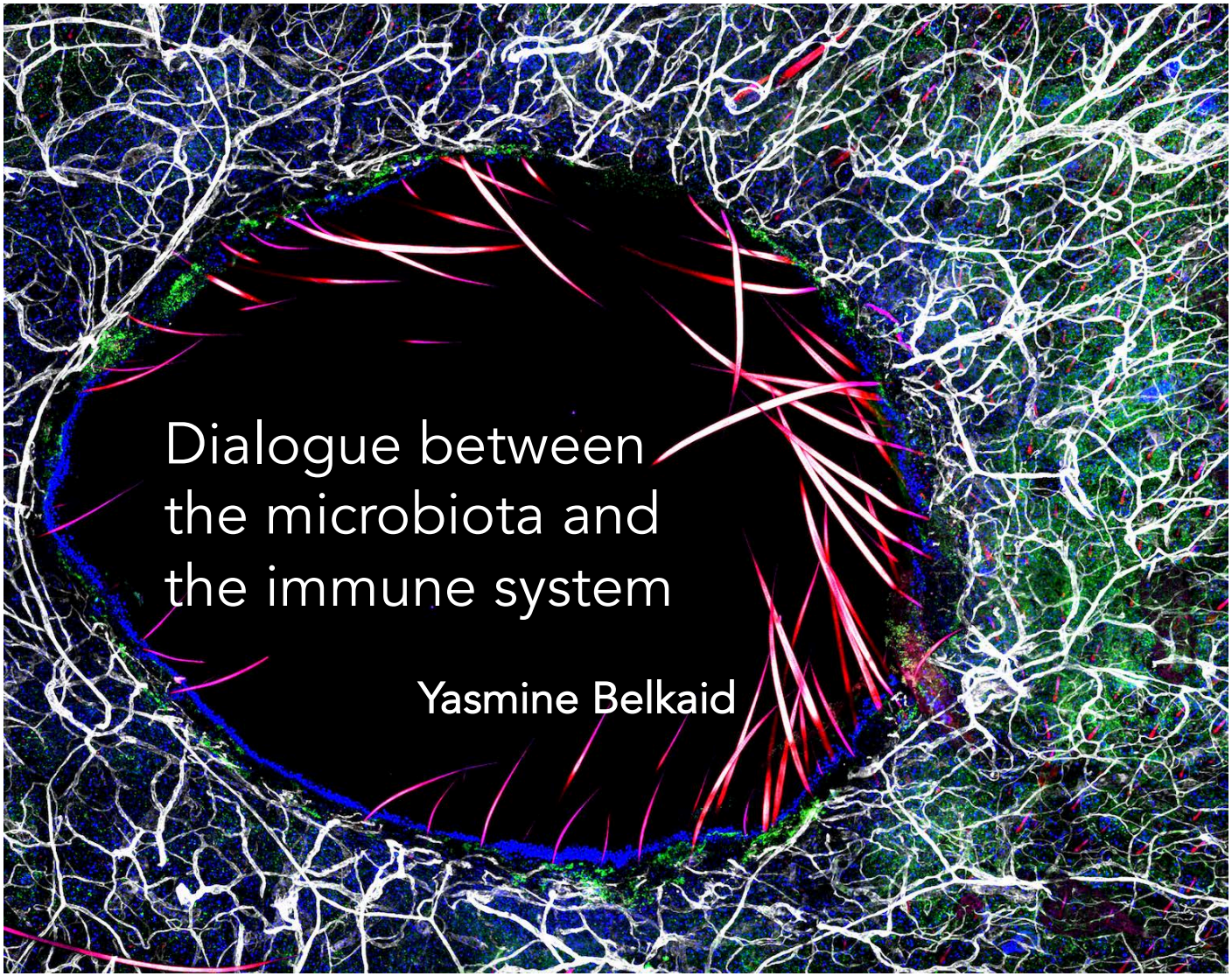


# Dialogue between the microbiota and the immune system

Yasmine Belkaid

NIH
NIAID

# Humans have co-evolved with microbial partners

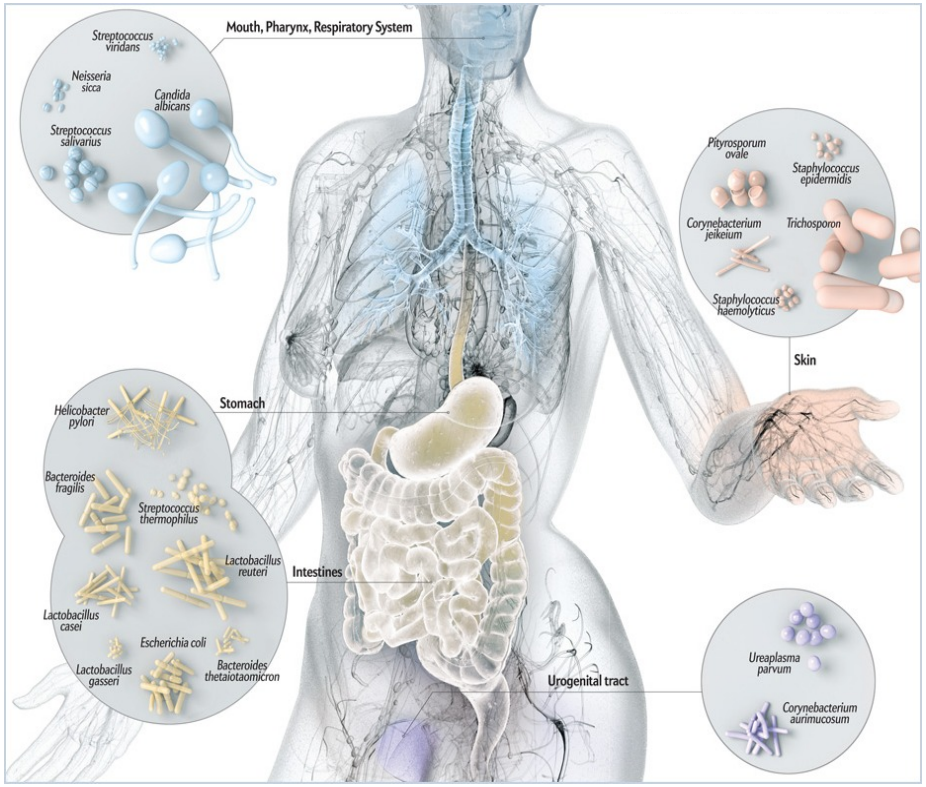



Illustration
Scientific American 2012

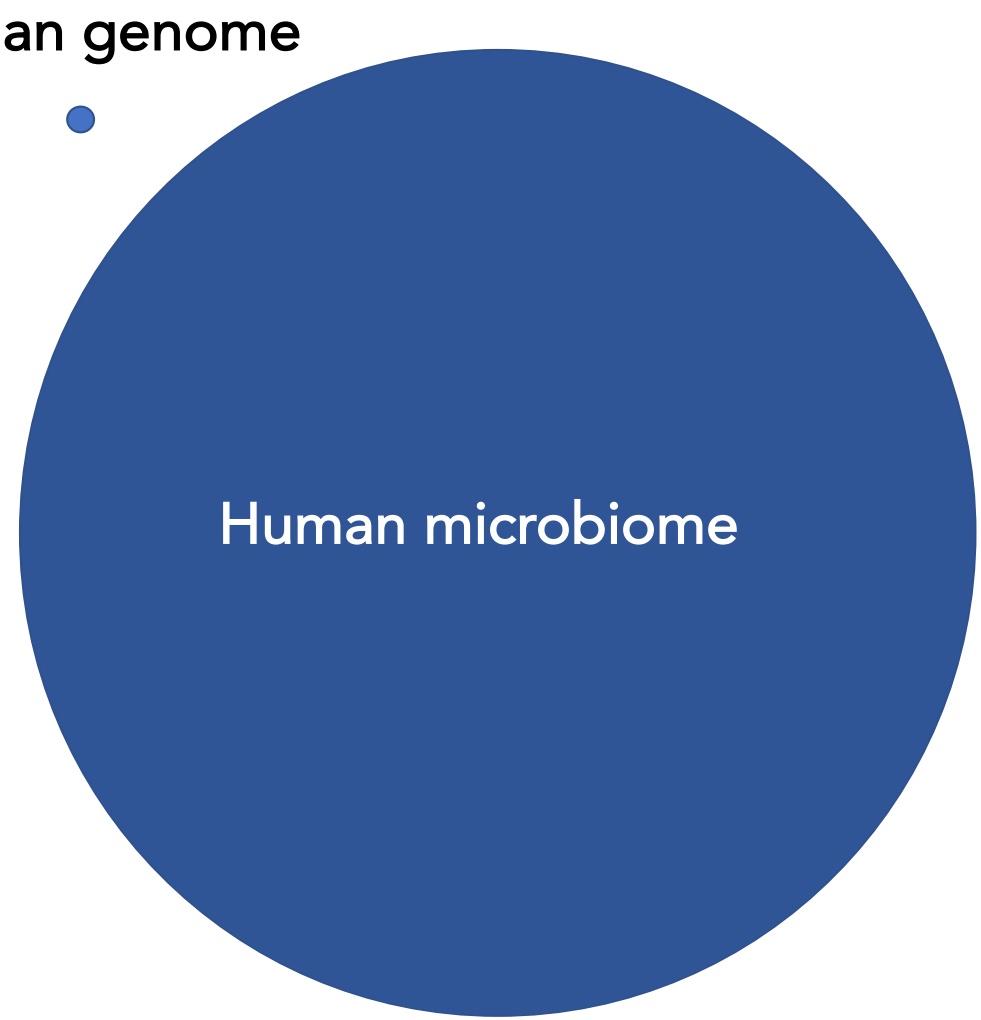
- We are a composite of species: bacteria, archea, protozoan, fungi, viruses, bacteriophages

- Commensal microorganisms
  - inhabit all barrier surfaces of our organism
  - are at least as numerous as human cells
  - their DNA (the microbiome) contains 100 times more genes than our 'own' human genome

- Humans are metaorganisms

composed of host and microbial cells with their own genes and shared metabolic processes and products

We are a composite of species:
bacterial, fungi, viruses…
a metaorganism



# Control of host physiology by the microbiota

Systemic effects

Local effects

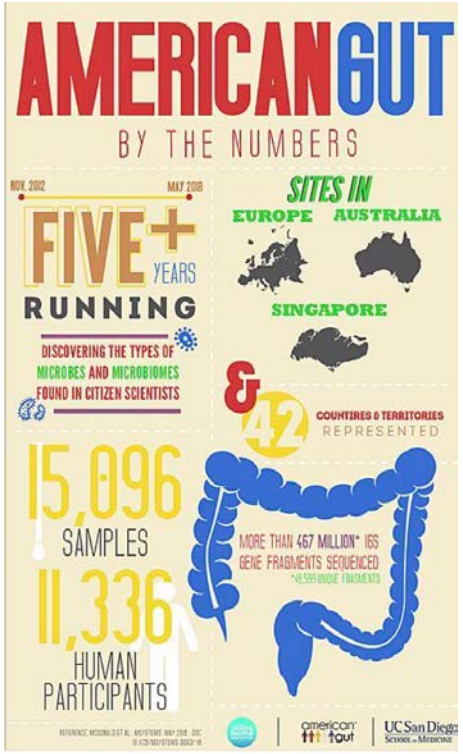
Immune system

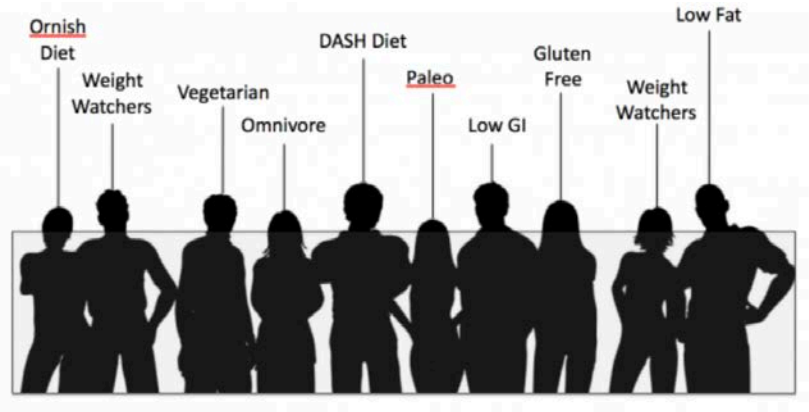
- Nutrient absorption
- Vitamin synthesis
- Metabolism of bile and hormones
- Fermentation of carbohydrate

Behavior and cognitive function

Metabolism

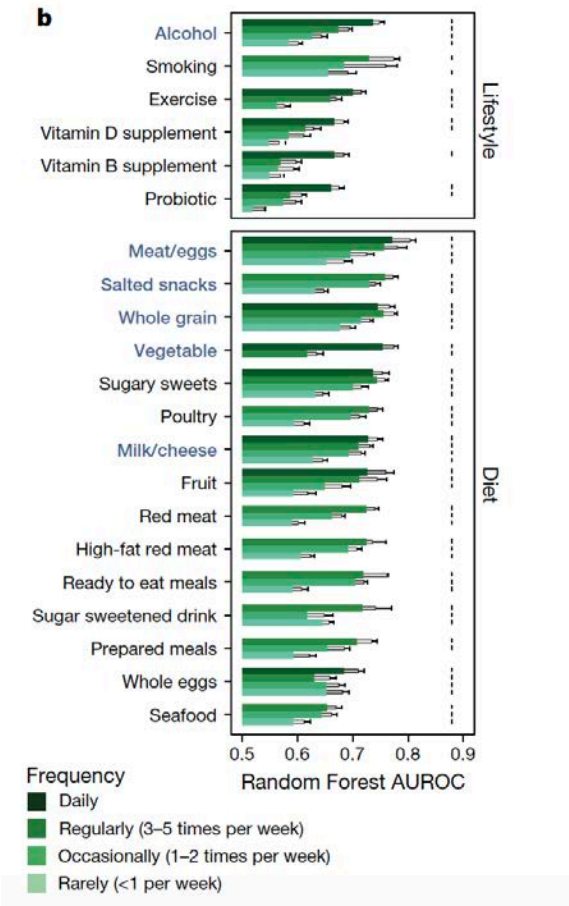
# Identifying sources of microbiome heterogeneity across human populations

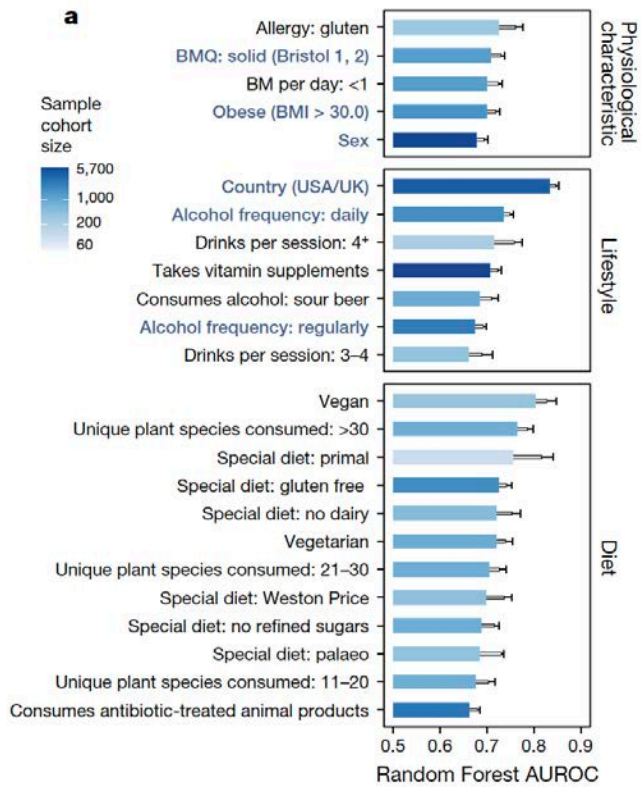


Ivan Vujkovic-Cvijin

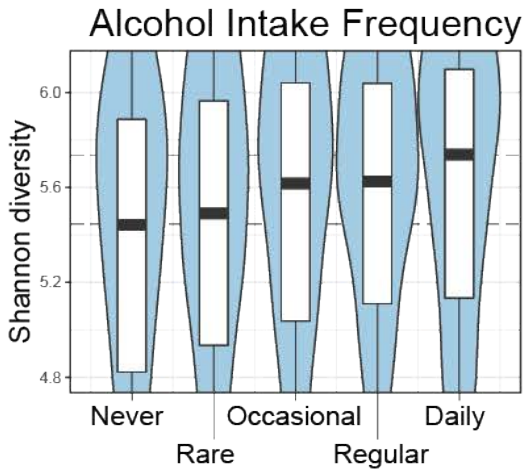
# Physiological, lifestyle and dietary characteristics strongly associate with the composition of the gut microbiota

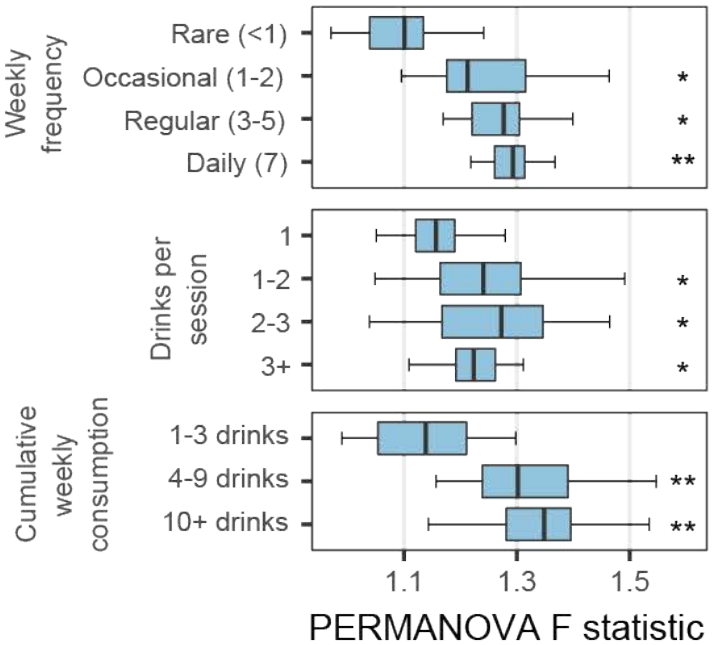


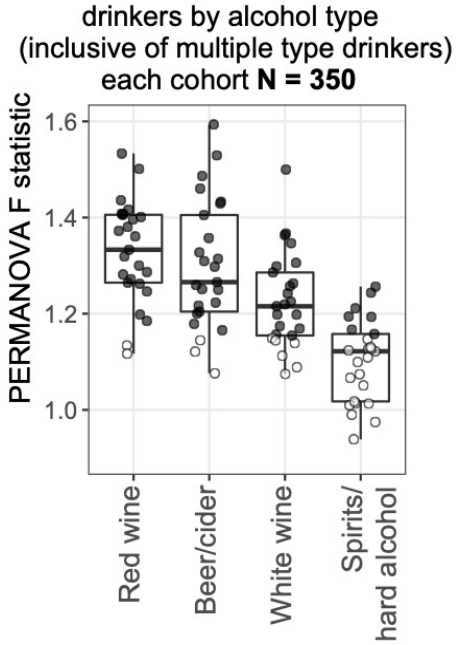




Vujkovic-Cvijin et al, *Nature*, 2020

# Alcohol affects gut microbiota composition in a dose-dependent manner

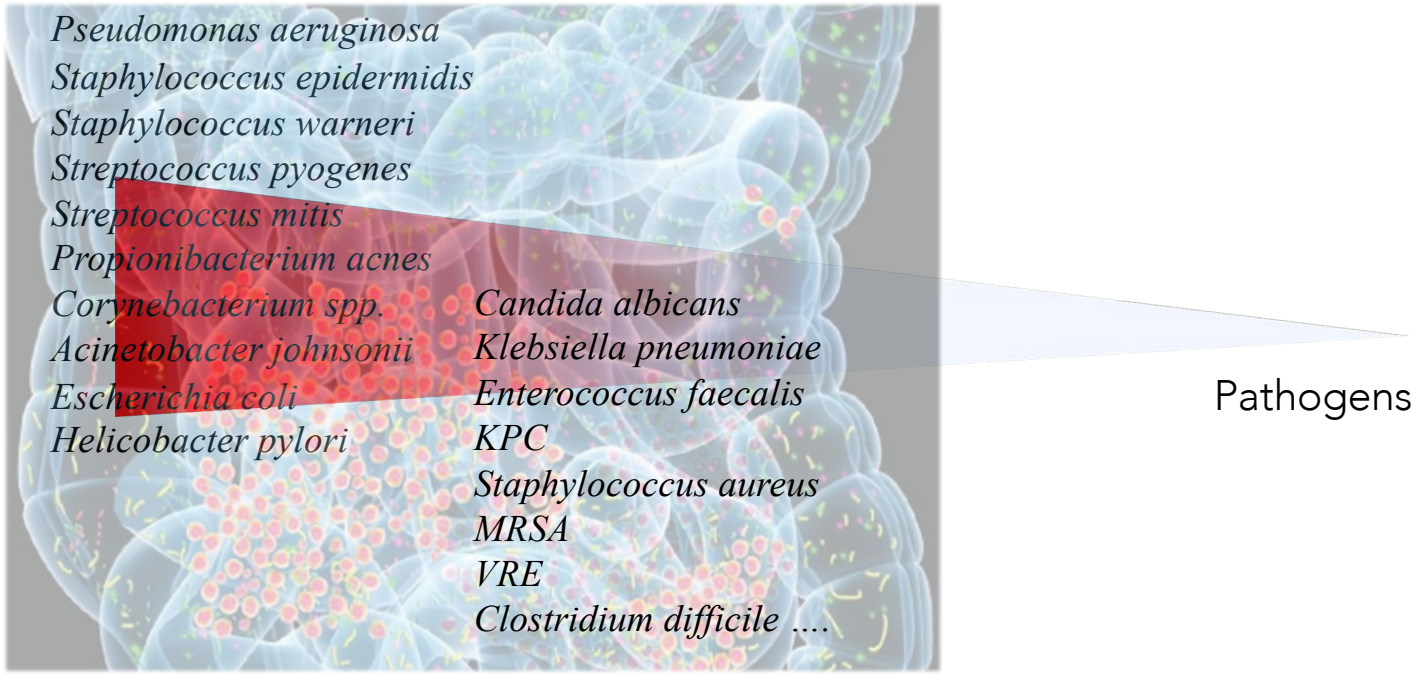



Vujkovic-Cvijin et al, *Nature*, 2020

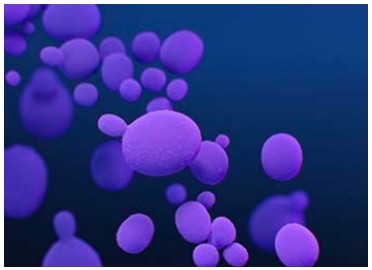
# A large number of microbes able to cause diseases are normal constituents of the microbiota



# Antimicrobial resistance

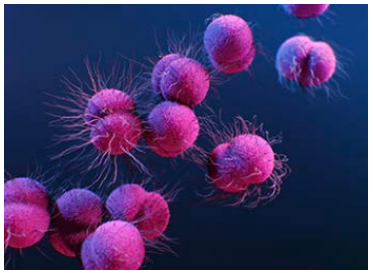
Photo: WHO (World Health Organization).

Drug-resistant *Candida auris*



Carbapenem-resistant Enterobacteriaceae (CRE

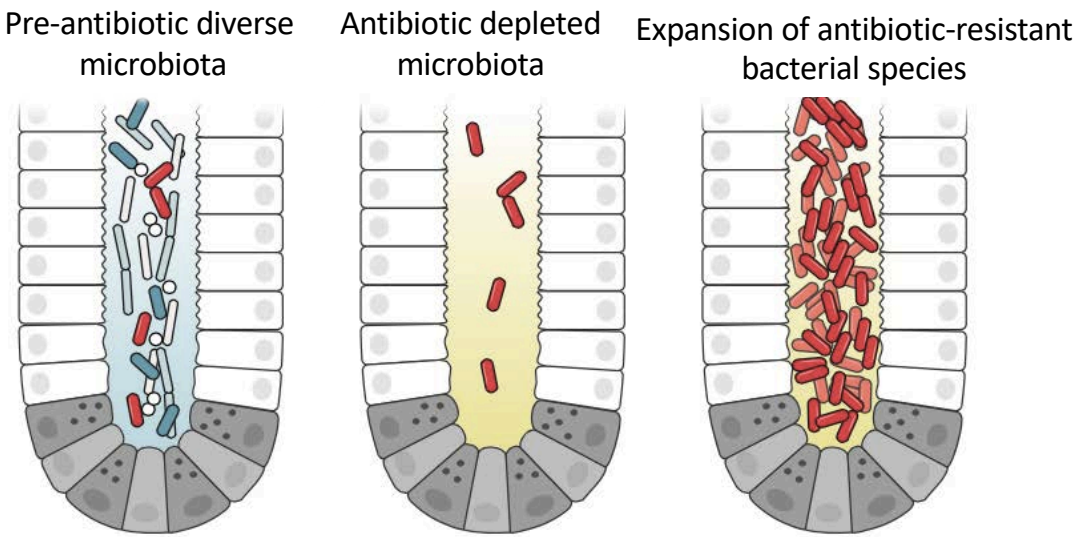
Drug-resistant *Neisseria gonorrhoeae*



*Clostridium difficile*

Carbapenem-resistant Acinetobacter

# Antibiotic treatment can lead to the expansion of antibiotic resistant species

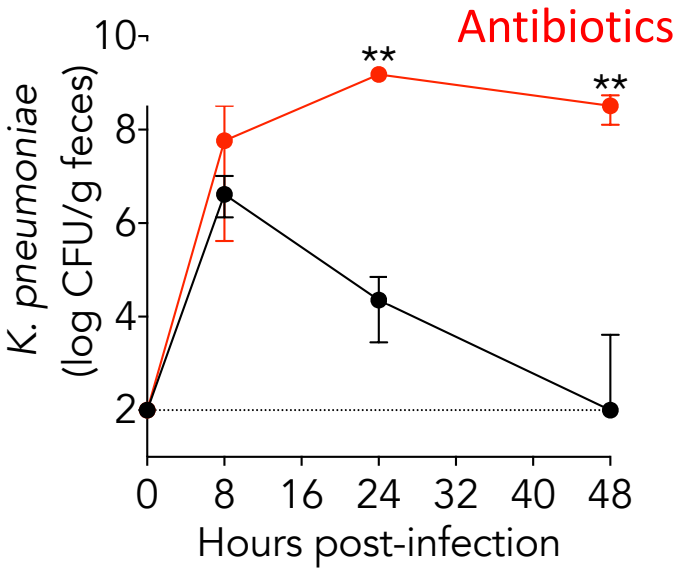



Adapted from Pamer et al, *Science,* 2016

# *Klebsiella pneumoniae* is a major cause of infection in individuals with compromised gut microbiota

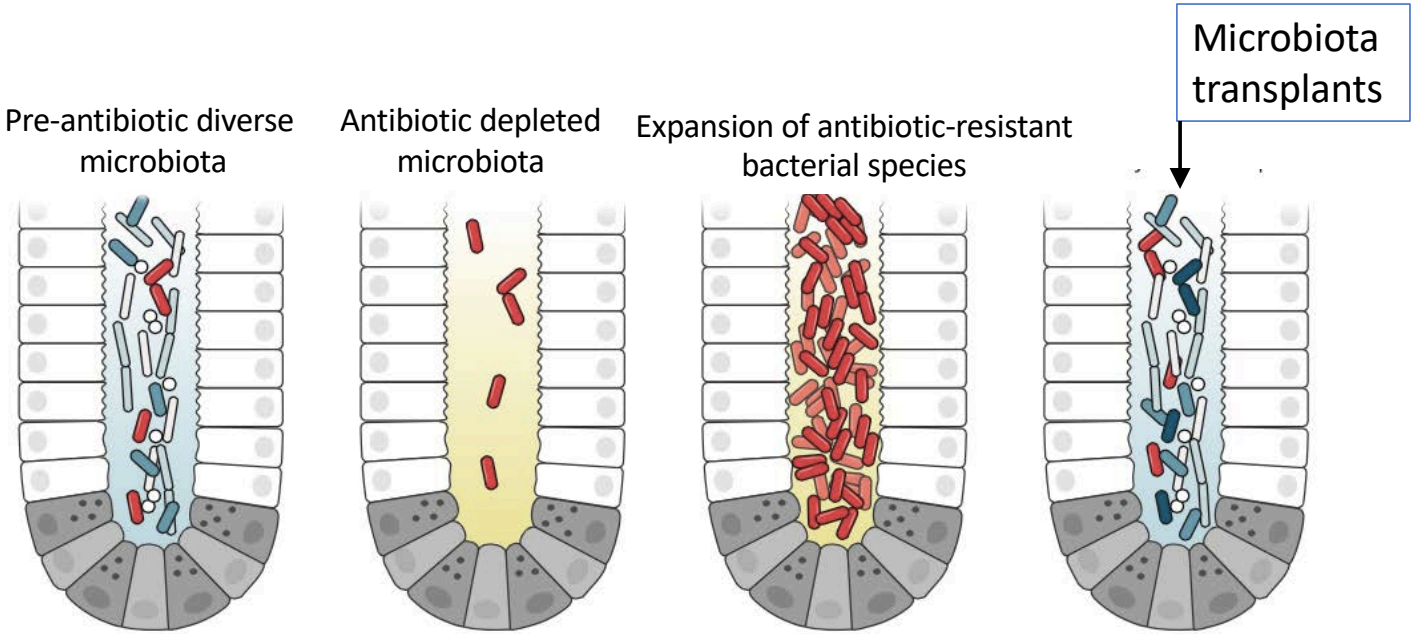
*Klebsiella pneumoniae*

fecal burden




Stacy, Cell, 2021

# Antibiotic treatment can lead to the expansion of antibiotic resistant species

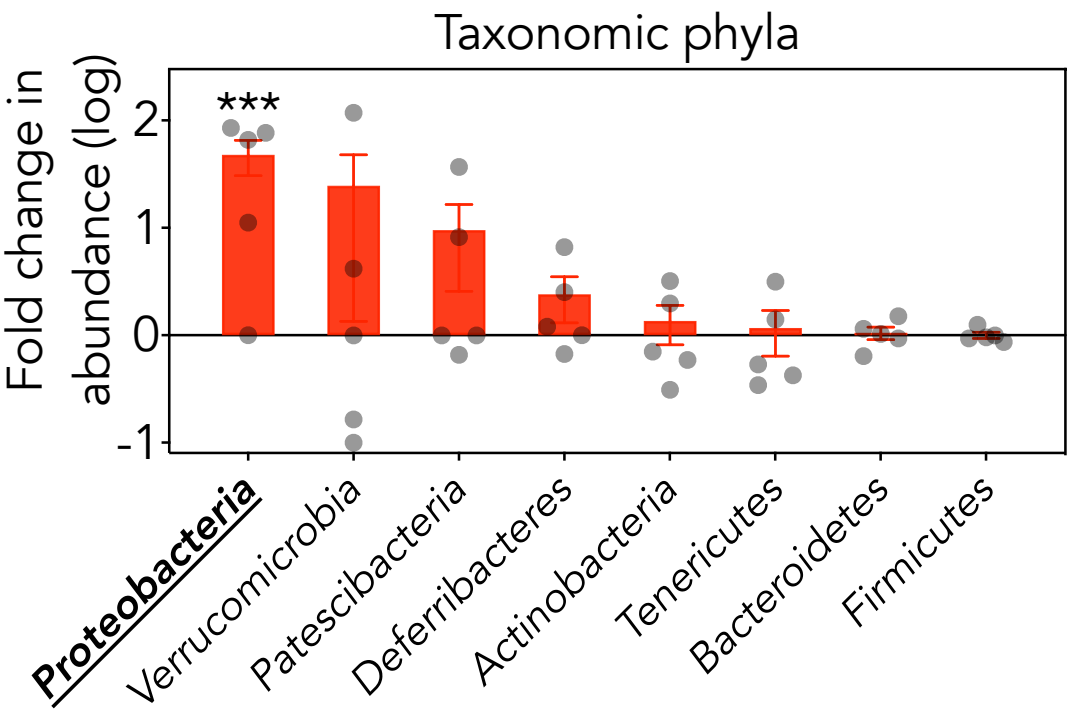


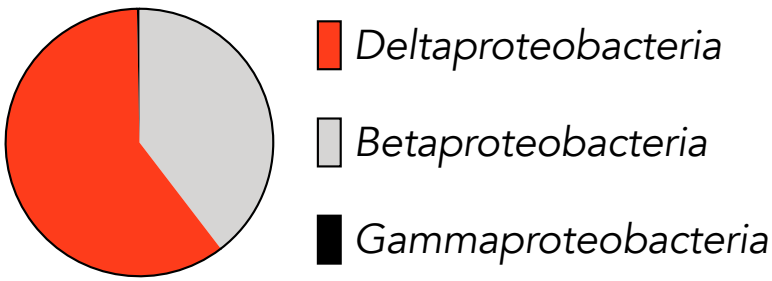

Adapted from Pamer et al, *Science,* 2016

# Can pathogen-induced microbiota shield against subsequent infections?

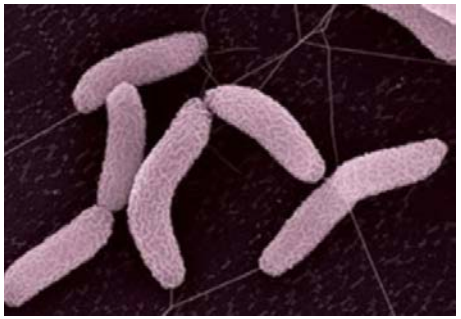
Apollo Stacy

# Prior infection elicits an expansion of *Deltaproteobacteria*



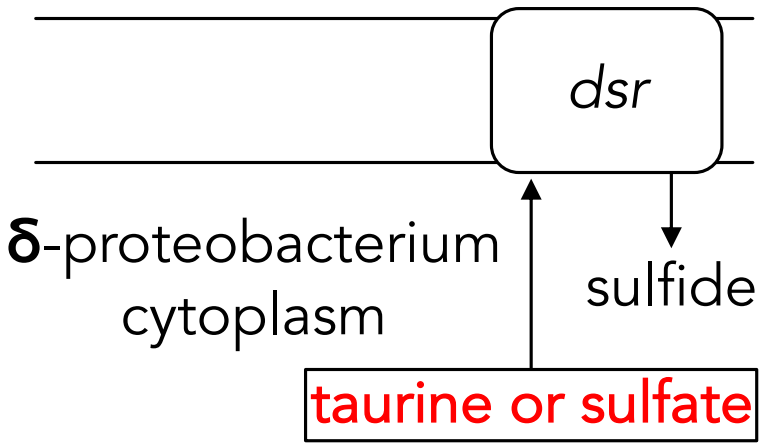




Stacy, Cell, 2021

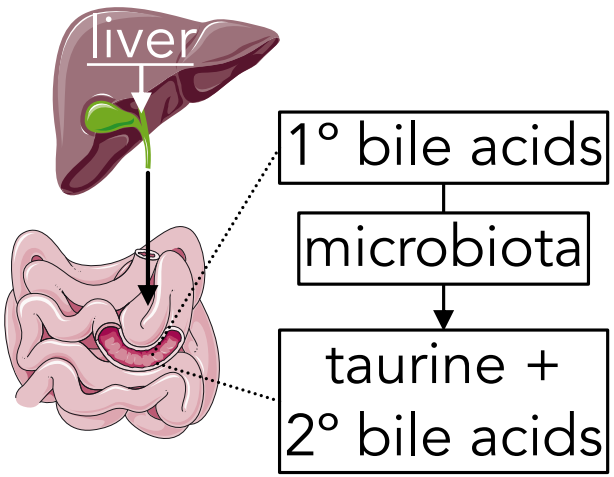


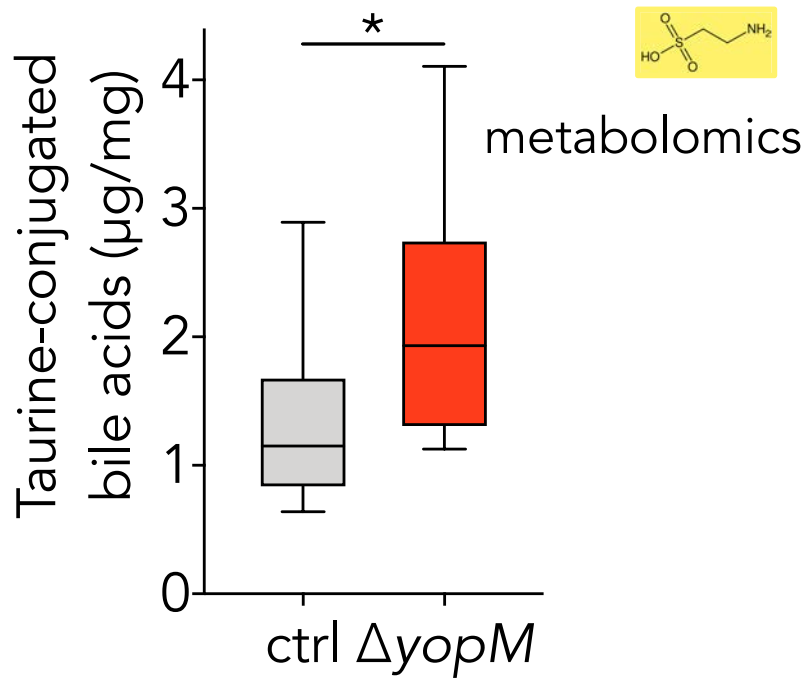
# *Deltaproteobacteria*

Generate energy by
respiring with sulfur-containing compounds



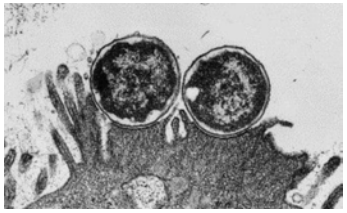
# Bile acids are the source of taurine



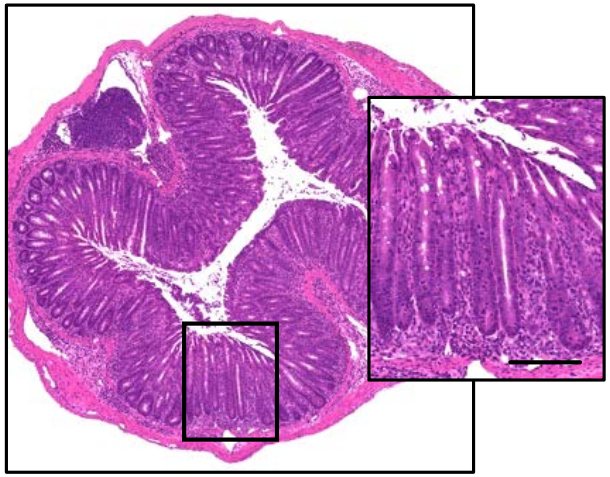



# Taurine enhances resistance to infection

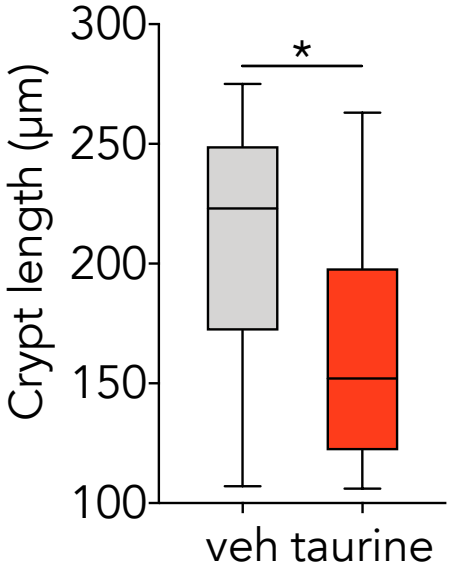
*Citrobacter rodentium*



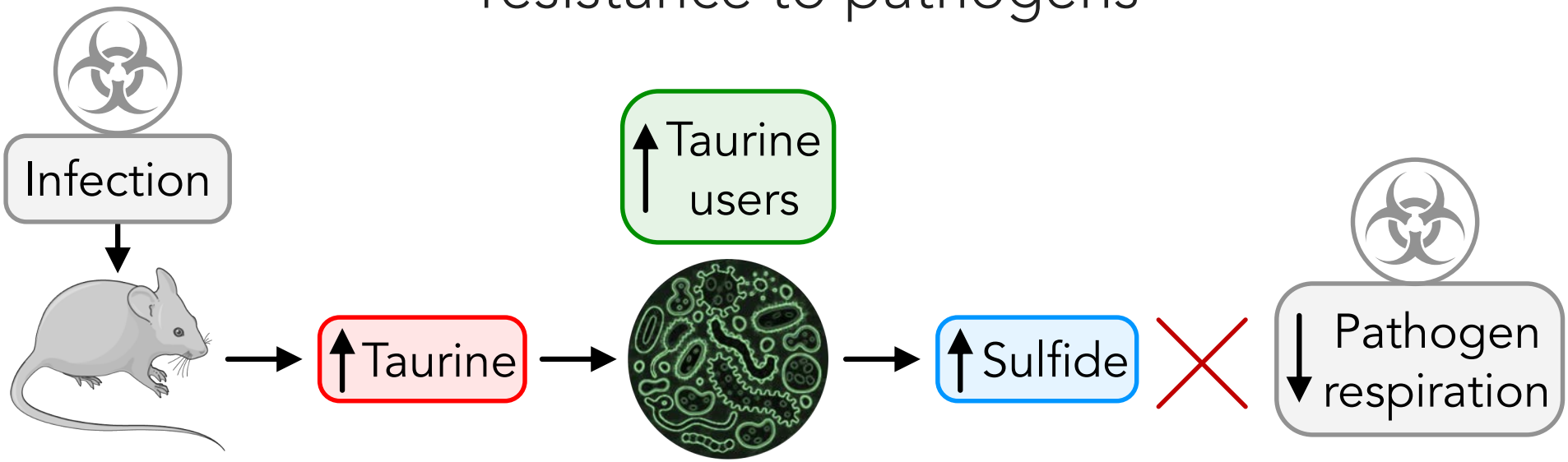
vehicle



taurine



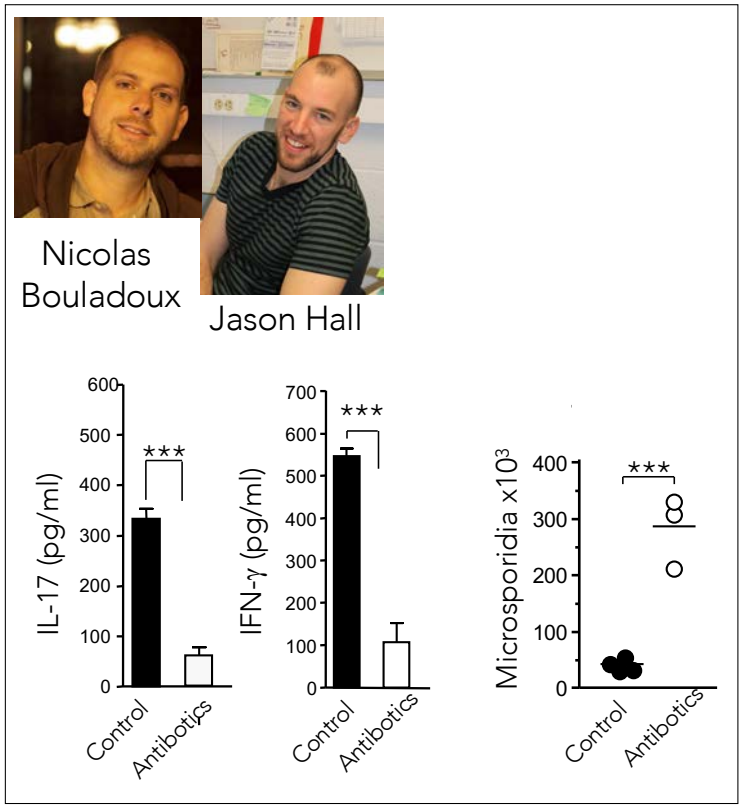
# Infection trains the host for microbiota-enhanced resistance to pathogens



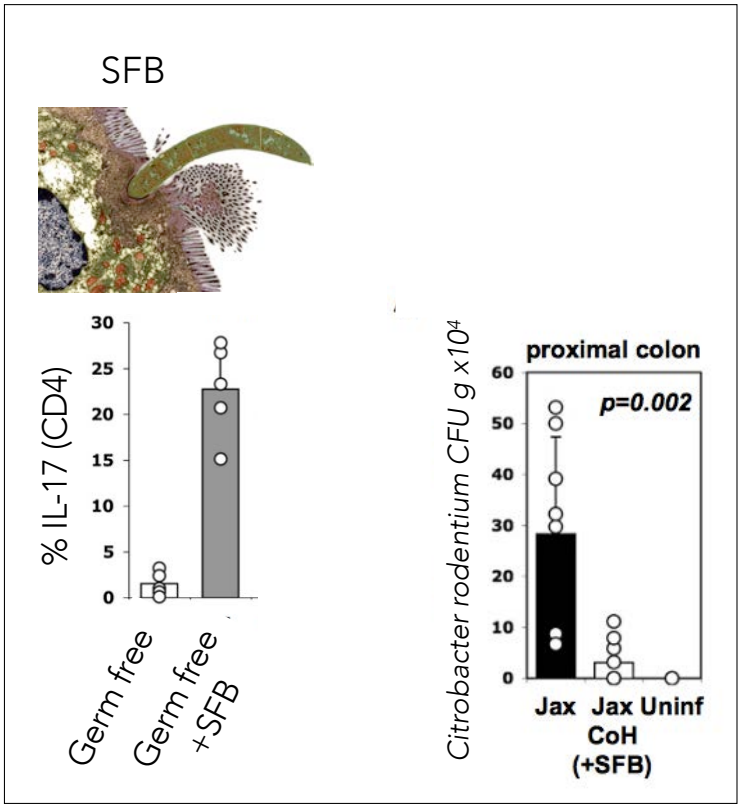

- Microbiota can be "trained," like immune system
- Training metabolite has potential therapeutic value

Stacy *et al.*, *Cell* (2021)

# The gut microbiota is an endogenous adjuvant for host protective immune responses

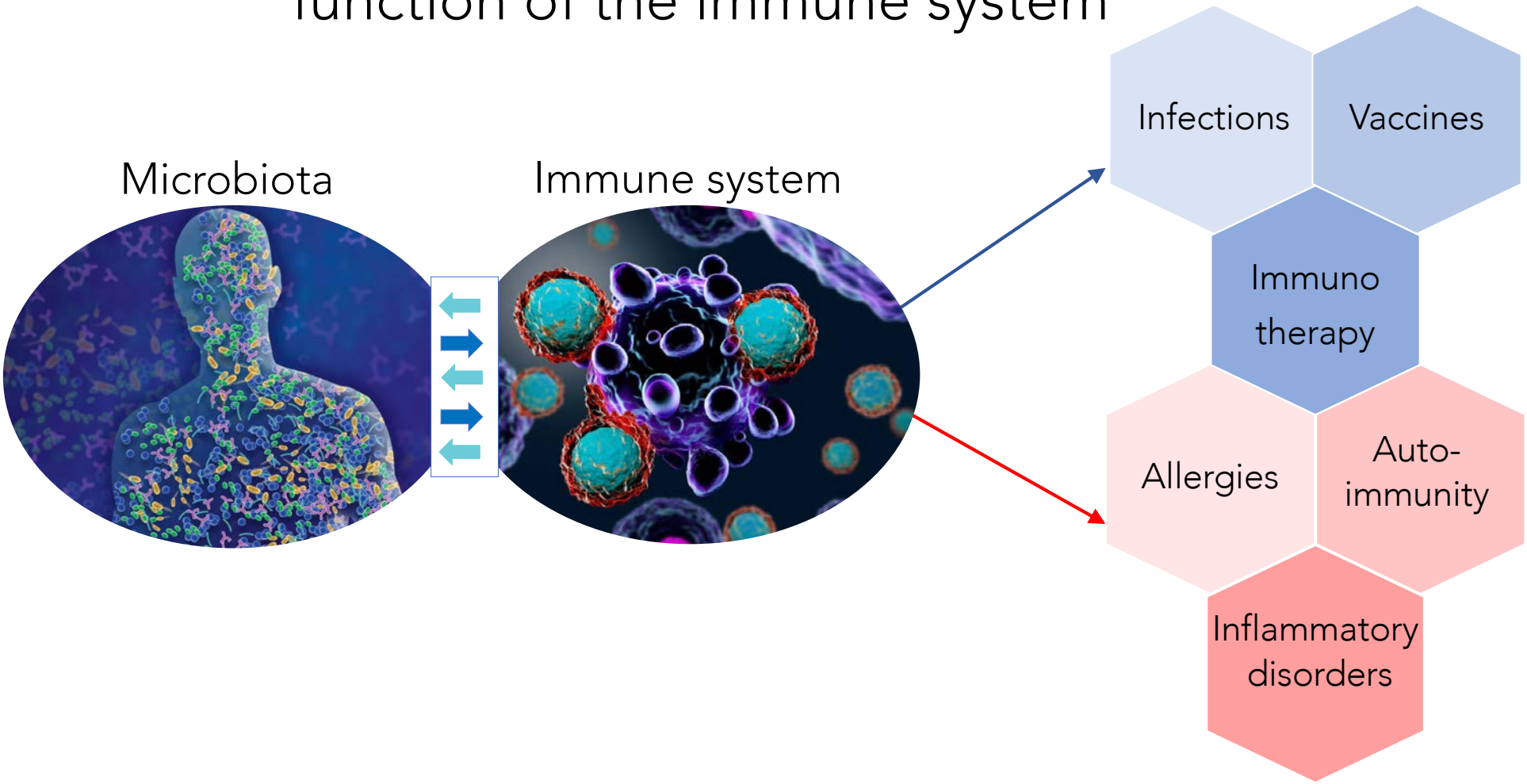


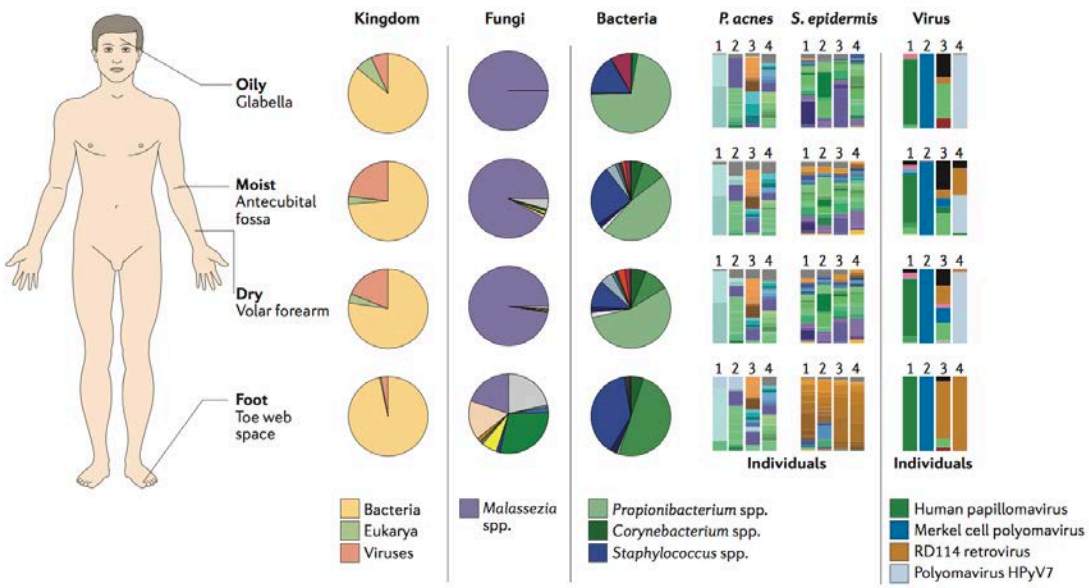

Hall & Bouladoux, *Immunity*, 2008

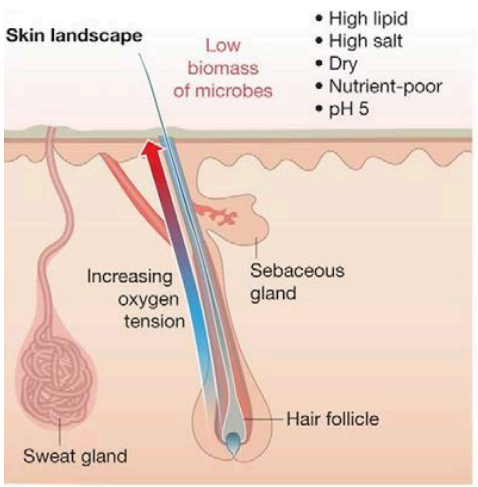



Ivanov, *Cell*, 2009

# The microbiota control the development and function of the immune system





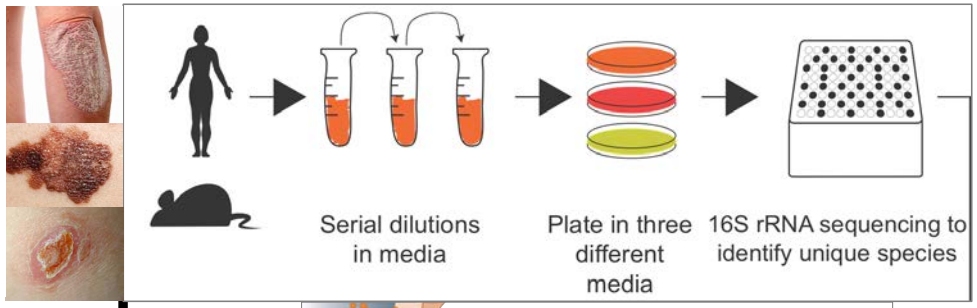

Chen, Nature 2018

# The skin microbiota control tissue immunity

Naik, Science 2012
Naik, *Nature* 2015

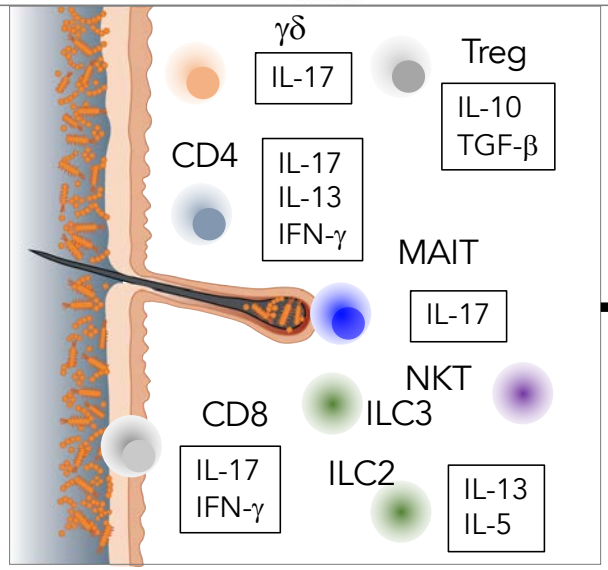
Shruti Naik
(Assistant Professor NYU)

# Defined microbes impose specific immune signature

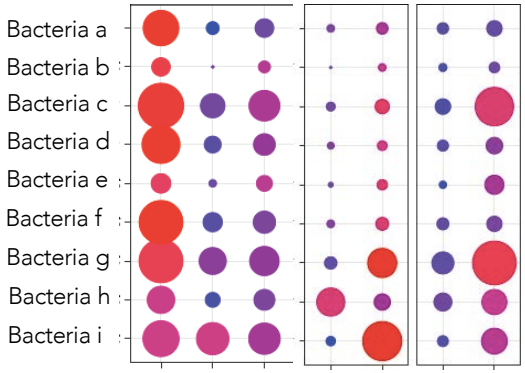


SPF mice

$10^{6/}$ cm$^2$




Cell subsets

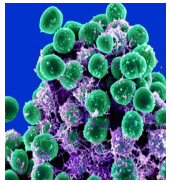


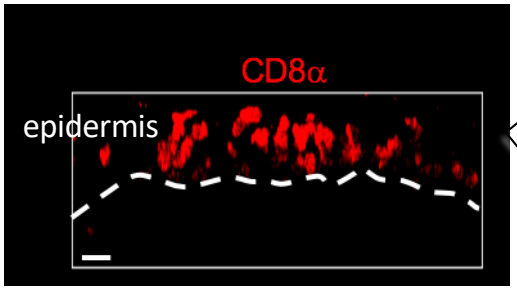

Skin immune signature

Naik, *Science*, 2012
Naik, *Nature*, 2015
Byrd, *STM*, 2017
Ridaura, *JEM*, 2018
Linehan, *Cell*, 2018
Tamoutounour, *PNAS*, 2019
Harrison, *Science*, 2019
Constantinides, *Science*, 2019

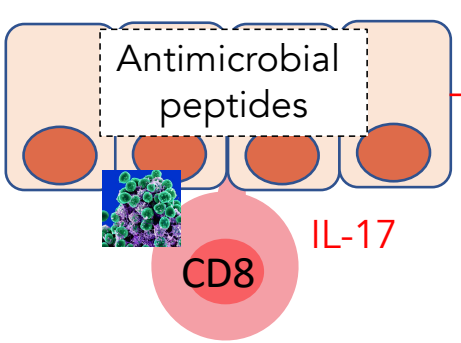
# *S. epidermidis*-induced CD8 T cells promote antimicrobial defense and tissue repair

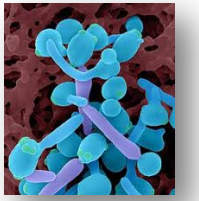
*S. epidermidis*





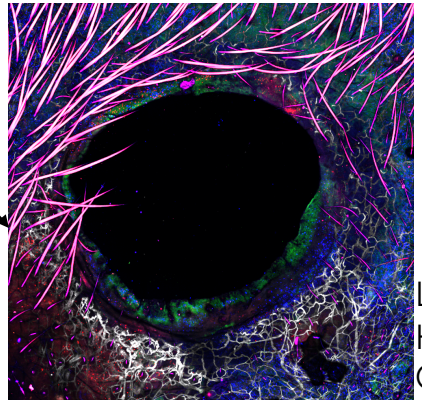

Keratinocytes

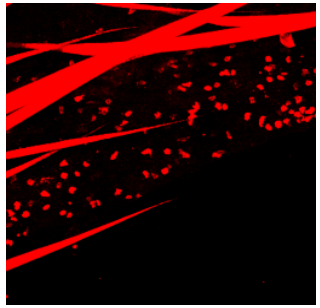


Naik, *Nature*, 2015

Skin wound





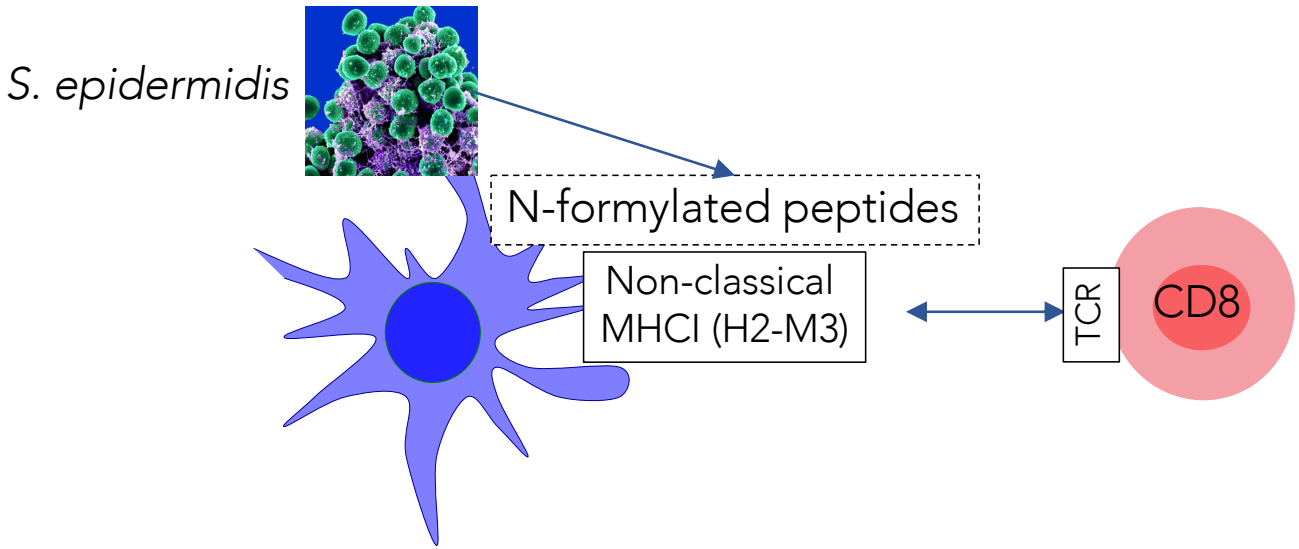
Linehan, *Cell*, 2018
Harrison, Science, 2019
Constantinides, Science, 2019

Microbiota derived Antigens

>

Self-antigens
Pathogens
Food derived antigens
Allergens

# *S. epidermidis* specific CD8 T cells recognize N-formylated peptides antigens via non-classical MHCI



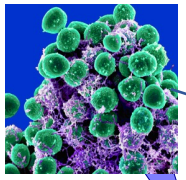

N-formyl methionine peptides: formylation required for initiation of translation in bacteria

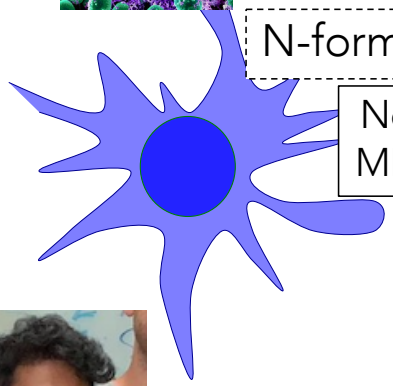
John Linehan (Genentech)

Linehan, *Cell*, 2018

# Commensal derived N-formylated peptides can be highly conserved

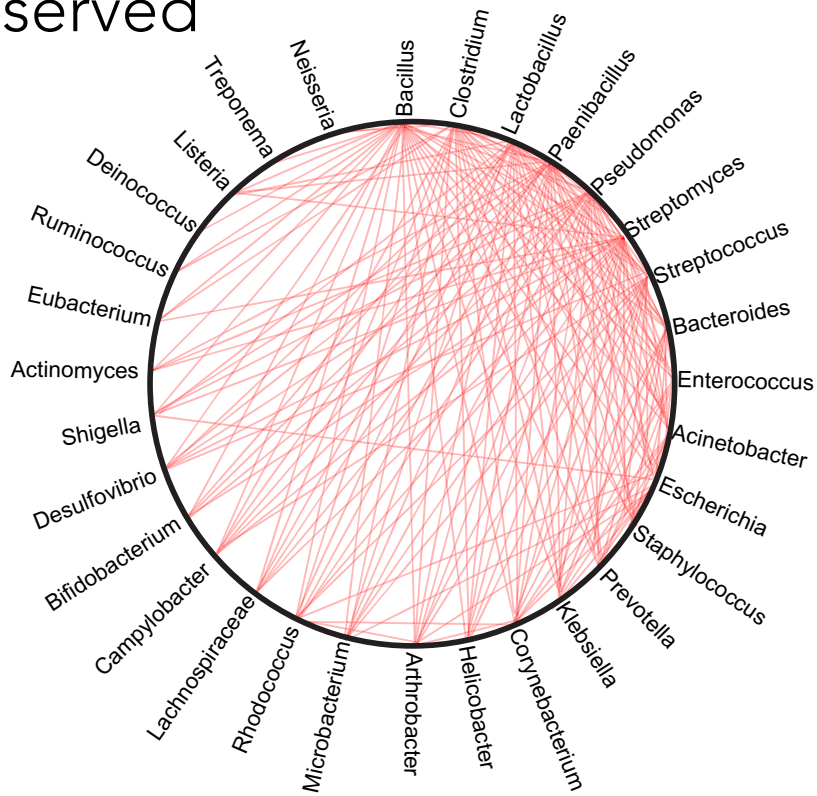
*S. epidermidis*





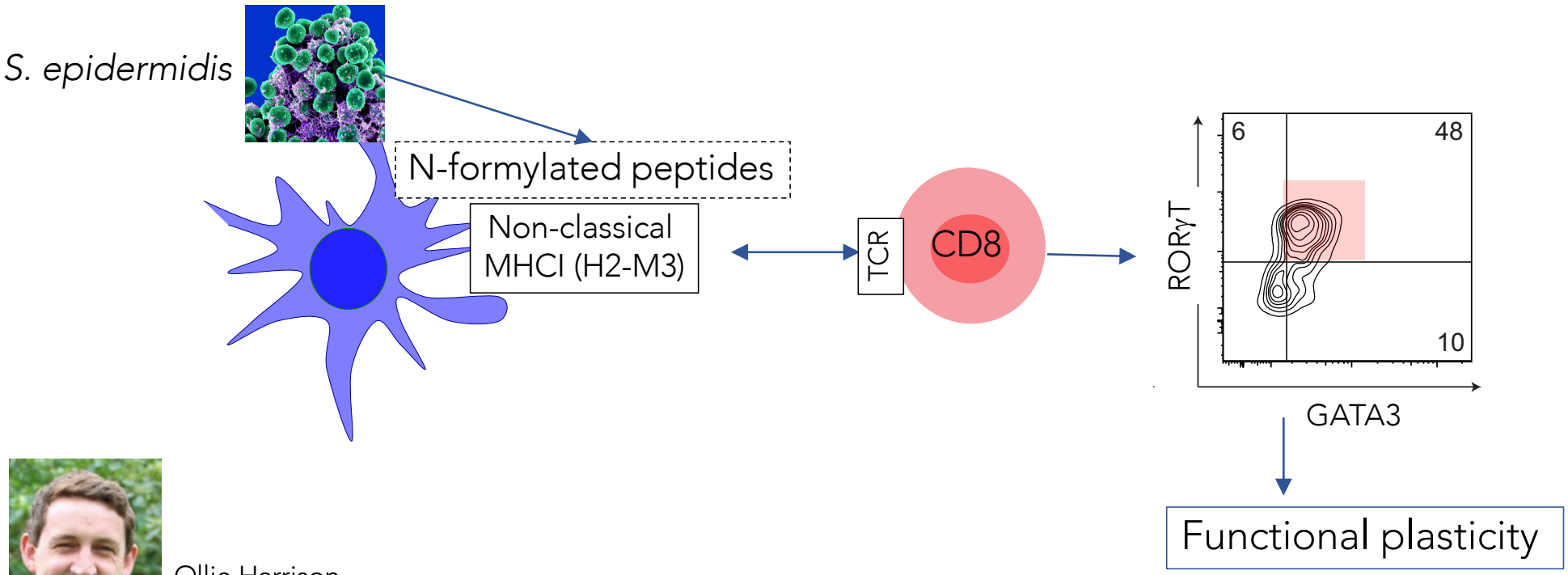
Taylor Farley  Siddharth Krishnamurthy

Fiona Powrie (Oxford) & Federica Sallusto (ETH Zurich)




Red lines connecting 2 genera indicate that they have at least 500 H2M3 Peptides shared between members of these taxa.

# Commensal specific CD8 T cells express a paradoxical Type 17/Type 2 signature

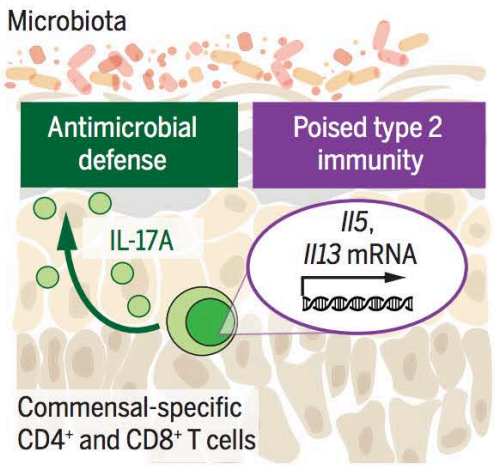


Ollie Harrison
(Assistant Professor Benaroya Institute)

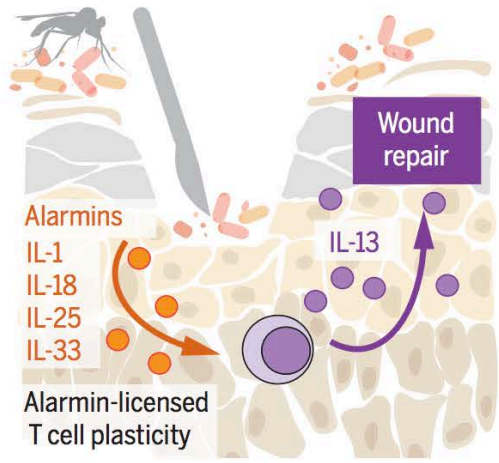
Harrison, *Science*, 2019

# Commensal-specific T cell plasticity promotes rapid tissue adaptation to injury

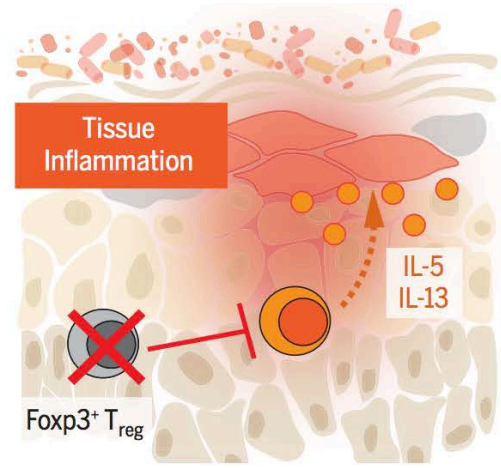
Homeostasis




Tissue injury

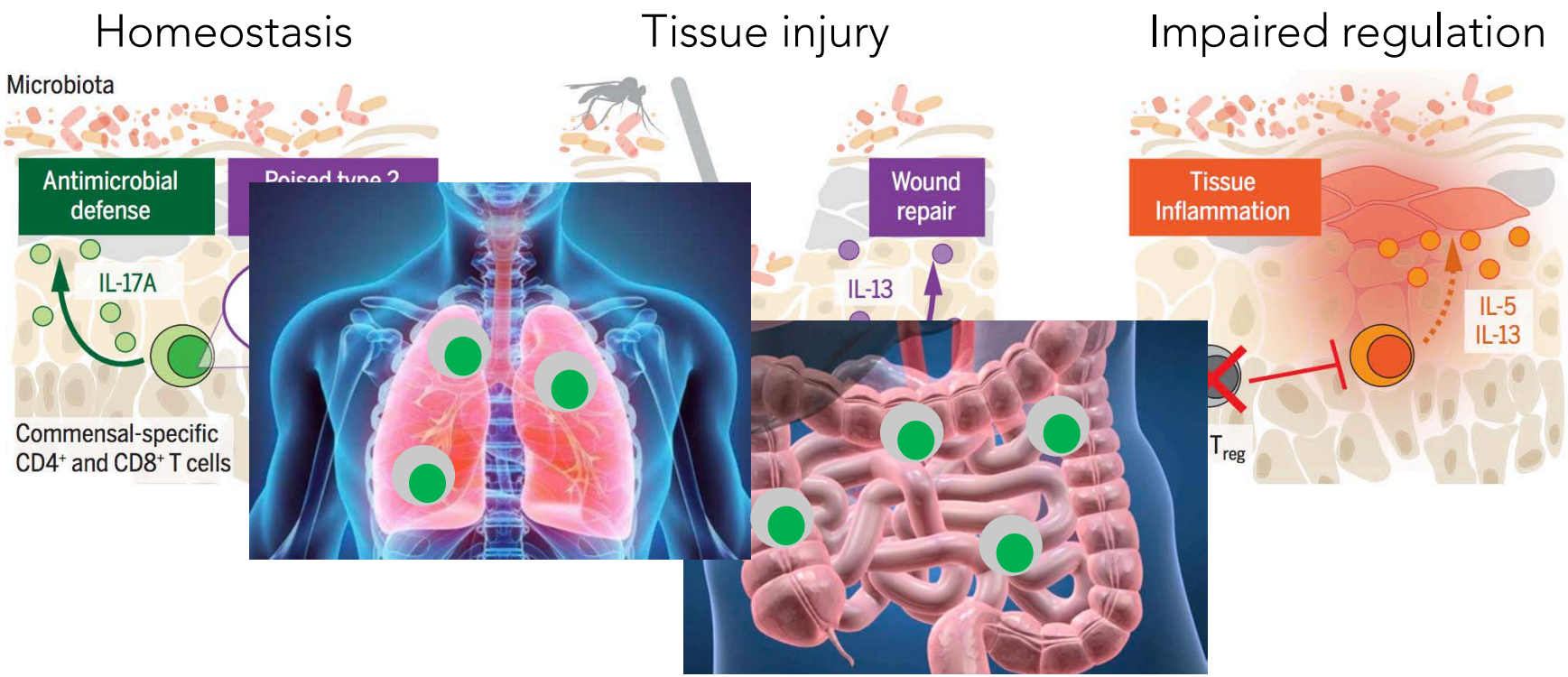



Impaired regulation

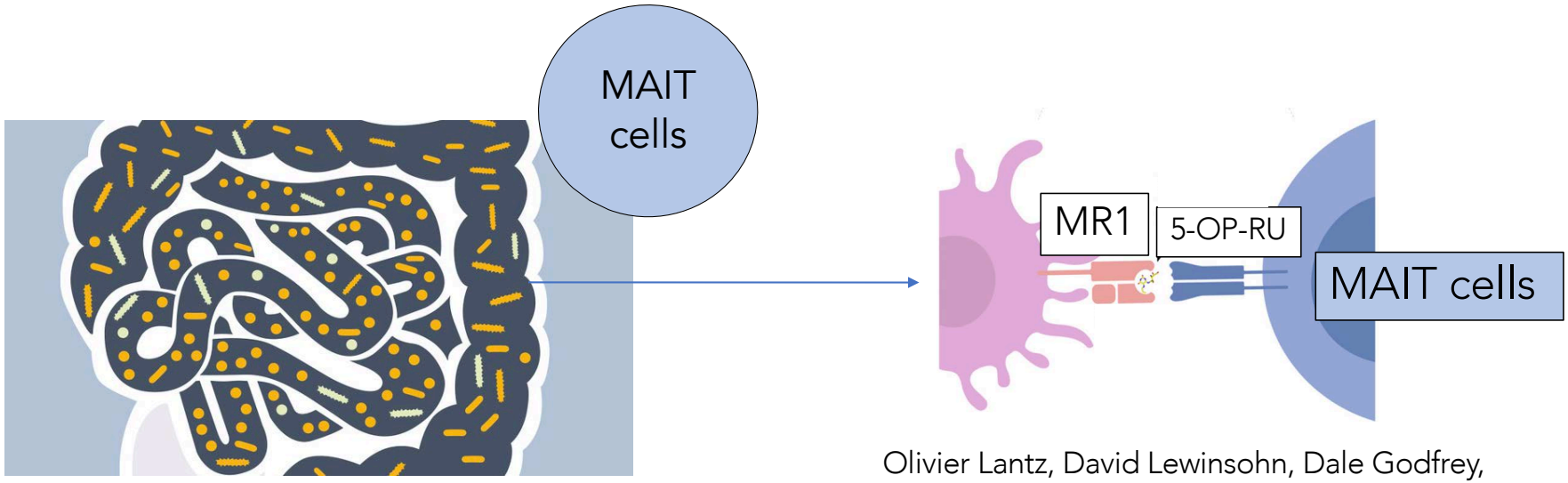



Harrison, *Science*, 2019

# Microbiota specific Tissue resident T cells



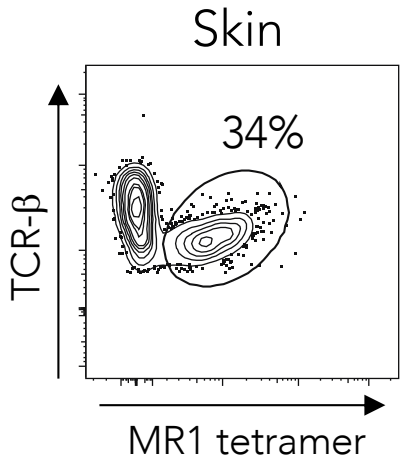
# MAIT cells recognize Antigens derived from the microbial vitamin B2 (riboflavin) metabolic pathway

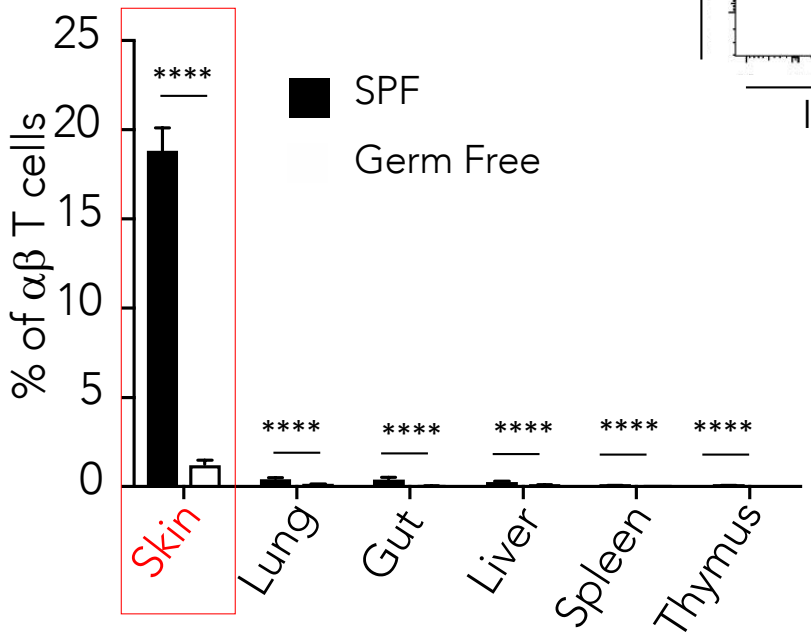


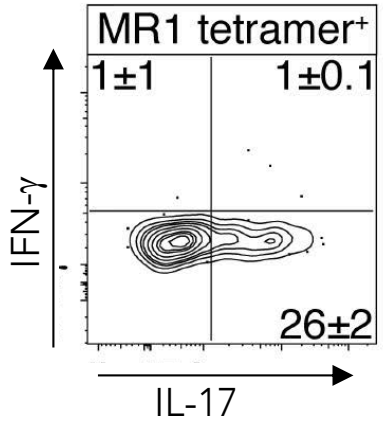

Olivier Lantz, David Lewinsohn, Dale Godfrey,
James McCluskey, Jamie Rossjohn, Paul Klenerman…

- 2-10 % of human blood and skin T cells (up to 45 % in the liver)
- Frequencies are low in mice (< 1%)….

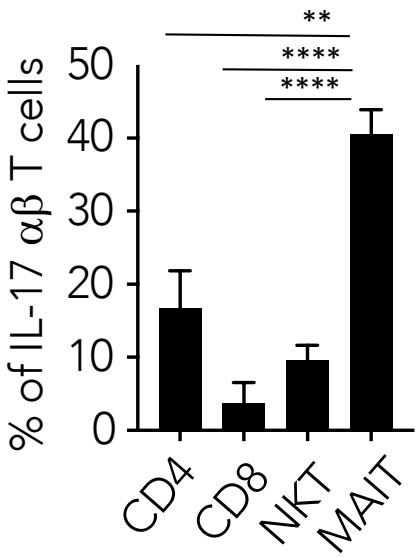
# MAIT cells are highly represented within the skin



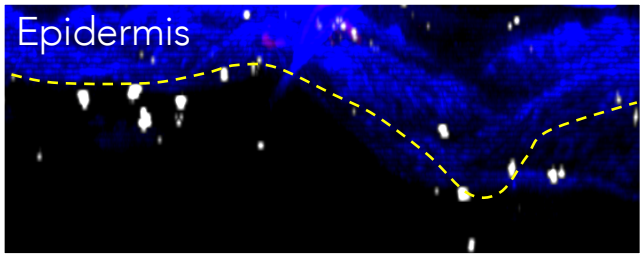

Skin



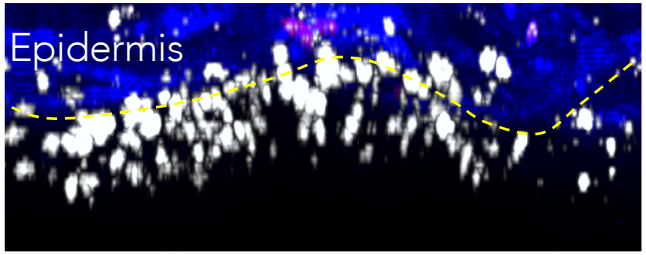
Mike Constantinides

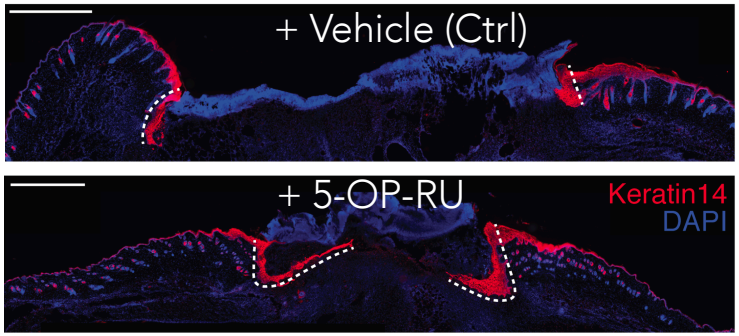
# Local increase of MAIT cells promotes Tissue repair

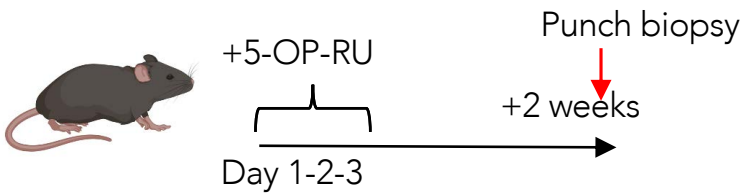
Vehicle (Ctrl)

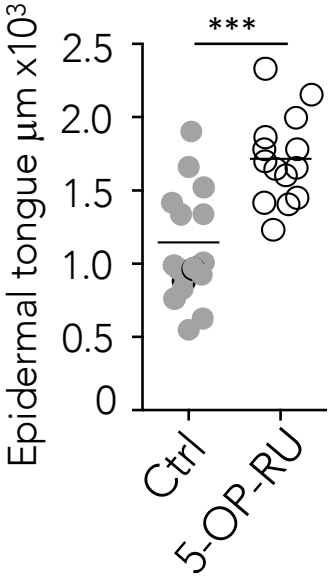



Topical 5-OP-RU

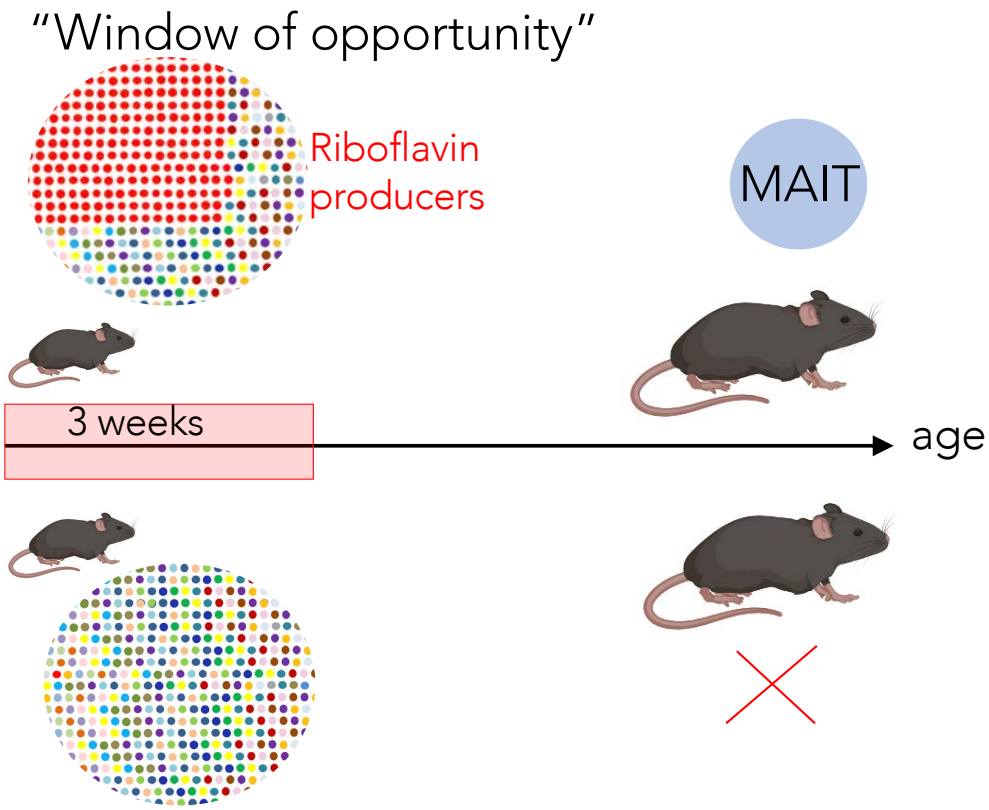


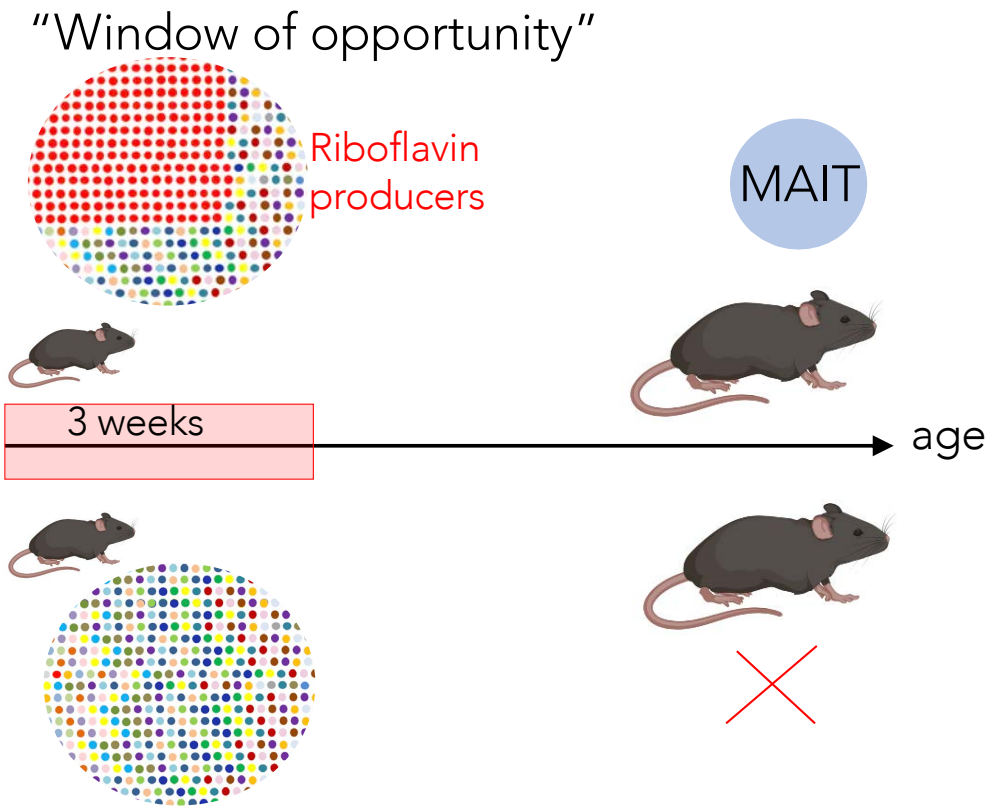



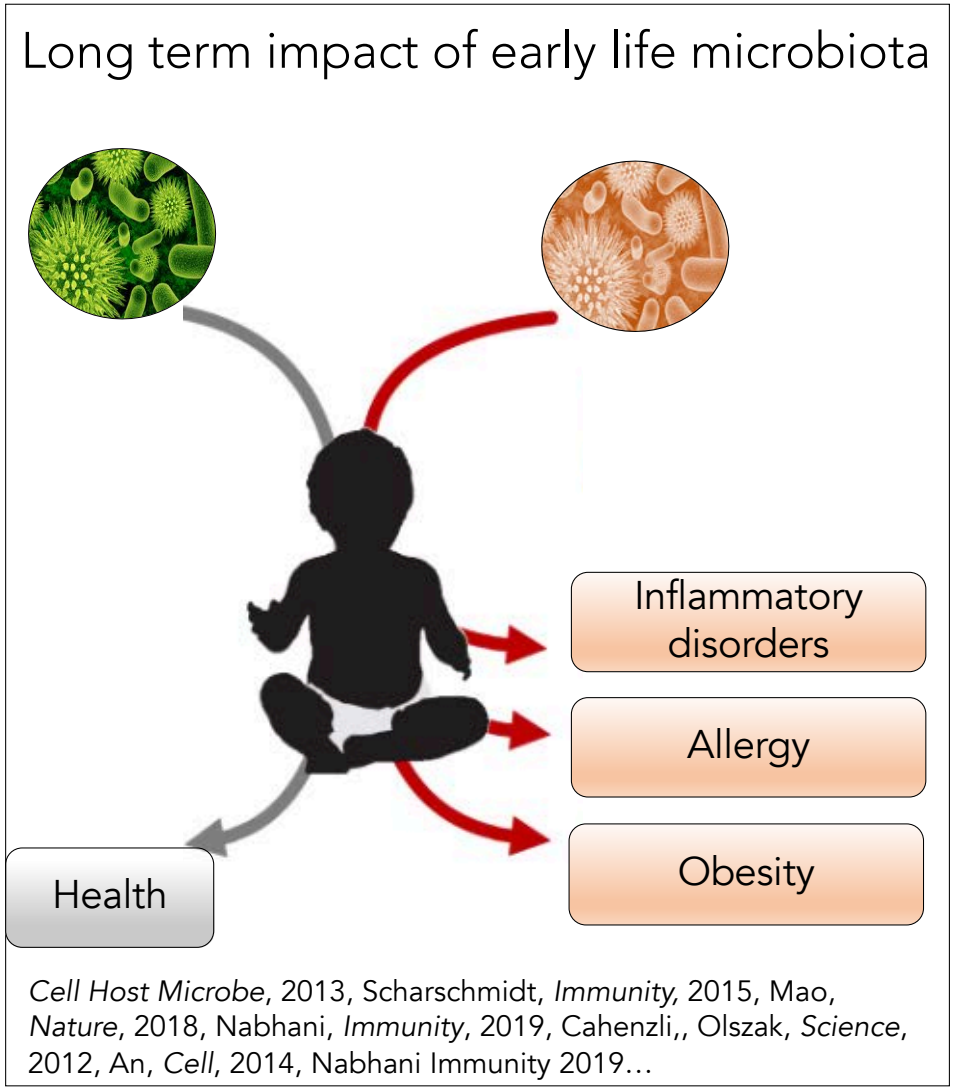



MAIT cells depend on exposure to defined microbes during a specific developmental window, after which development is permanently impaired



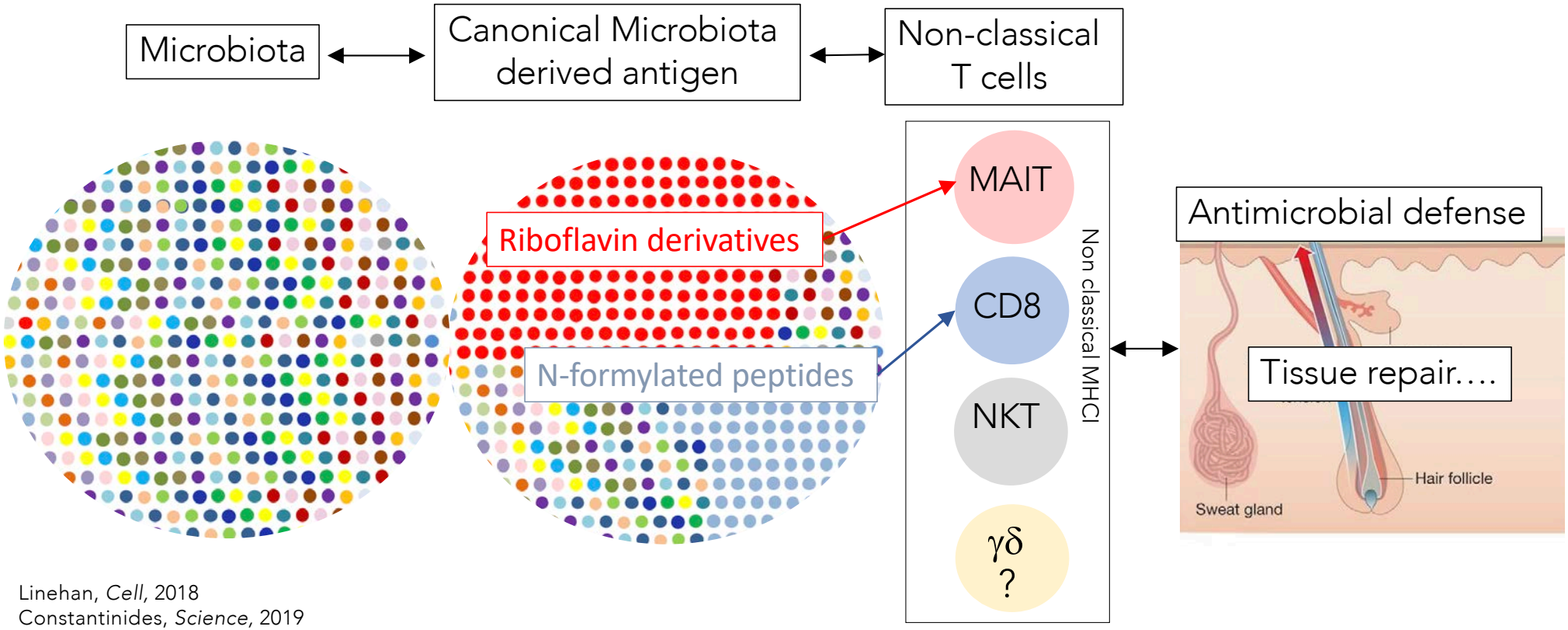

Constantinides, *Science*, 2019




*Cell Host Microbe*, 2013, Scharschmidt, *Immunity*, 2015, Mao, *Nature*, 2018, Nabhani, *Immunity*, 2019, Cahenzli,, Olszak, *Science*, 2012, An, *Cell*, 2014, Nabhani Immunity 2019…

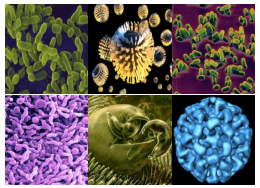
# Conserved microbiota antigens/non-conventional T cell: promotion of tissue homeostasis



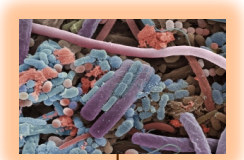

Linehan, *Cell*, 2018
Constantinides, *Science*, 2019

# Pathogenic immunity to the microbiota

Infection



Immunity

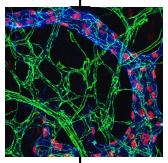


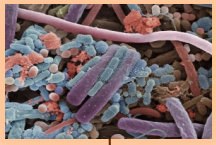
Tissue inflammation

Oldenhove, *Immunity*, 2011
Hand, *Science*, 2012
Hill, *Nature*, 2014
Byrd, STM, 2017
Harrison, *Immunity* , 2017

Infection/defect in immuoregulation

Tissue damage

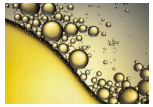


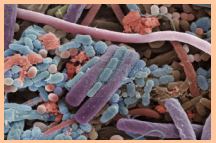


Loss of tolerance/ Inflammation

Morais de fonceca, *Cell*, 2016
Xu, *Nature*, 2018
Linehan, *Cell*, 2018

Diet





Immunity

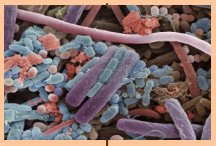
Tissue inflammation

Ridaura , JEM, 2018
Harrison, *Science*, 2019

Primary Deficiencies

Gain-of-function mutations in PI3Kδ

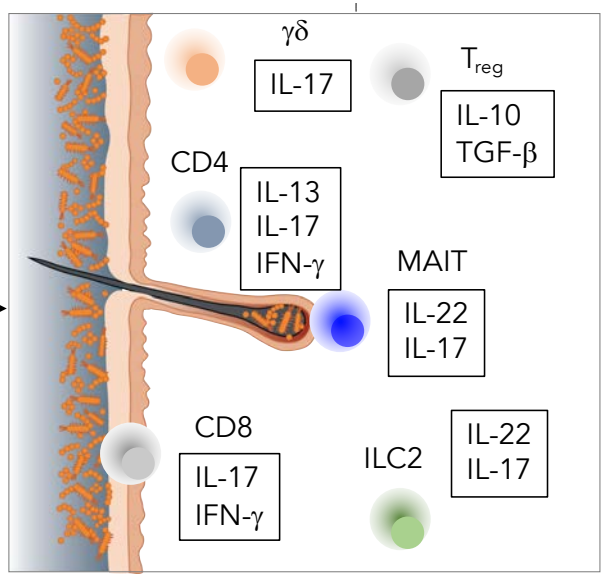
Immunity



Self-reactivity

Preite & Schwartzberg, *Nature Immunology*, 2018

# Mining the Microbiome…




For a novel class of therapies

- Microbiota transplant
- Microbiota consortium
- Microbiota derived products/antigens
- Prebiotic

Control of Infection

Vaccine

Immunotherapy

Autoimmunity

Metabolic syndrome

Allergy

Inflammatory Disorder

As a biomarker

- Microbial communities
- Function
- Metabolites
- Immune response to the microbiota

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