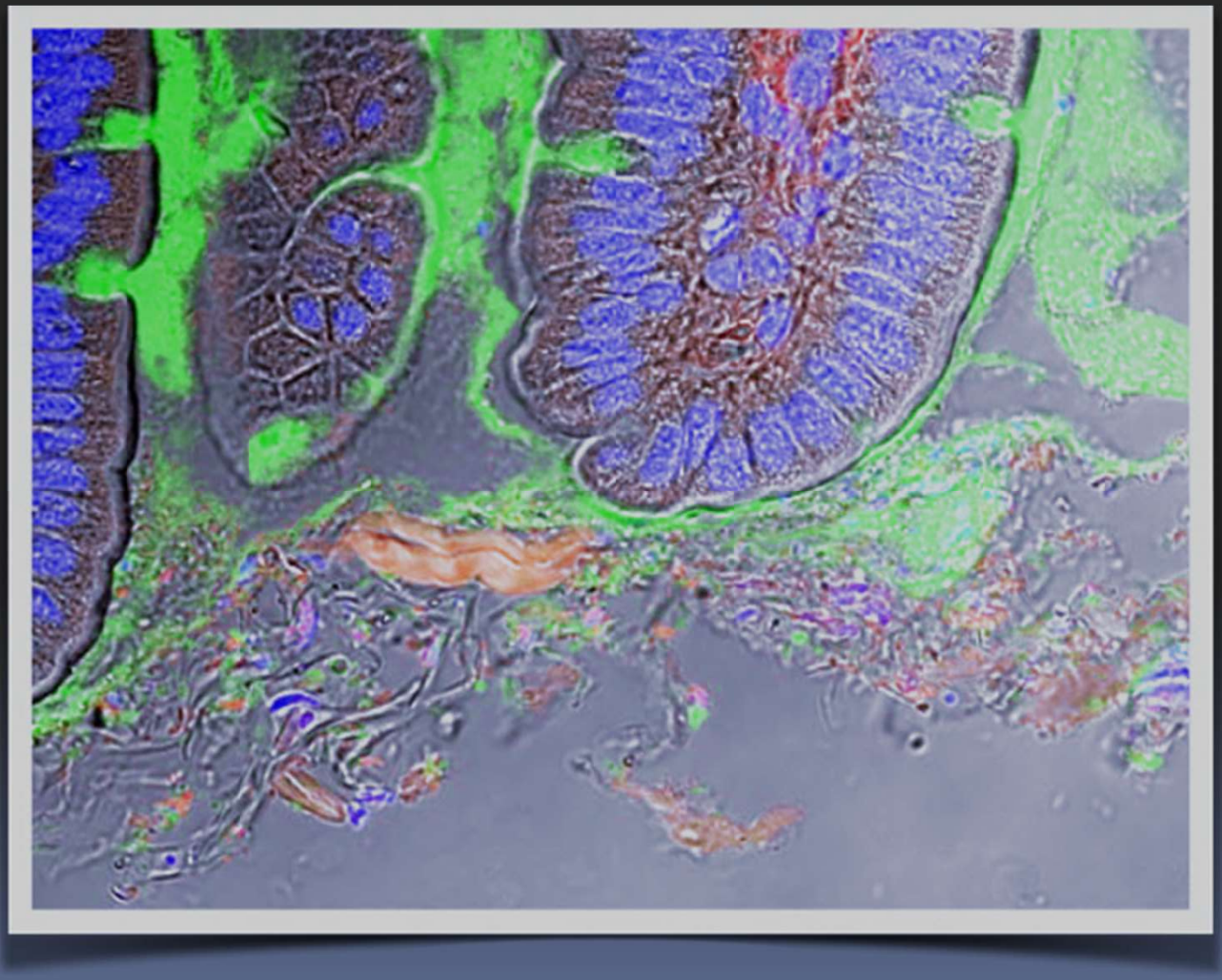
Intestinal Microbiota and Enteric Vaccine Design



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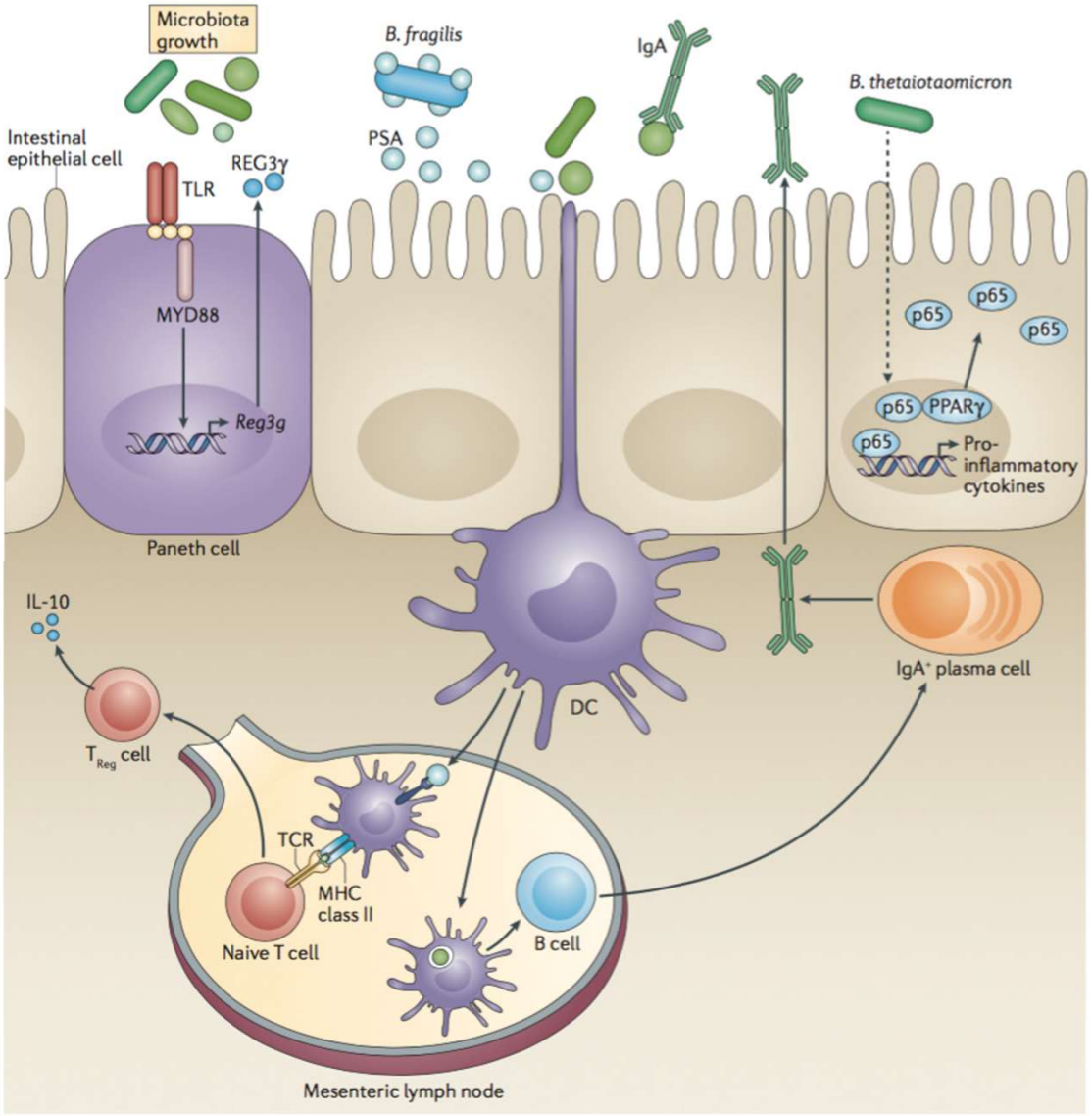
Global Vaccine and Immunization Research Forum
Johannesburg, South Africa 2016

World Health Organization
Bill & Melinda Gates foundation
NIH National Institute of Allergy and Infectious Diseases

modulation of intestinal immunity
by commensal microorganisms

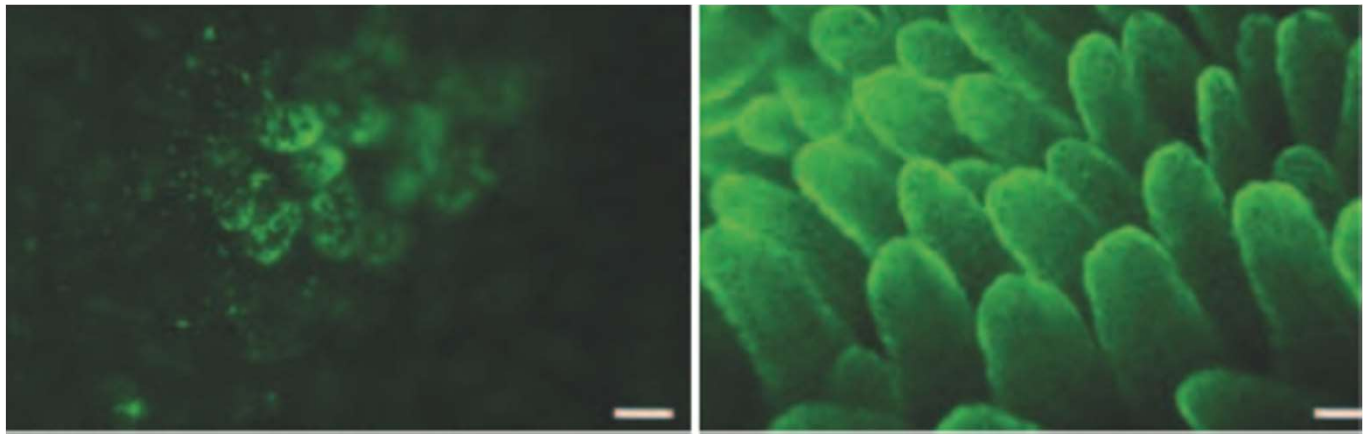


microbiota prepare us for attack

- stimulate TLRs
- sustain gut “innate immune tone”
- stimulate regulatory T cells
- induce IgA production
- modulate pro-inflammatory cytokines

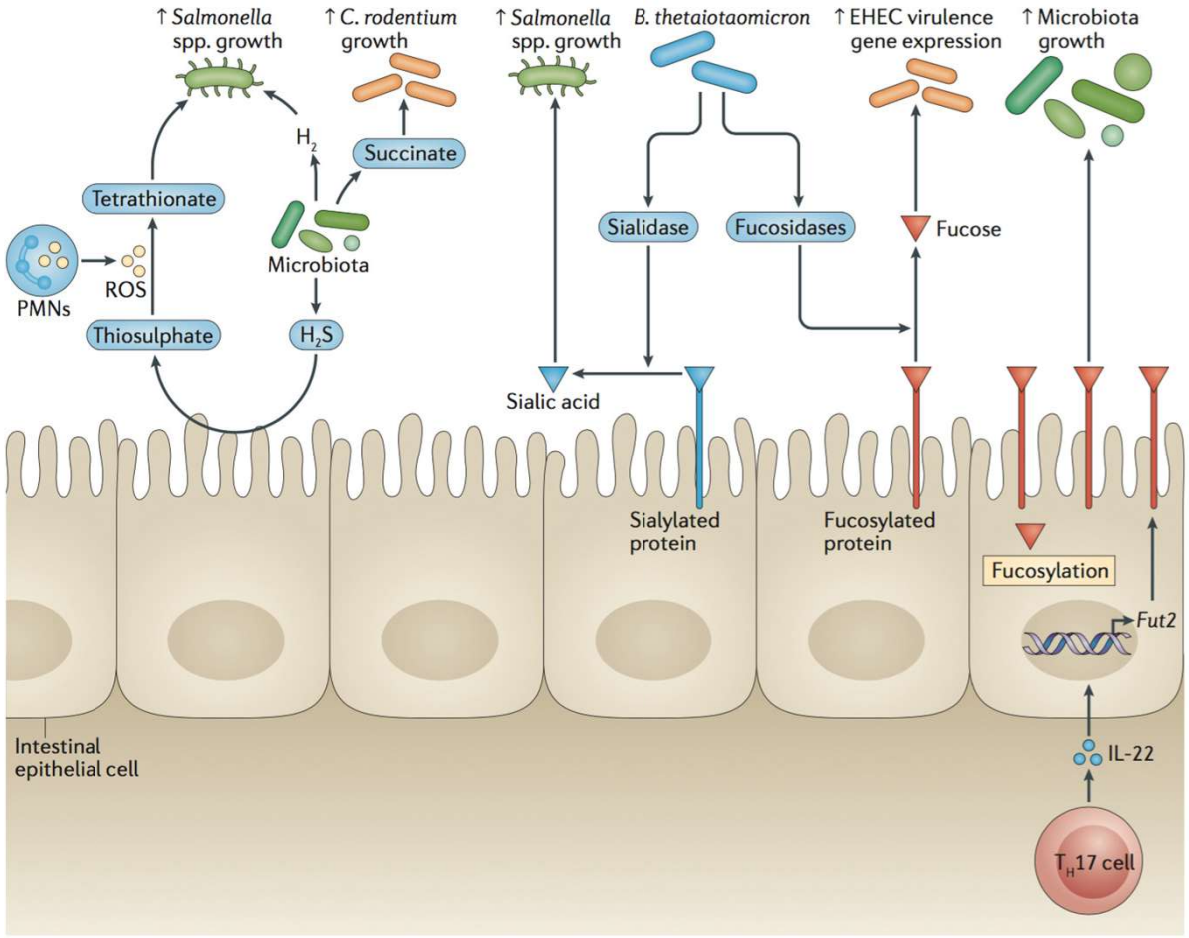
Perez-Lopez, *et al* Nature Rev Immunology 2016

TLR4 sensing changes the sugar landscape in the intestine



Pickard, *et al* Nature, 2014

pathogens exploit microbiota to colonize

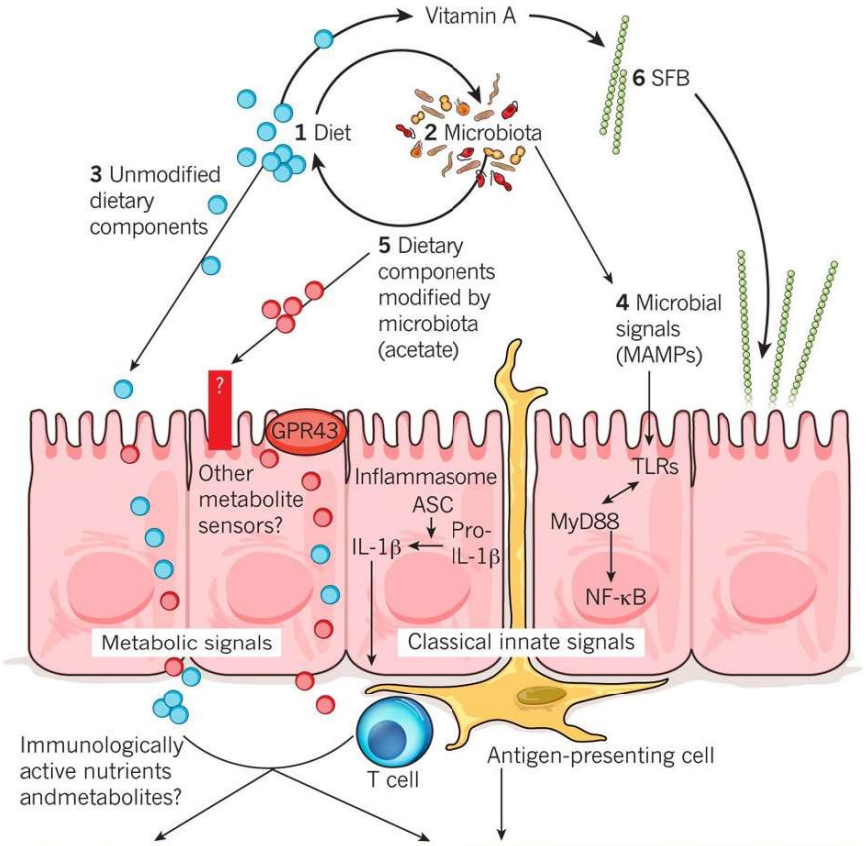


use byproducts of microbiota

- for anaerobic respiration
- as carbon sources
- alternative energy source (H_2)
- to modulate gene expression

Perez-Lopez, *et al* Nature Rev Immunology 2016

nexus of nutrient metabolism and immunity



T cell

mTOR
Promotes T_H1, T_H2, T_H17 cell differentiation; inhibits T_{reg} cell differentiation

RAR–RXR
Promotes intestinal T-cell homing; promotes T_H2 and T_{reg} cell differentiation

VDR–RXR
Promotes T_{reg} cell differentiation; inhibits T_H1 and T_H17 cell differentiation

AHR
Promotes T_H17 and T_{reg} cell differentiation

LXR and PPAR
Control T-cell differentiation

Antigen-presenting cell

TLRs

Inflammasomes

mTOR
Modulates DC function and differentiation

RAR–RXR and VDR–RXR

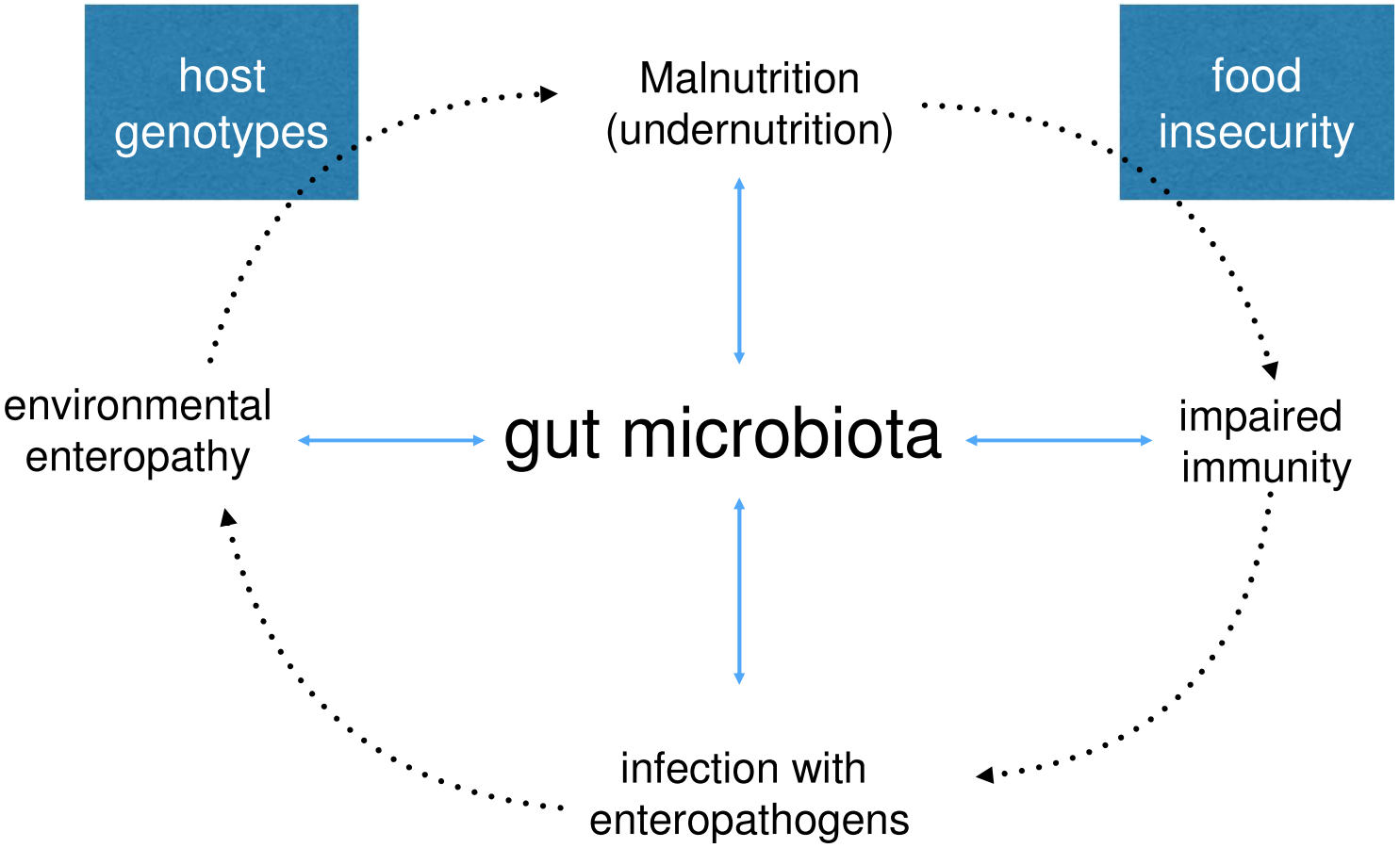
AHR
Modulates DC differentiation

PKR
Regulates inflammatory responses

GPR120
Inhibits inflammatory responses in macrophages

- nutrients shape microbial community
- microbes alter nutritional value
- MAMPs>modify local immunity
- immune system responds to microbial products

Andy Kau, Nature 2011

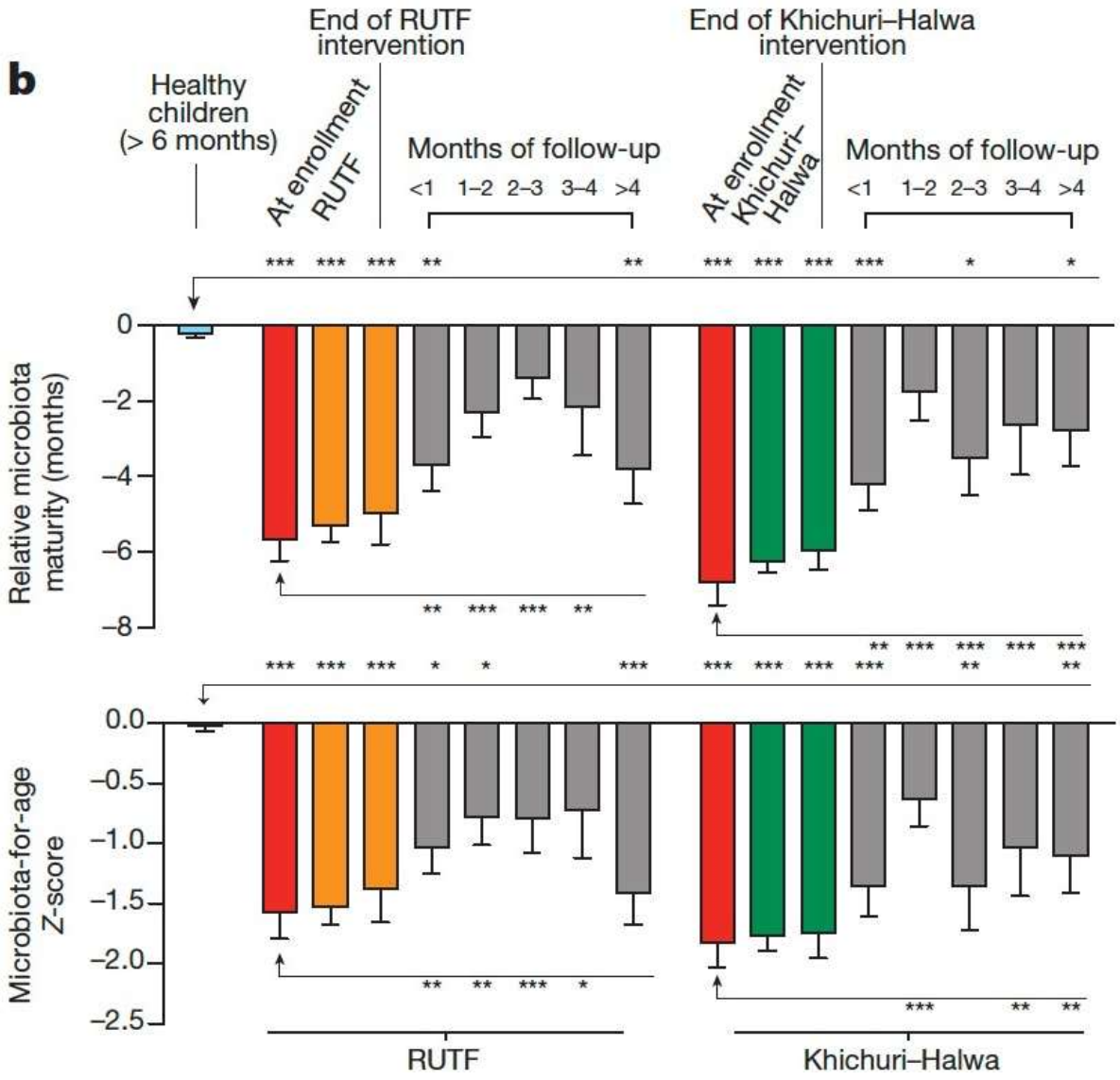


Andy Kau, Nature 2011

microbiota considerations for vaccines

- nutritional interventions to optimize vaccine efficacy?
  - severe acute malnutrition impacts on microbiota
  - can we optimize nutrient supplementation?

immaturity in gut microbiota
persists after nutritional replacement

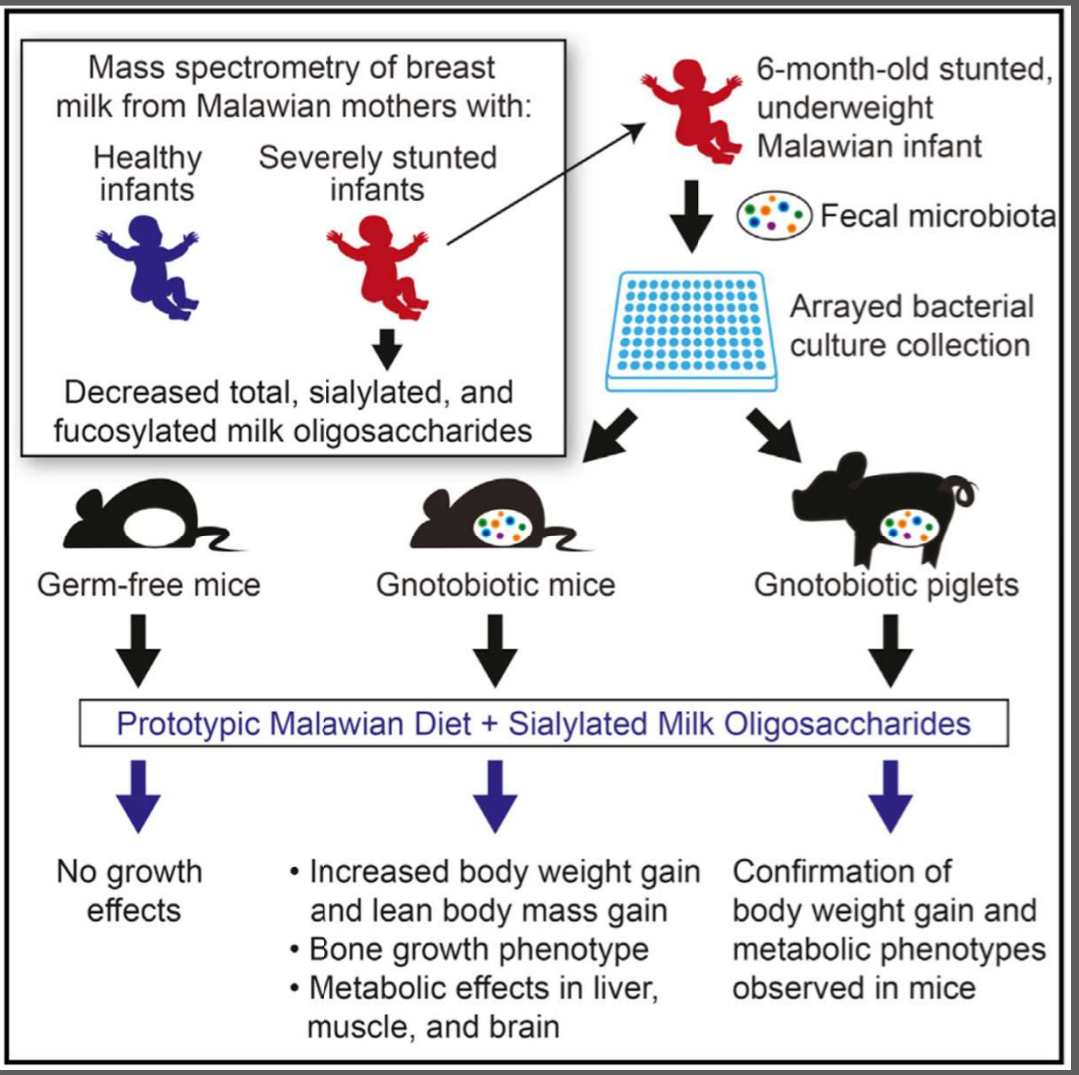


severe acute malnutrition

- microbiota immaturity
- only partially ameliorated by nutritional interventions

Subramanian, *et al. Nature* 2014

human milk oligosaccharides
effects on microbiota



HMOs as prebiotics

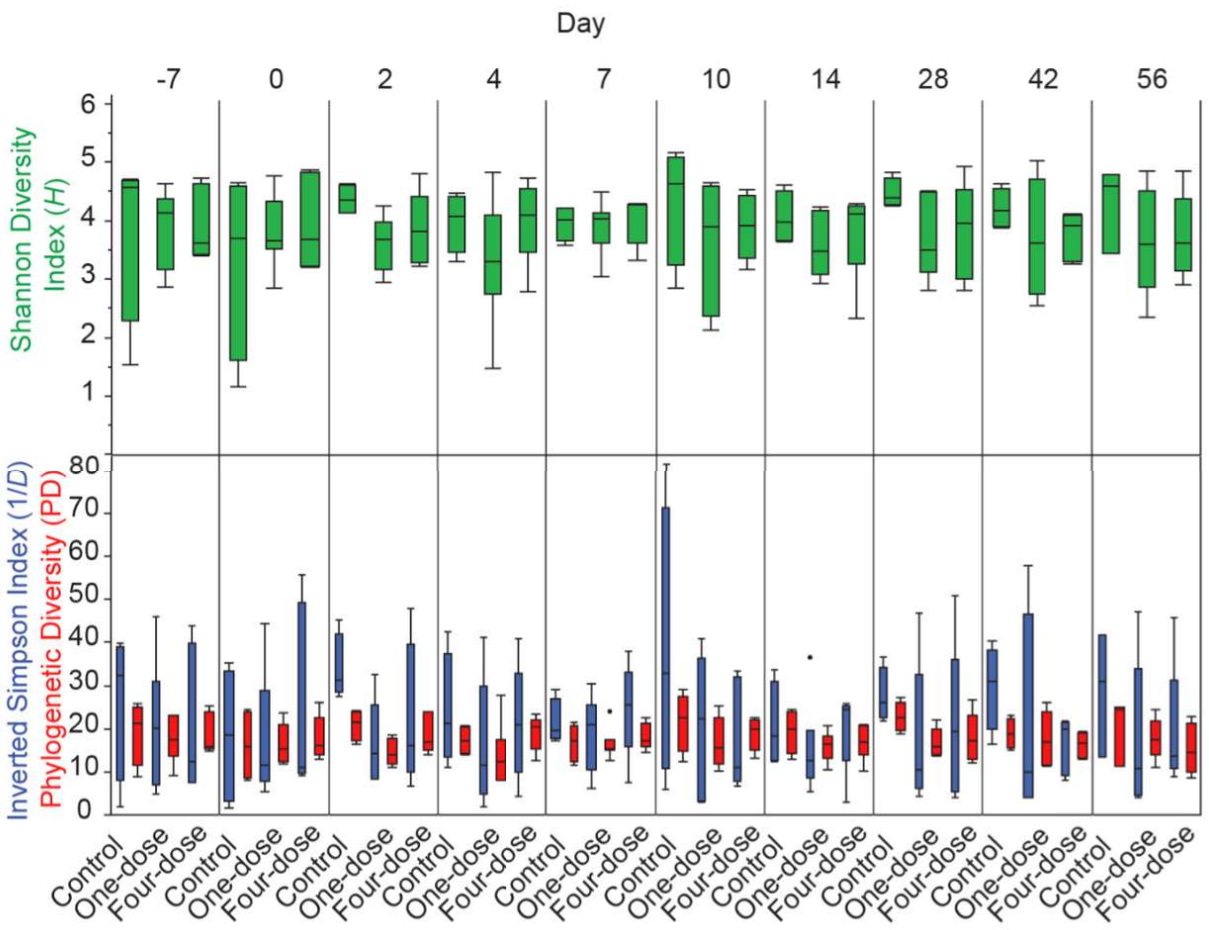
- promote beneficial bacteria
- compete for pathogen binding
- shape microbiota development

De Leoz J Proteome Research 2014

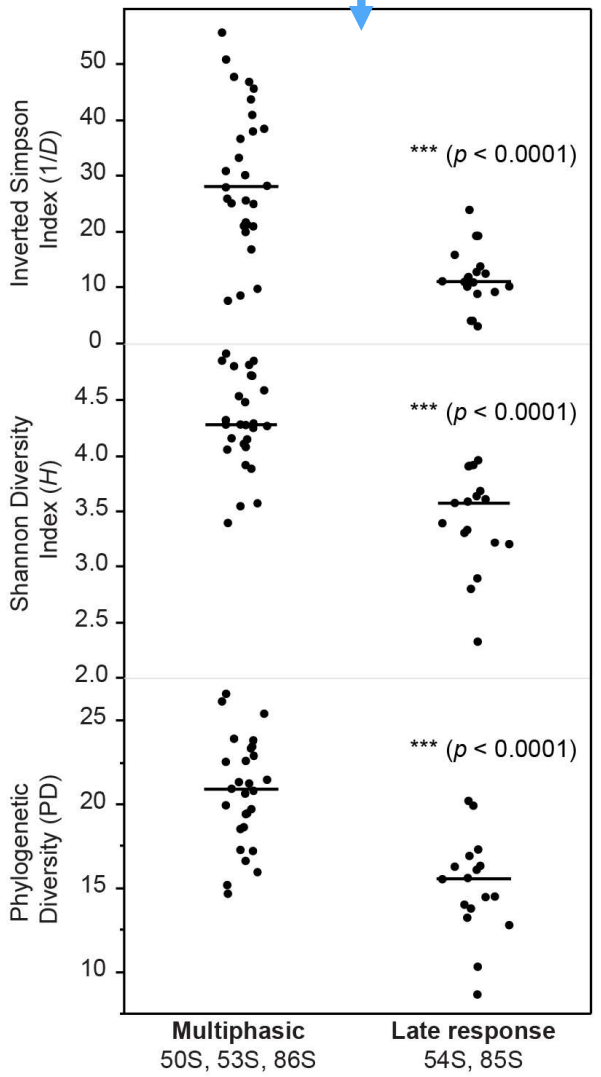
Charbonneau *et al.* Cell 2016

Ty21a live-attenuated oral typhoid vaccine

vaccine effects on microbiota

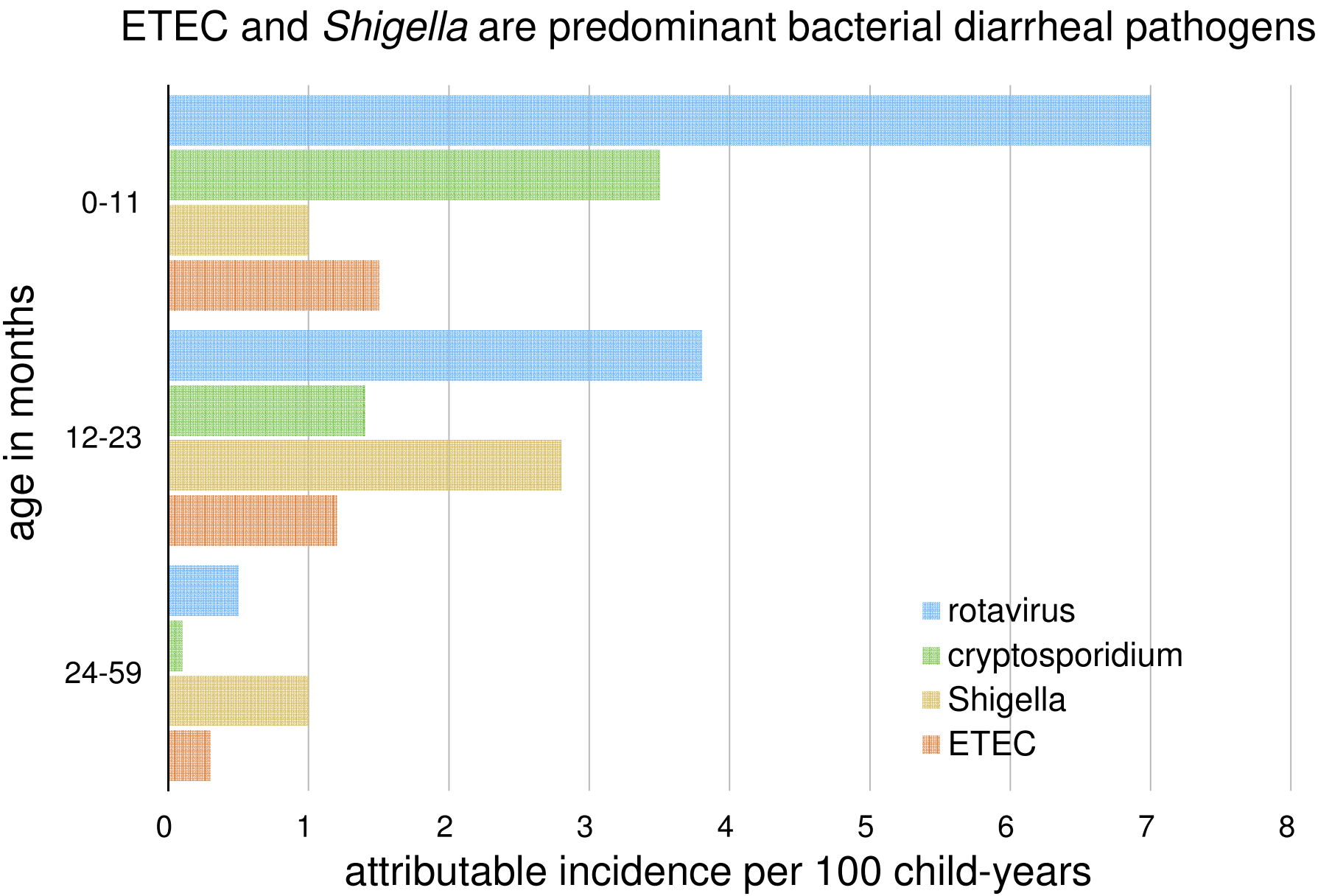


microbiota effects on vaccine



Eloe-Fadrosh, *et al PlOS One* 2013

Global Enteric Multicenter Study (GEMS)



from Kotloff et al. Lancet 2013; 382: 209-222

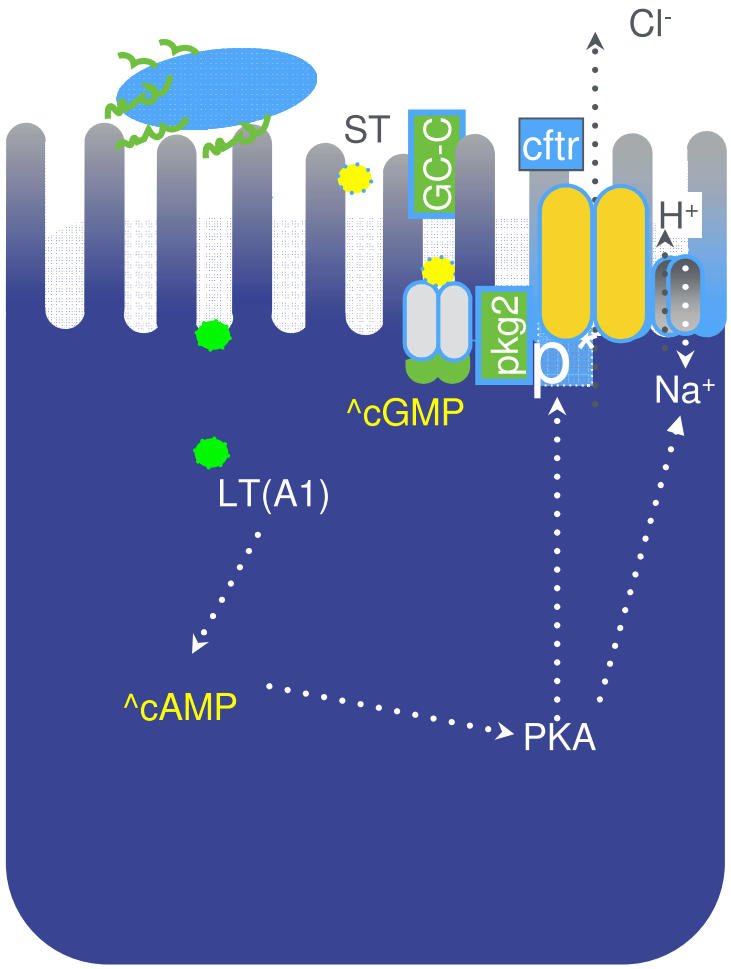
Pathogens associated with deaths due to diarrhea

GEMS data

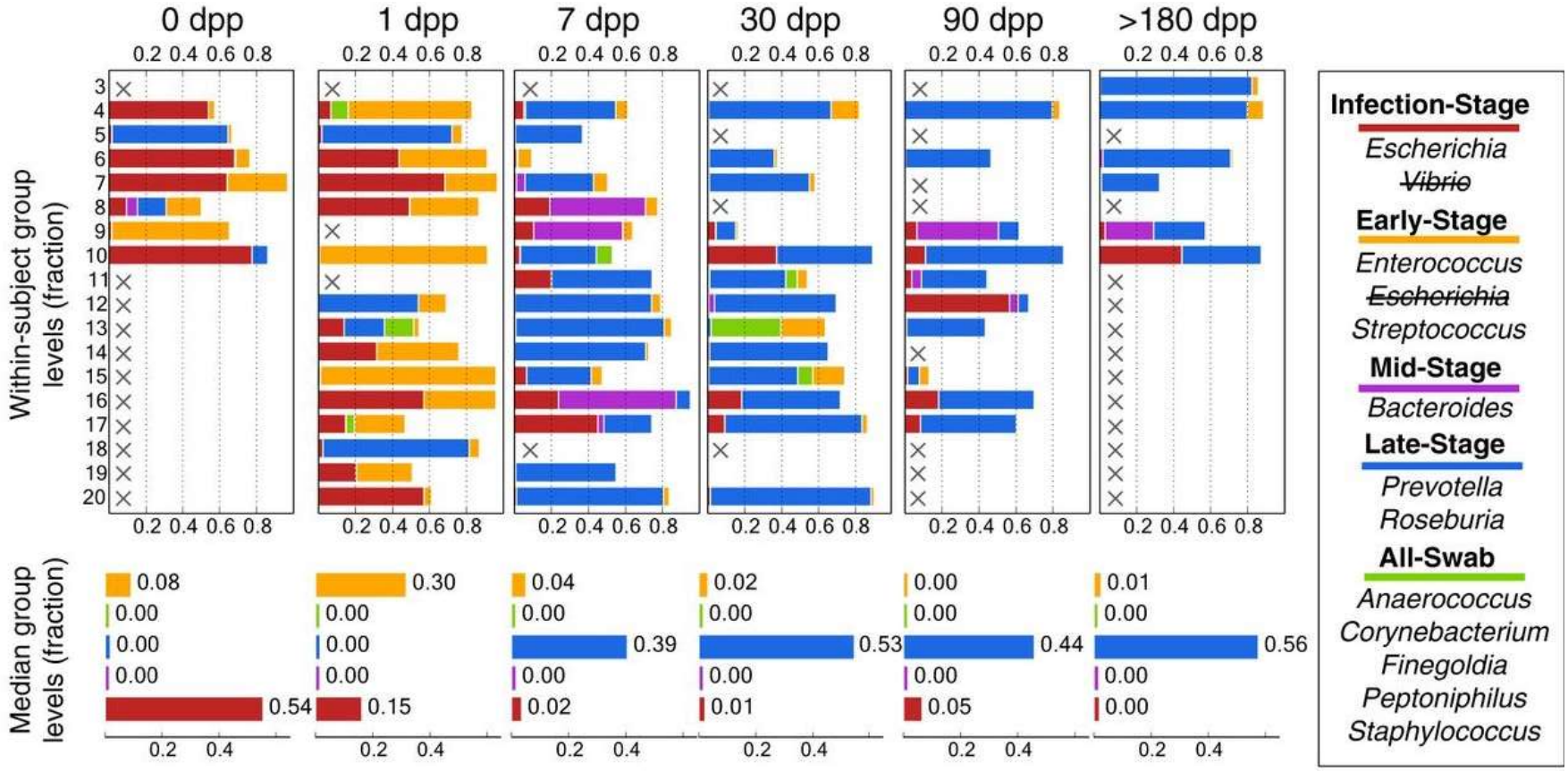
Kotloff et al. Lancet 2013; 382: 209-222

ETEC pathogenesis

classical paradigm



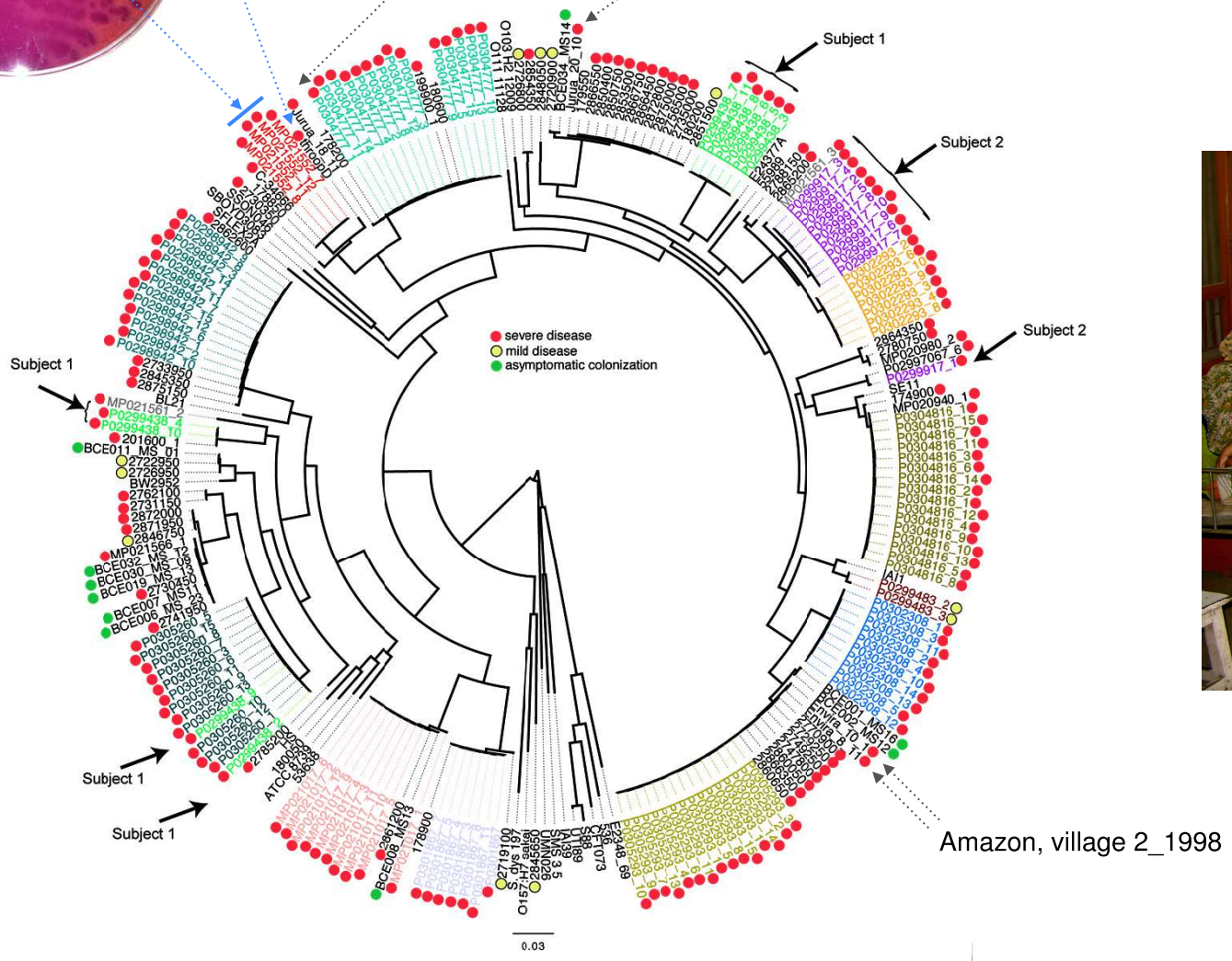
Gut microbial succession after ETEC infection



Lawrence A. David et al. mBio 2015; doi:10.1128/mBio.00381-15

Parkland, 1975

Amazon, village 1_1998

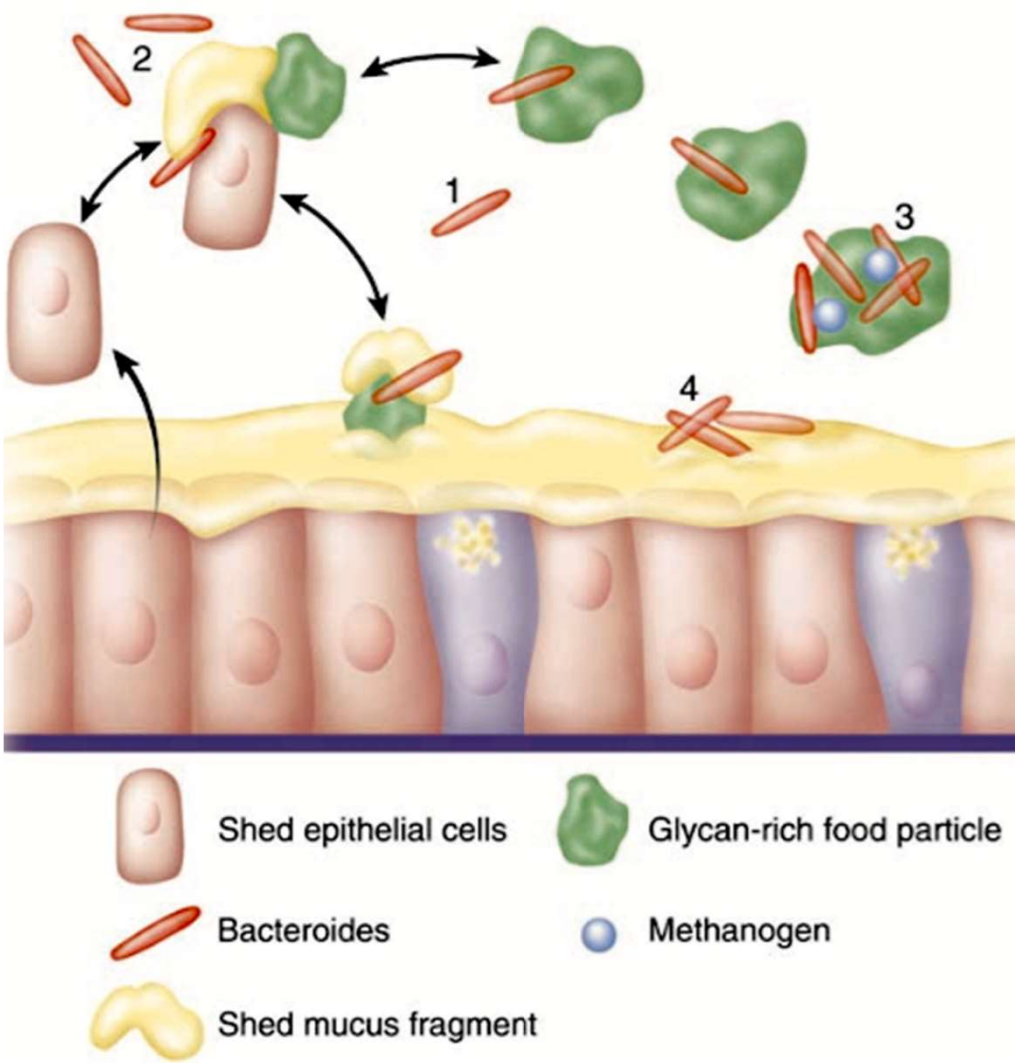


Amazon, village 2_1998

Clonality of ETEC in stool cultures from patients with severe diarrheal illness

mBio 2015

Gut microbiota are “glycophiles”



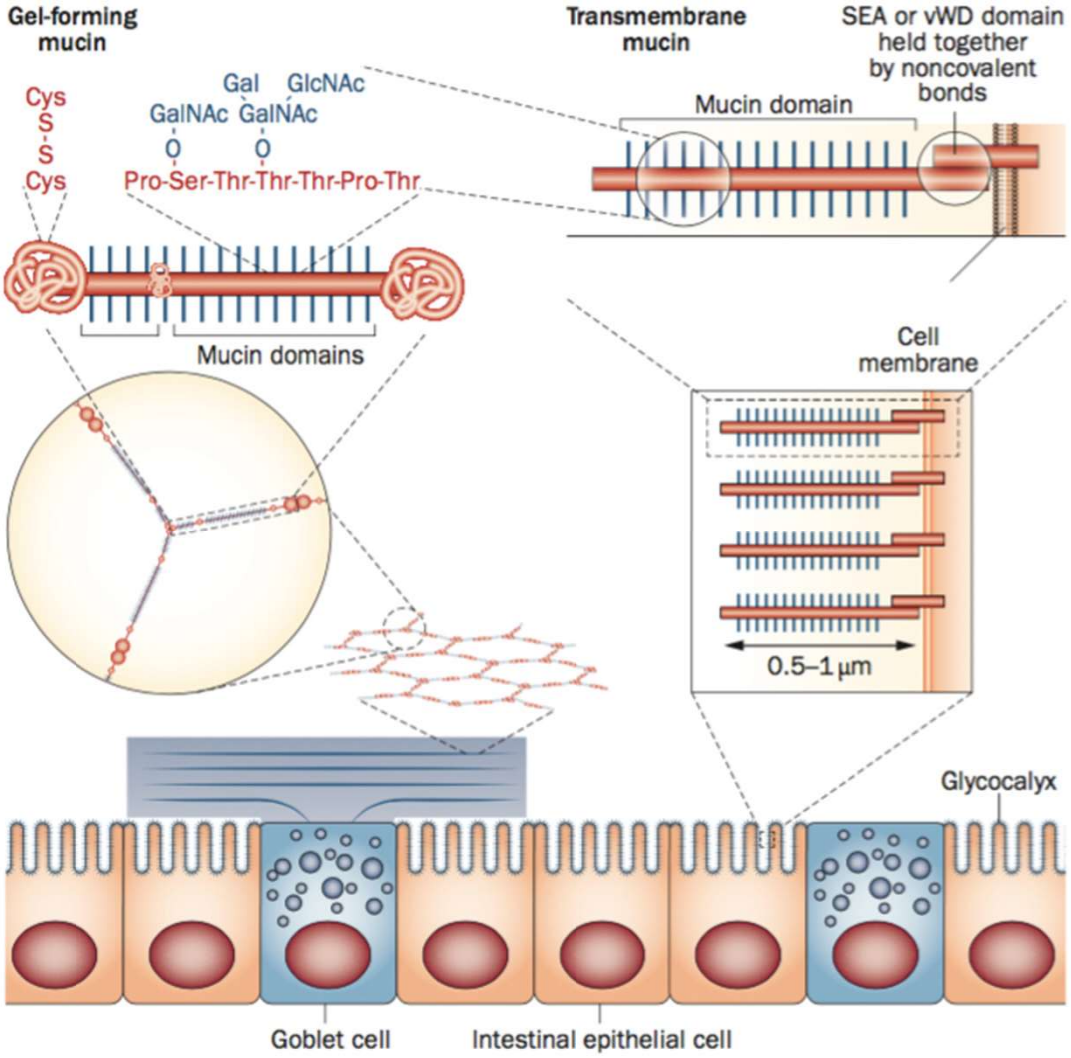
seminal studies on *B.* “*theta*”

- gut glycans induce OMP lectins, hydrolases
- in absence of exogenous dietary glycans digest mucins

Sonnenburg, *et al*. Science 307 (25) March, 2005

intestinal glycans

targeting and manipulation by pathogens

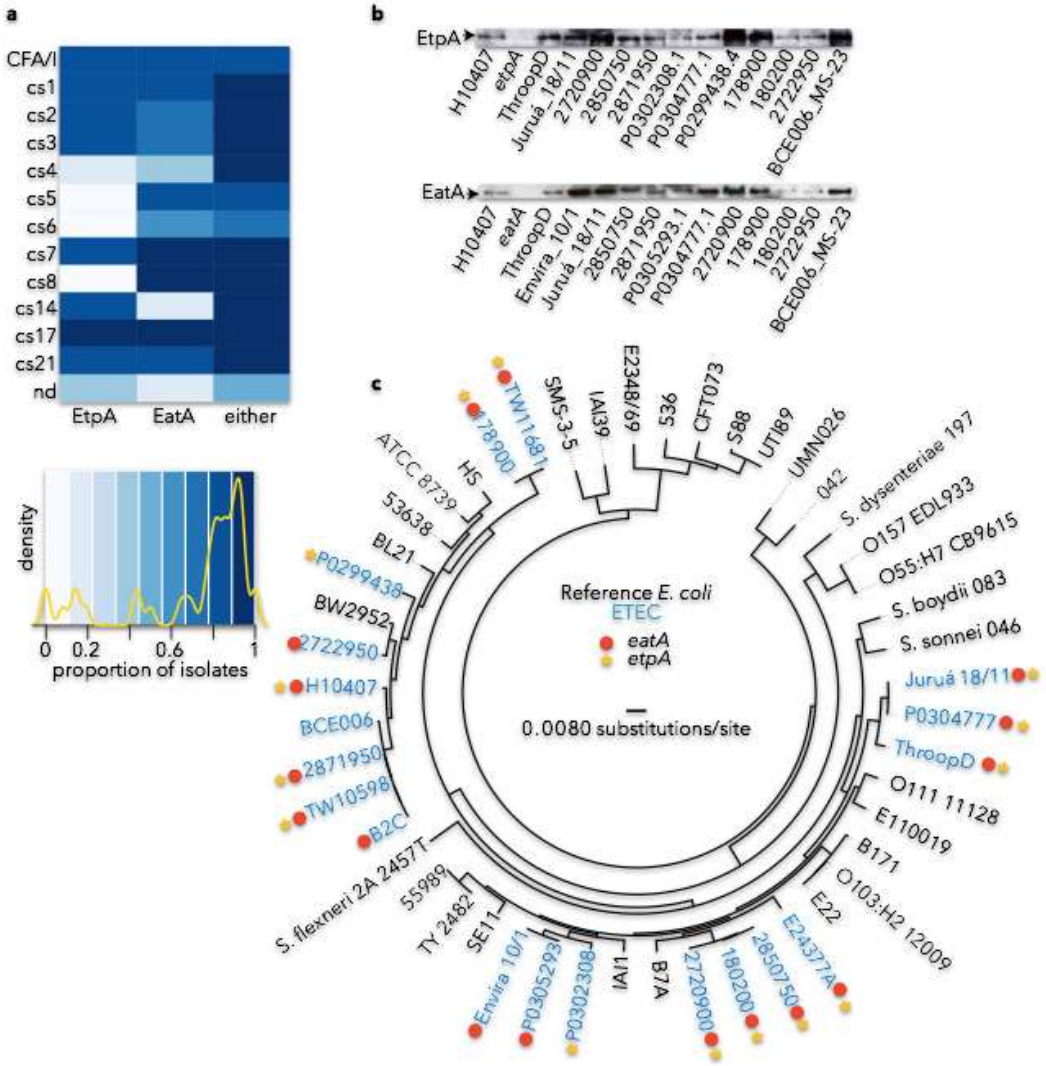


Johansson, *et al* Nature Biotechnology, 2013

ETEC as pathogens must:

- compete with commensals
- traverse protective mucin
- engage the epithelial surface
- deliver toxin payloads

conservation of novel ETEC antigens

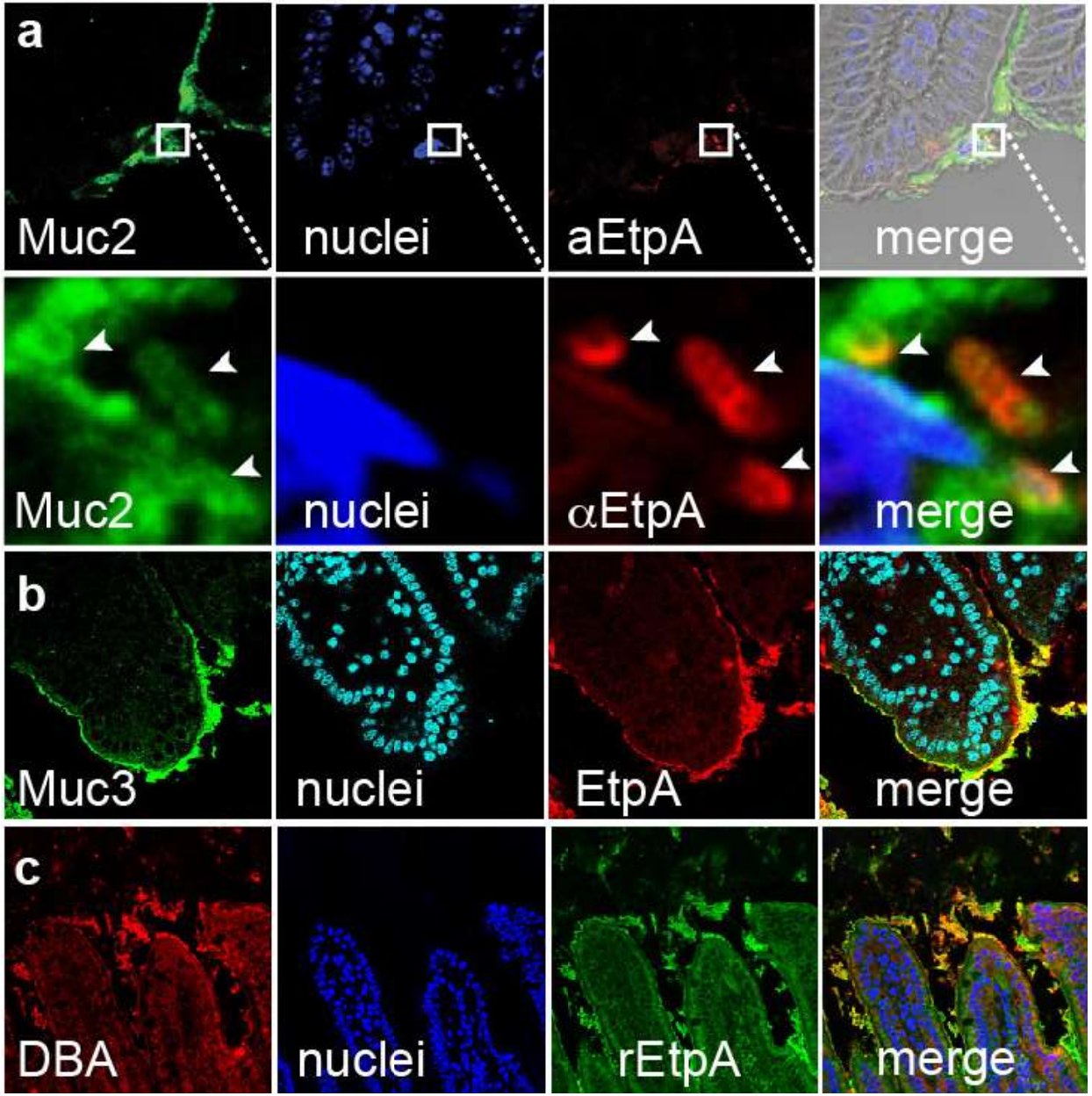


getting a seat at the table

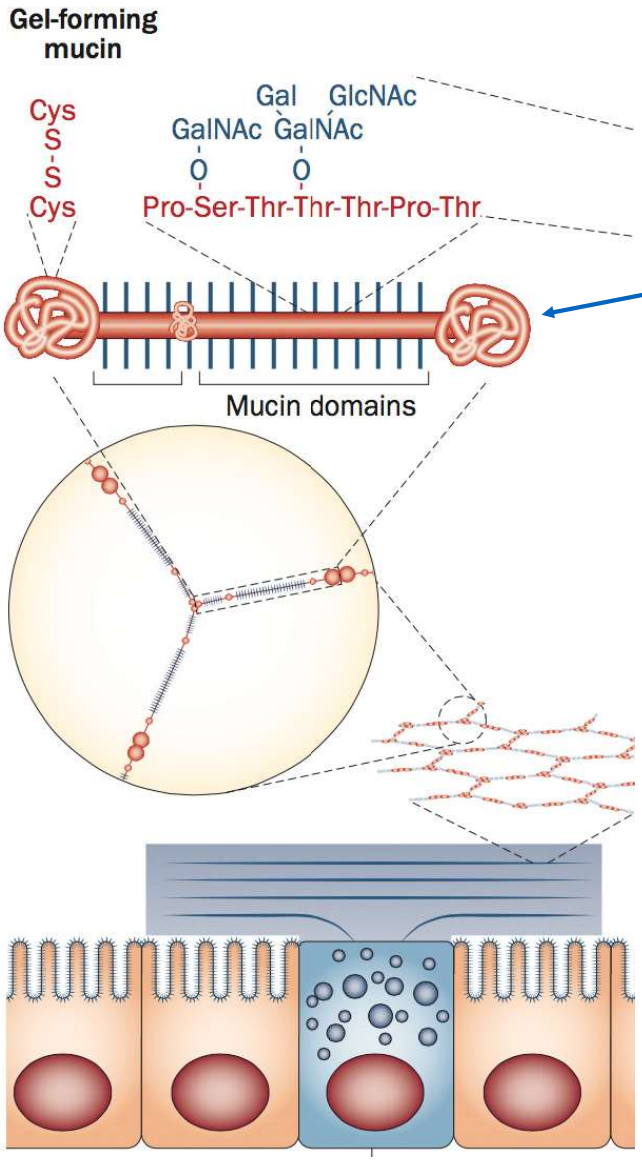
- ETEC secrete highly conserved proteins
- not shared with E. coli commensals
- not found in other microbiota

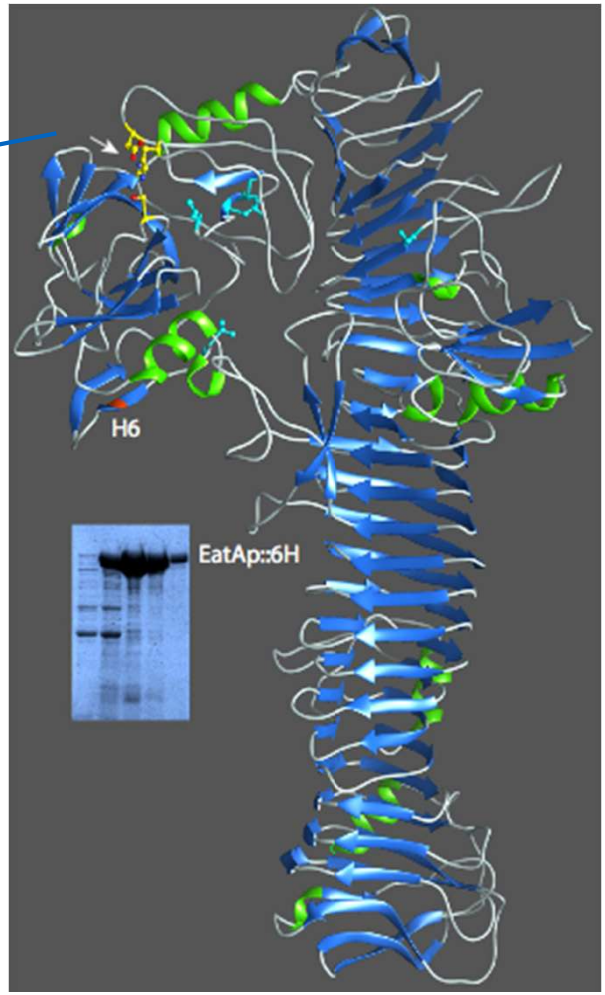
Luo et al PLoS NTD, 2015

ETEC make a sugar-binding secreted lectin



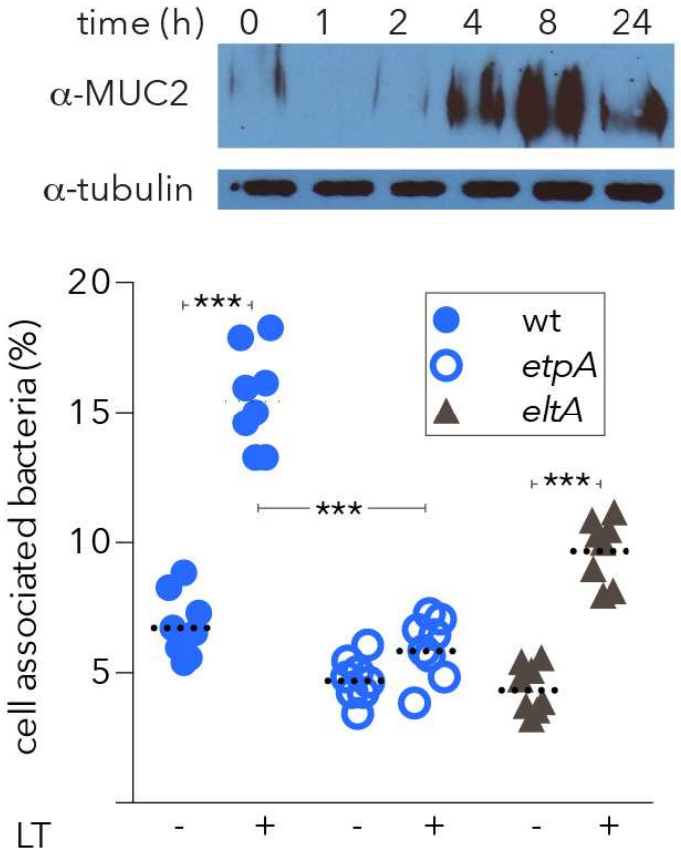
EatA dissolves MUC2 gel matrix

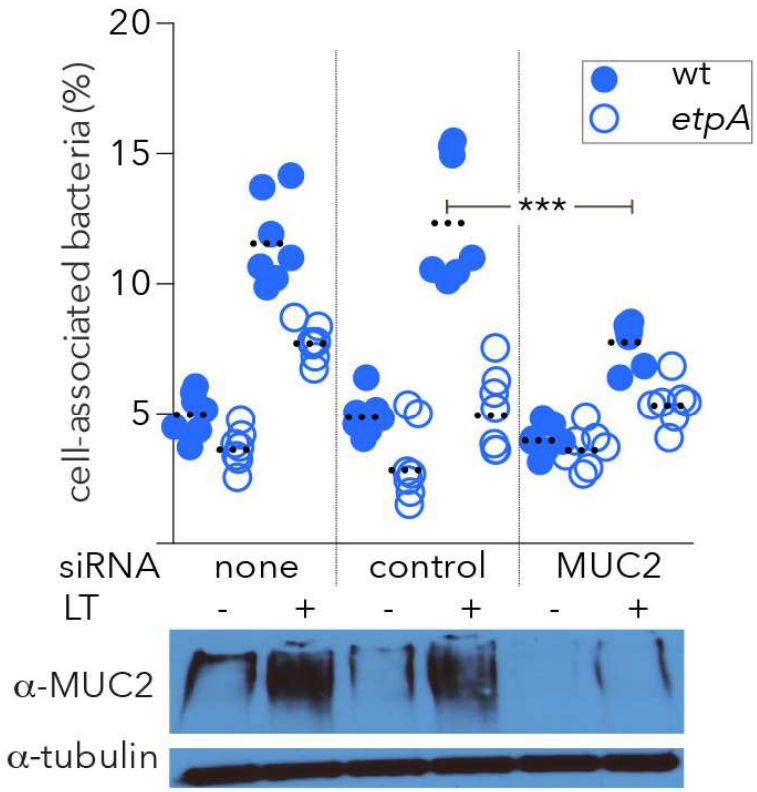




ETEC toxin glycoscaping

LT induces MUC2 expression and promotes adhesion

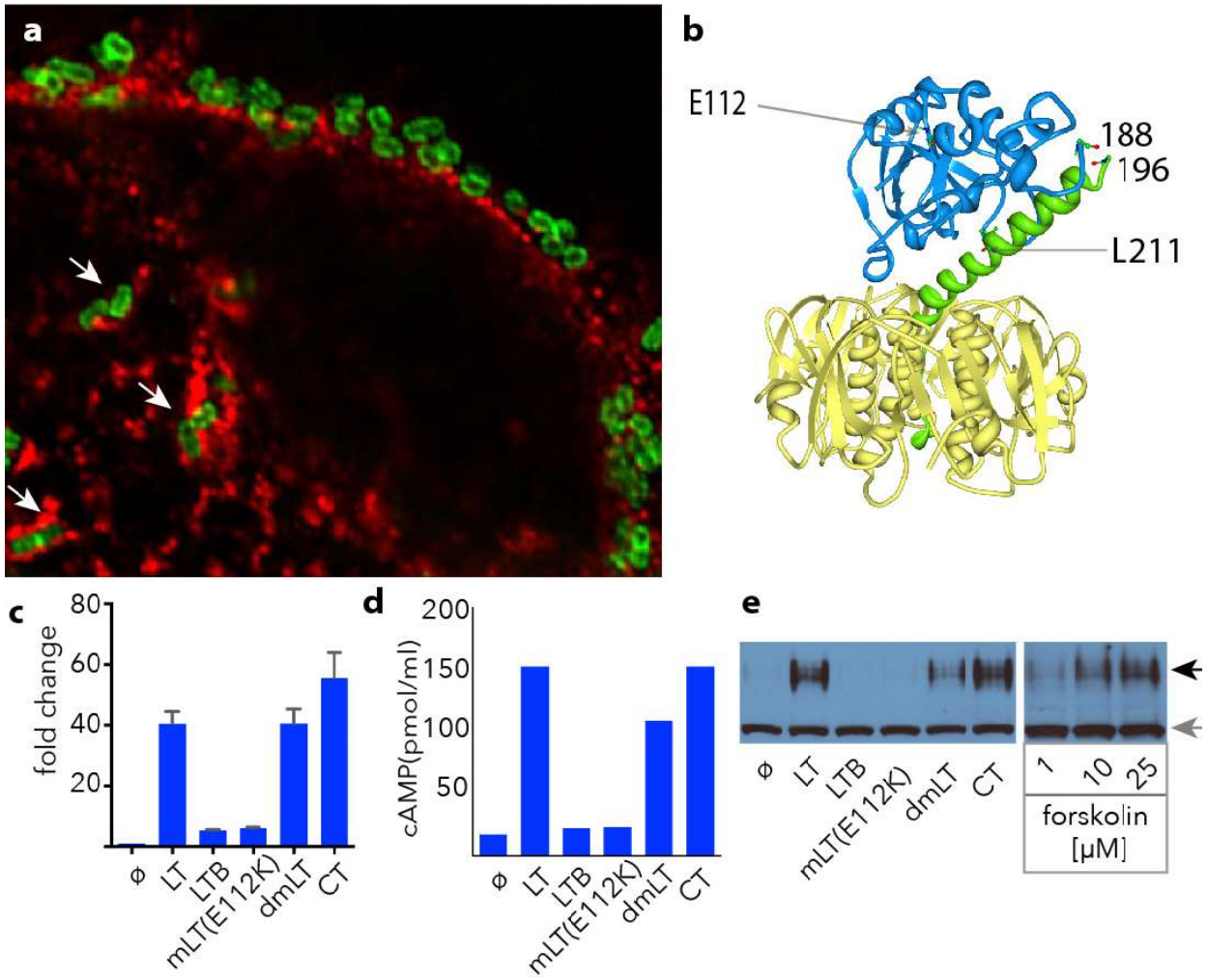




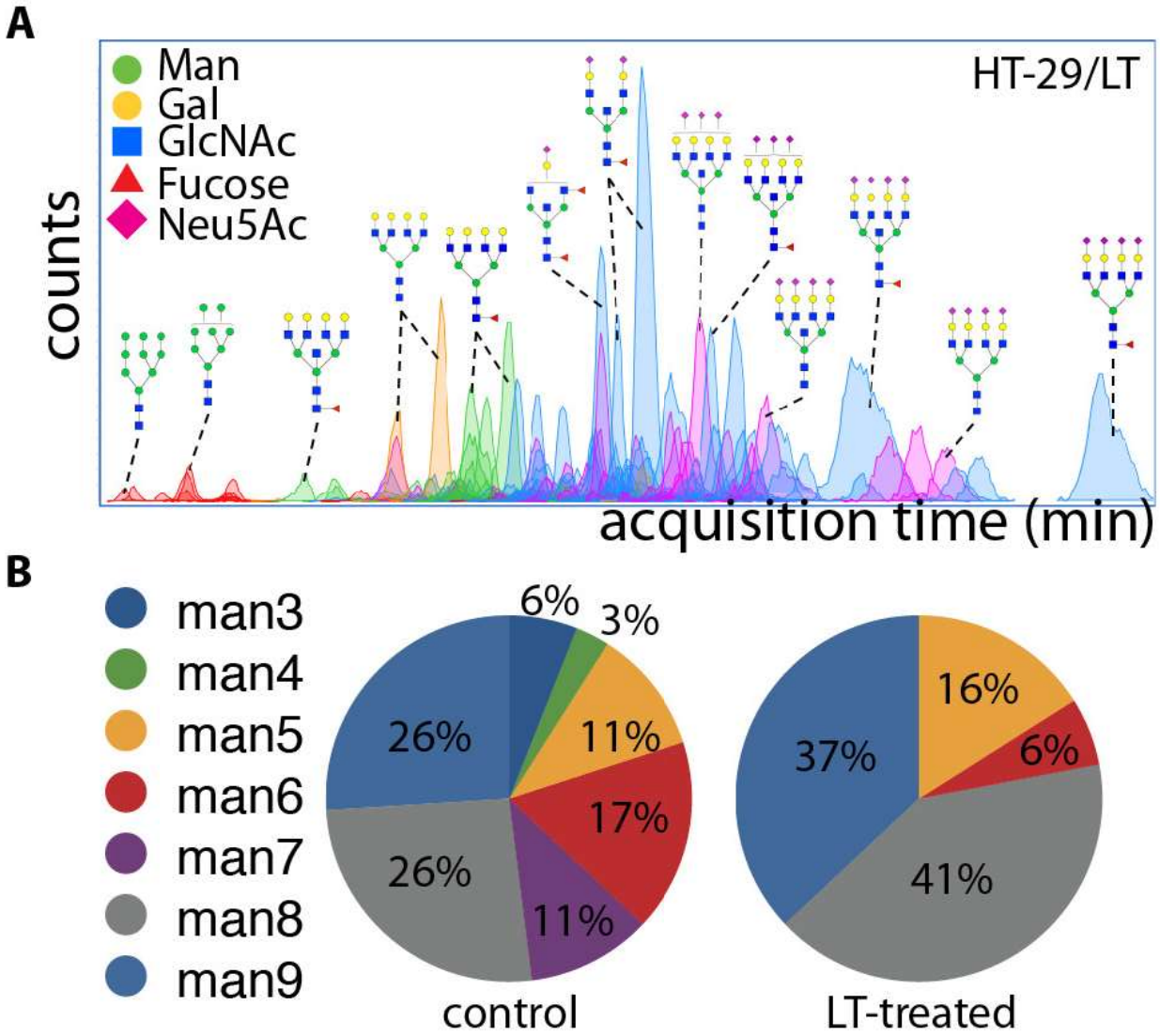
ETEC glycoscaping

LT modulation of intestinal glycoproteins

CEACAM6

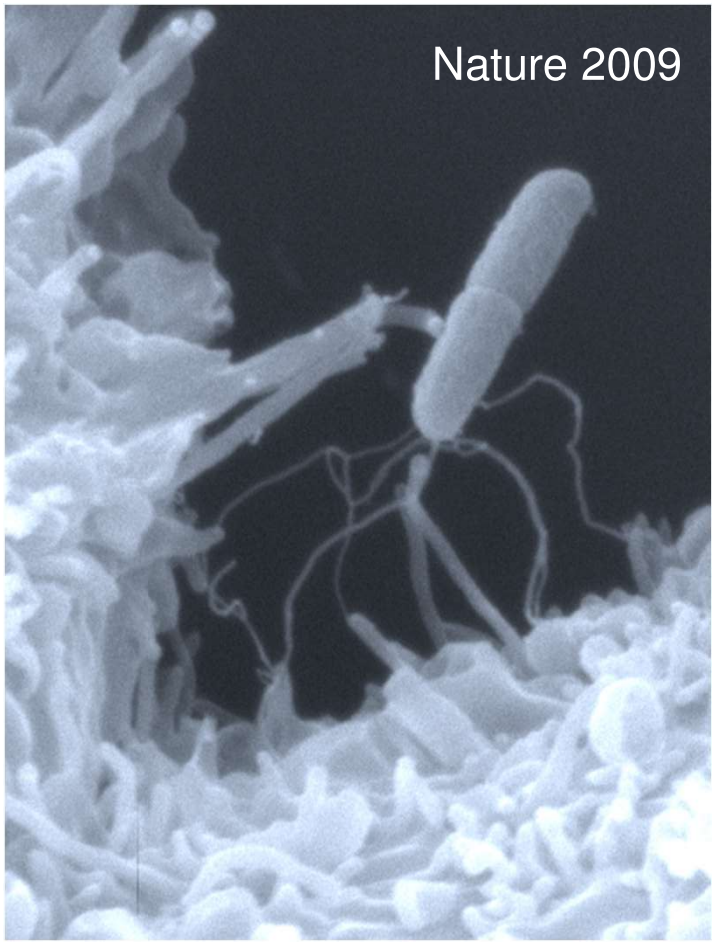


heat-labile toxin
changes the glycan landscape of intestinal epithelia



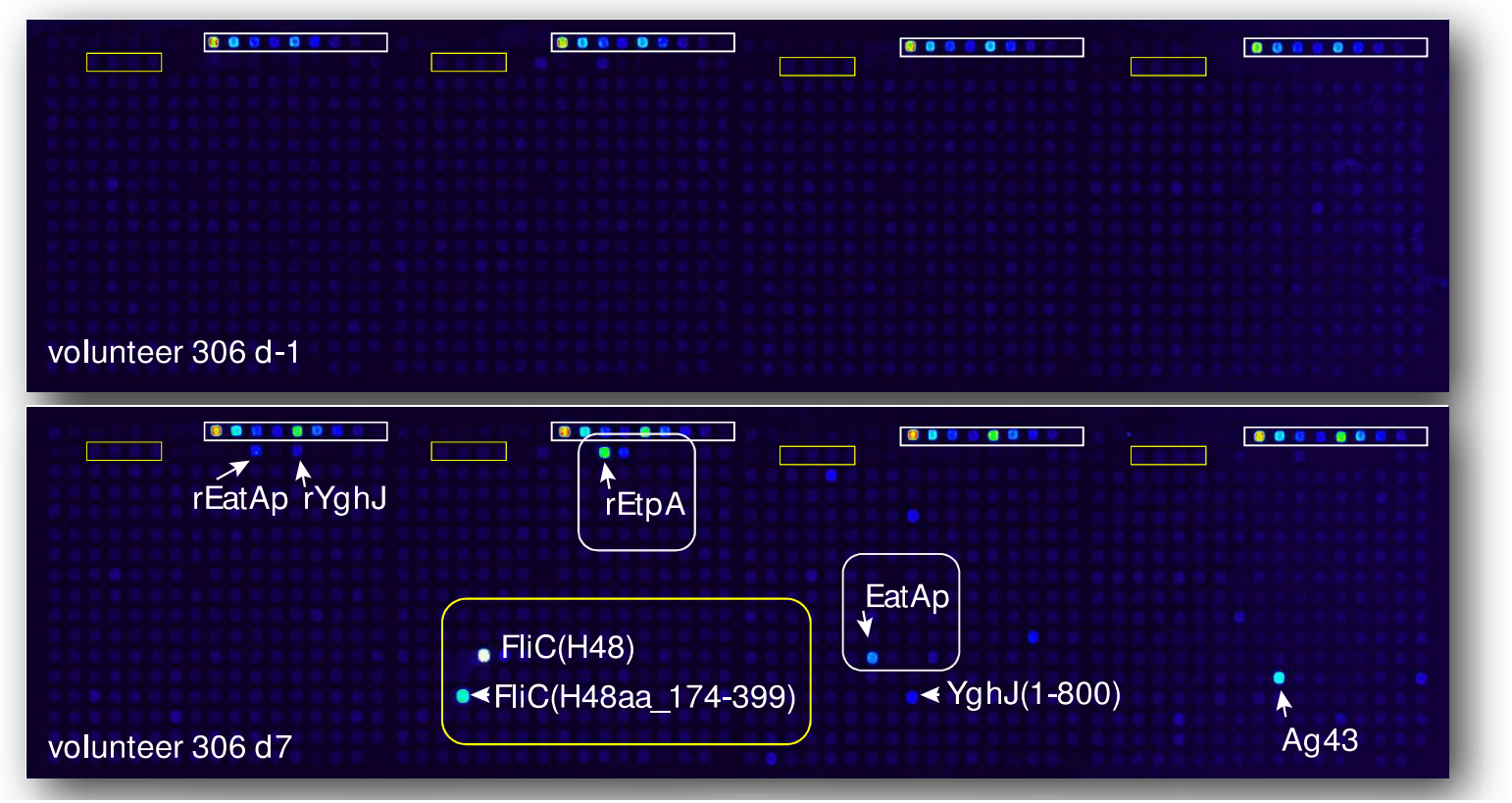
Carlito Lebrilla, University of California, Davis

flagellin and ETEC vaccinology



- *all* ETEC are flagellated
  - motility
  - mucin penetration
  - adhesion
- flagellin
  - most abundant secreted antigen
  - highly immunogenic
  - protective
  - TLR5 agonist

ETEC protein microarray studies



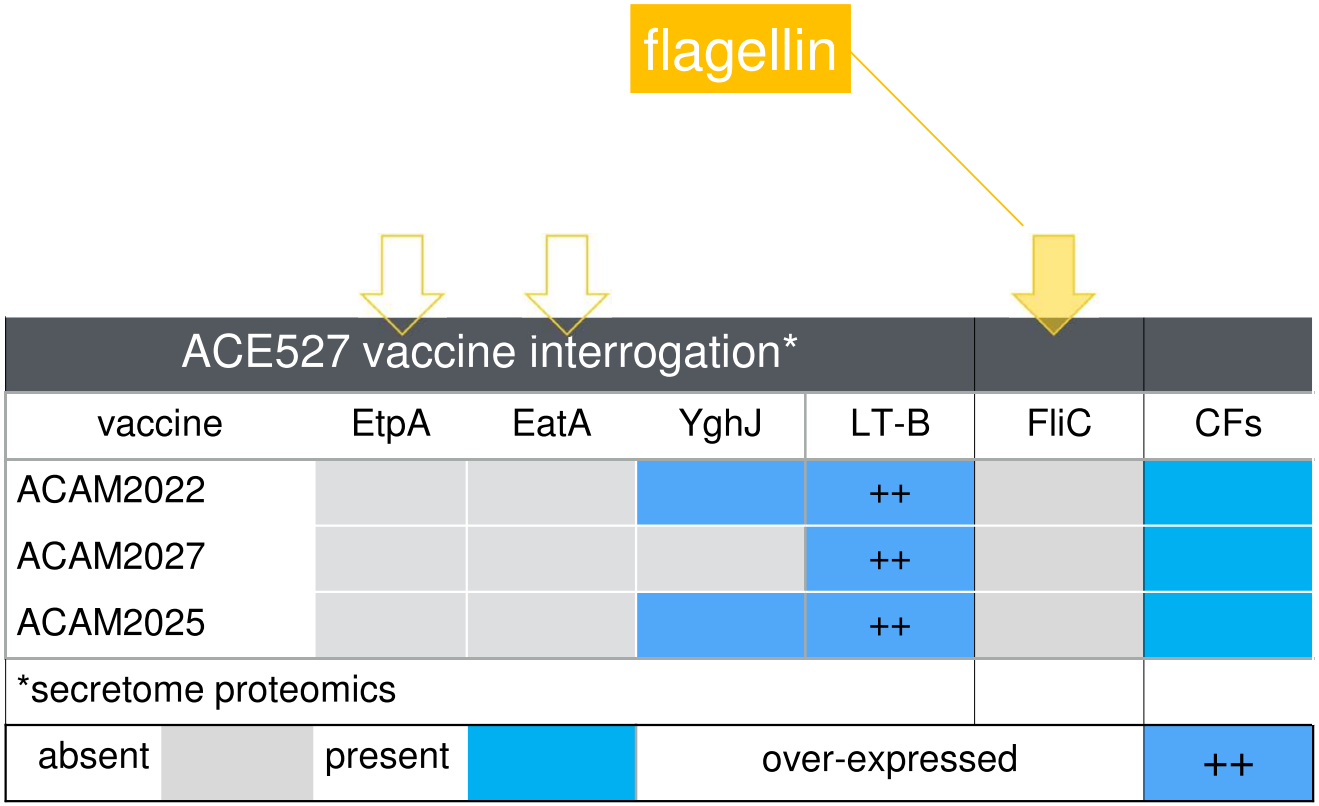
PATH

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

ANTIGEN DISCOVERY INC The Proteome Company

Washington University in St.Louis SCHOOL OF MEDICINE

Live-attenuated ACE527 vaccine
secreted antigen production



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Washington University in St. Louis
School of Medicine

intestinal microbiota and enteric vaccines

microbiota

- shape immune responses
- are altered by infection and nutrition
- respond to changes in glycan content
- can impact vaccine efficacy
- are involved in recovery from infection

enterotoxigenic *E. coli* ETEC

- are highly diverse pathogens
- secrete conserved proteins
- engage specific glycans/glycoproteins
- toxin(s) glycoscape to enhance colonization
- virulence factors that impact microbiota can inform novel vaccine strategies

Washington University in St. Louis
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- Jerry Pinkner
- Reid Townsend
- Mark Miller
- Matt Ciorba
- Sri Santhanam

the lab

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- Alaullah Sheikh
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- Matt Kuhlmann

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- Chase Westra

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- Yasmin Begum
- Rashed Rashu
- Salma Sharmin
- Firdausi Qadri

glycobiology

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Imperial College, London, UK
- Anne Dell
- Stuart Haslam

NIH/CCR
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University of British Columbia
- Bruce Vallance
- Kiran Bhullar

University of Oklahoma
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University of California, Davis
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genomics/microarray development

PATH Enteric Vaccine Initiative
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- Heather Wentzel

U of Maryland, Institute for Genome Sciences
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- Subhra Chakraborty
- David Sack

Antigen Discovery, Inc
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- Joe Campo
- Xiaowu Liang
- Doug Molina

University of California, Irvine
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NIH National Institute of Allergy and Infectious Diseases

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Veterans Health Administration R&D www.research.va.gov