THE ROLE OF THE MICROBIOME IN TYPE 1 DIABETES

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JDRF

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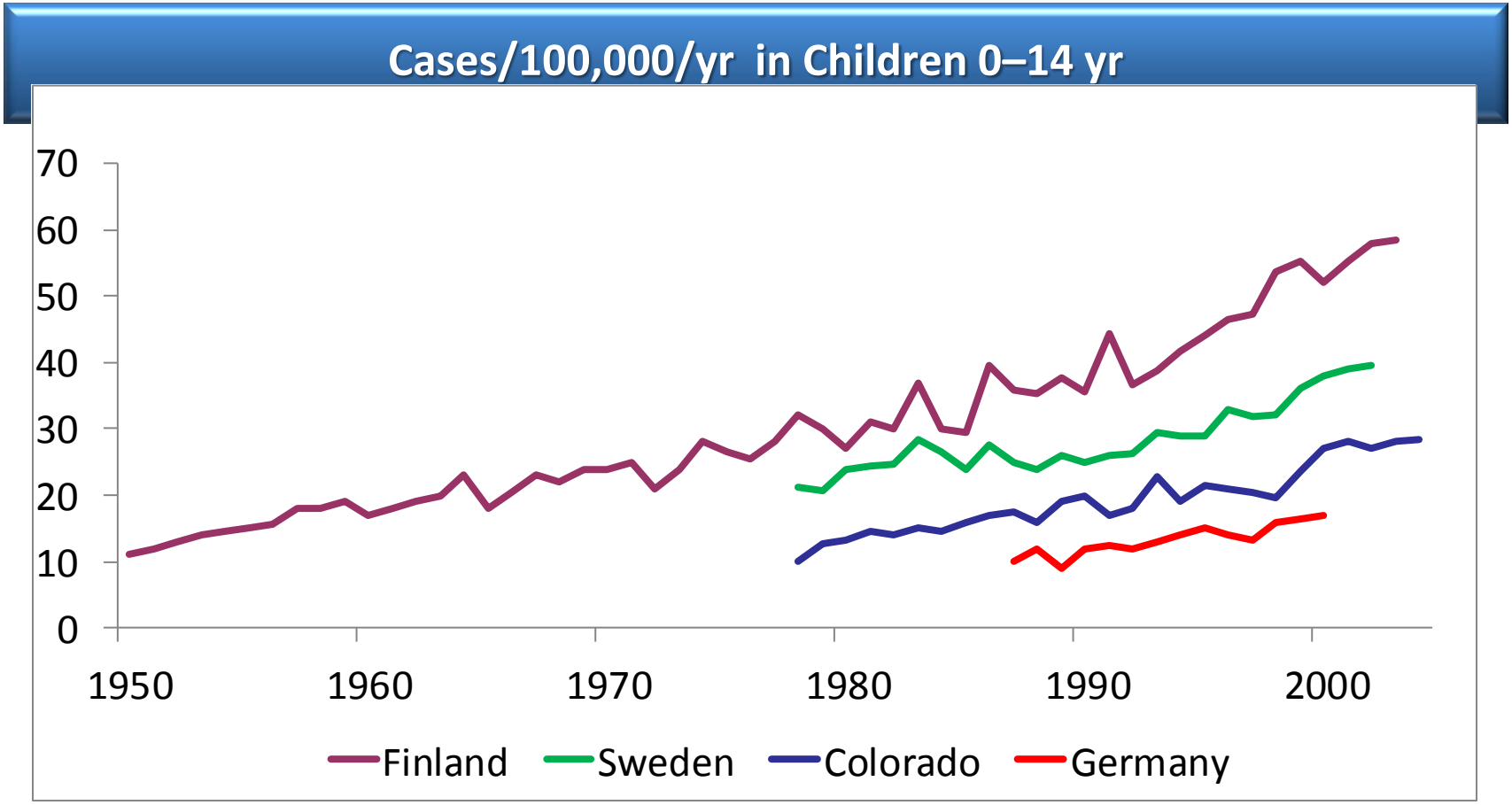
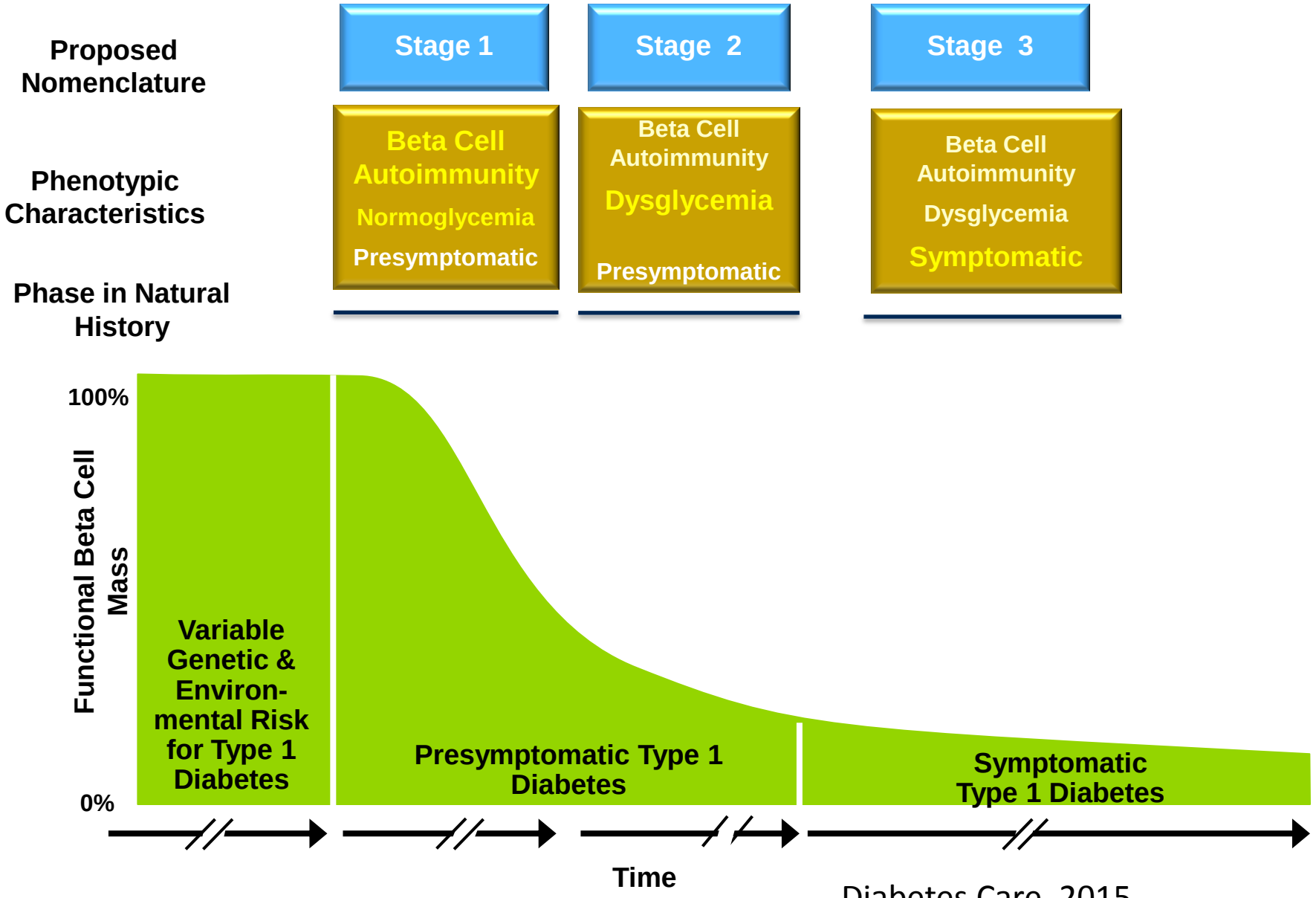
Incidence and Prevalence of T1D Increasing and Occurring at Earlier Age





Diabetes Care. 2015 Oct;38(10):1964-74

JDRF T1D Prevention Goals

- **Short-term goals:**
  - Preservation of beta cell function in pre-diabetes → Delay symptomatic T1D
  - Validated biomarkers for staging progression and trial intermediate endpoints
- **Intermediate goal:** Secondary prevention of childhood onset and adult onset symptomatic T1D in at-risk individuals
- **Long-term goal:** Primary prevention of childhood onset T1D with universal childhood immunization with safe vaccines without screening for risk

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Microbiome

- Based on the available body of literature, it is feasible to suggest that the well-described increased incidence in T1D over the past 50 years arises, at least in part, from one or both of the two primary mechanisms related to the intestinal microbiome:
  - defective development and/or alteration of healthy microbiota in an individual at genetic risk for T1D may result in abnormal immunoregulation that enables autoimmune destruction of insulin producing beta cells.
  - enhanced leakiness of the gut epithelial barrier either results from an altered microbiome or, is a key determinant of an altered microbiome, or “dysbiosis”
- Need to determine whether and how an altered microbiome contributes to either defective immunoregulation and/or gut leakiness in T1D

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Gut Microbiome and T1D: Strategy

- JDRF has catalyzed this field in T1D, and published a review article on the topic through the JDRF Microbiome Consortium (Clin Exp Immunol. 2014 Jul;177)
- JDRF Microbiome Consortium: Role of Microbiome in T1D
- Assess potential for primary prevention, secondary prevention
- Identify and evaluate safe interventions to establish, maintain, reset healthy microbiome-induced immunoregulation
- Partner and Leverage (JDRF Human Microbiome Consortium, ADA-JDRF Microbiome Conference, JDRF Infant Diet Meeting, NIH, Other Foundations, Industry, VC)
- Recent publications and unpublished observations confirm a role for dysbiosis in T1D

JDRF Microbiome Consortium

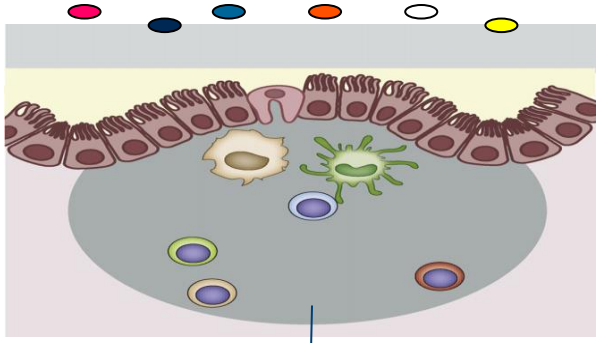
- Collaborative network
- Work with JDRF staff and an external advisory group
- 1° Goal: Define what microbial communities are positively or negatively associated with T1D in both humans and mouse models of the disease.
- 2° Goals: Identify biomarkers (immune, metabolomic, mucosal, etc.) of a positive or negative microbiome association with T1D; **Understanding mechanism and identifying targets to manipulate the microbiome for therapeutic effect.**

Microbiome in At-Risk Infants Progressing to T1D

- Decreased bacterial community complexity
- Decreased diversity
- Increased inflammation-favoring bacteria

Intestinal Microbiota

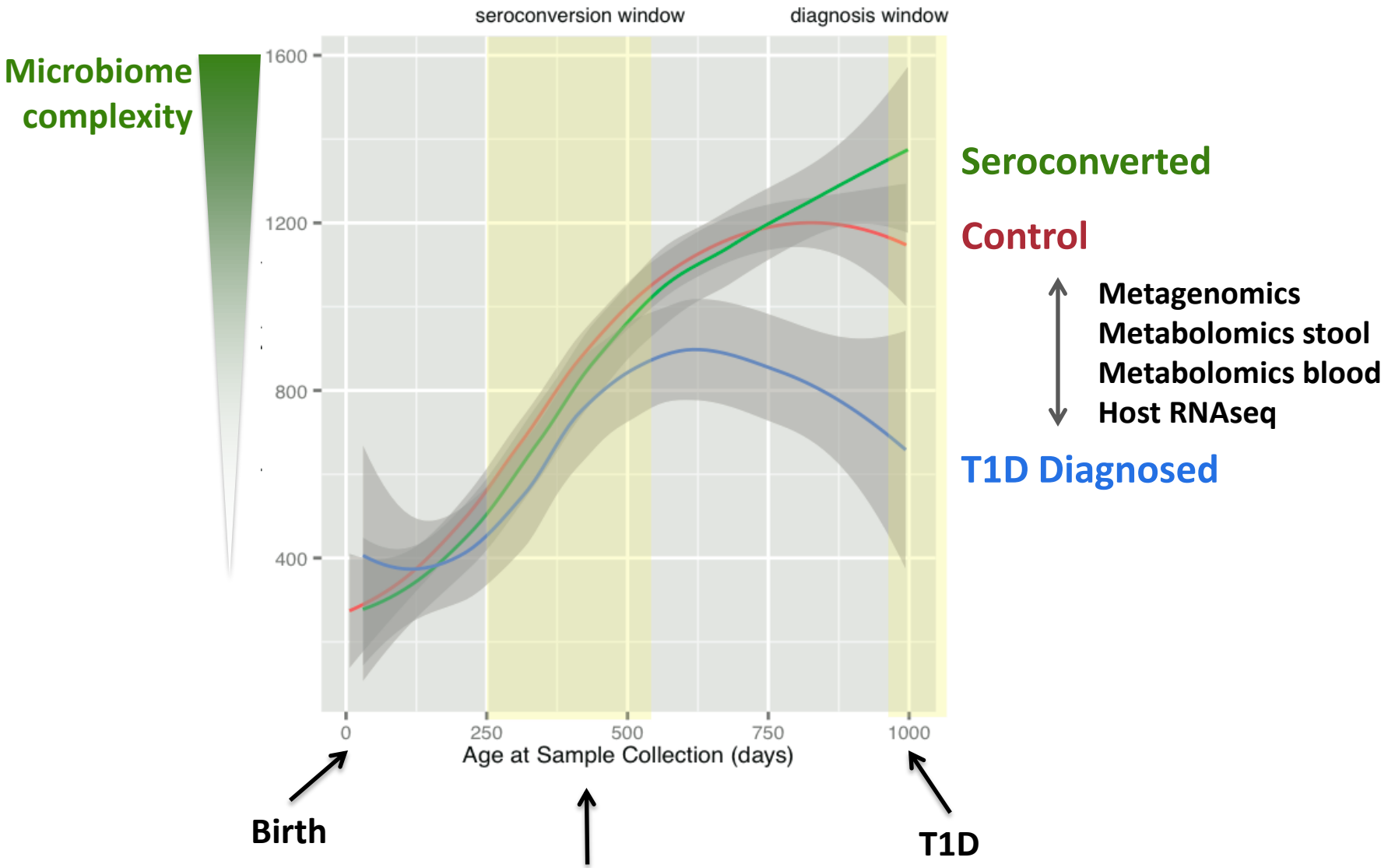
Intestine



Innate, Adaptive Immune System, Immunoregulation

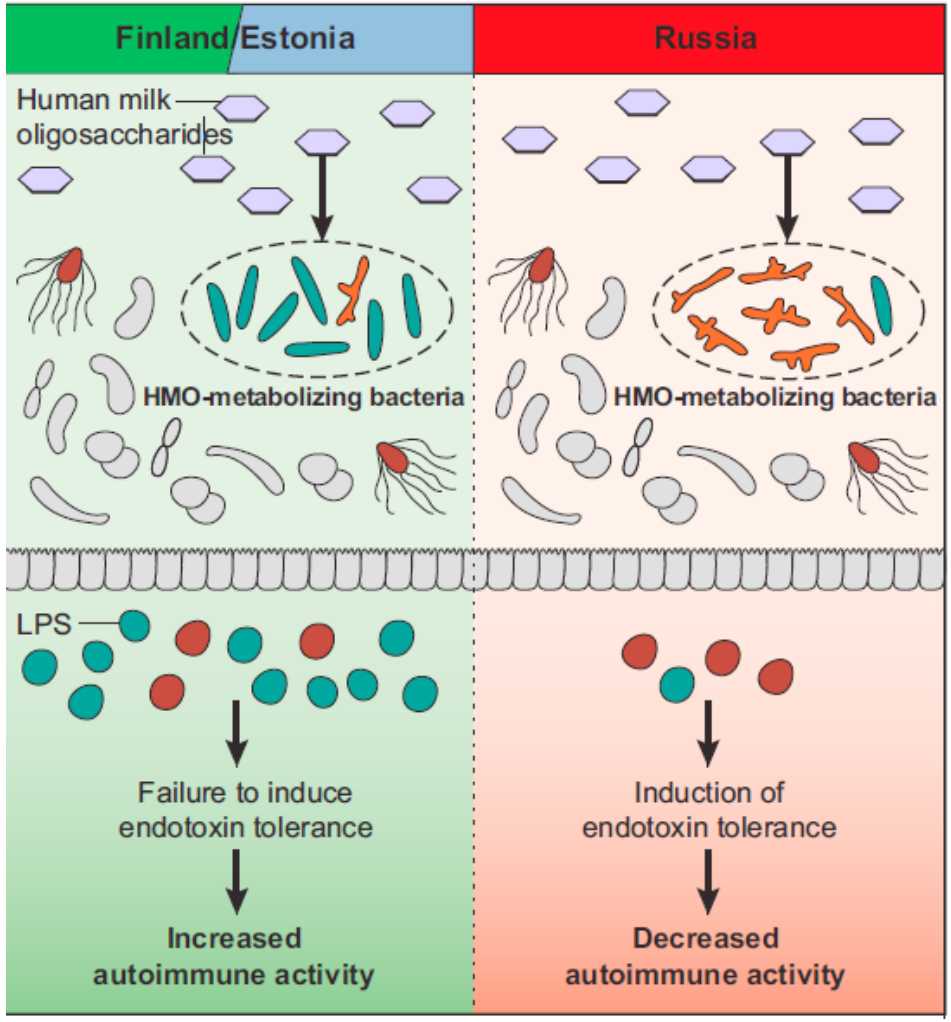
Setting threshold for immune signaling, Innate immunity

The microbiome shifts before T1D diagnosis



Cell Host Microbe. 2015 Feb 11;17(2):260-73

Differential immune education

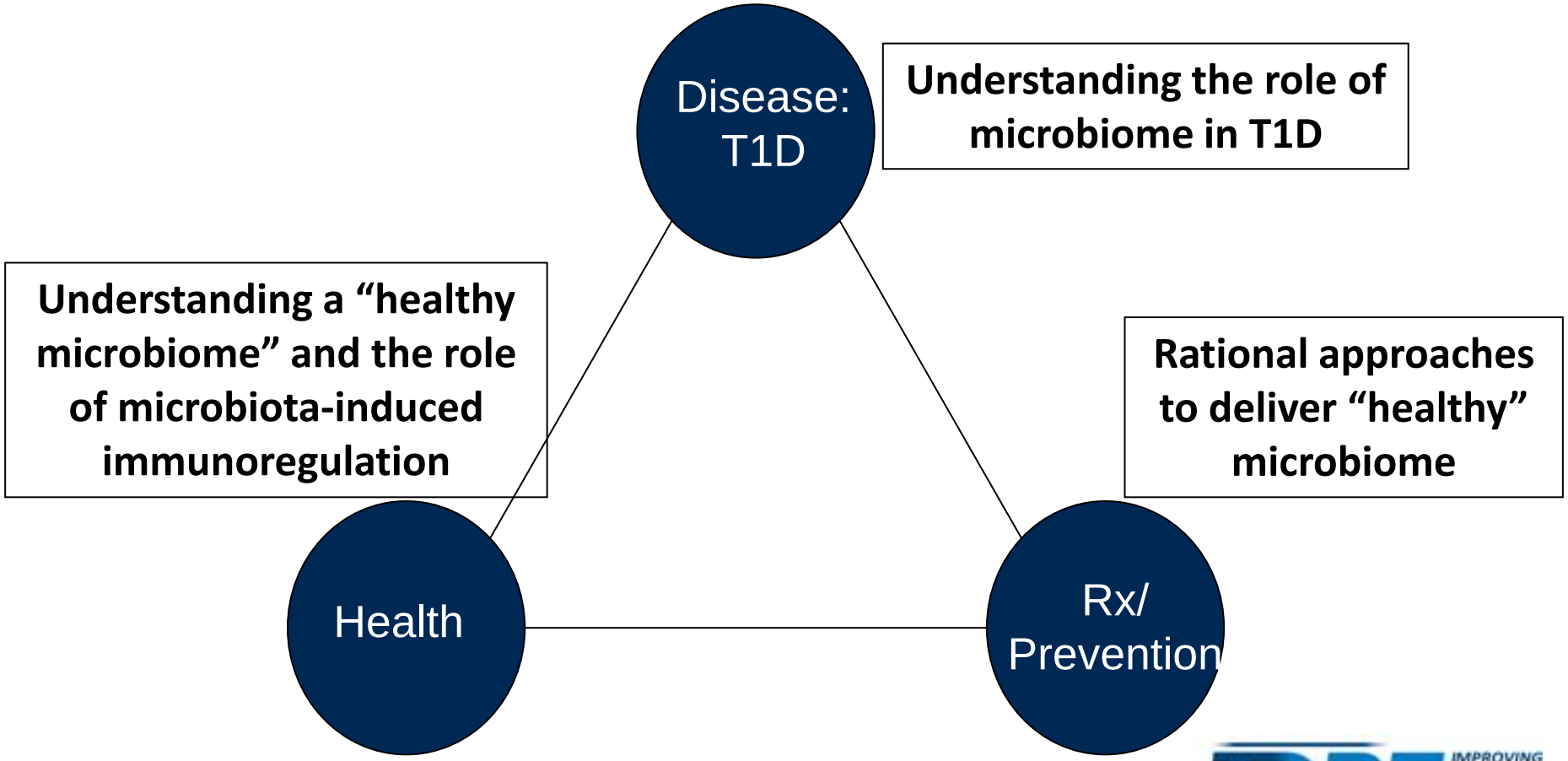


- Finnish and Estonian infants have a distinct early gut microbiome compared to Russians
- B. dorei and other Bacteroides species are highly abundant in Finland and Estonia
- B. dorei LPS inhibits the immunostimulatory activity of E. coli LPS
- LPS from B. dorei does not protect NOD mice from type 1 diabetes

Vatanen et al., 2016, Cell 165, 1–12

GI Microbiome Challenges

Unraveling the Microbiome Role in T1D



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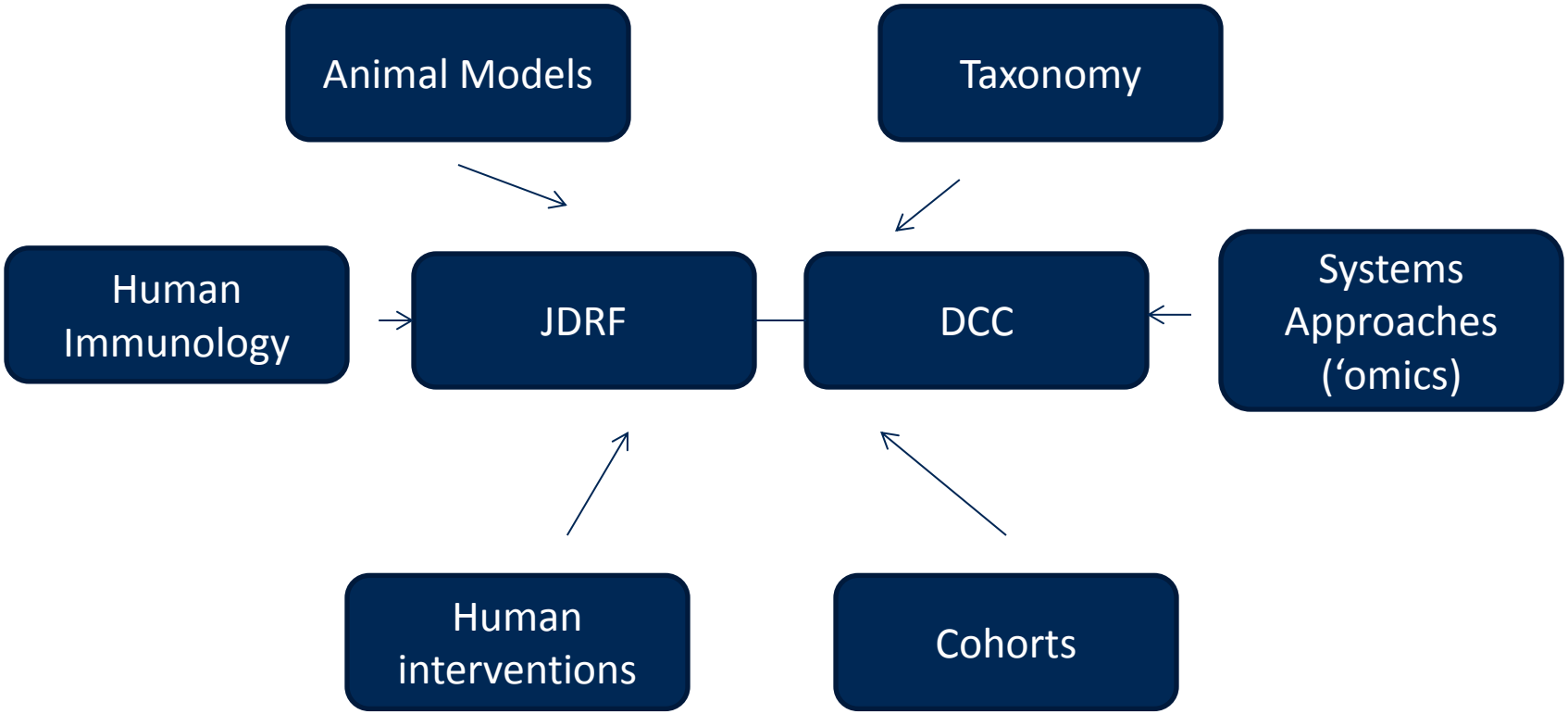
Possible questions to address

- Development. Does perturbed development of the intestinal microbiota in early childhood contribute to susceptibility to T1D? If so, what are the mechanisms? What are the effects on intestinal integrity, immune system, metabolism and beta cell development and function?
- Microbiota containment. Does altered intestinal permeability/integrity contribute directly to susceptibility or pathogenesis of T1D? If so, what are the mechanisms? How can its detection be refined and quantified? What interventions can correct?
- Health. What is the basis of healthy microbiota-induced regulation? How can this be detected in the periphery? Does trained innate and adaptive immunity via epigenetic programming play a role?
- Prevention and therapy. What interventions can induce or preserve the development of a healthy microbiota-induced regulation in infancy?

JDRF Microbiome Consortium Structure



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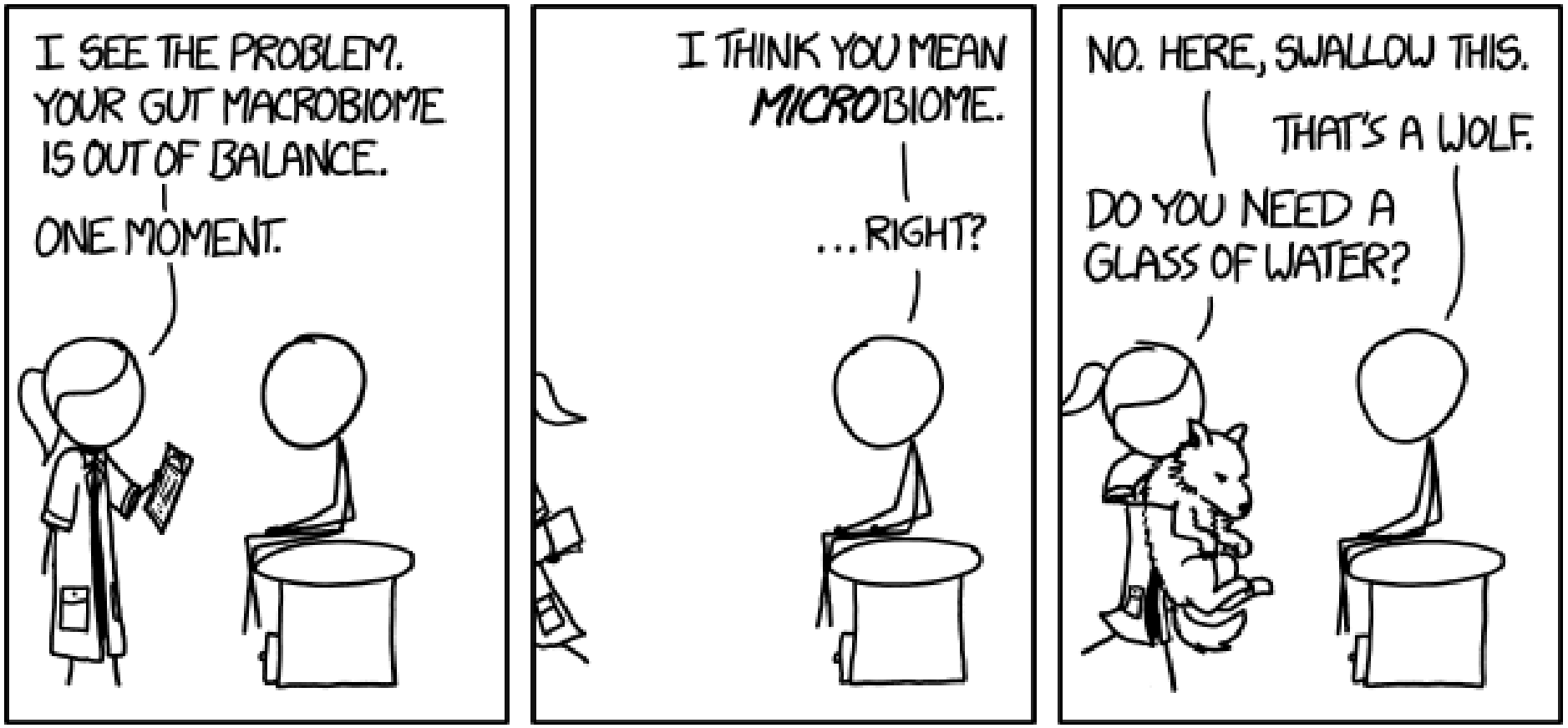
QUESTIONS?


I SEE THE PROBLEM. YOUR GUT MACROBIOME IS OUT OF BALANCE.
ONE MOMENT.
I THINK YOU MEAN MICROBIOME.
...RIGHT?
NO. HERE, SWALLOW THIS.
DO YOU NEED A GLASS OF WATER?
THAT'S A WOLF.