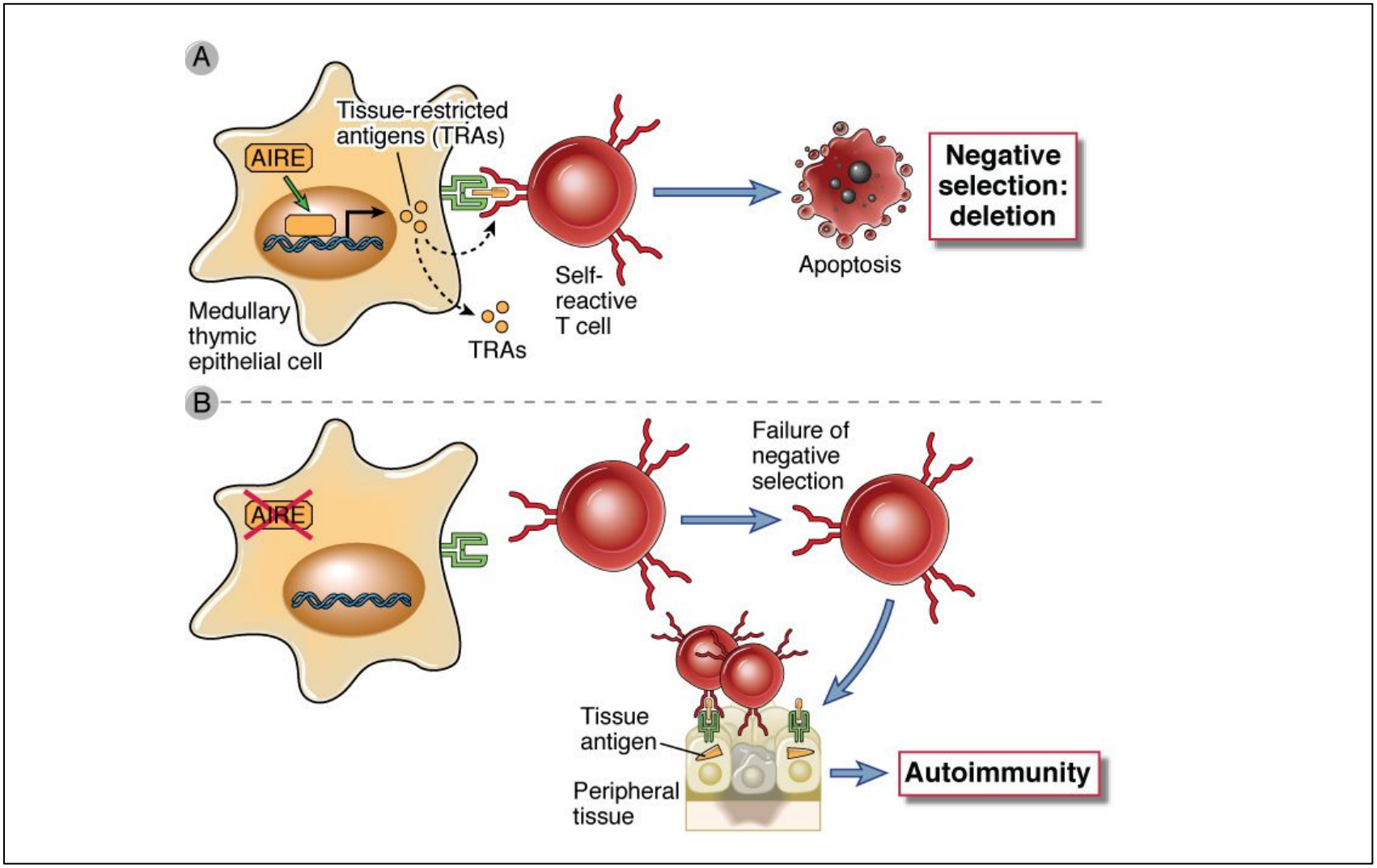
Diabetes Center University of California San Francisco

Case Presentation of Autoimmune Polglandular Syndrome Type 1 (APS1 or APECED) a Mendelian form of autoimmunity

- R.V. 51 year old female

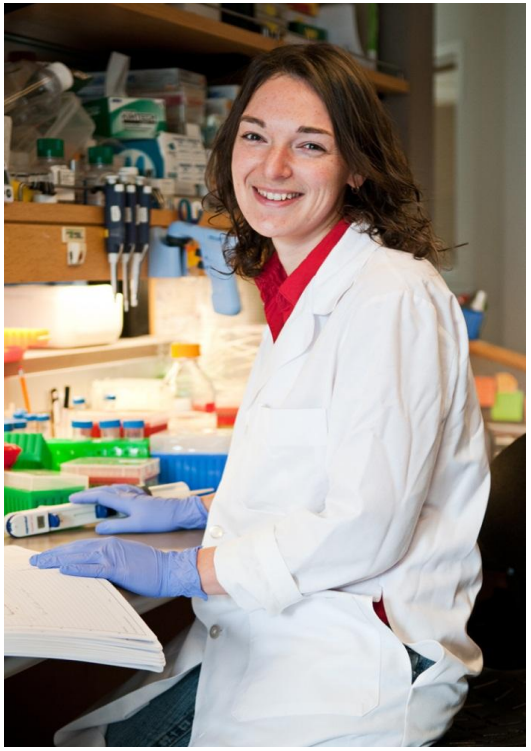
- Age 7: Hypoparathyroidism
- Age 8: Mucocutaneous candidiasis
- Age 13: Addison's disease
- Age 16: Premature ovarian failure
- Age 20: Alopecia areata universalis
- **Age 40: Type I DM**

Model

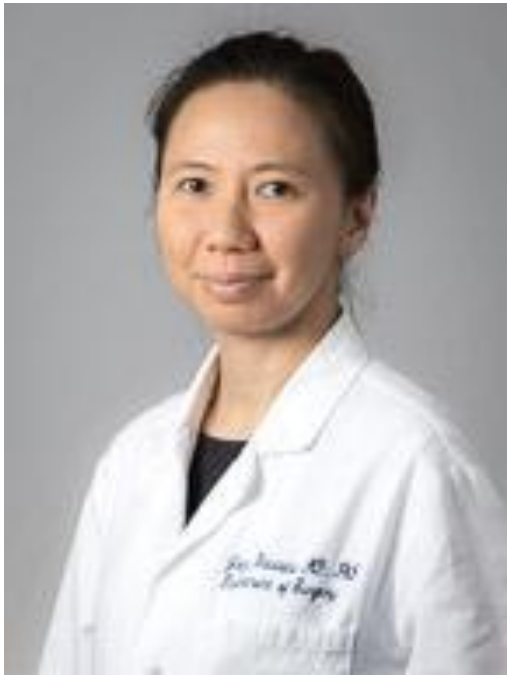


Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology, 8th edition, 2014*

What about human thymic stromal cells?

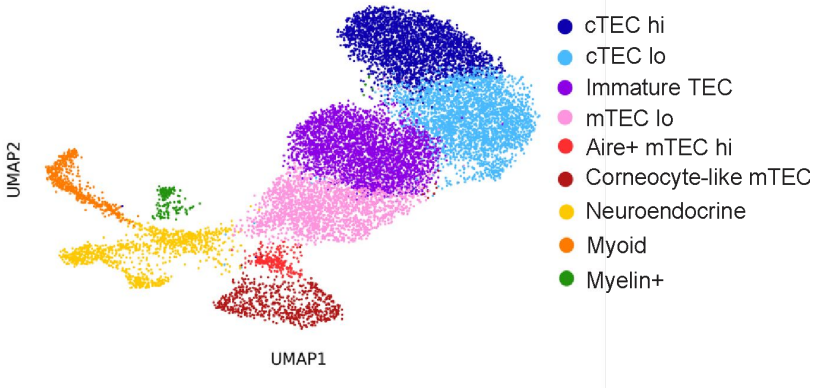


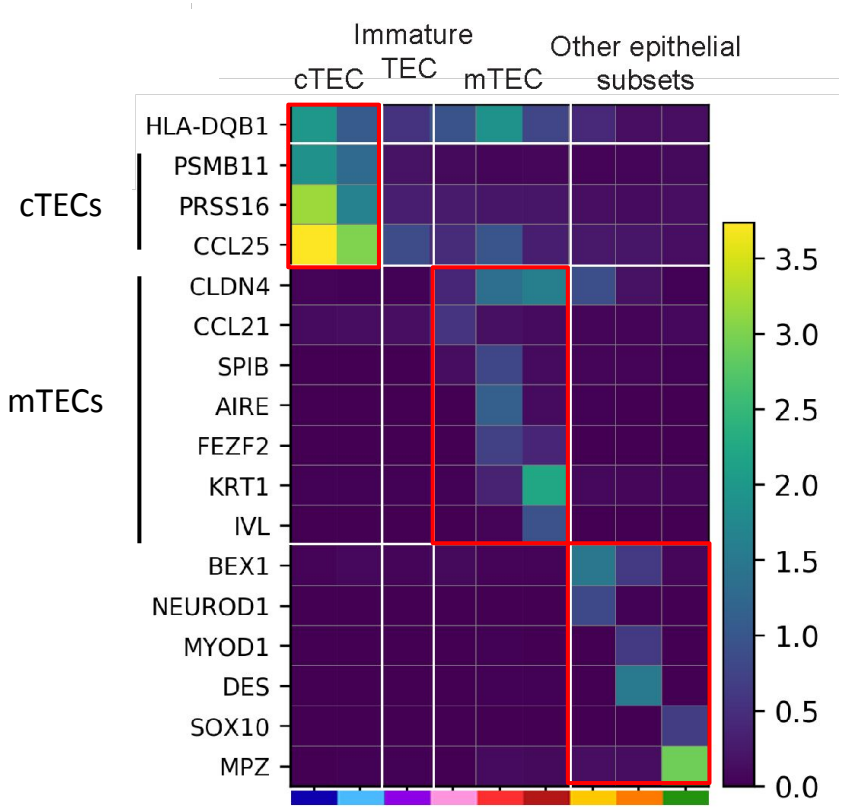
Audrey Parent



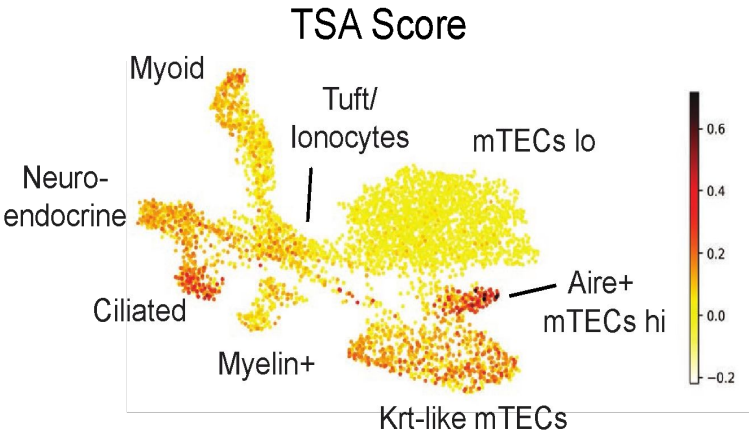
Joey Bautista

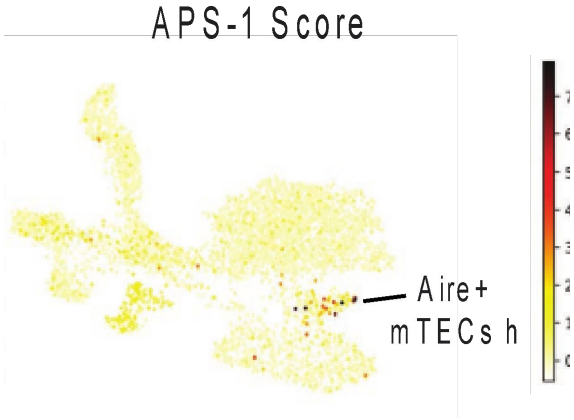
Focus on thymic epithelial cells



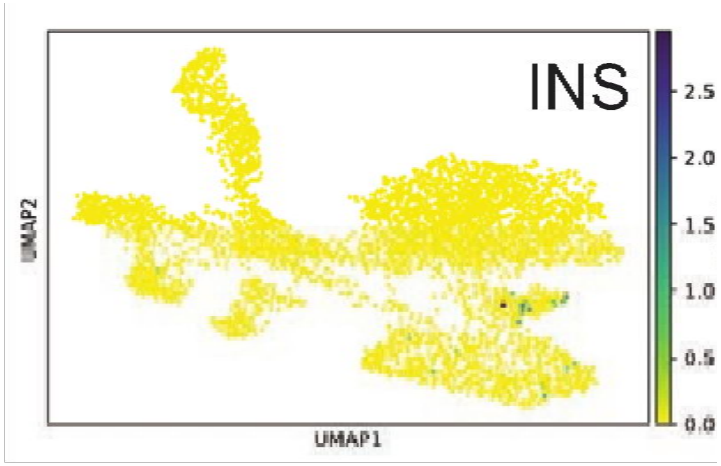


Tissue-specific antigen (TSA) expression in human TECs



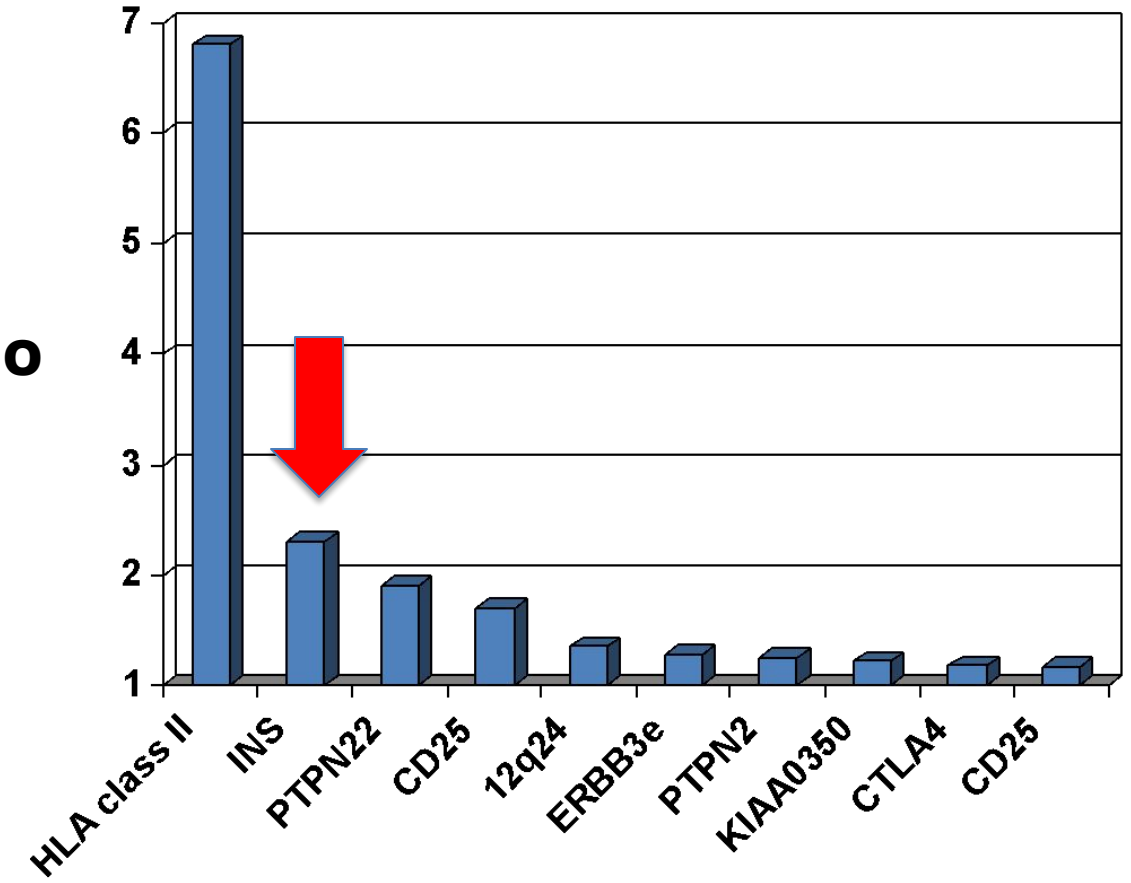


Type 1
Diabetes



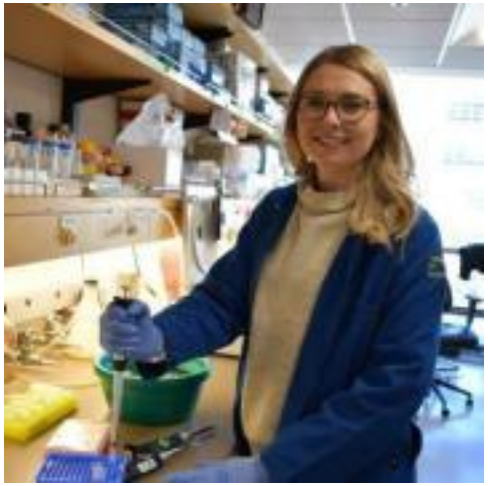
Genetic risk for T1D

ODDS RATIO



Modified from Todd et al. Robust Associations of four new chromosome regions from genome-wide anlayses of type 1 diabetes Nature Genetics June 6 2007

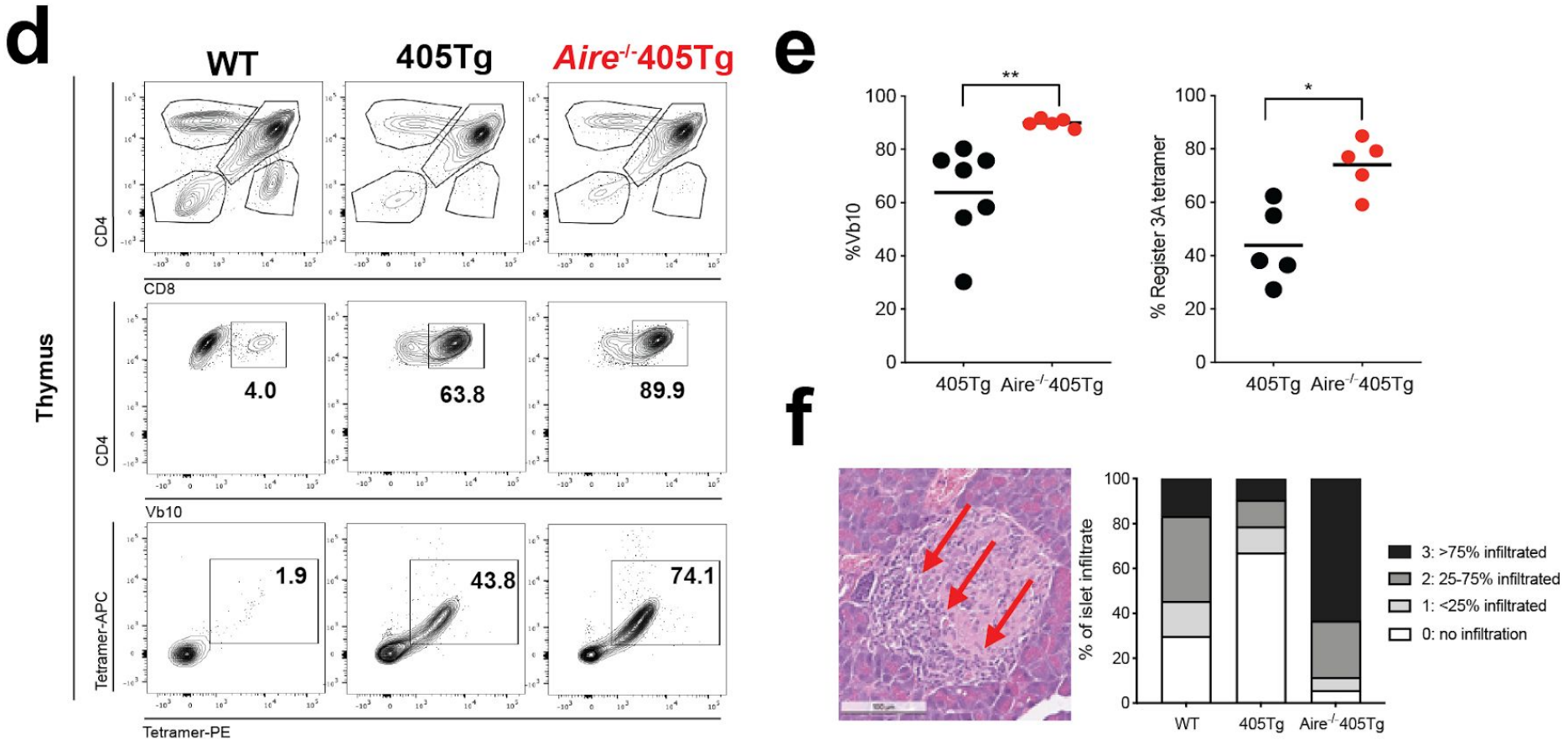
What about Ins-specific CD4+ T cells and their selection?



Jennifer Bridge

John Kappler, PhD
U of Colorado National Jewish Health

Aire-405TCR is dependent on Aire expression



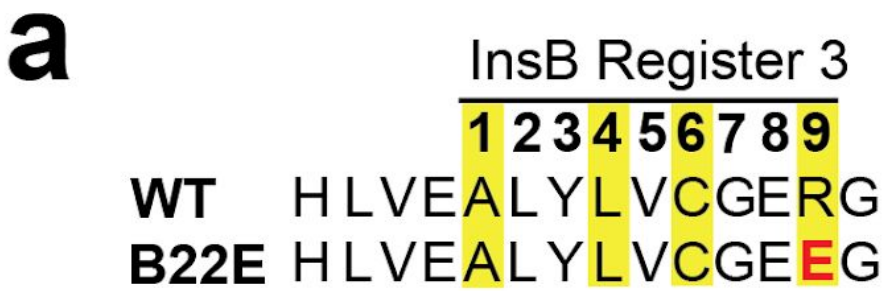
Could one alter Insulin's display to the immune system to promote tolerance?

John Kappler, PhD
U of Colorado
National Jewish Health

Ins2 mutants: B22E

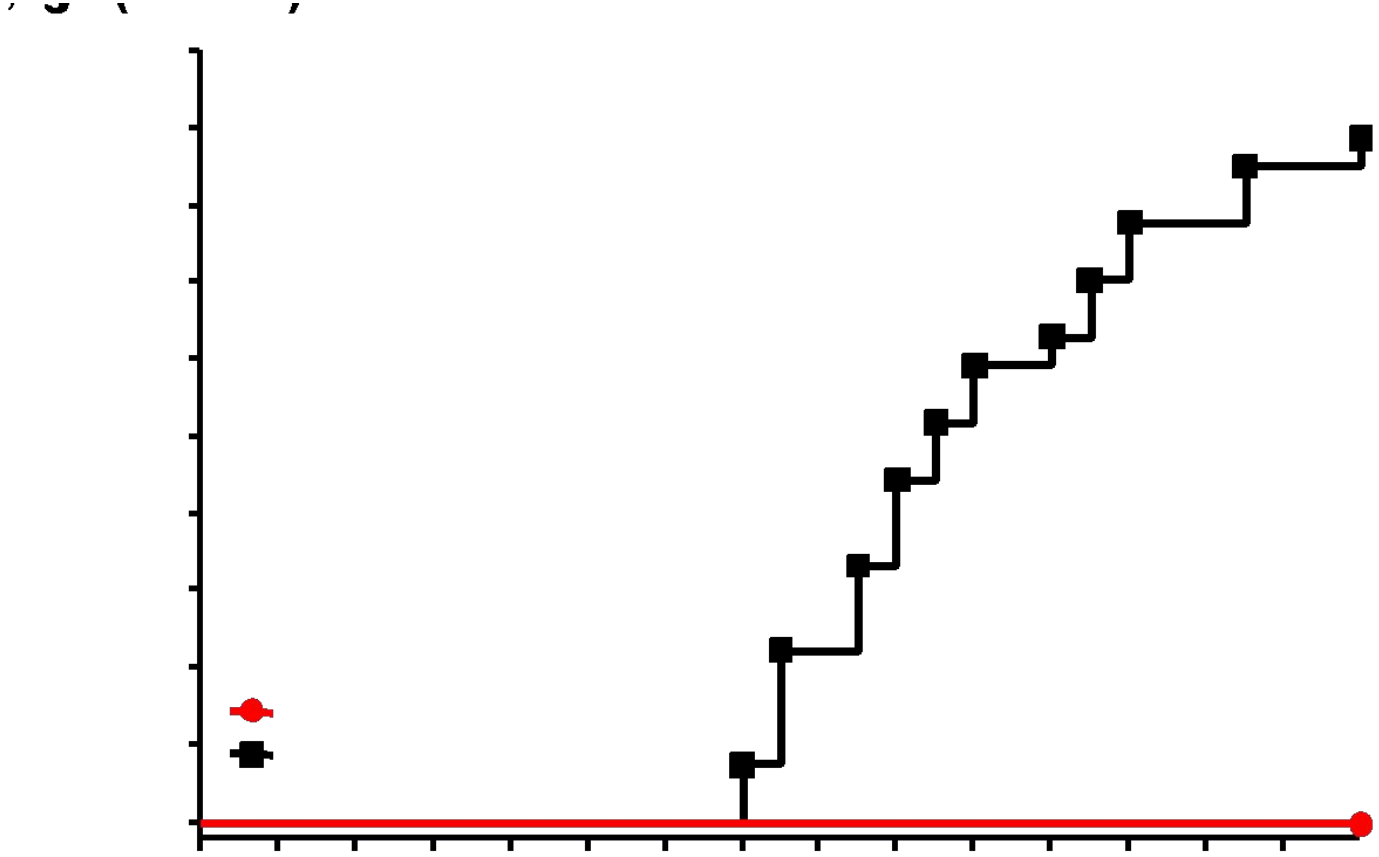
Introduction of Insulin super-agonists into the Ins-2 gene

```
                                  <————————Register 3————————>
                                   1  2  3  4  5  6  7  8  9
GCACCTTTGTGGTTCCCACCTGGTGGAGGCTCTCTACCTGGTGTGTGGGGAGGAGGGCTTCTTC
                                           |————————Guide———————>PAM
  H  L  C  G  S  H  L  V  E  A  L  Y  L  V  C  G  E  R  G  F  F
  H  L  C  G  S  H  L  V  E  A  L  Y  L  V  C  G  E  E  G  F  F)
<————————————————Ins2 B Chain————————————————————————————————>
```



John Kappler & Niyun Jin

Summary of the T1D development data



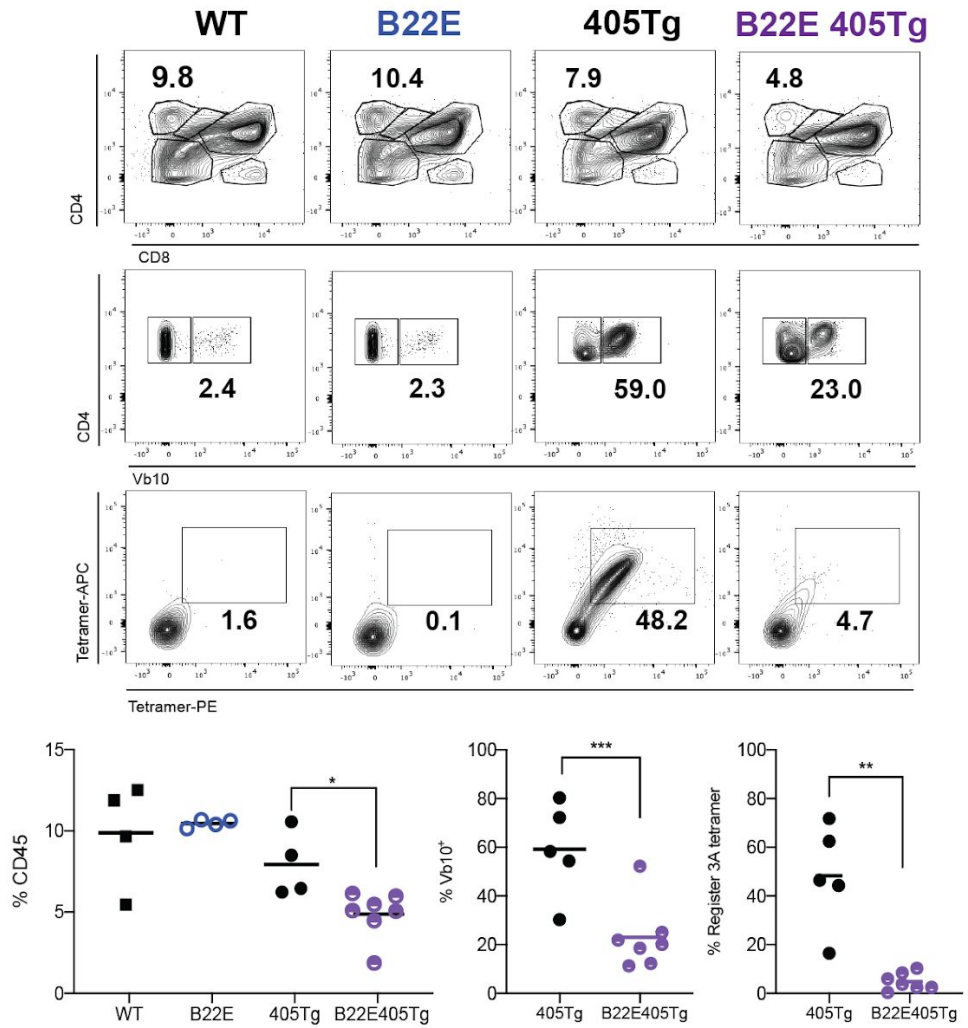
Aire-405 TCR specific deletion in the thymus via Ins2EE expression

a

InsB Register 3

	1	2	3	4	5	6	7	8	9
WT	H	L	V	E	A	L	Y	L	V	C	G	E	R	G
B22E	H	L	V	E	A	L	Y	L	V	C	G	E	E	G

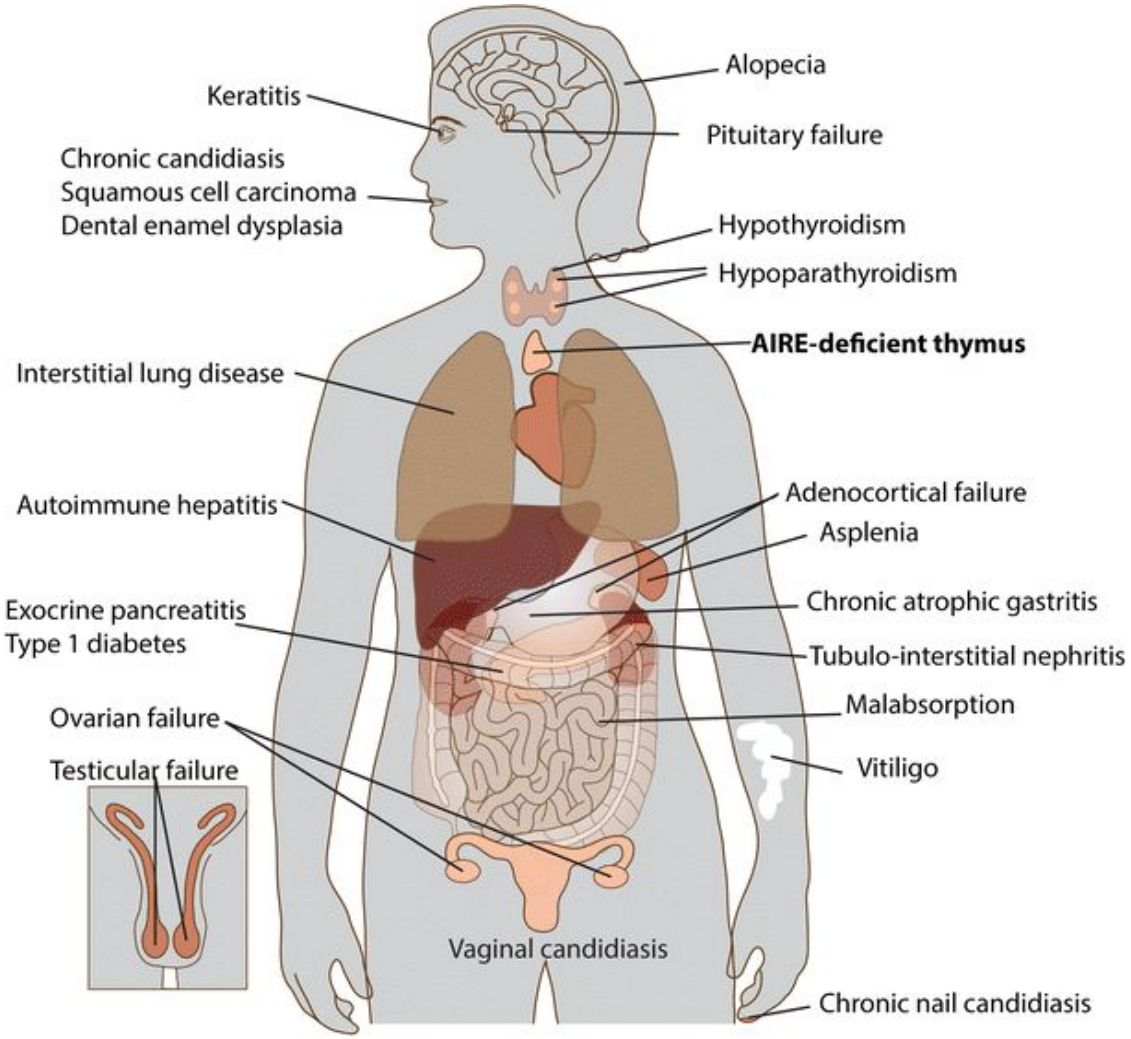
c



Summary 2

- The influence of Aire on insulin-specific T cell selection in the thymus is subtle
- Such T cells appear to be selected by thymic-derived insulin supporting a "pruning" model for unusual high affinity register 3 T cells
- Improving Insulin peptide binding to MHC Class II can **completely** protect against diabetes

APS-1 Disease spectrum



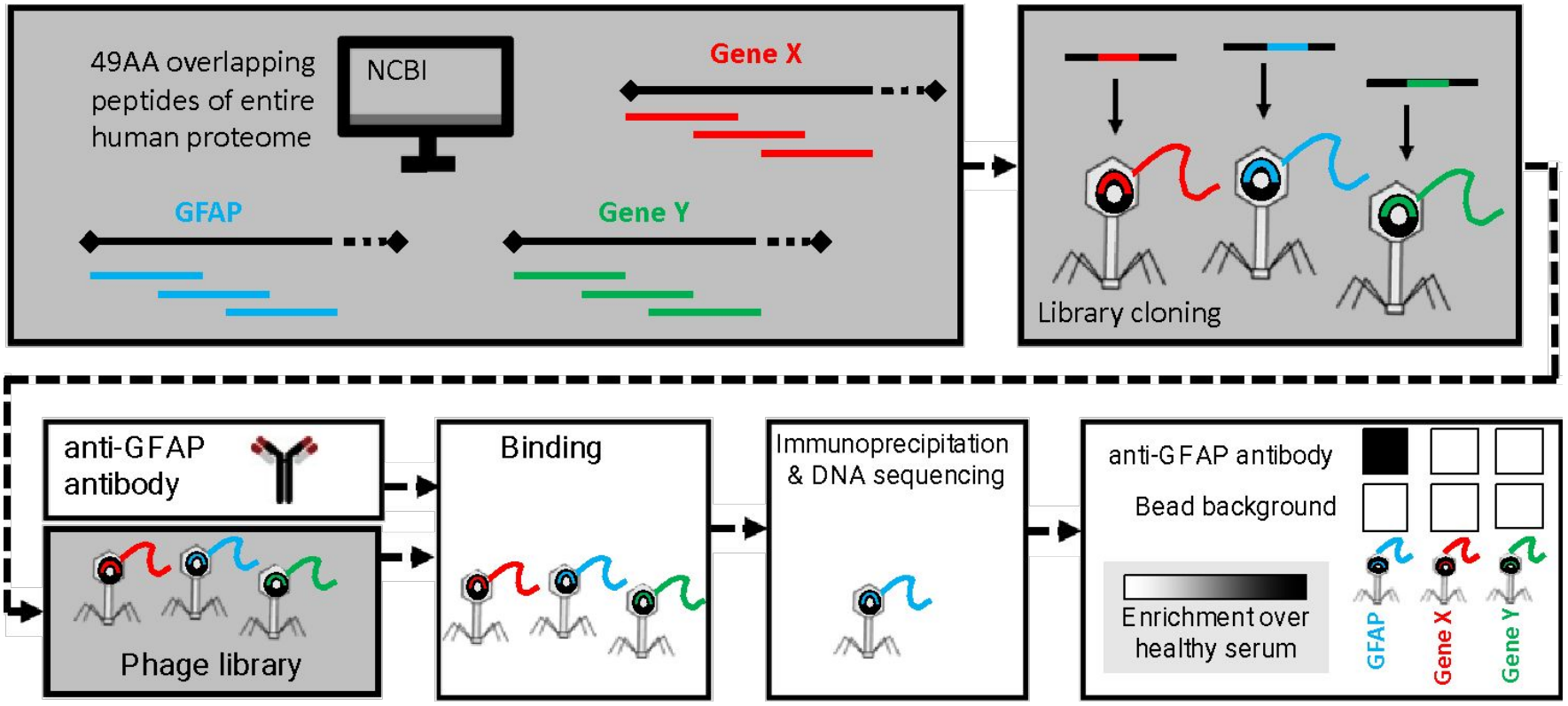
Kisand &

Autoantibody Discovery Project

Joe DeRisi
UCSF

Sara Vazquez
UCSF MD/PhD Student

Phip-Seq:
Synthetic Phage library of the entire human "orfeome"



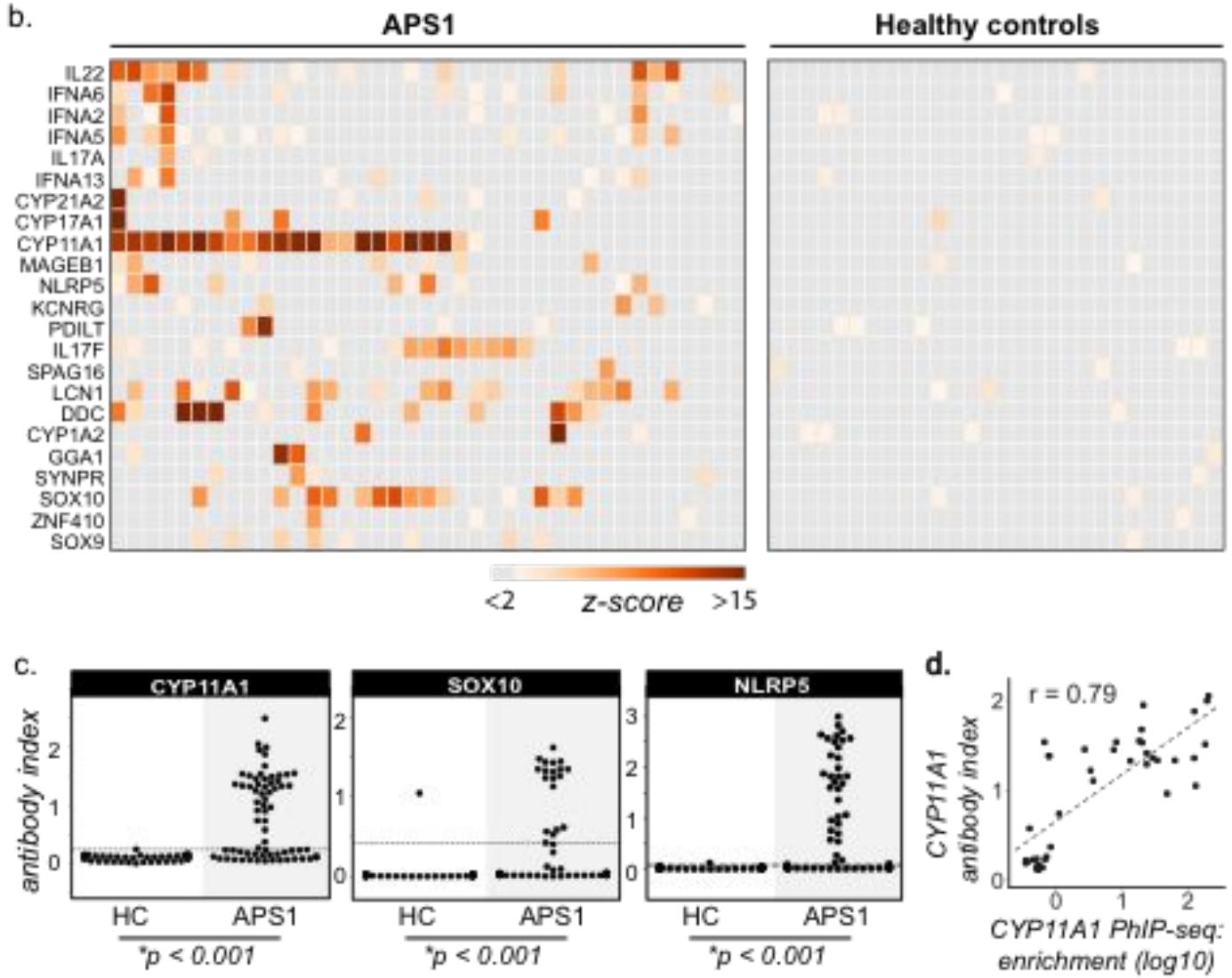
Adapted from Steve Elledge
Current Library has 700,000 unique 49 AA mers that overlap (new one coming with 64)

A collaborative effort

- Collaboration with Dr. Mihalis Lionakis at NIH- North American APS1 cohort

- Combined over 80 APS1 serum samples to mine

PhIP-seq detects known antigens in APS1

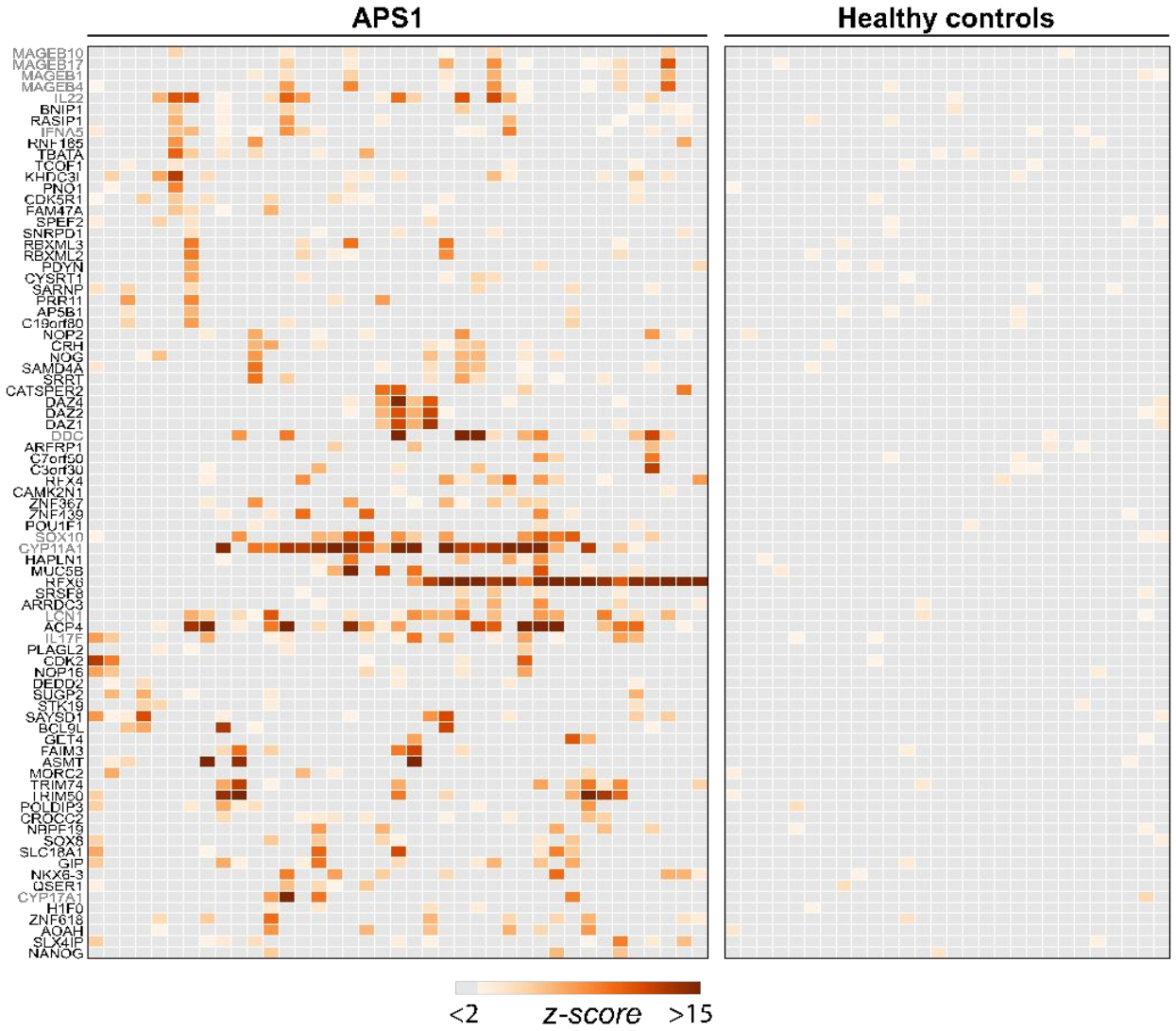


APS1 phage display: novel (potential) autoantigens

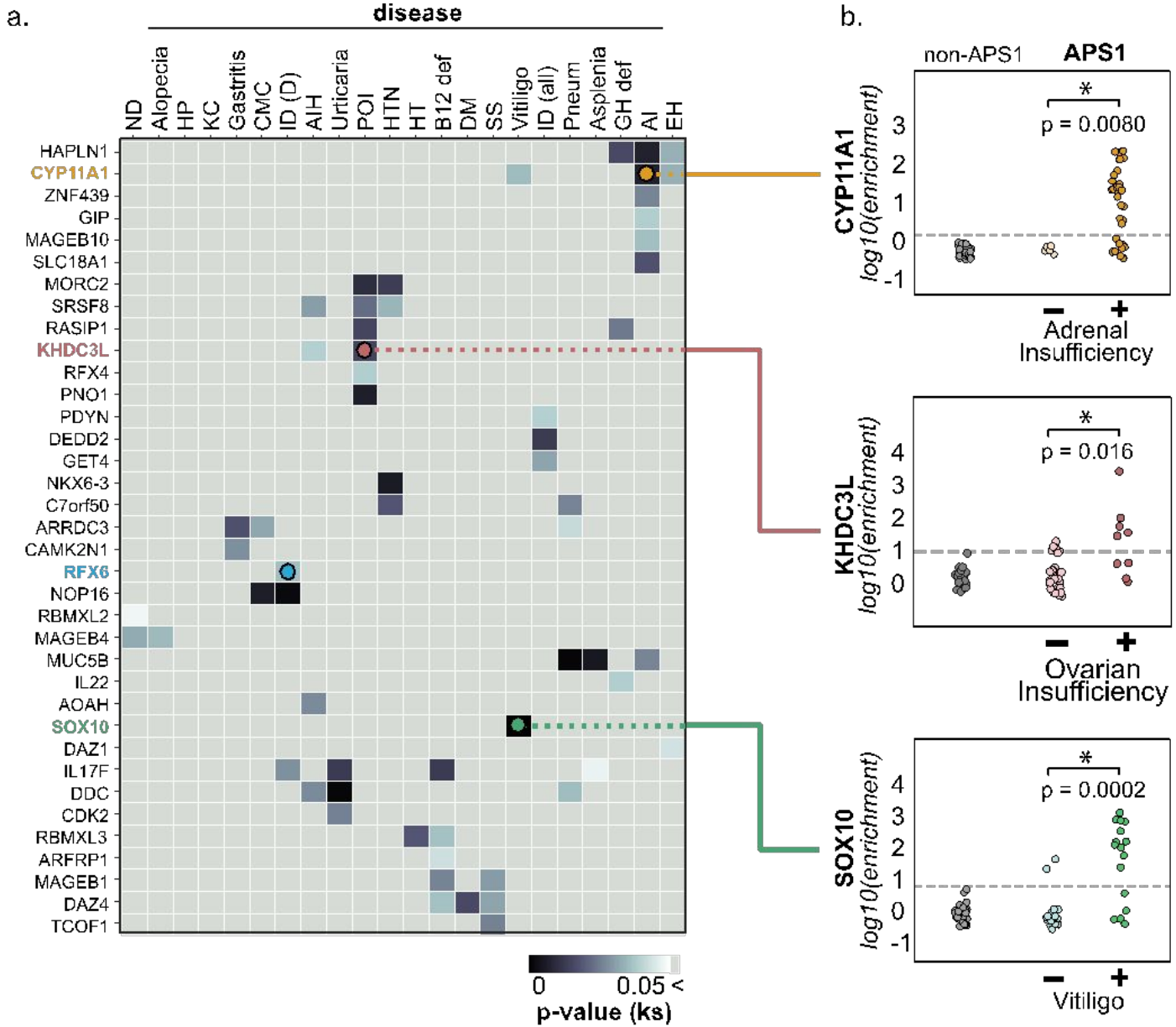
Filtering cutoffs:

APS1 > 3 *AND* **10-fold over mock-IP**

0/29 Healthy Controls

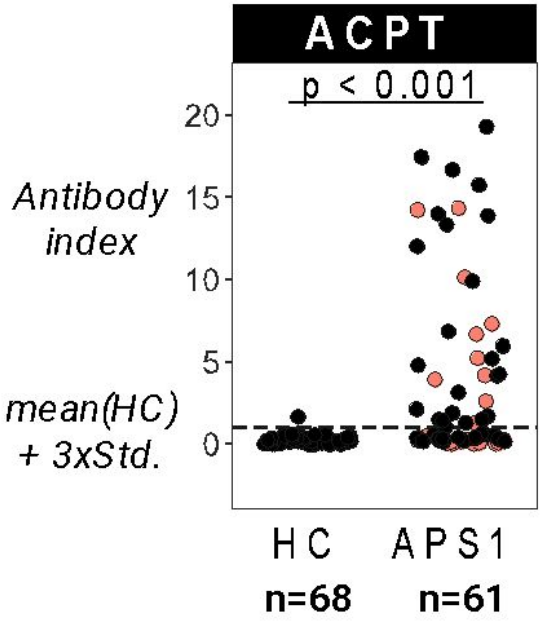


APS1 Clinical correlation with autoantibodies



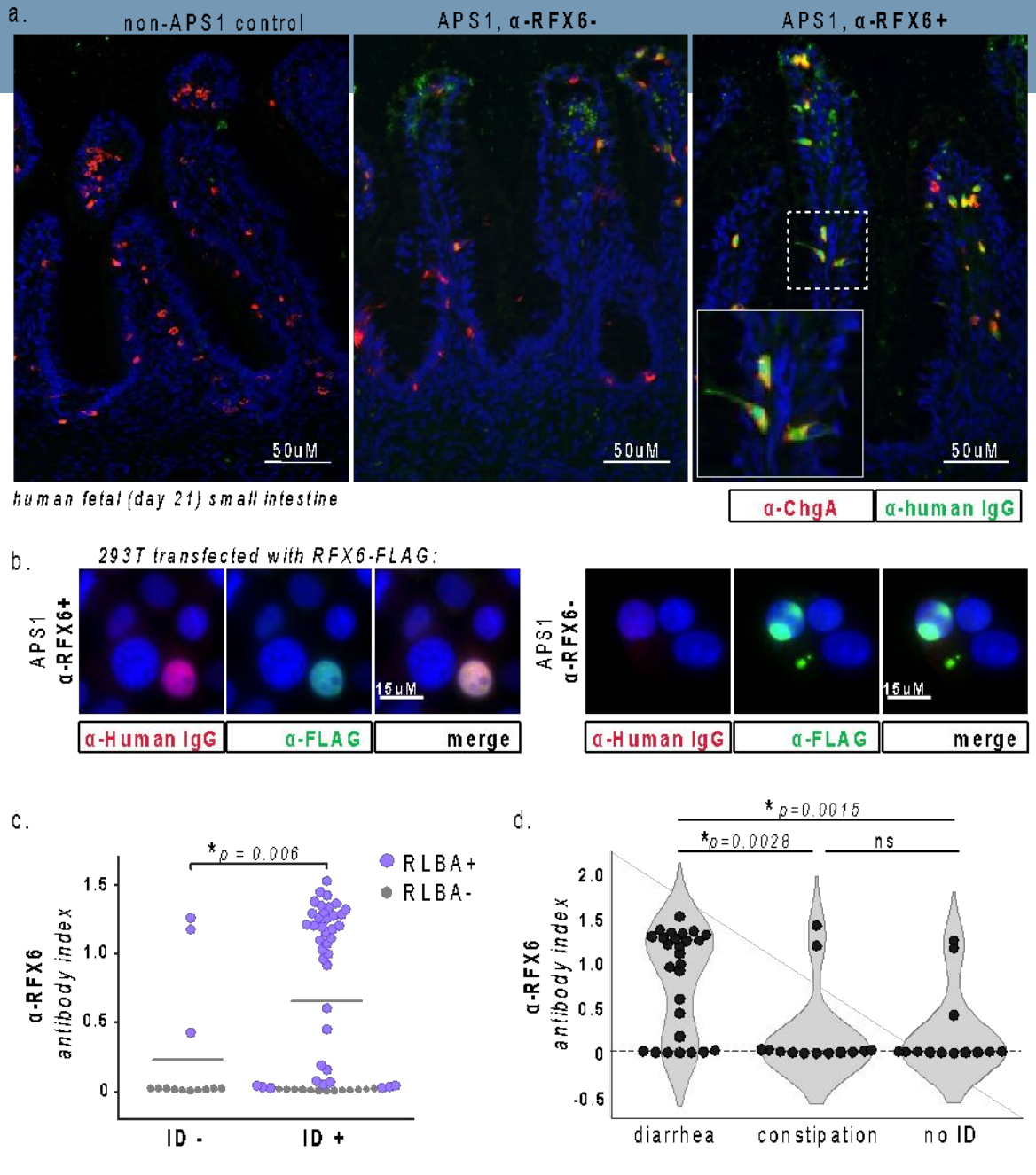
Novel Antigen #1:
Mutations in Testicular Acid Phosphatase (ACPT) cause enamel hypoplasia

85% + of APS1 patients have enamel hypoplasia



Smith et al. 2017
Seymen et al. 2016

APS1 Rfx6 autoantibodies and intestinal dysfunction



Summary

- Phip-Seq is a powerful new tool to mine for autoreactive specificities
- Identified several new targets in APS1 subjects that may provide predictive value for ovarian failure and intestinal dysfunction
- Identified antigens are tissue specific and controlled by Aire in mTEC's
- Cost effective (<$5 per sample)

Acknowledgements

Zoe Quandt
Audrey Parent
Joey Bautista
Jennifer Bridge
Ben Yuen
Sara Vazquez
Corey Miller
Alice Chan
Irina Proekt
Yi Wang
Jared Balolong

UCSF
Joe DeRisi
Jimmie Ye
COMET Consortium
NIH
Mihalis Lionakis
Rockefeller
Paul Bastard
JL Casanova
U of Colorado
John Kappler
Jen Matsuda
Fran Crawford

Funding
NIAID, NIDDK, JDRF, Helmsley Trust, Hillblom Foundation, CZ Biohub
Robert and Michelle Friend

UCSF University of California San Francisco

IMMUNO
Harnessing Immunology To Improve Human Health