Autoimmune research in the U.S.

A presentation to the NASEM Committee for the Assessment of NIH Research on Autoimmune Diseases

Jane Hoyt Buckner, MD

President, Benaroya Research Institute at Virginia Mason

November 18, 2020

Benaroya Research Institute
Virginia Mason

Goals of the Committee

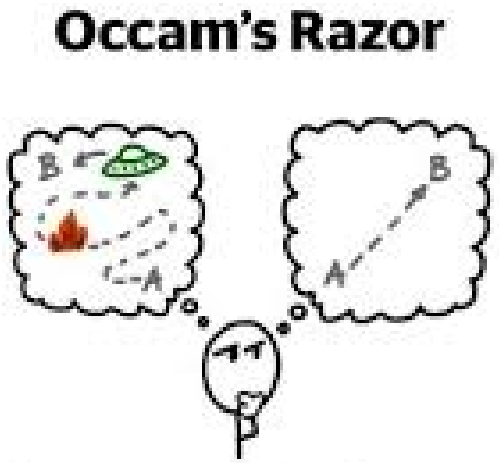
An assessment of NIH research activities on autoimmune diseases with an emphasis on risk factors, diagnostic tools, barriers to diagnoses, treatments, and **prospects for cures**.

.

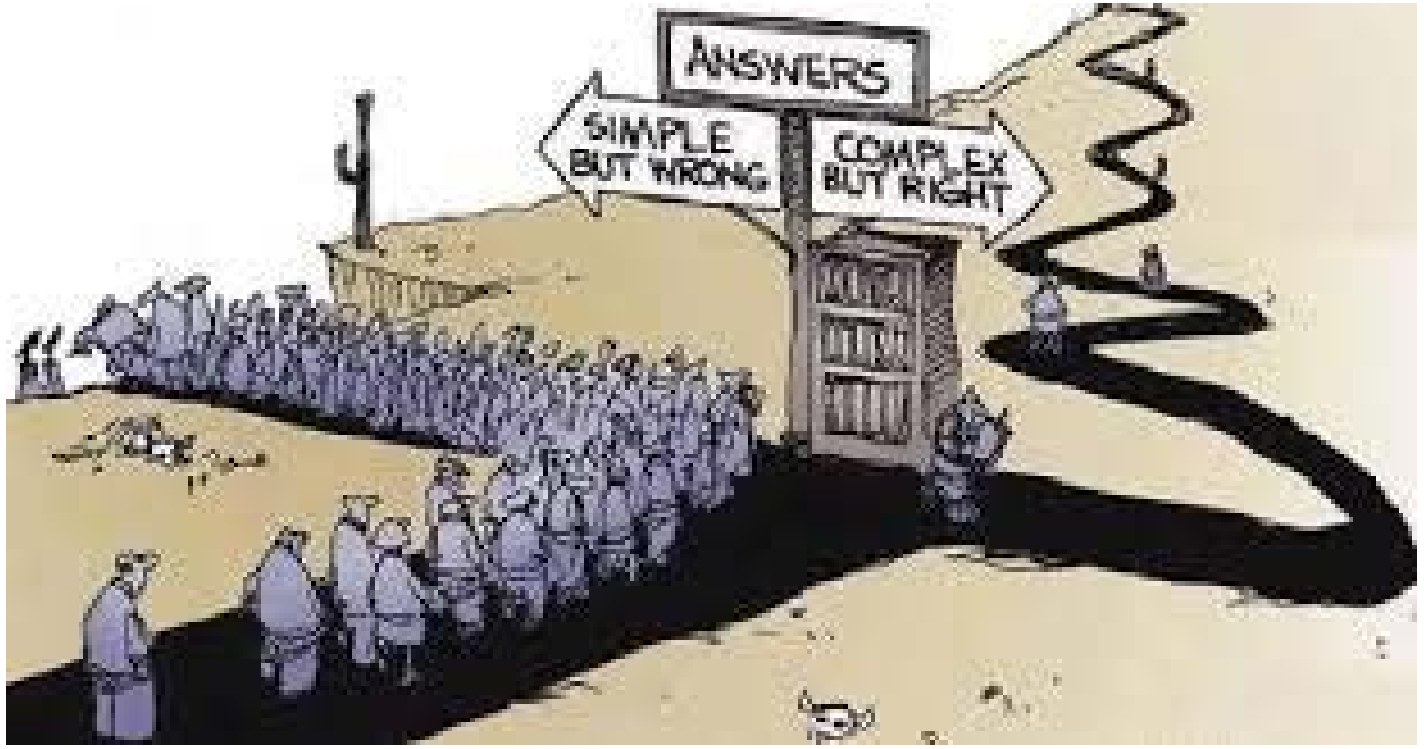
The committee will identify **barriers** to NIH-sponsored research, research **gaps**, and **promising areas** for future NIH-sponsored research that would benefit the greatest need

How we think about autoimmunity matters

Searching for a single unifying mechanism for AI diseases has blinded us to their complexity.



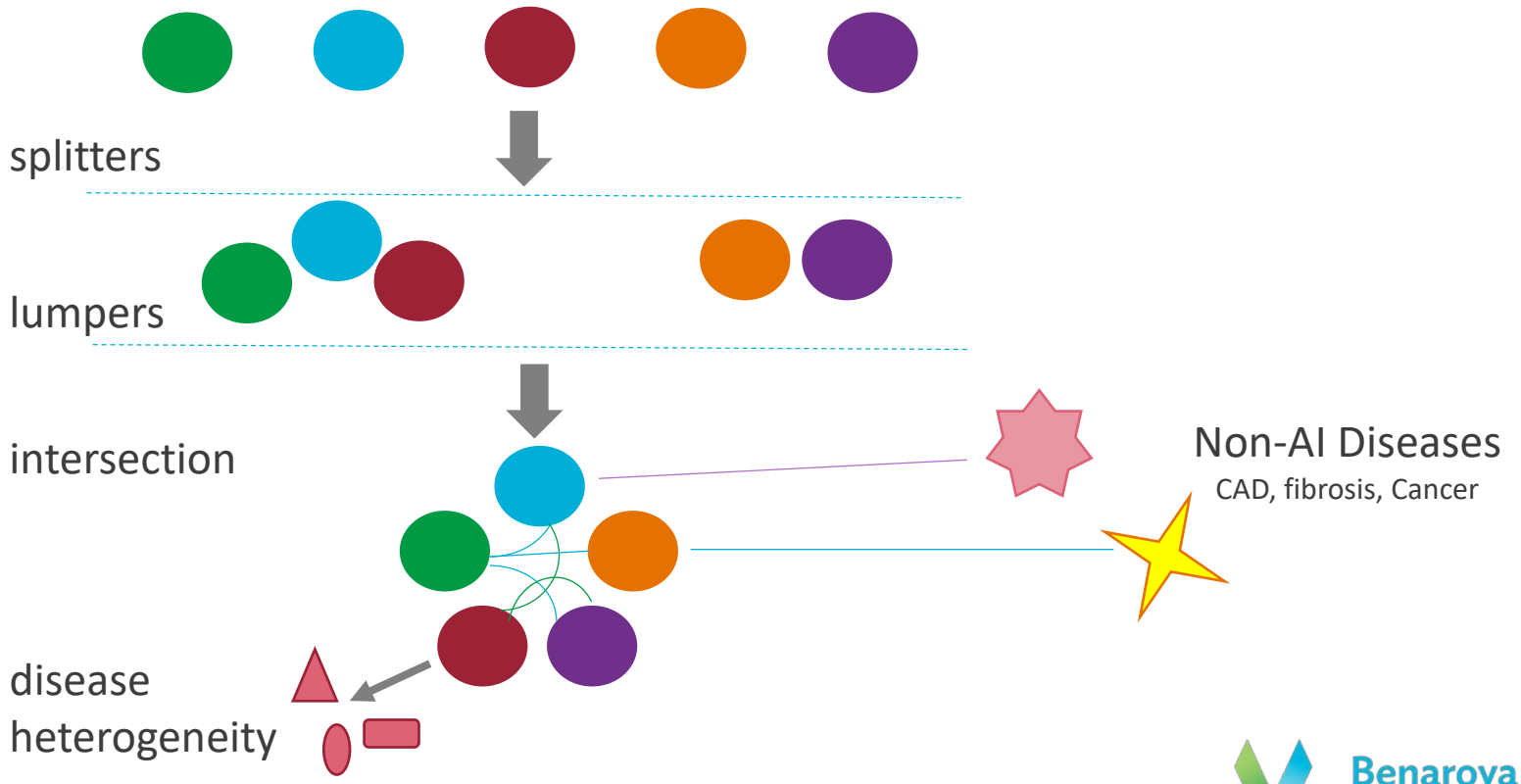
"When faced with two equally good hypotheses, always choose the simpler."



Benaroya Research Institute
Virginia Mason

How we think about autoimmunity matters

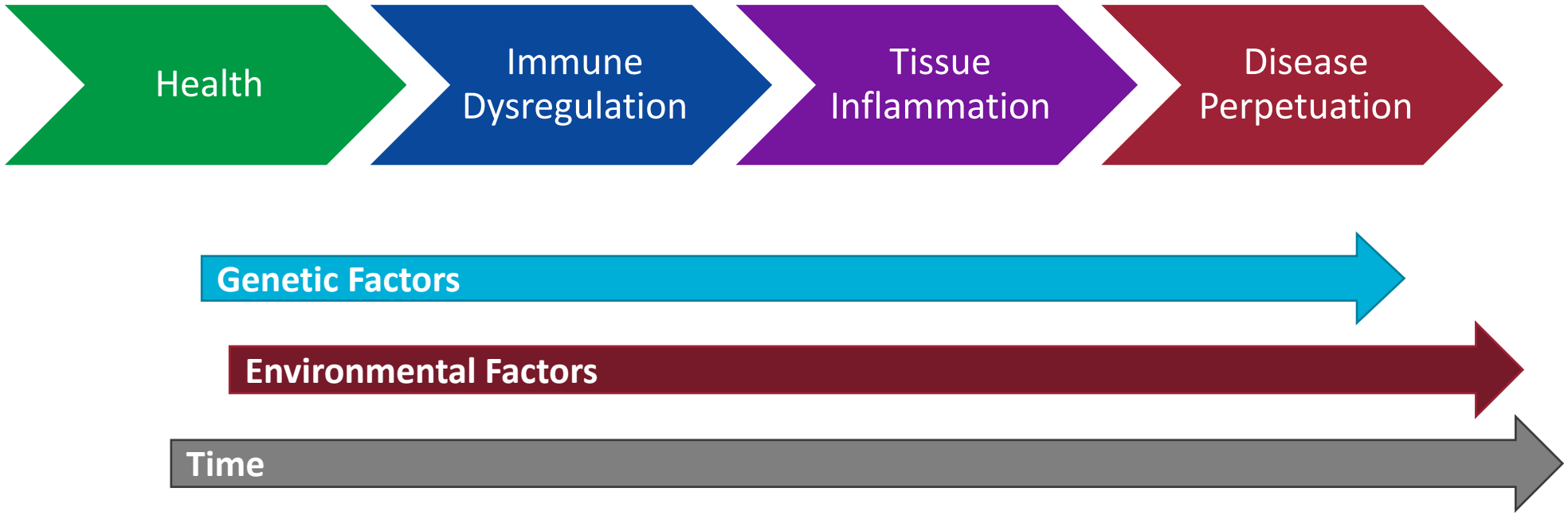
Acknowledging common features while also embracing disease heterogeneity is vital to moving research forward.



Benaroya Research Institute
Virginia Mason

Autoimmunity-

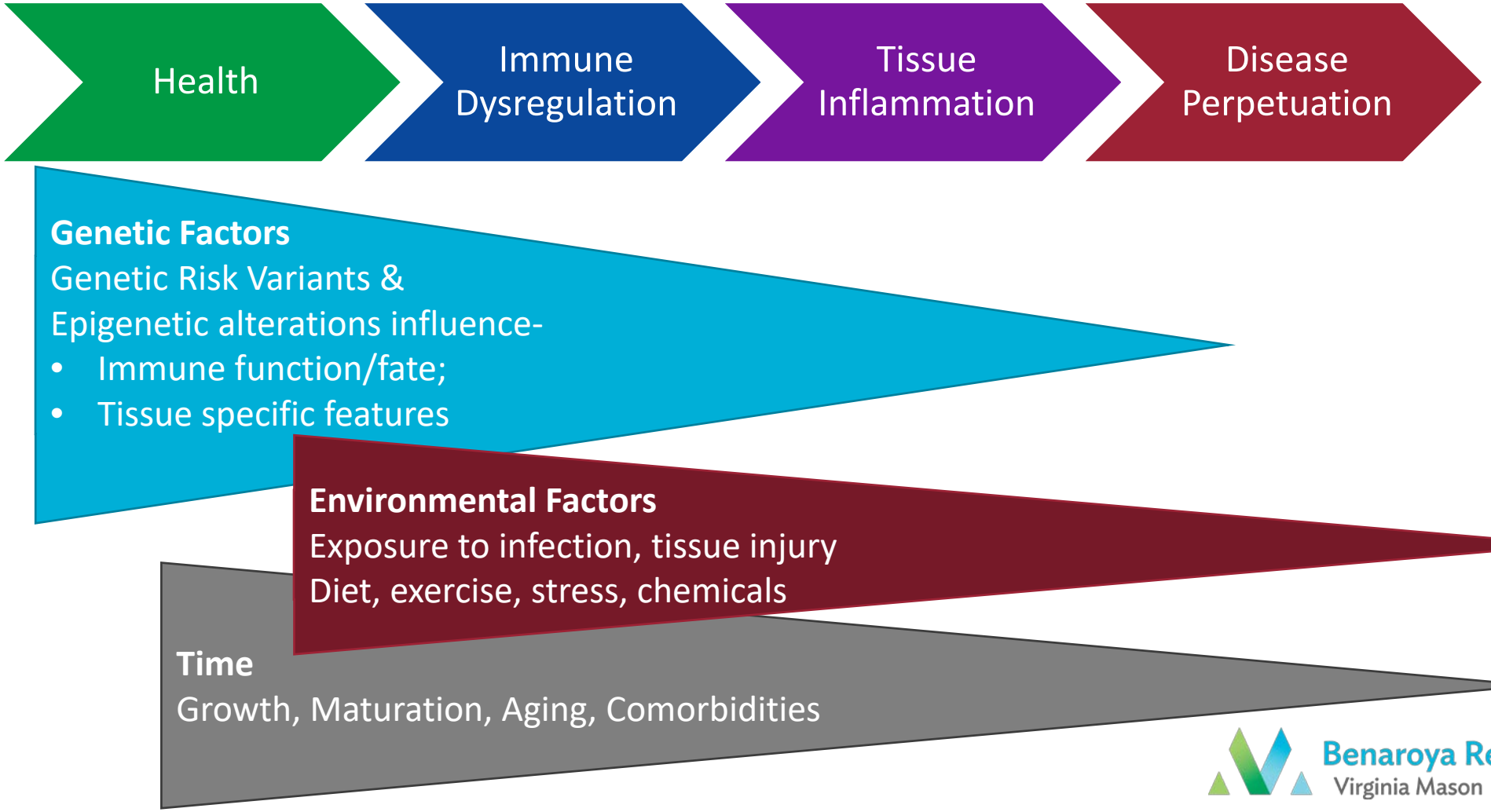
Failure of Immune Homeostasis and Tolerance



Benaroya Research Institute
Virginia Mason

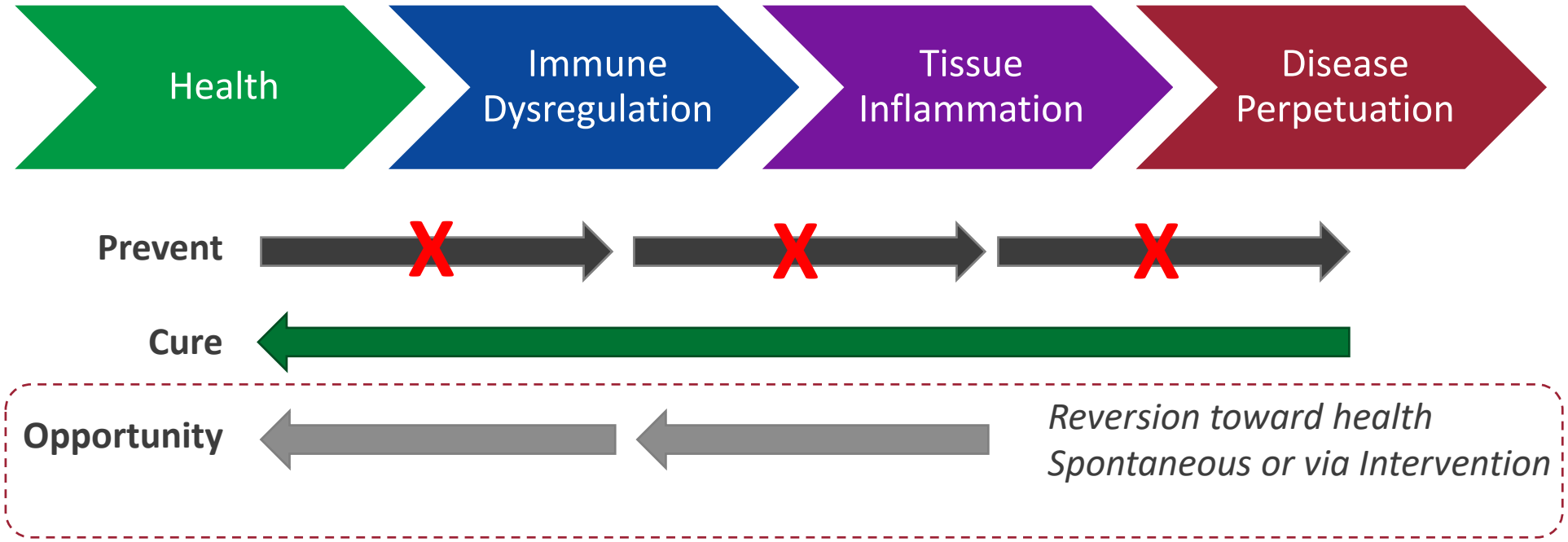
Autoimmunity-

Failure of Immune Homeostasis and Tolerance



Benaroya Research Institute
Virginia Mason

Autoimmunity- Our Challenge and Opportunities



Benaroya Research Institute
Virginia Mason

To induce tolerance in the setting of autoimmunity- we need to know why tolerance was broken

Leo Tolstoy, Anna Karenina

*"**Happy families** are all alike; every unhappy **family** is unhappy in its own way."*

Heathy immune systems are not all alike- when we look at individuals components.

But they achieve the same purpose

Autoimmune Diseases share common mechanisms.

But the complex interact between these mechanisms and tissue result in many different forms and presentation of disease.

Benaroya Research Institute
Virginia Mason

What are the road blocks to tolerance in autoimmunity

Good News

Mechanisms of failed tolerance are shared across autoimmune diseases

Genetic risk

Immunologic Functional features

Response to therapies

Bad News

The immune system is built to be redundant and complex

Multiple Mechanisms are involved in retaining tolerance

Modest alterations to several pathways in combination are the norm

complex multigenic diseases

Autoimmunity diseases arise over time, and the mechanisms that lead to failed tolerance by differ based on stage of disease; initiation, progression and perpetuation may be different

Where have we fallen short in research?

- Focused too frequently on individual diseases or disease models
  - Yet alterations in target tissue that may drive disease are ignored
- We fail to embrace and tackle complexity
  - Simple or novel hypothesis are favored
    - New approaches, models and analytical tools need to be established to tackle complexity
- We fail to include the aspect of time in our studies
  - Cross-sectional studies focused on established disease
    - Natural History studies yield novel insights into the mechanisms that drive each step of disease
      - Initiation through perpetuation
- We lack an understanding of what immune health looks like
  - Response to immune perturbation in health may uncover causes for failed tolerance

Successful Research Strategies

What can these teach us about how to move forward

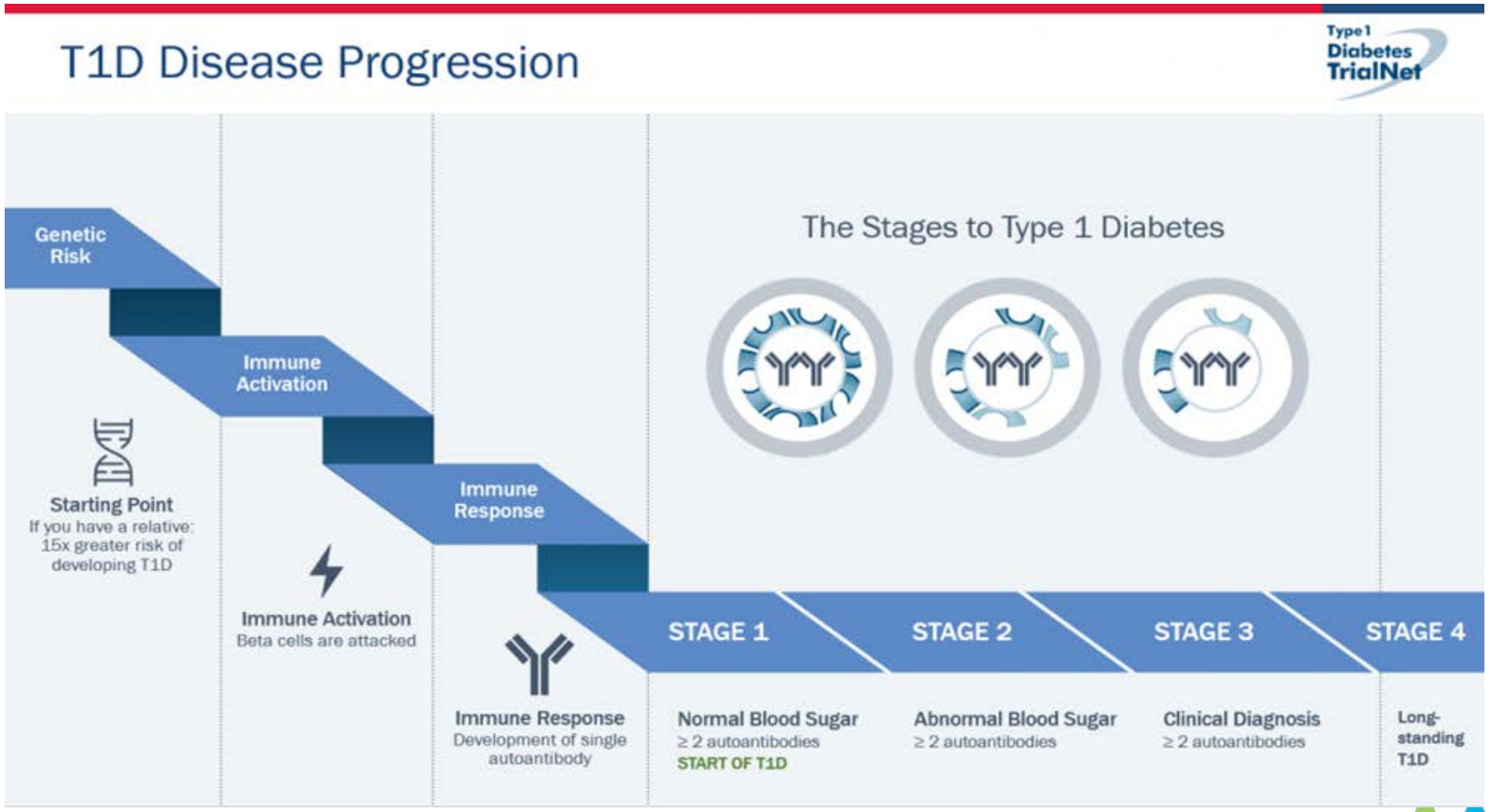
I will discuss

- Genetic Association to altered immune function to disease heterogeneity to therapy
- Mechanistic Studies of samples from clinical trials enlighten our understanding of response
- Studies in health and their implications for understanding autoimmunity

I won't be talking about:

- Advances in understanding fundamentals of Immune system through models
- Application of new tools to study the immune system
- Expanding understanding of microbiome

Genetic Risk is presumed to initiate and environmental trigger to propagate Autoimmunity

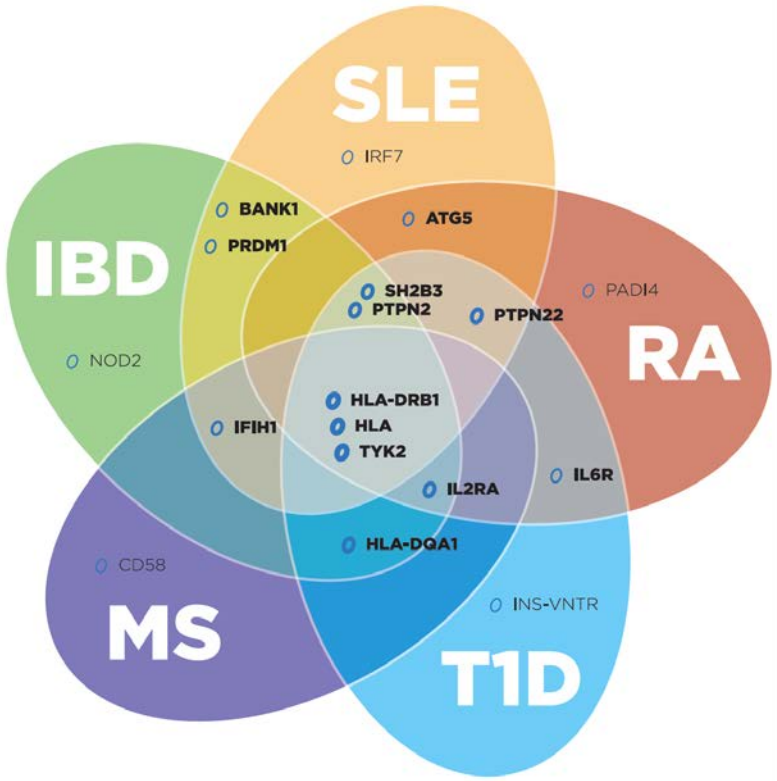


Benaroya Research Institute
Virginia Mason

Genetics has given us a window into autoimmunity

Genetic Risk are shared across autoimmune diseases

Good News



Bad News

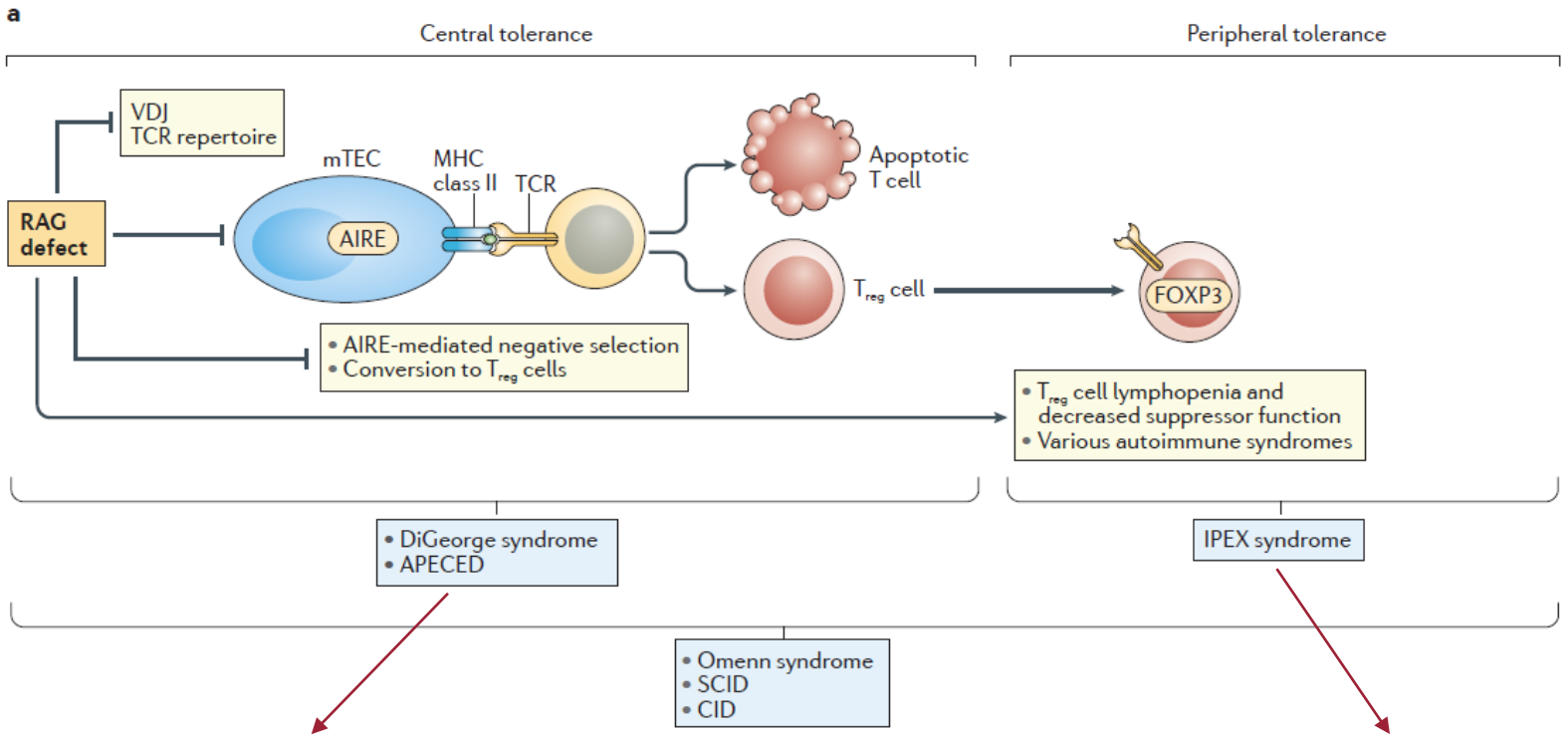
- Typically >100 genes associated with disease risk.
- Each gene confers only a modest increase in risk
- The genetics of autoimmune disease indicates complexity.
- Traits conferred by genetics are fixed

- Genes are predominantly but not exclusively involved in immune function

Benaroya Research Institute
Virginia Mason

Genetics has given us a window into autoimmunity

Rare genetic mutations have helped define pathways important in autoimmunity



Schmidt et al. 2018
Nature Reviews Rheumatology

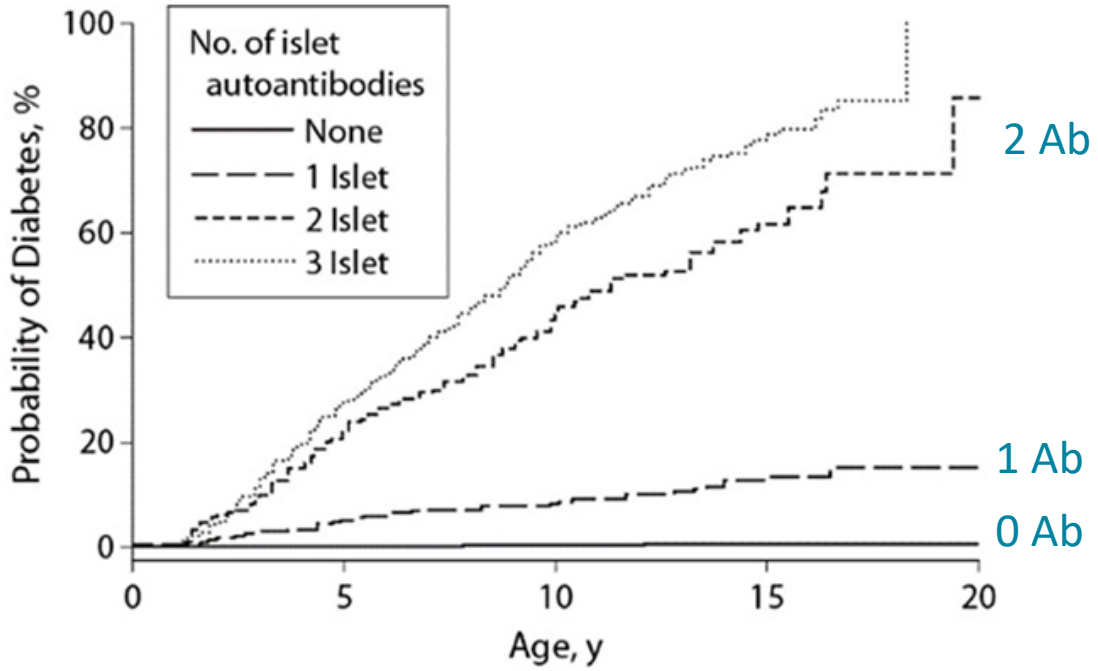
APECED patients played a central role in the recognition that T1D was an autoimmune disease.

IPEX patients demonstrate the powerful role of Treg in restraining autoimmunity

Bottazzo, G. F et al. 1974. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet
MacCuish, A. C. et al,. 1974. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. Lancet.

Natural History Studies have established the role of B cells in T1D

Autoantibodies specific for islet antigens predate disease and predict disease development



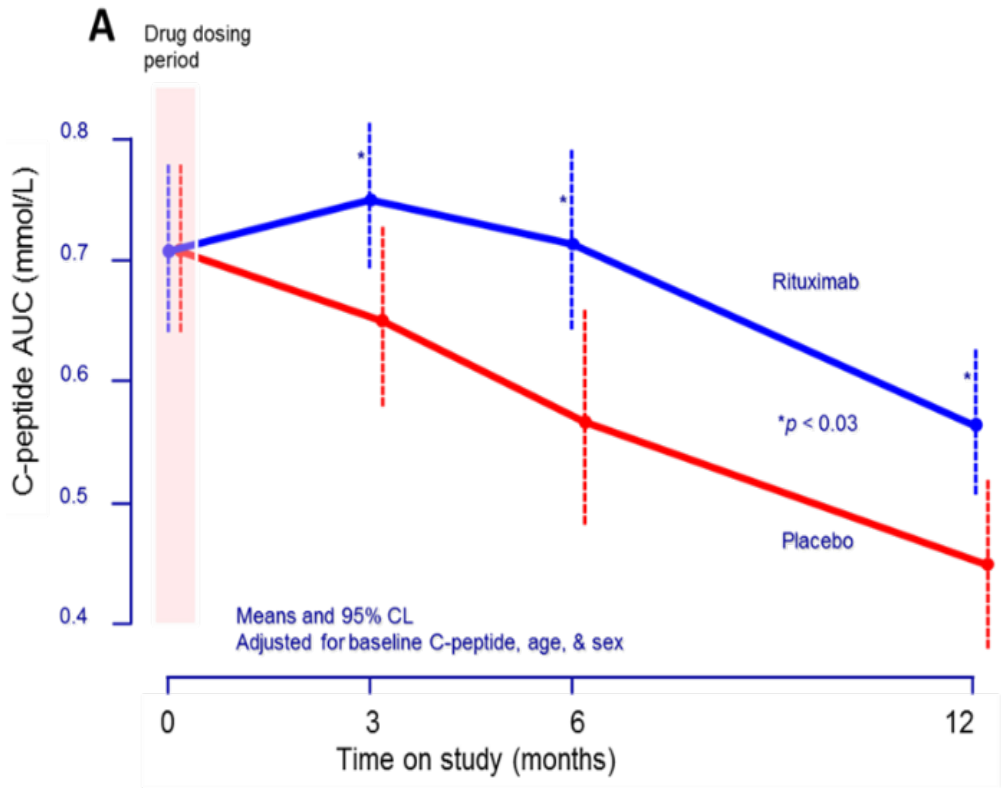
No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

Ziegler A et al JAMA. 2013

Benaroya Research Institute
Virginia Mason

B cell depletions in T1D

In new onset disease B cell depletion delays beta cell loss



- Insulin requirement remains but c-peptide loss is slowed
- Protection is not maintained
- Autoreactive B cells return after therapy
- Response is not uniform
- Response is better in the youngest subjects

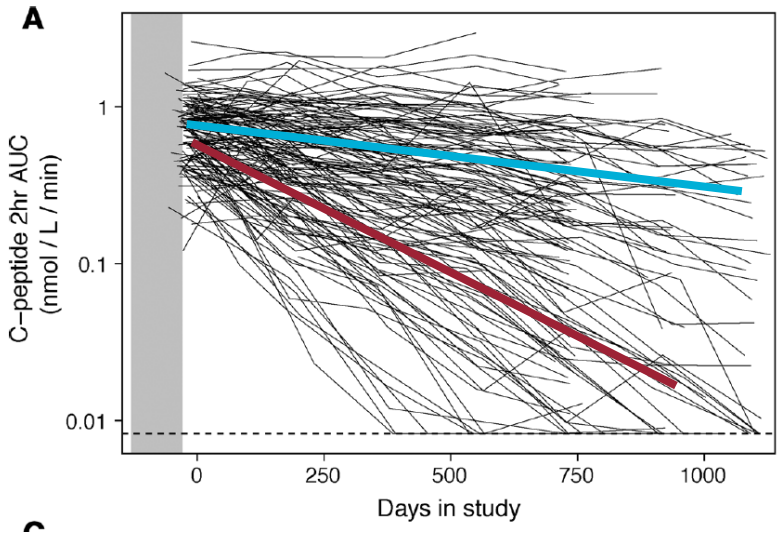
Pescovitz et al, NEJM 2009

Benaroya Research Institute
Virginia Mason

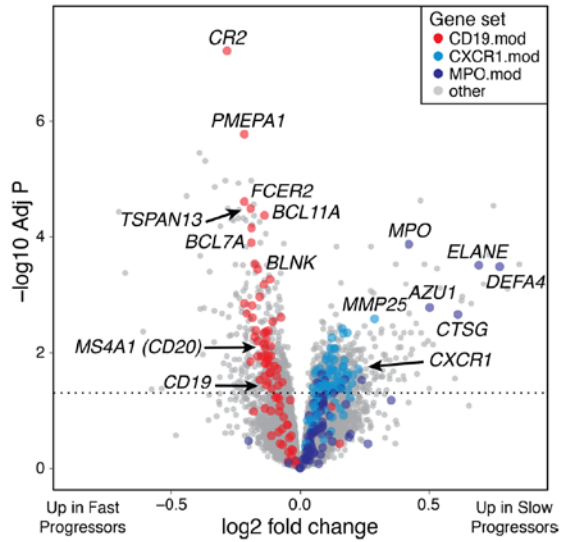
Natural History Studies Reveal Heterogeneity in T1D

Role of B cells in T1D progression in the young

C-peptide loss in T1D patients shows wide variation among and within subjects over time.
Answer: linear regression models of C-peptide AUC



Whole blood RNAseq profiles differ betweenT1D subjects with fast and slow progression



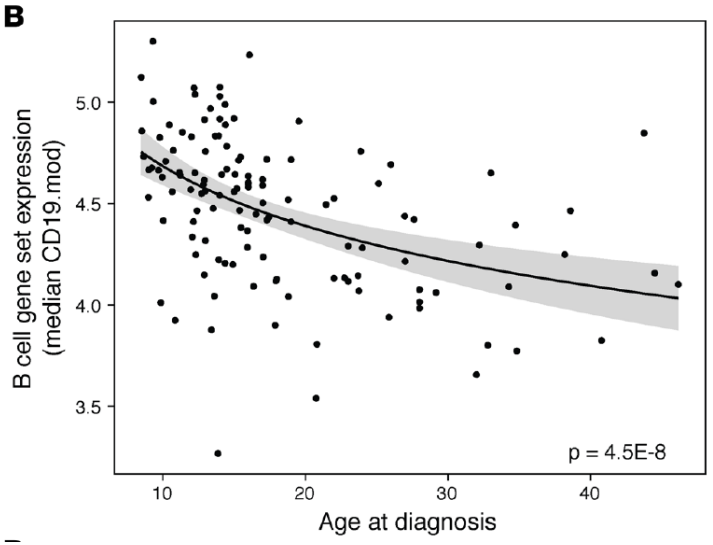


Figure 2. Whole blood gene expression profiles differ between T1D subjects with fast and slow loss of C-peptide.

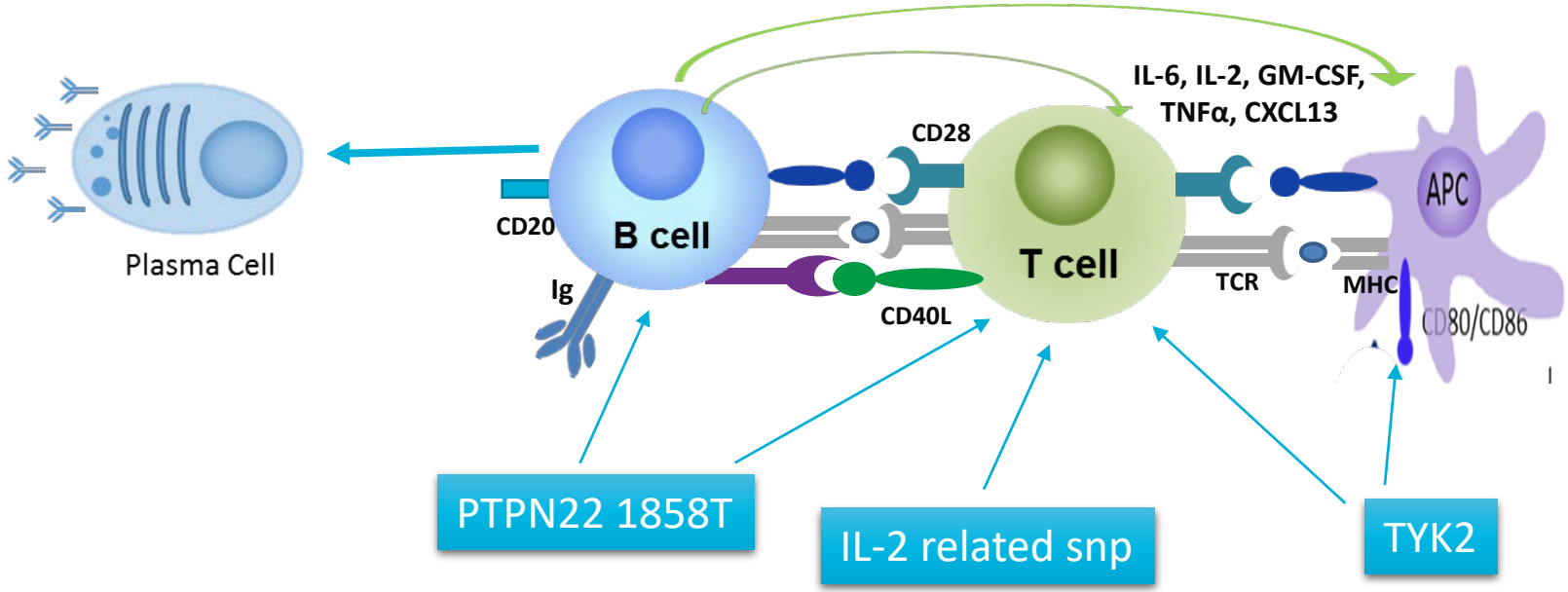
- **Rate of c-peptide loss is faster in young.**
- **B cell signatures are higher in young individuals.**
- **Rate of loss of C-peptide is associated with B cell signature in the young.**

Dufort Met al. 2019 JCI Insight

Benaroya Research Institute
Virginia Mason

Genetics of T1D expands our understanding of this process

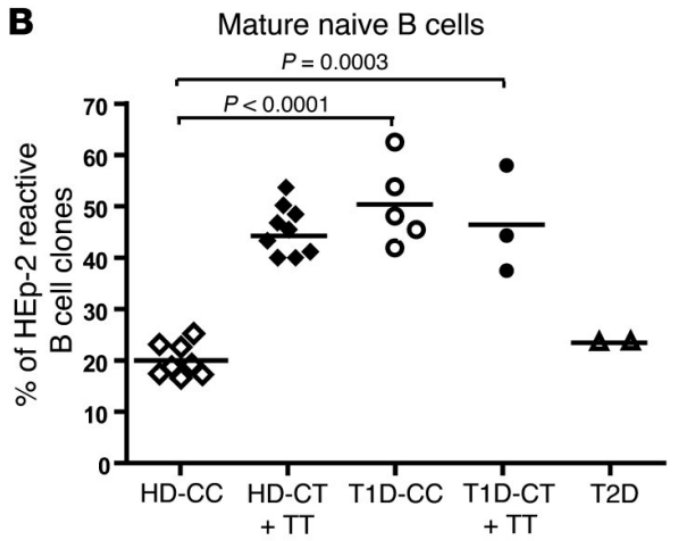
Common genetic variants associated with T1D promote B cell autoimmunity

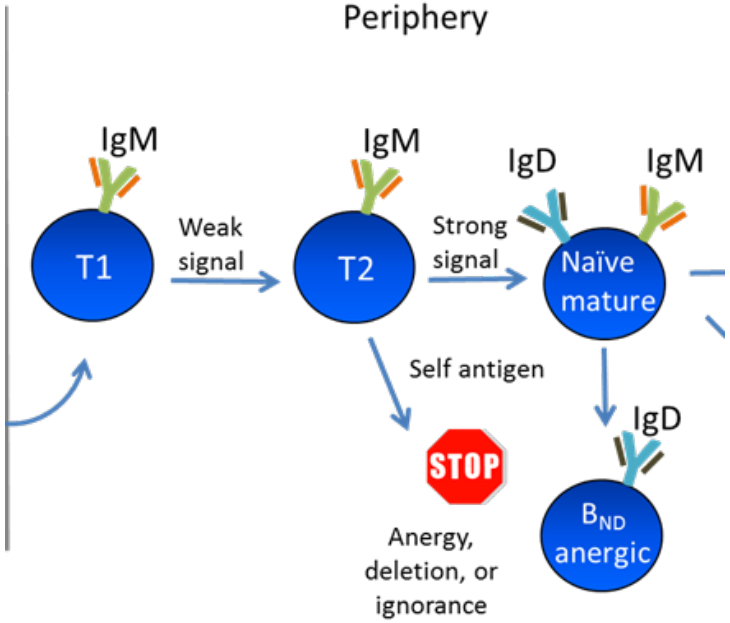


- PTPN22 1858T SNP is associated with multiple autoimmune diseases
- TYK2 Pro1104Ala variant (rs34536443) is associated with protection for autoimmune disease
- *IL2RA and PTPN2(rs1893217)* , IL-2 related SNPs are associated with multiple autoimmune diseases

Benaroya Research Institute
Virginia Mason

The PTPN221858T variant is associated with alterations in B cell development in the periphery that is also present in T1D.



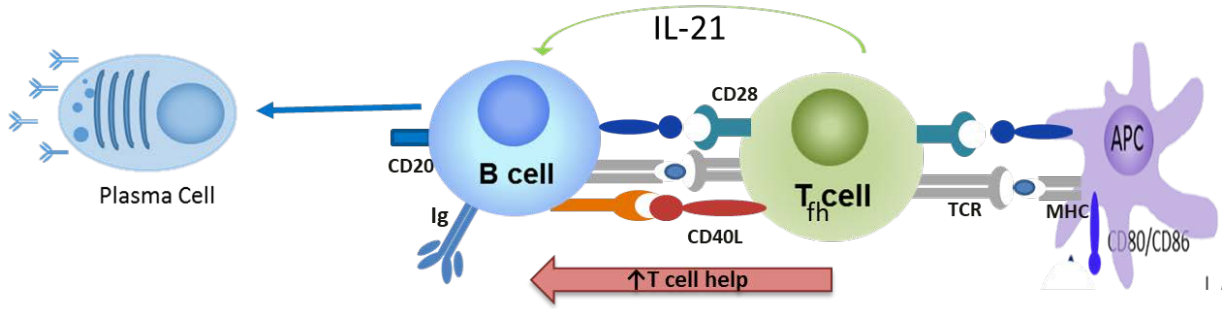


PTPN22 risk and T1D naïve B cells are enriched for autoreactive B cells

Menard et al JCI 2011

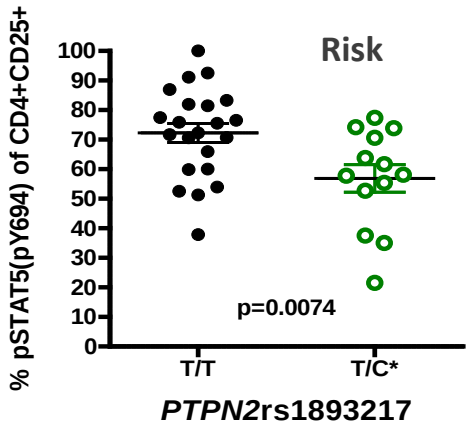
Benaroya Research Institute
Virginia Mason

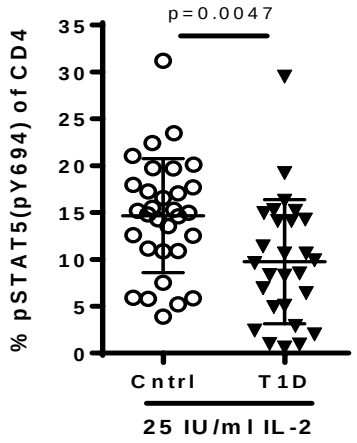
Common genetic variants associated with T1D promote B cell autoimmunity- IL-2 signaling linked to Tfh

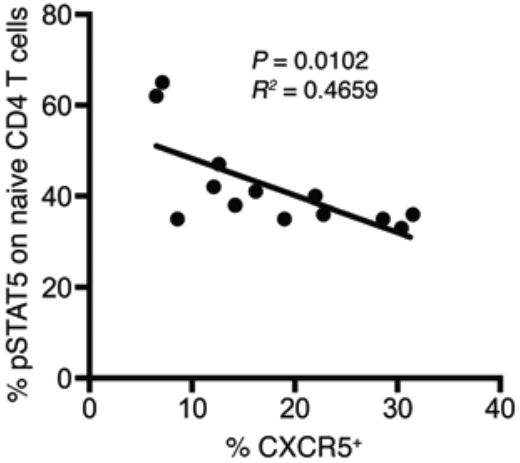


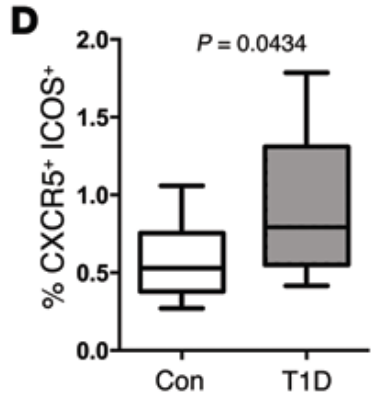
CD4 T cells of risk snps and T1D subjects have impaired IL-2 response

CD4 T cells of T1D subjects have impaired IL-2 response









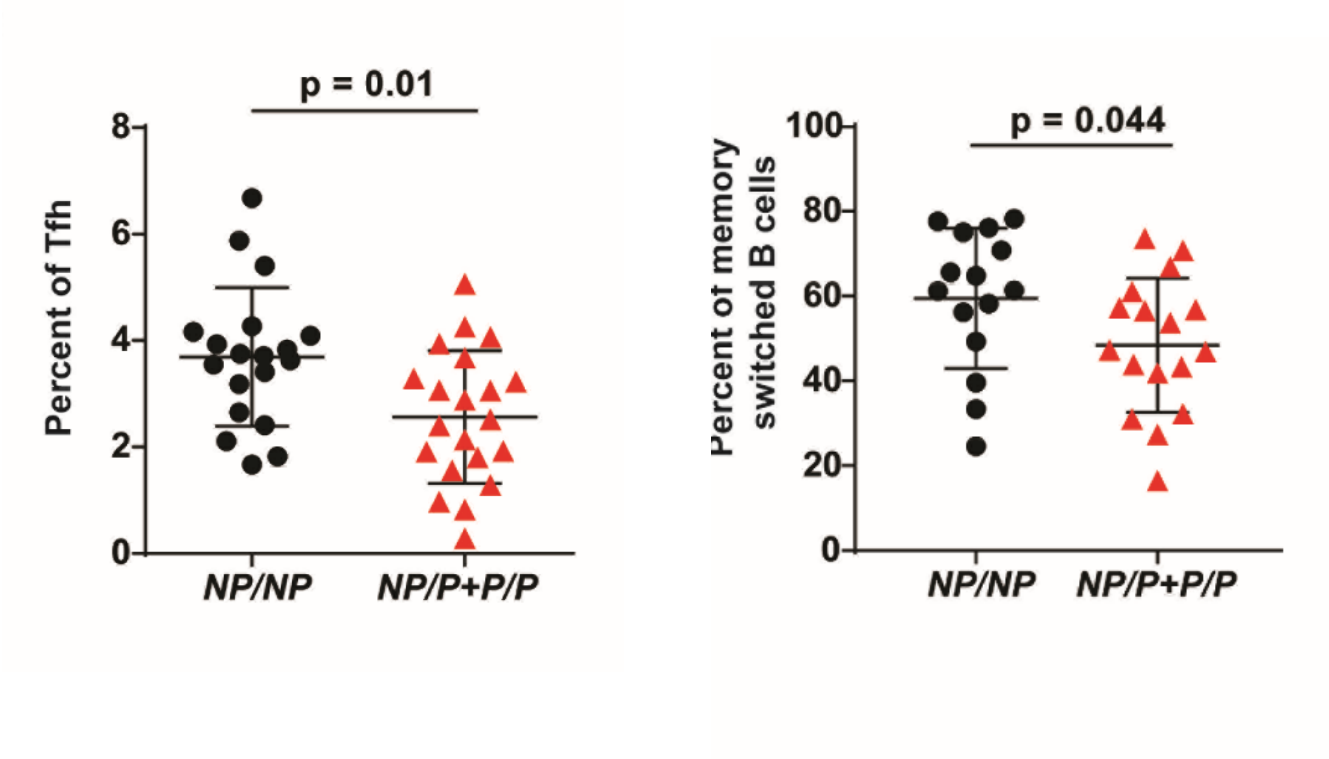
Cerosaletti et al. PLOS ONE 2013
Long Diabetes 2010

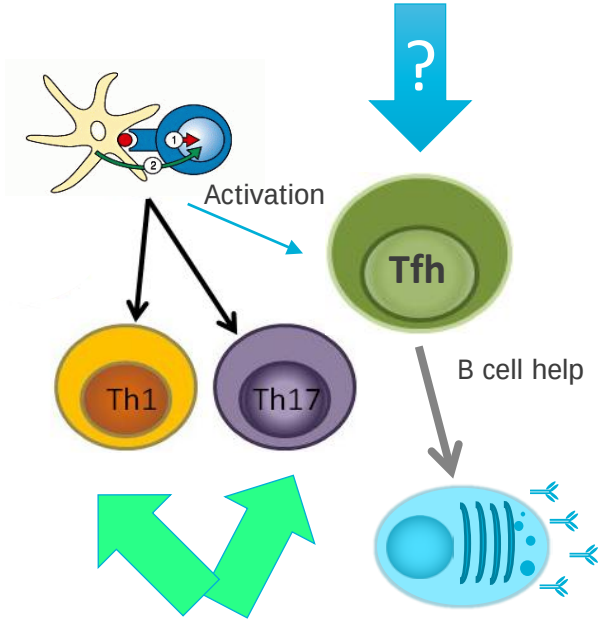
Kenefeck R. et al JCI 2014

Benaroya Research Institute
Virginia Mason

Common genetic variants associated with T1D promote B cell autoimmunity- TYK2 variants influence Tfh

TYK2 protective variant is associated with a decrease in Tfh and decreased switched memory B cells.





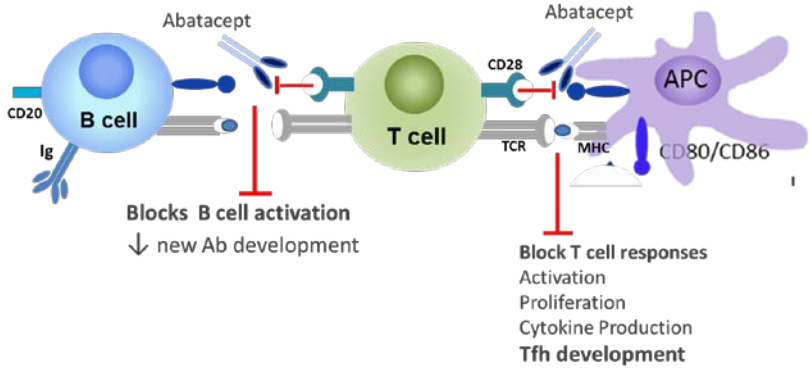
Dendrou et al., Sci Transl Med 2016

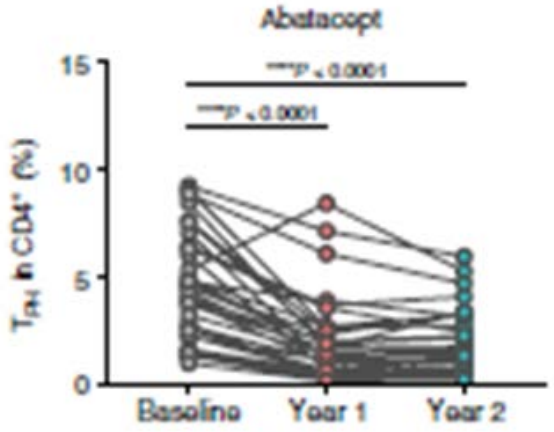
Gorman, Hundhausen et al Frontiers 2018

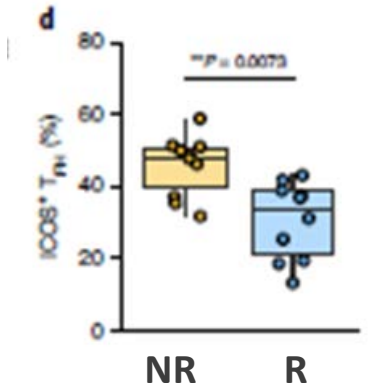
Benaroya Research Institute
Virginia Mason

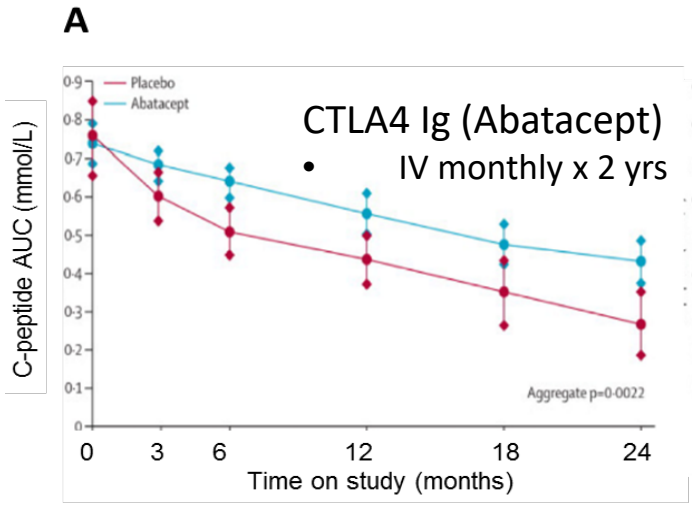
Predictive Biomarker Identified in T1D

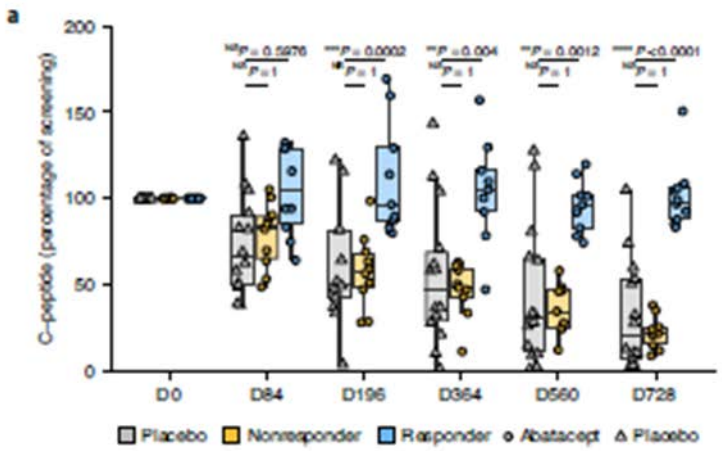
Abatacept responders have low Tfh at baseline

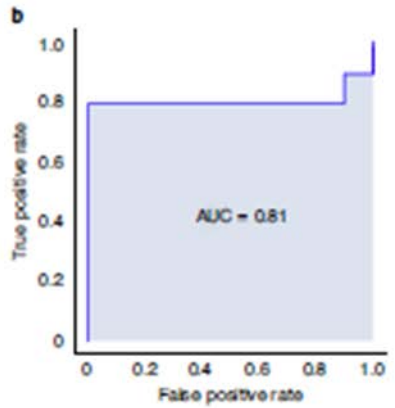












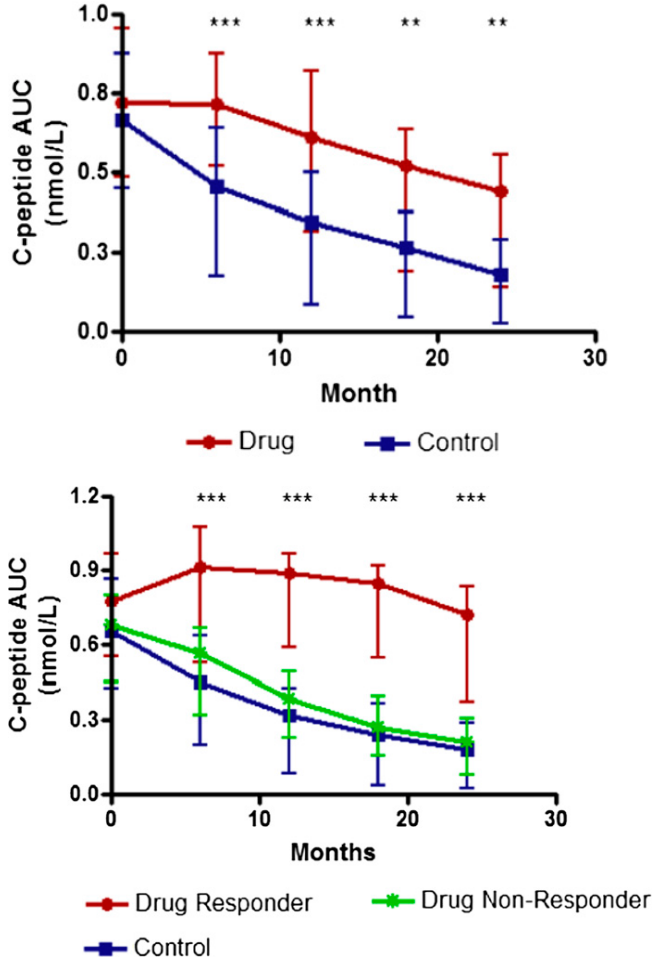
Orban et al, Lancet 2011

Edner N et al Nature Medicine 2020

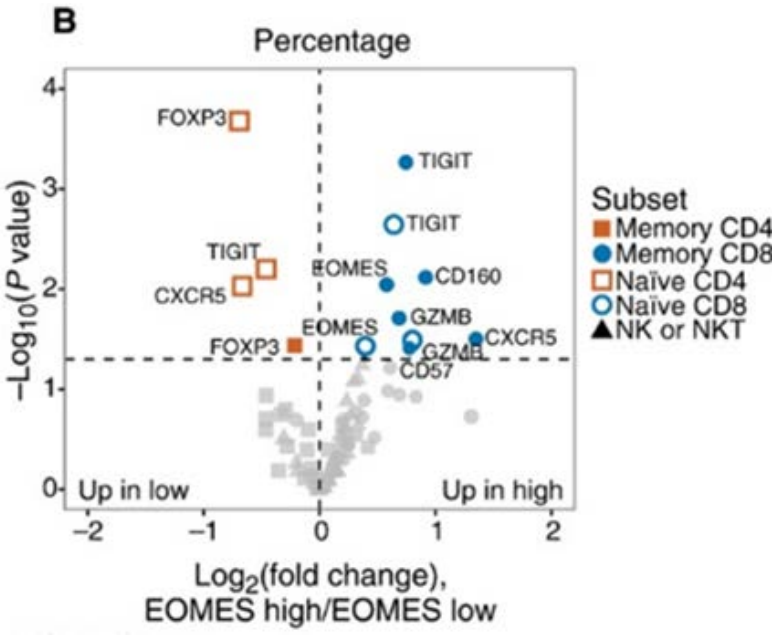
Benaroya Research Institute
Virginia Mason

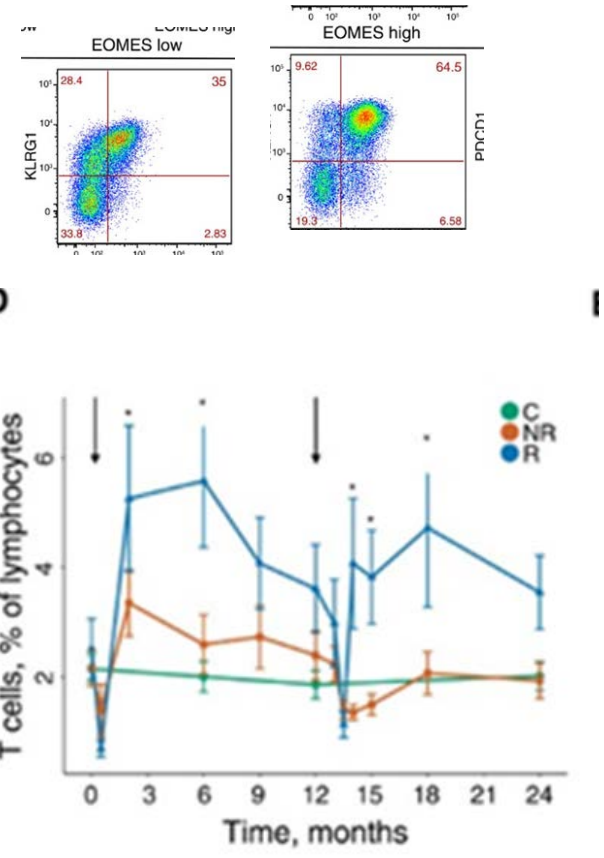
Mechanistic Studies identify a new cell involved in maintenance of tolerance

Teplizumab (Anti-CD3 mAb) Preserves beta cell function in Patients With T1D



Herold KC et al Diabetes 62:3766–3774, 2013

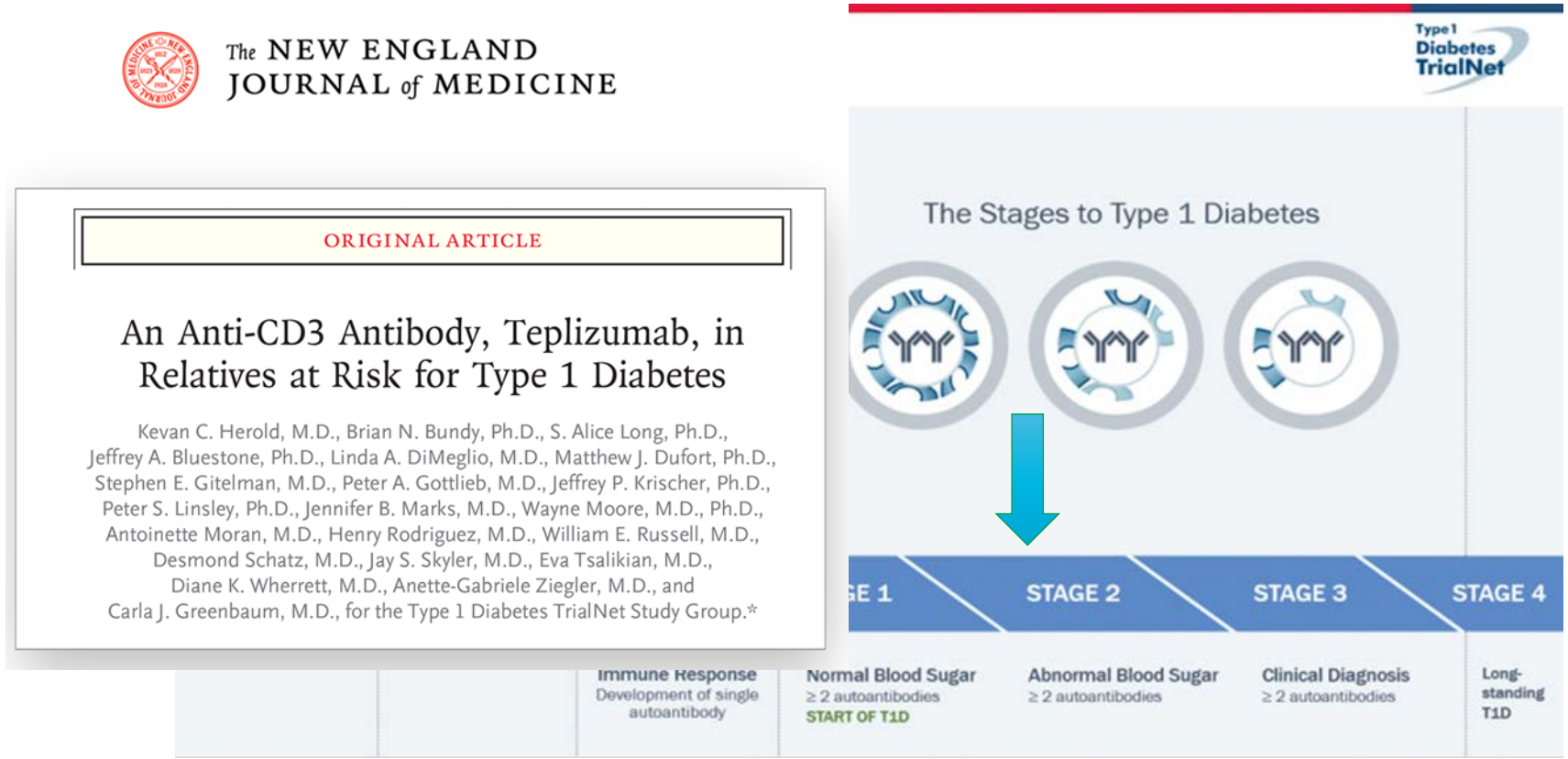




S. Alice Long et al. Sci. Immunol. 2016;1:eaai7793

Benaroya Research Institute
Virginia Mason

Prediction could lead to prevention



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group.*

Type 1 Diabetes TrialNet

The Stages to Type 1 Diabetes

STAGE 1 | STAGE 2 | STAGE 3 | STAGE 4

Immune Response
Development of single autoantibody

Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

Abnormal Blood Sugar
≥ 2 autoantibodies

Clinical Diagnosis
≥ 2 autoantibodies

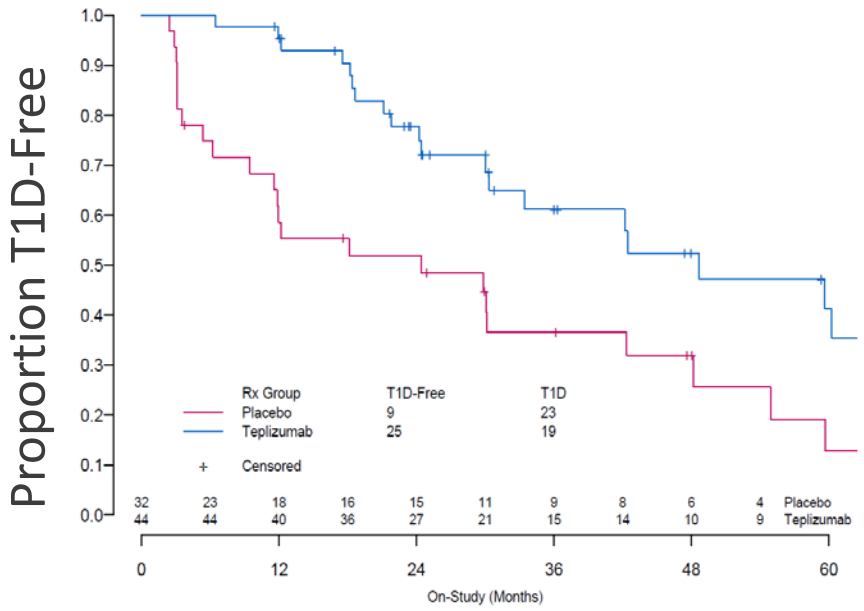
Long-standing T1D

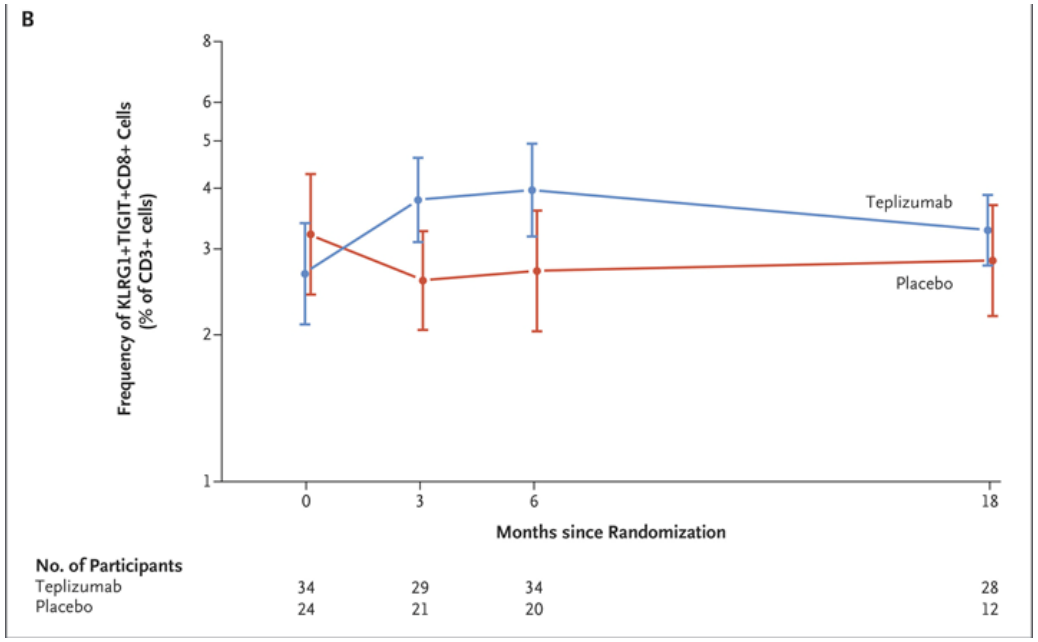
Ziegler A et al JAMA. 2013 J

Benaroya Research Institute
Virginia Mason

Prediction and possibly prevention

Mechanistic studies confirm exhaustion profile is protective





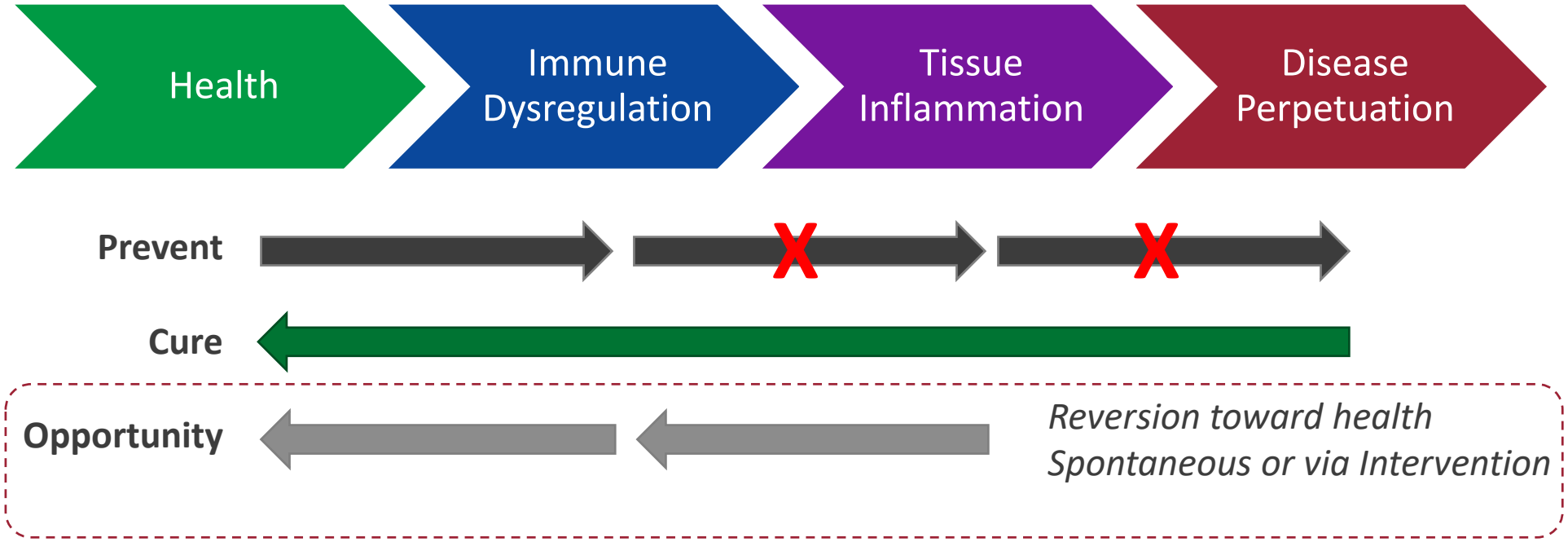
- T1D was diagnosed in **19 (43%)** in teplizumab and **23 (72%)** in placebo groups.
- The median time to diabetes increased in teplizumab as compared with placebo groups from 24 to 48 mos.

Type 1 Diabetes TrialNet

Benaroya Research Institute
Virginia Mason

Autoimmunity- Our Challenge and Opportunities

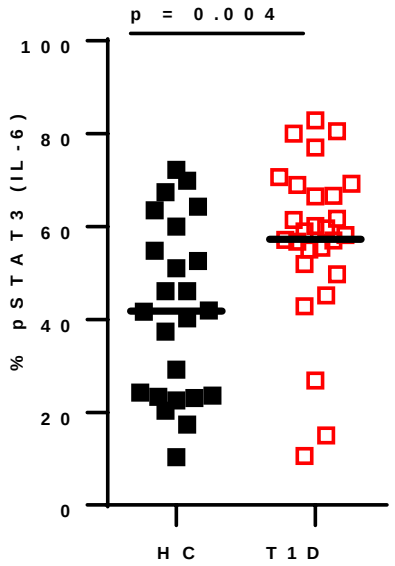
To attain a cure we need to understand the target- healthy immune system

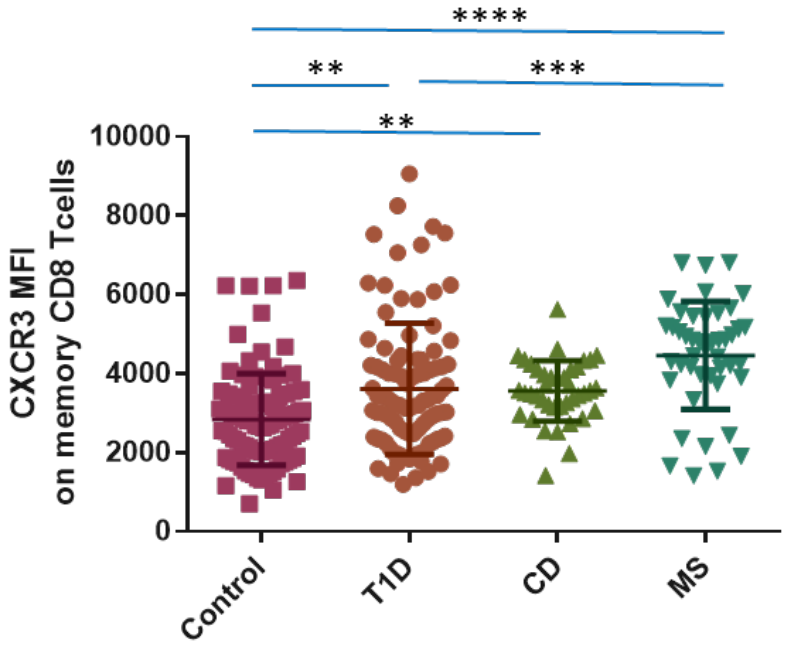


Benaroya Research Institute
Virginia Mason

Broad Immune Heterogeneity is Seen in Health

Heterogeneity of individuals parameters is found in Healthy AI subjects



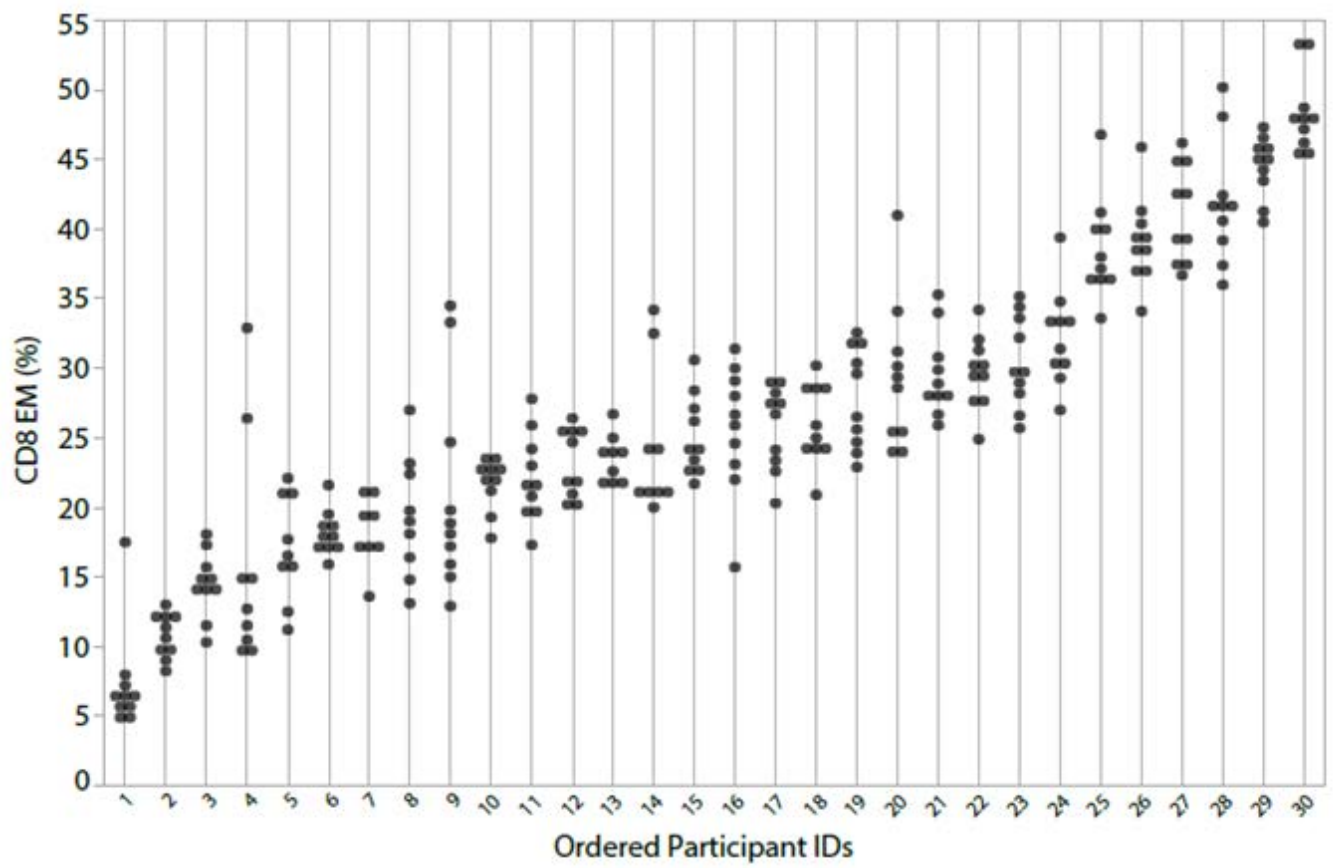


- There is overlap between what is seen in healthy subjects and immune diseases.

Benaroya Research Institute
Virginia Mason

An Individual's Immune Profile is Unique and Stable

Example of Intra and Inter- individual variation over time

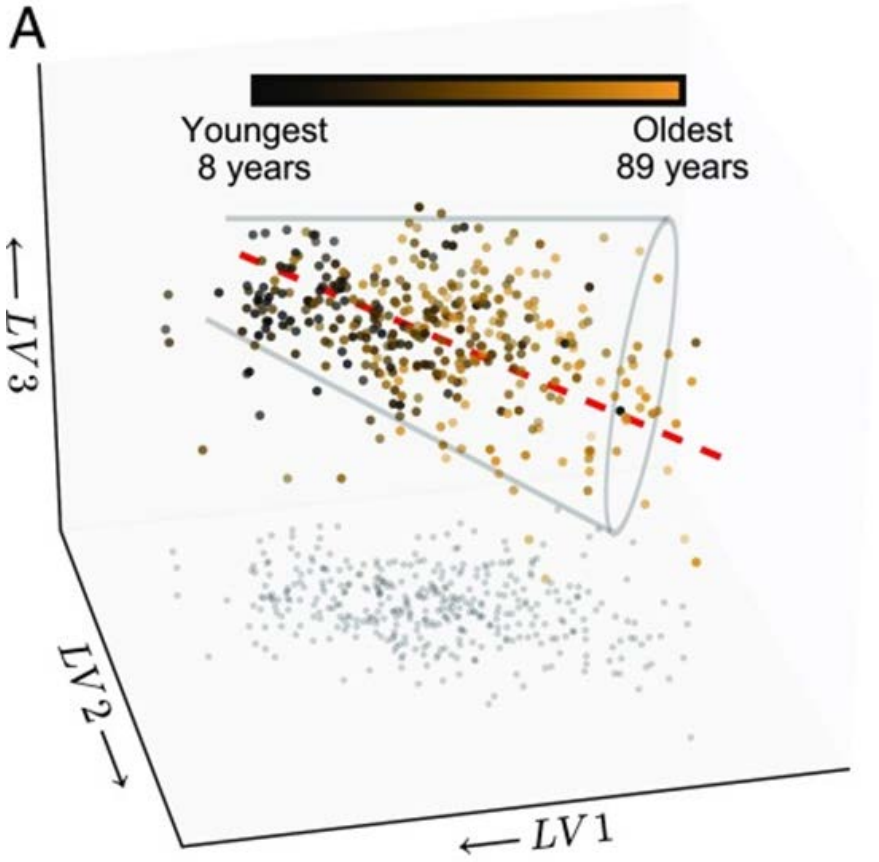


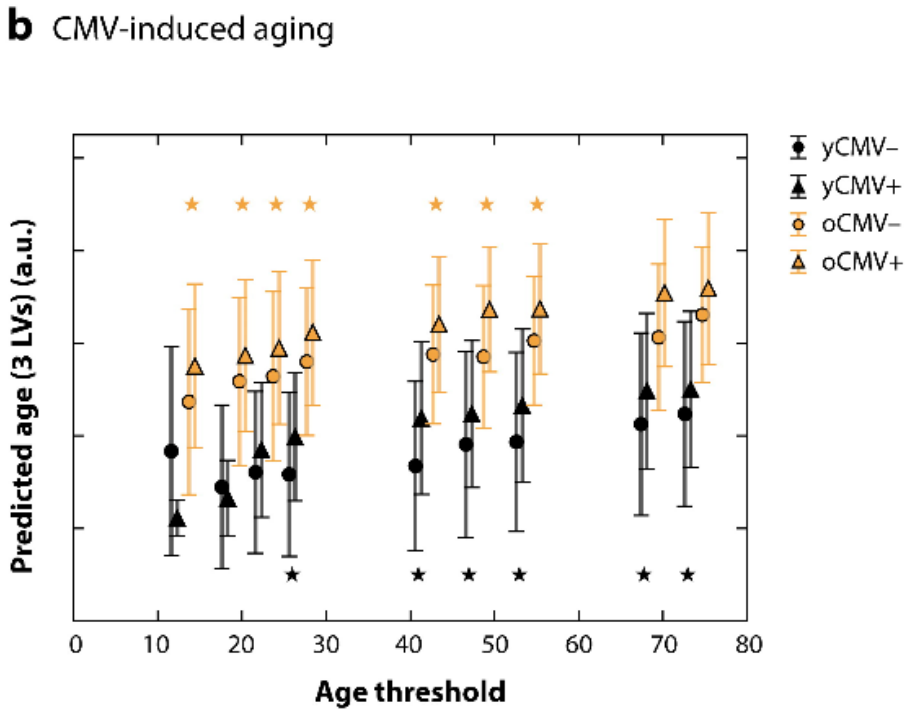
Speak et al Frontiers Immunol 2019

Benaroya Research Institute
Virginia Mason

Immune Experience is a Source of Immune Heterogeneity

Age and CMV contribute to variations across individuals

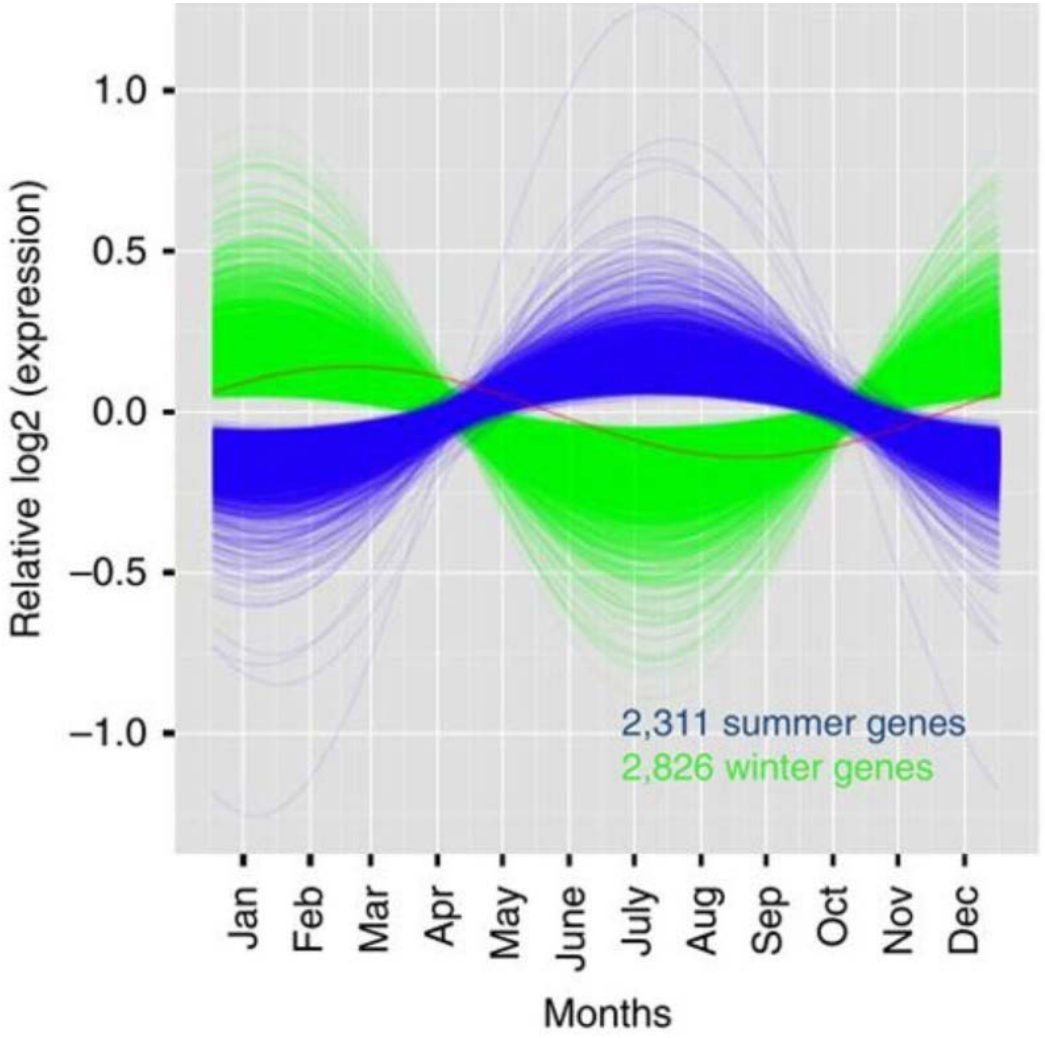




Kaczorowski KJ et al PNAS 2017

Benaroya Research Institute
Virginia Mason

Seasonal Variation as a Source of Immune Heterogeneity



nature COMMUNICATIONS

Article | OPEN | Published: 12 May 2015

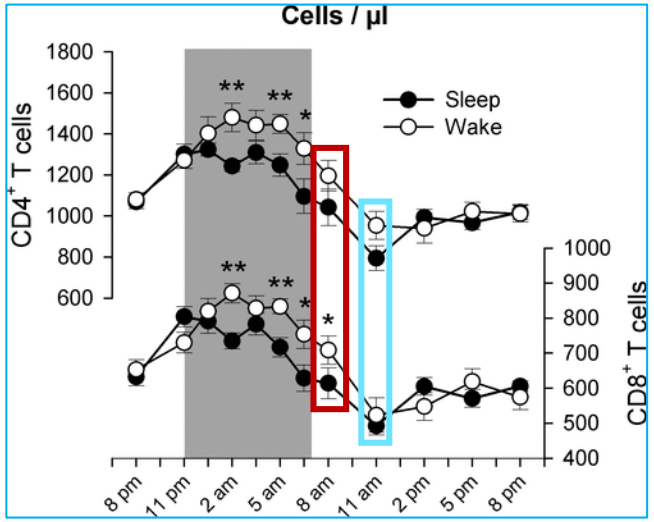
Widespread seasonal gene expression reveals annual differences in human immunity and physiology

Xaquin Castro Dopico, Marina Evangelou, Ricardo C. Ferreira, Hui Guo, Marcin L. Pekalski, D
J. Smyth, Nicholas Cooper, Oliver S. Burren, Anthony J. Fulford, Branwen J. Hennig, Andrew M
Prentice, Anette-G. Ziegler, Ezio Bonifacio, Chris Wallace & John A. Todd

Nature Communications **6**, Article number: 7000 (2015) | Download Citation

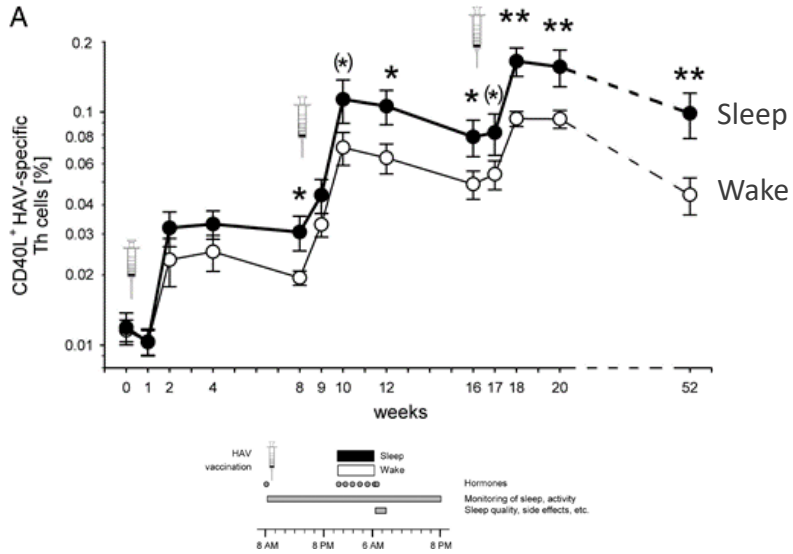
Benaroya Research Institute
Virginia Mason

Diurnal Variation as a Source of Immune Heterogeneity



Nocturnal sleep uniformly reduces numbers of different T-cell subsets in the blood of healthy men.

Am J Physiol Regul Integr Comp Physiol. 2016

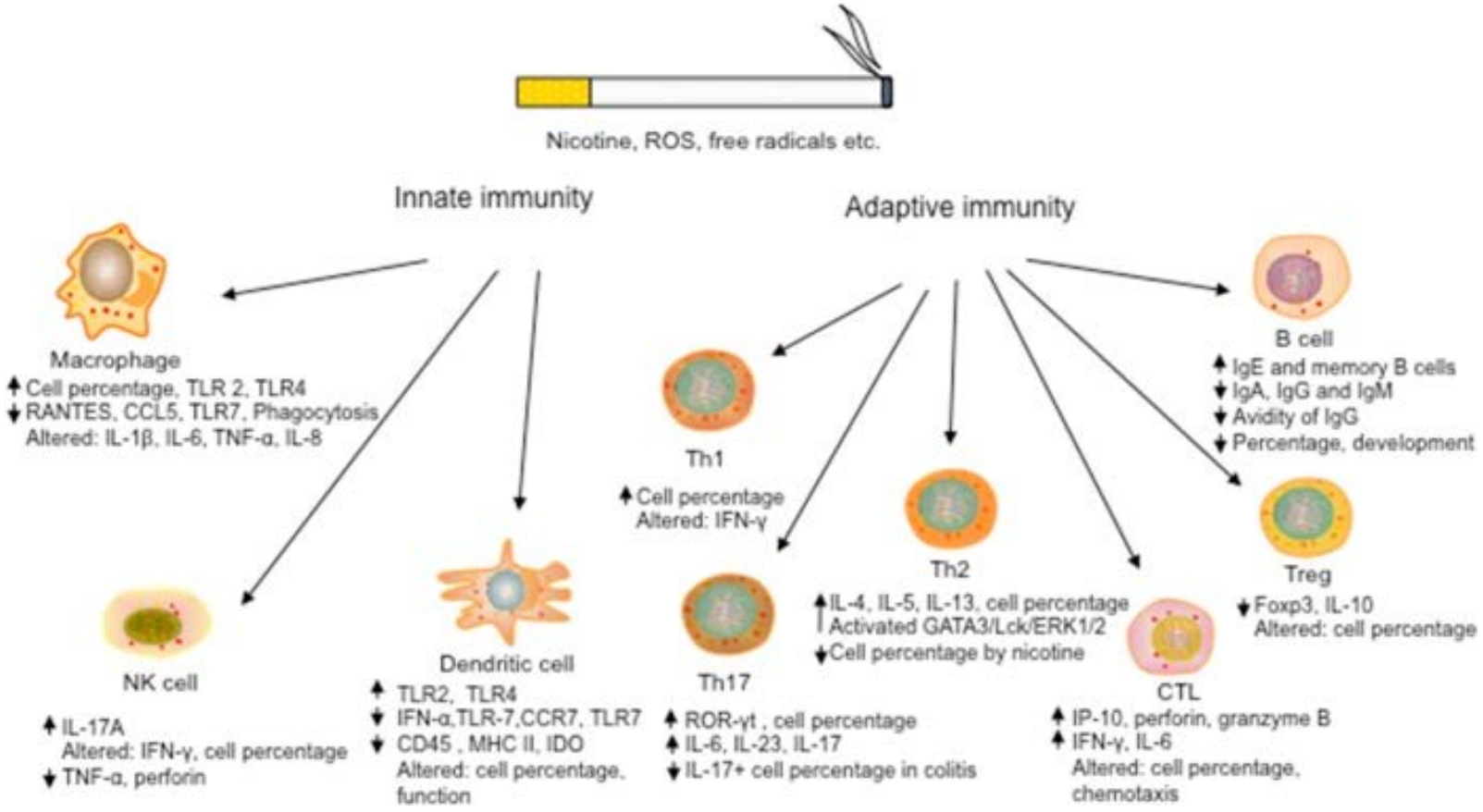


Sleep after Vaccination Boosts Immunological Memory

Tanja Lange et al J Immunol, 2011,

Environment and Lifestyle are Sources of Immune Heterogeneity

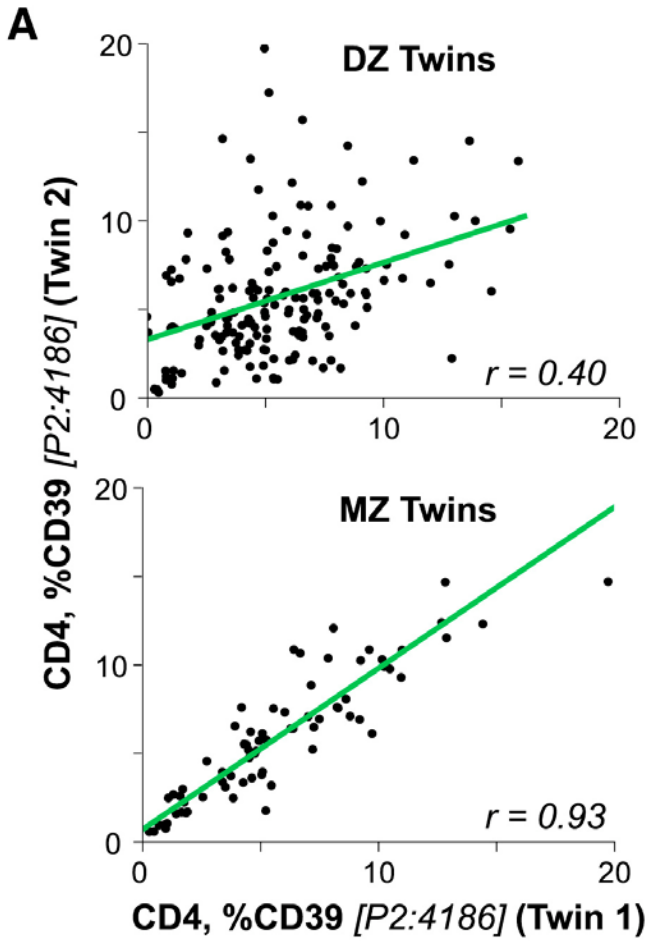
Smoking a lifestyle choice that influences the immune system



Benaroya Research Institute
Virginia Mason

Teasing apart the influence of genes and environment

Twin studies control for environment in context of genetics



Resource

Cell

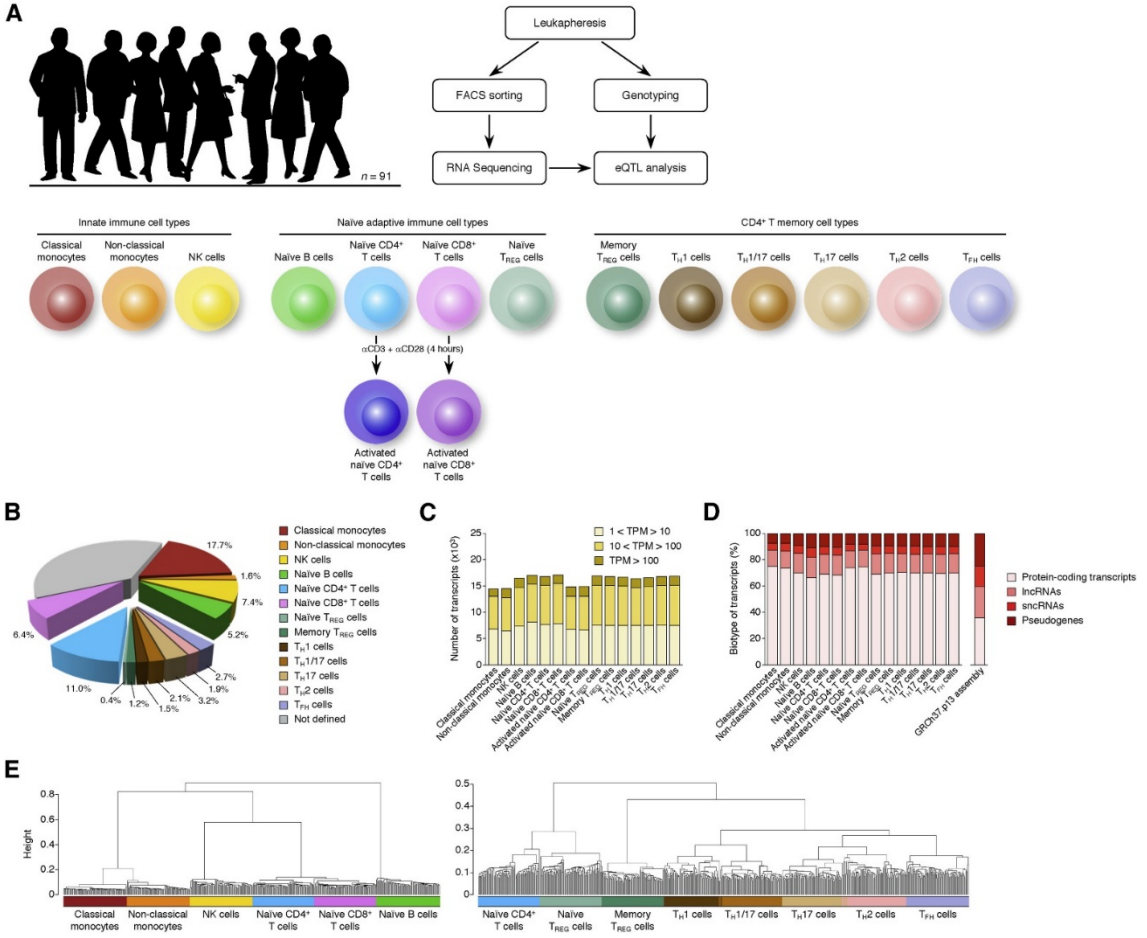
The Genetic Architecture of the Human Immune System: A Bioresource for Autoimmunity and Disease Pathogenesis

Mario Roederer,[1,7,*] Lydia Quaye,[2,7] Massimo Mangino,[2,4,7] Margaret H. Beddall,[1] Yolanda Mahnke,[1,5] Pratip Chattopadhyay,[1] Isabella Tosi,[3,4] Luca Napolitano,[3] Manuela Terranova Barberio,[3] Cristina Menni,[2] Federica Villanova,[3,4] Paola Di Meglio,[3,6] Tim D. Spector,[2,8,*] and Frank O. Nestle[3,4,8]

[1]ImmunoTechnology Section, Vaccine Research Center, NIAID, NIH, Bethesda, MD 20892, USA
[2]Department of Twin Research & Genetic Epidemiology, King's College London, London SE1 7EH, UK
[3]Cutaneous Medicine Unit, St. John's Institute of Dermatology, King's College London, London SE1 9RT, UK
[4]NIHR Biomedical Research Centre at Guy's and St. Thomas' NHS Foundation Trust, London SE1 9RT, UK
[5]Present address: Translational and Correlative Sciences Laboratory, Translational Research Program, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, PA 19104, USA

Benaroya Research Institute
Virginia Mason

Genetic and epigenetic factors contribute to immune heterogeneity

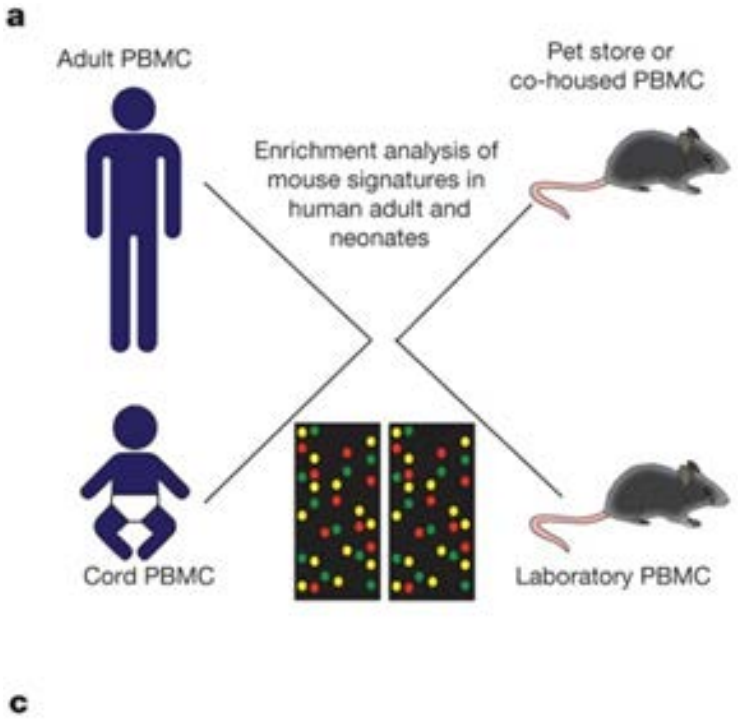


Cell 2018 1751701-1715.e16DOI: (10.1016/j.cell.2018.10.022)

Benaroya Research Institute
Virginia Mason

Murine Models begin to imitate human biology

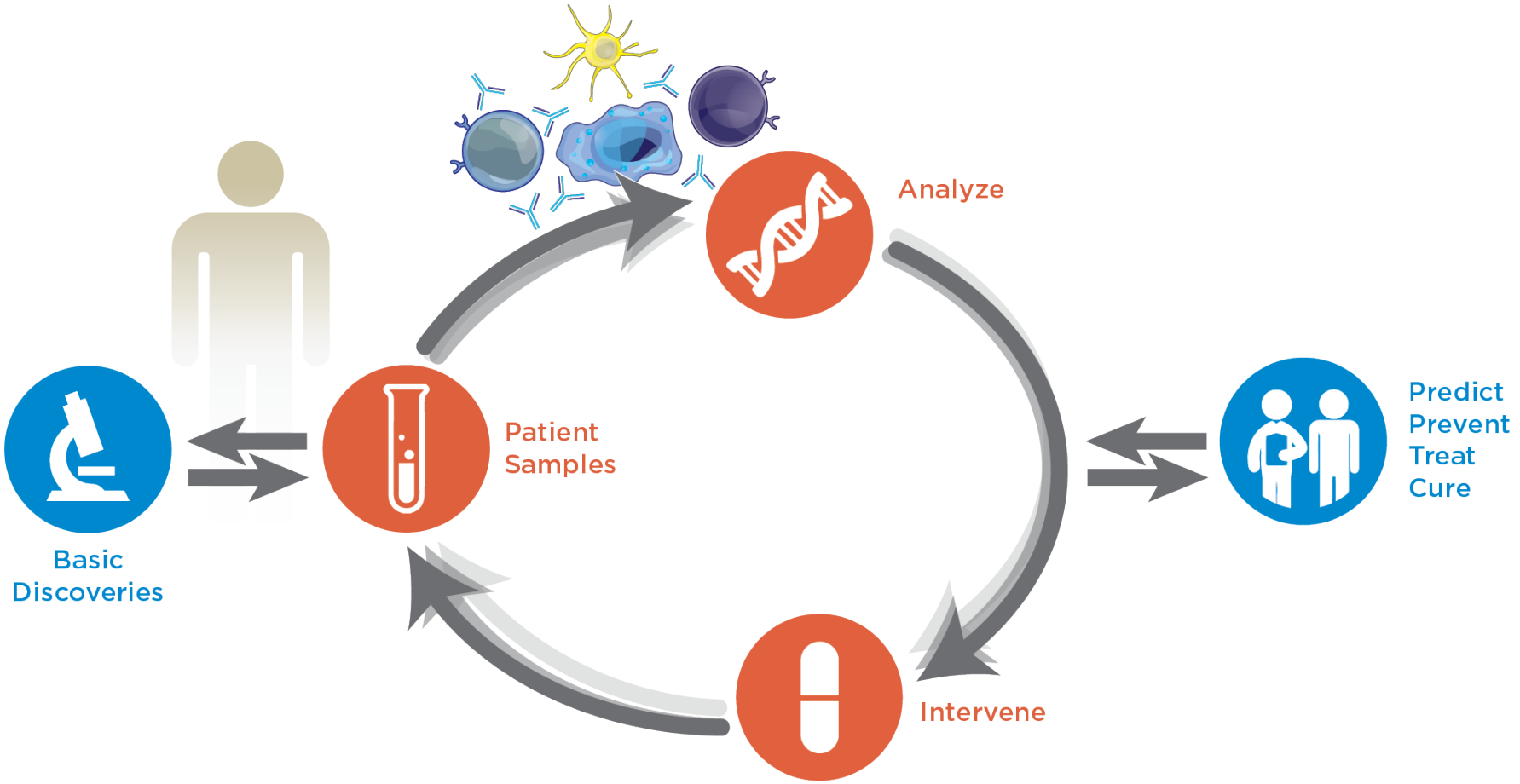
Maturation and microbial exposures promote immune maturation



L K Beura *et al. Nature* 1–5 (2016) doi:10.1038/nature17655

Benaroya Research Institute
Virginia Mason

A Diversified Research Portfolio that Promotes Integration



Well-orchestrated Deep Dive

Benaroya Research Institute
Virginia Mason

Barriers to NIH Funded Research

- Projects that require development and maintenance of infrastructures over time. (longitudinal studies or natural history studies).
- Large consortia- can be excellent, but can become ungainly and hard to administer. Smaller committed groups may prove to be more productive
- Human immunology has increased challenges to demonstrate productivity and high impact publications. Lessens the desire for junior investigators to pursue this path.
- Pathway for computational biologists to develop recognition as independent investigators while encouraging collaboration.

Potential Pitfalls

Too Big or Too small

- Too Big
- Too small
- Blinded by shiny new technologies

    When Innovation becomes the point instead away to an answer

Gaps

How could we accelerate discoveries that improve human health

- Develop improved models of human disease –
- Embrace studies of disease heterogeneity- disease mechanisms and interventions
- Expand studies of disease develop and course over time
- Bringing Big Data and Bench research together as partners in moving our understanding forward. How do we truly integrate our understanding of pathways
- Define Health- so that we have a target to shoot for if we are to cure AI
- Expand the inclusion of environmental, lifestyle, demographic features as variables that influence health and disease.

Promising Avenues

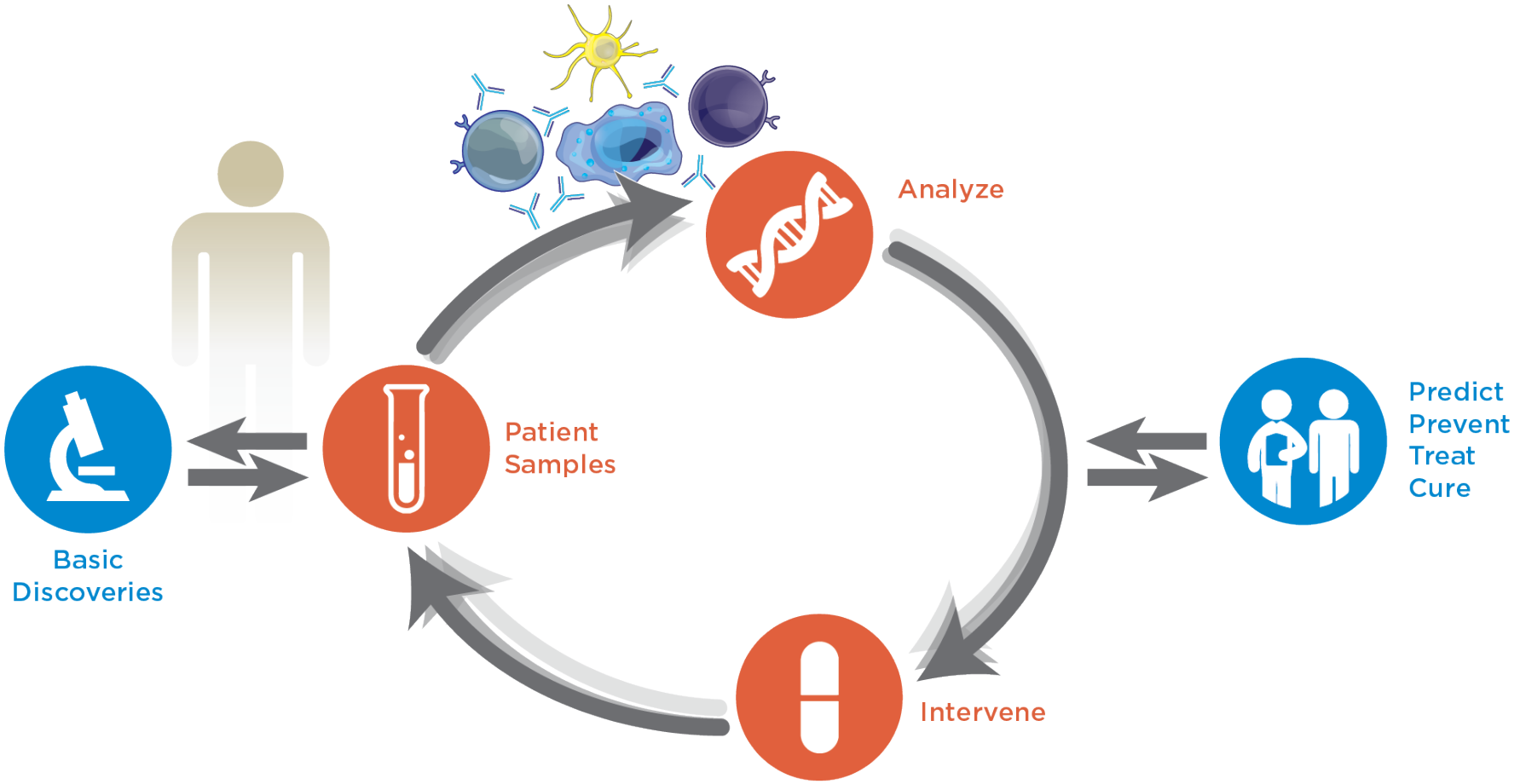
Ways to increase our understanding of the human immune response

- Perturbations in vitro and in vivo hold promise for expanding our understand of immune modulation, plasticity, resilience and regulation .

- In vivo immune interventions with currently available therapeutics offers a window into the global impact of individual pathways in vivo.

- Studies that take advantage of interventions that target specific subtypes or stages of AI disease may yield significant progress both in fundamental understanding of disease and achieving the ultimate goal of prevention and cure.

A Diversified Research Portfolio that Promotes Integration



Well-orchestrated Deep Dive

Benaroya Research Institute
Virginia Mason