Exploiting strain richness limits for targeted alteration of the gut microbiome

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Conflicts of interest

▶ Scientific Advisory Board

  – Vedanta Biosciences

▶ Consulting

  – Genfit

  – Vedanta Biosciences

▶ Funding

  – Janssen Research & Development

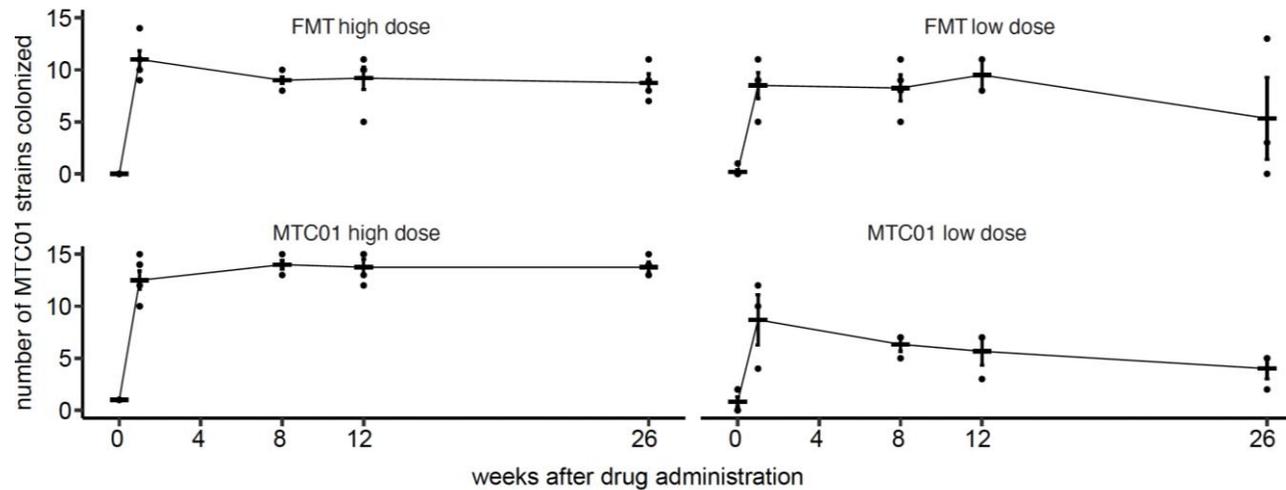# Building capacity to perform strain addition/replacement in humans

Anaerobic manufacturing facility

sterilization port

in vitro drug culture

MTC01

Lukas Bethlehem

Ari Grinspan, Clinical PI
Sari Feldman
Phyu Mar

Bethlehem et.al., medrxiv 2025

rCDI clinical trial FMT vs defined consortium (same donor)

Phase Ib Trial rCDI

D283.FMT Donor 283 feces

1. Array culture library from stool
2. Remove poor engrafters
3. Remove MDROs

MTC01 (15 bacterial strains) Donor 283 LBP

stool

10^{10} CFU $\quad$ 10^{11} CFU $\quad$ 10^{10} CFU $\quad$ 10^{11} CFU

Engraftment prevention:

Bethlehem etal medrxiv 2025

recurrent C. difficile infection microbial therapy is a *restoration* of the healthy microbiota

What if the microbiota is intact and we want to replace or suppress specific strains?

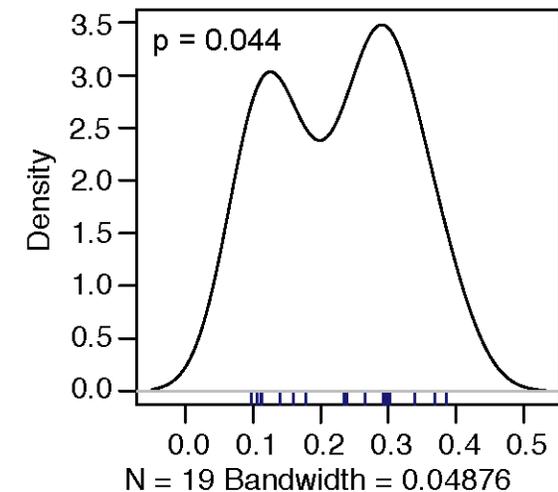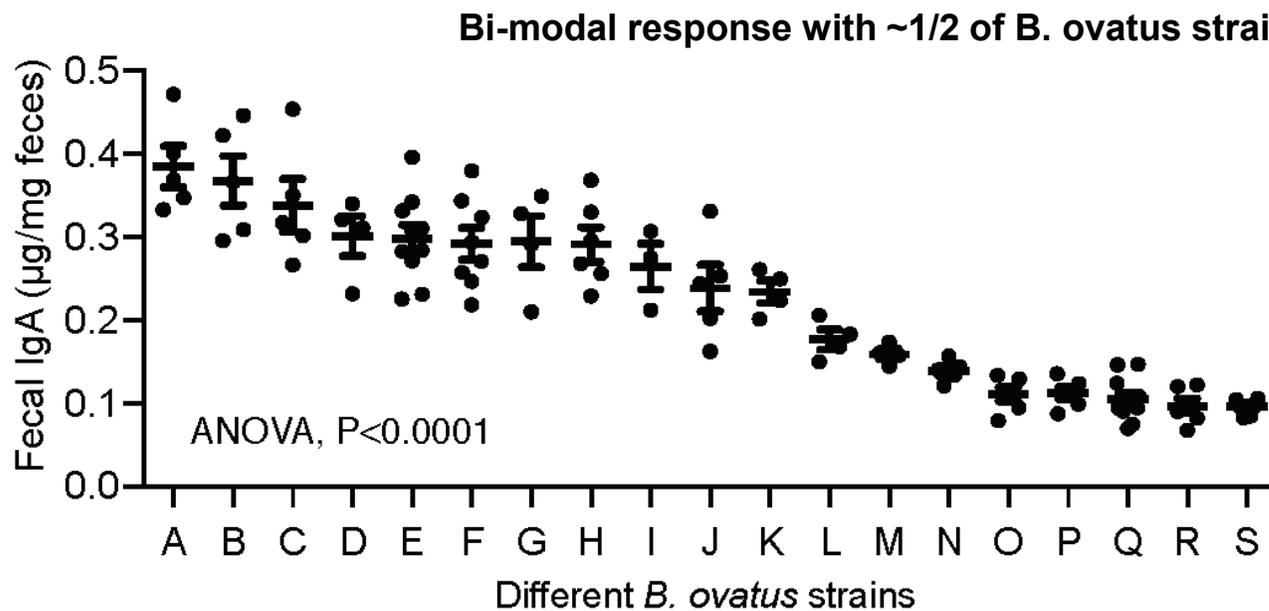# Strain-level differences in microbiome composition determine fecal IgA
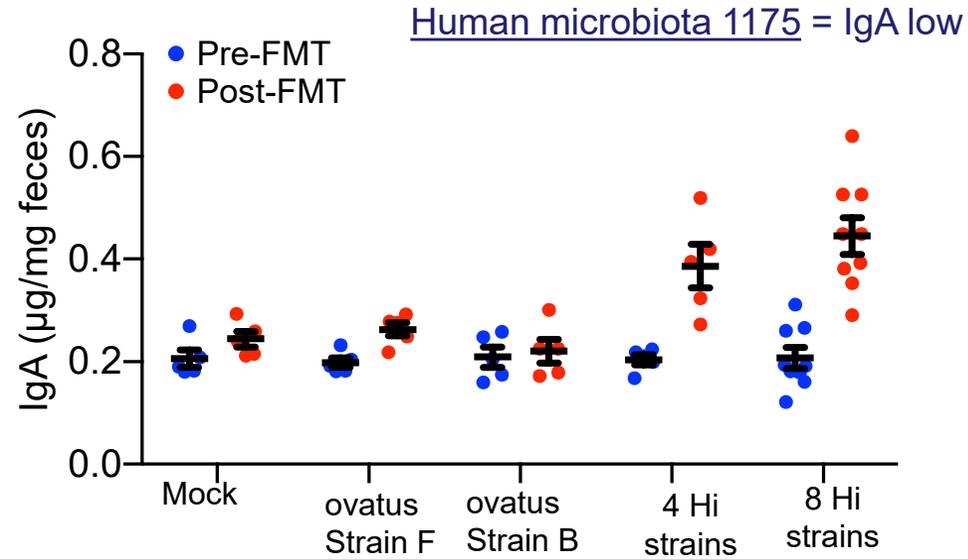

Chao Yang

Bacteroides ovatus drives fecal IgA

Monocolonizations

Yang, et.al., CHM 2020

Bi-modal response with ~1/2 of B. ovatus strains inducing IgA[HIGH]

ANOVA, P<0.0001

p = 0.044

N = 19 Bandwidth = 0.04876
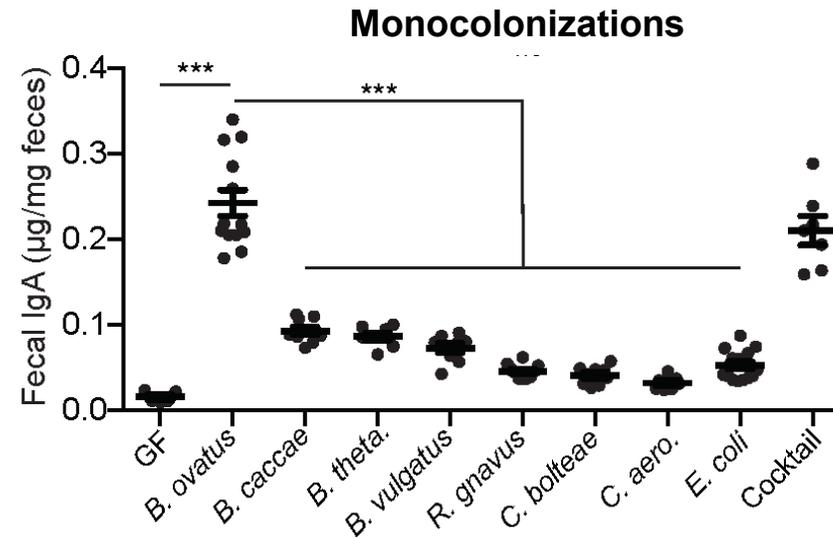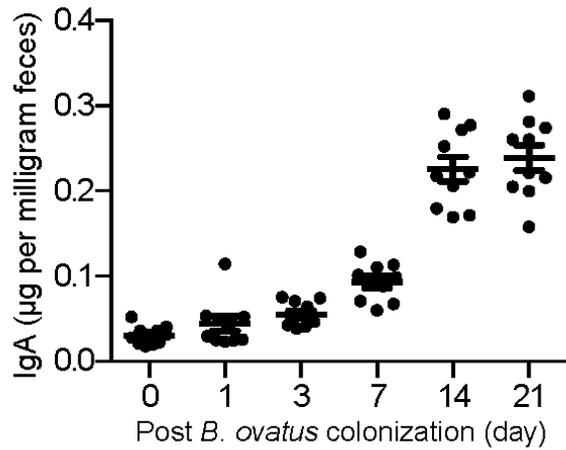
# Immune modulation of a recessive microbial strain phenotype

Human microbiota 1175 = IgA low

A cocktail of microbial effector strains induces high IgA
no single high IgA strain can do so

Human microbiota 1271

Human microbiota 88
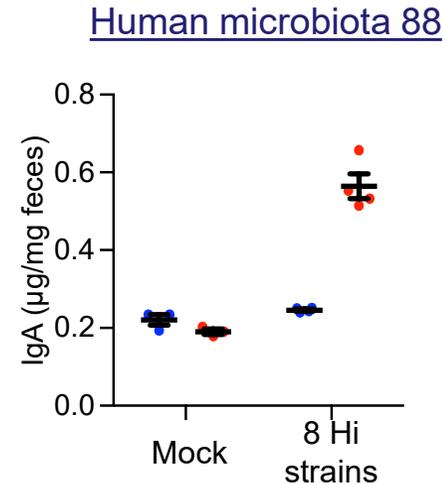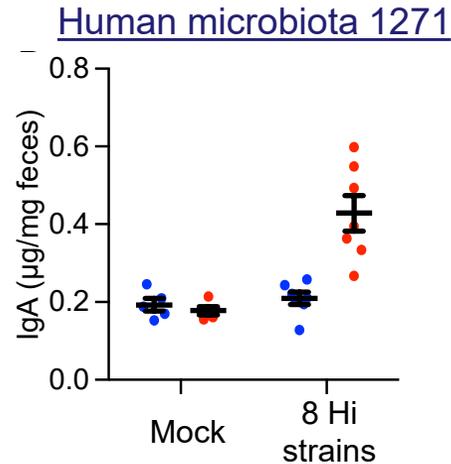
The multiplex cocktail is robust
across multiple recipients

Yang, et.al., CHM 2020

Multiple strains of ovatus share the same niche!

Yang, et.al., CHM 2020
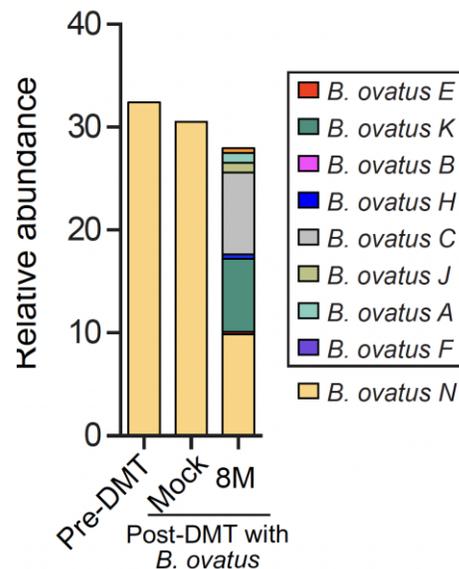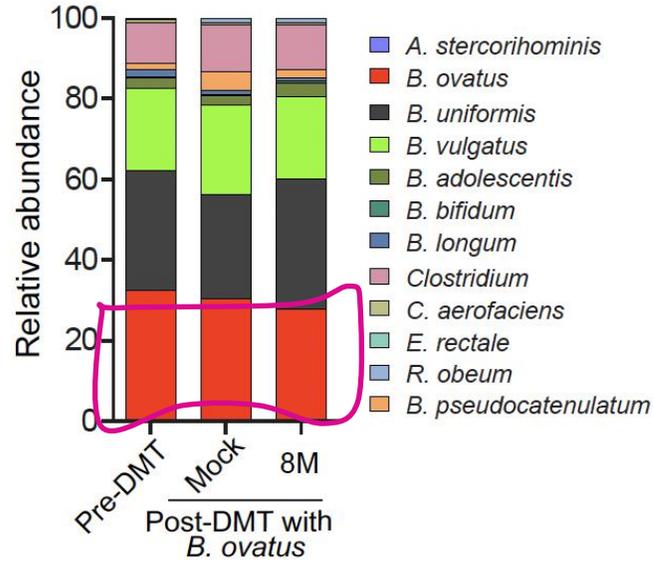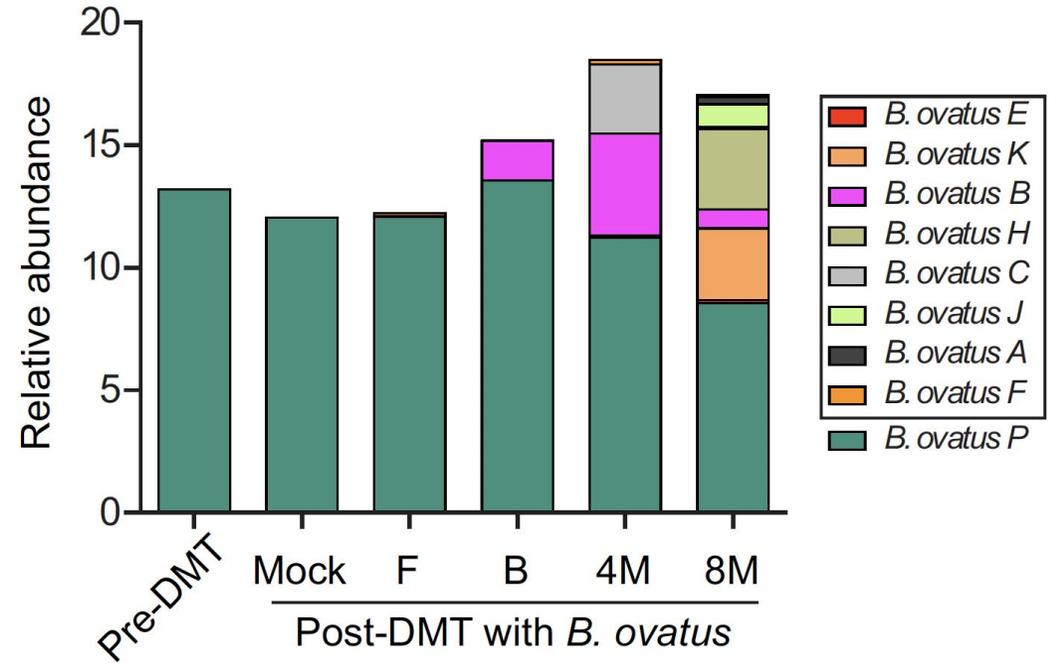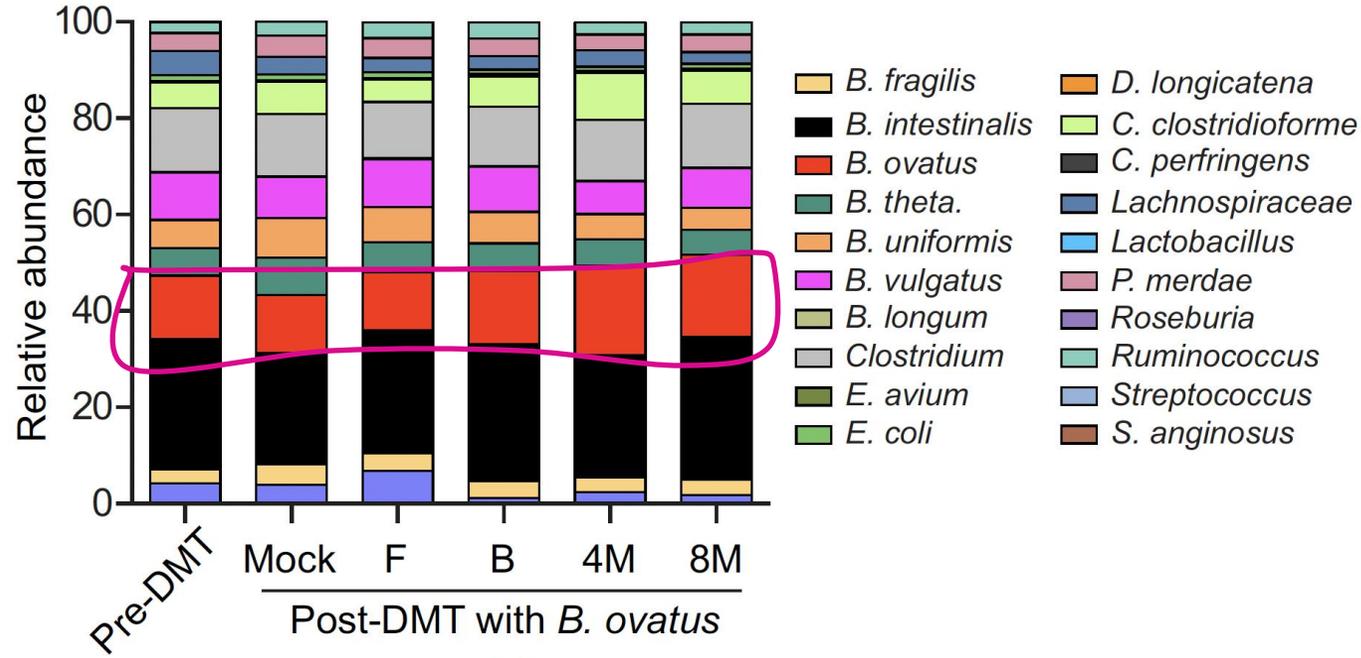
Not all B. ovatus seem to get in…

Gut microbiome structure

carrying capacity

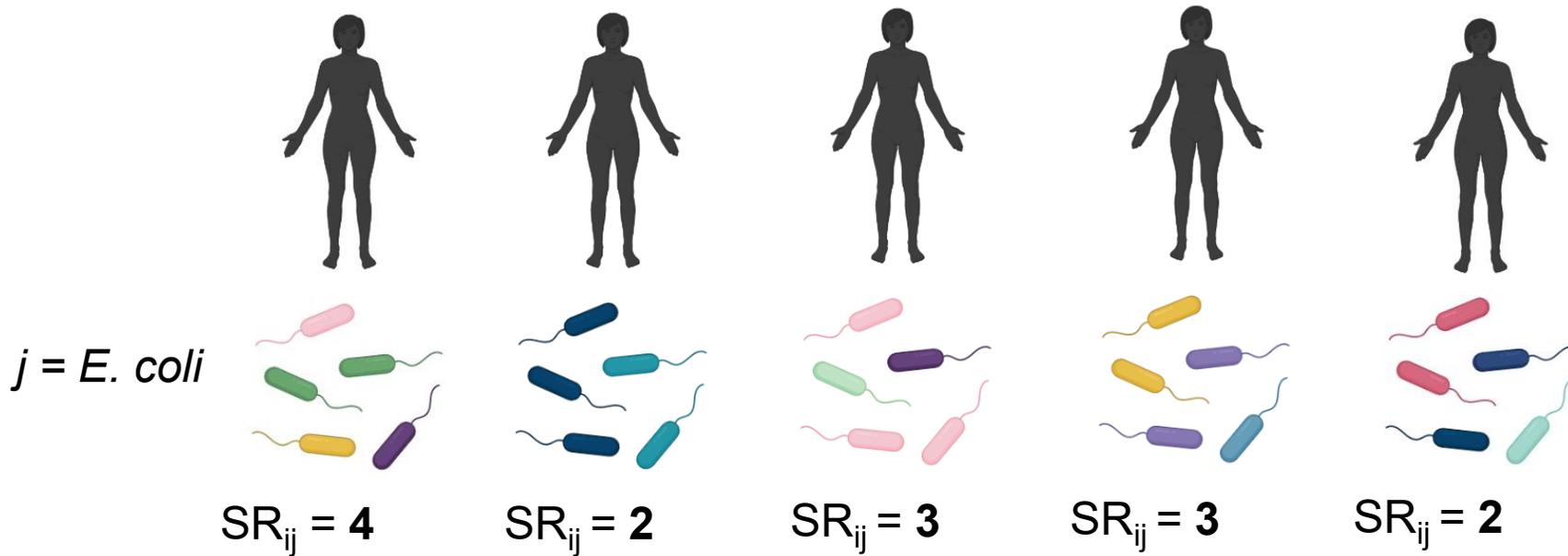Is there a limit on how many strains of a species can inhabit a gut?

Alice Chen-Liaw
MDPhD student

Calculating strain richness of a species

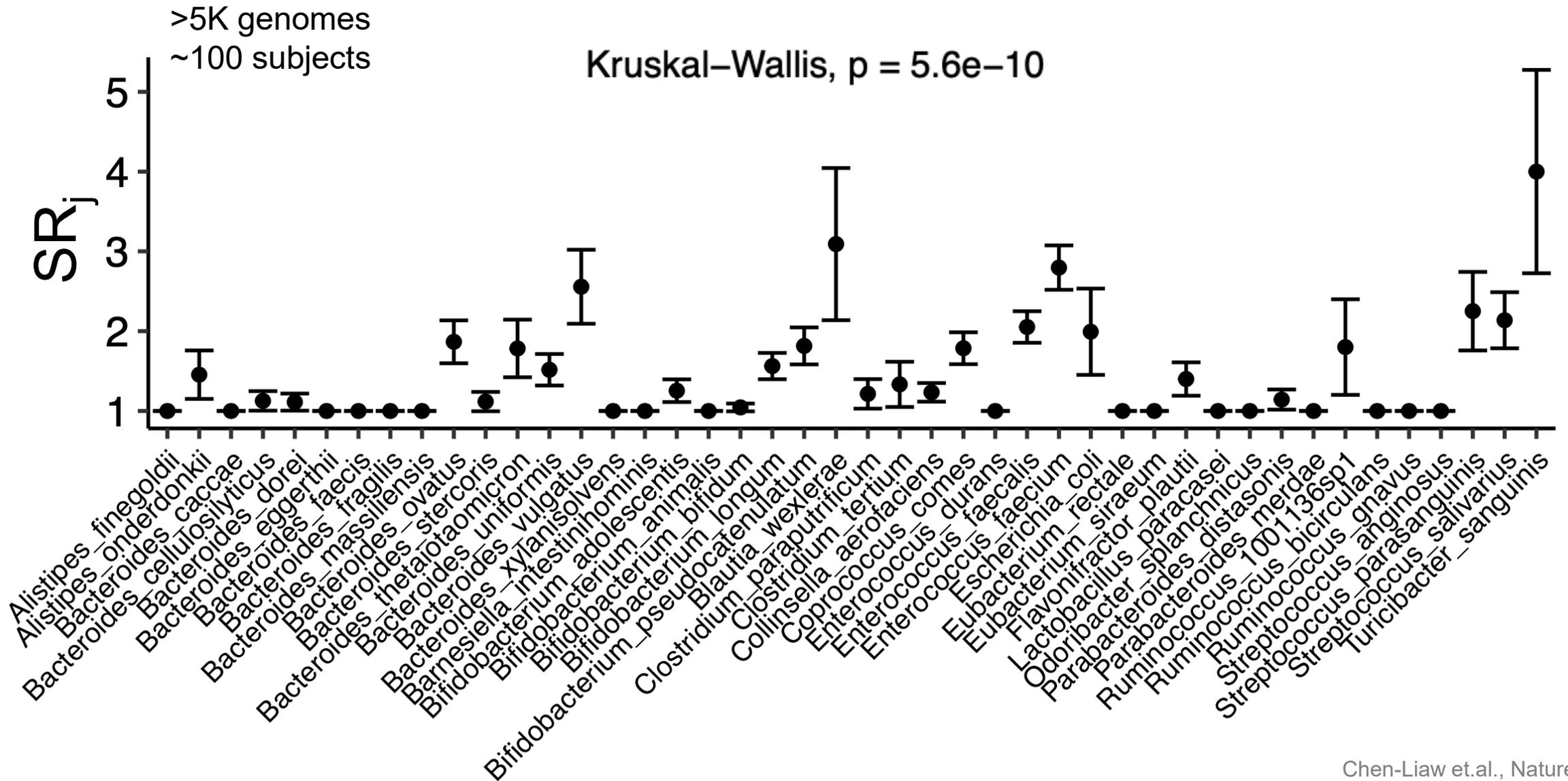SR_{ij} = the number of unique strains of bacterial species j in person i

SR_j = the average SR_{ij} for species j across all people

j = E. coli

SR_{ij} = **4**	SR_{ij} = **2**	SR_{ij} = **3**	SR_{ij} = **3**	SR_{ij} = **2**

SR_j = **2.8**

[Same strain: >96% genome similarity; all counts from draft genomes]

Strain richness per species in human gut microbiome usually ranges from 1-2

Chen-Liaw et.al., Nature 2024

Strain richness per species per individual (SR_{ij}) is transferable

rCDI FMT
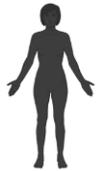
Donor SR_{ij}

FMT

Recipient SR_{ij}

Supraphysiologic strain richness therapeutics test the limits of strain carrying capacity
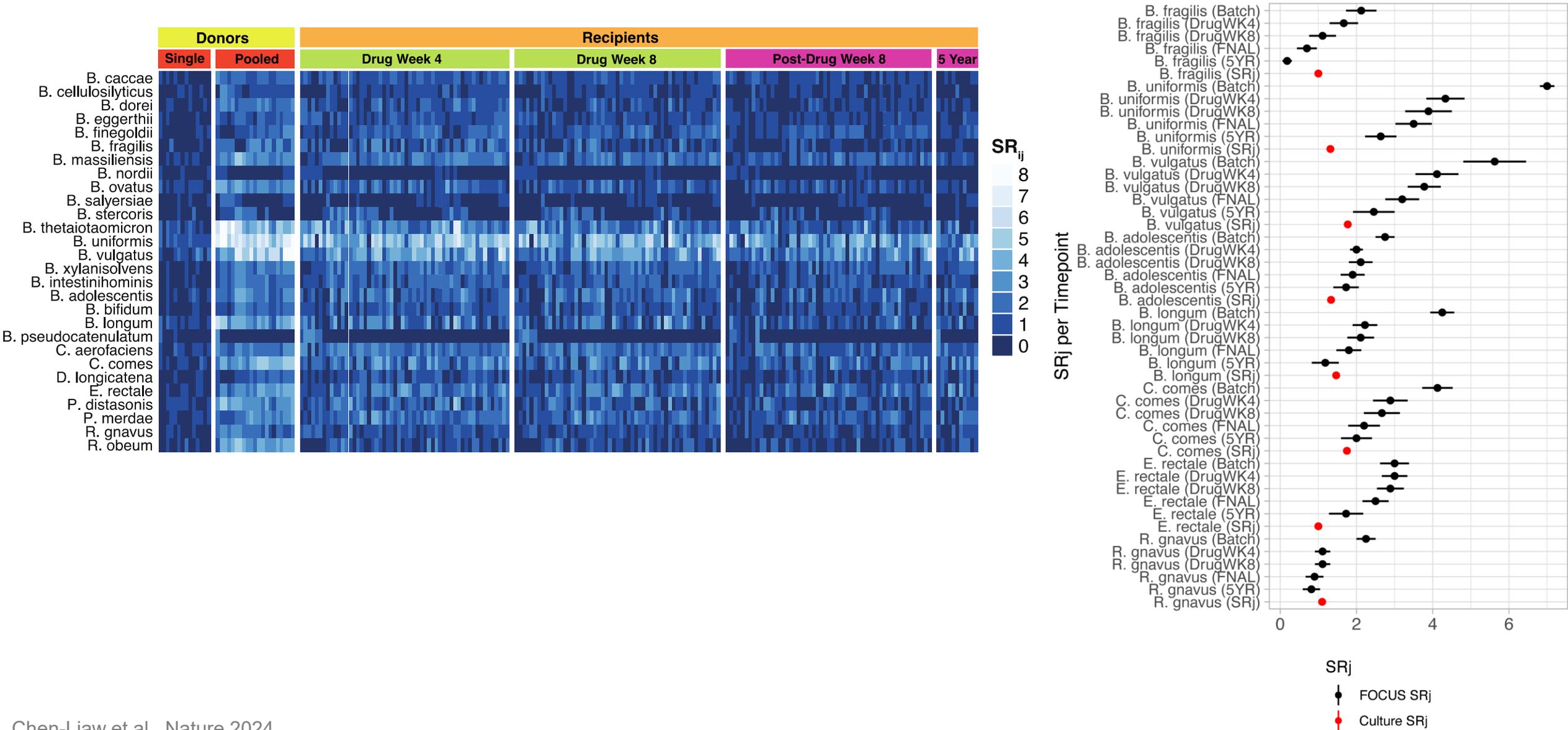
Ulcerative colitis FMT
FOCUS trial

13 donors

3-7 donors per recipient
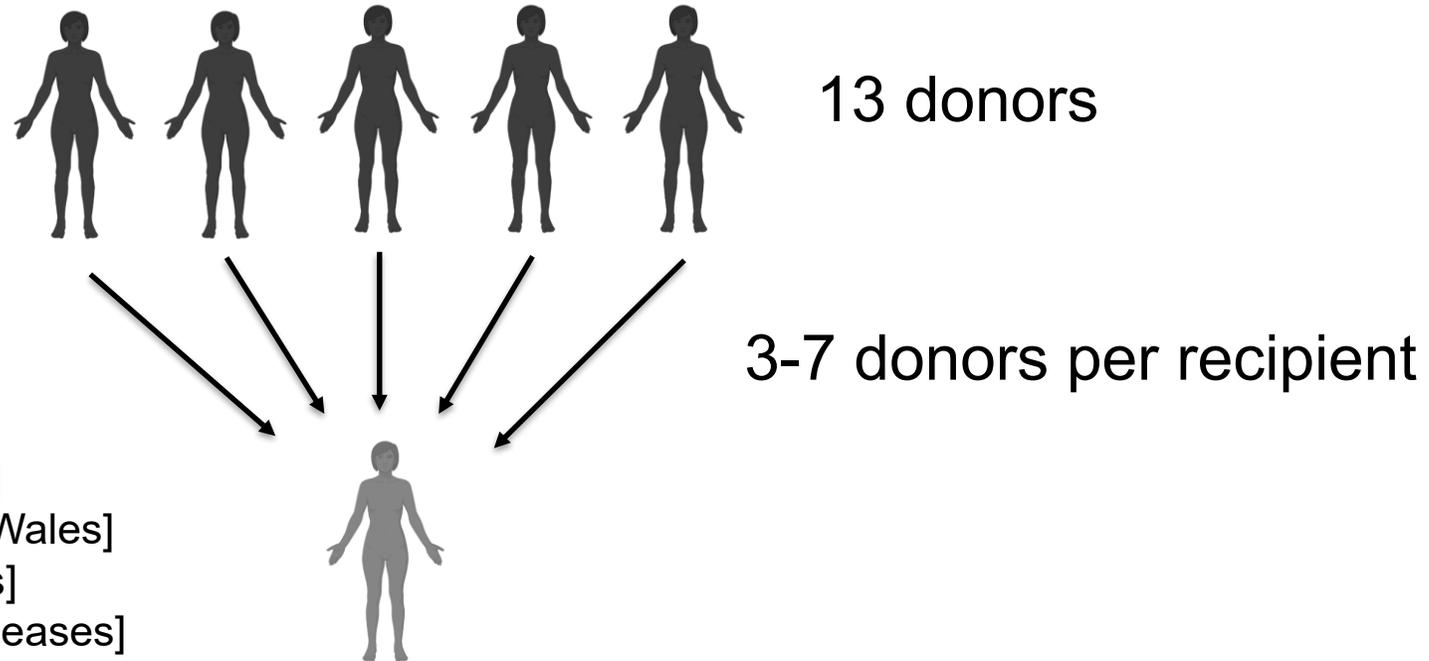
FOCUS
Sudarshan Paramsothy [U Sydney]
Nadeem Kaakoush [U New South Wales]
Hazel Mitchell [U New South Wales]
Thomas Borody [Center for Dig Diseases]
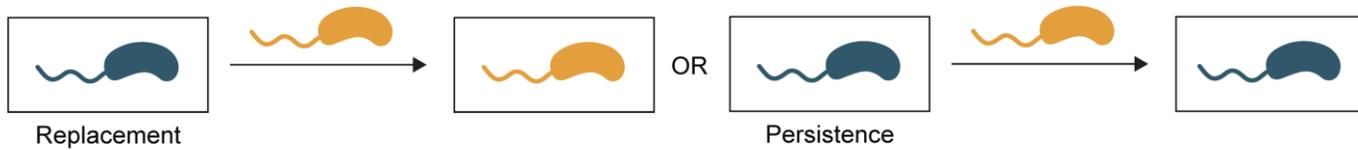Michael Kamm [U Melbourne]

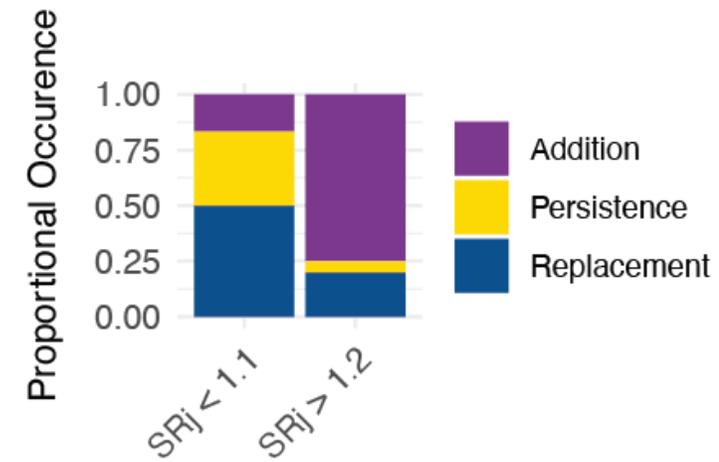# Strain richness overdose converges to population average over time

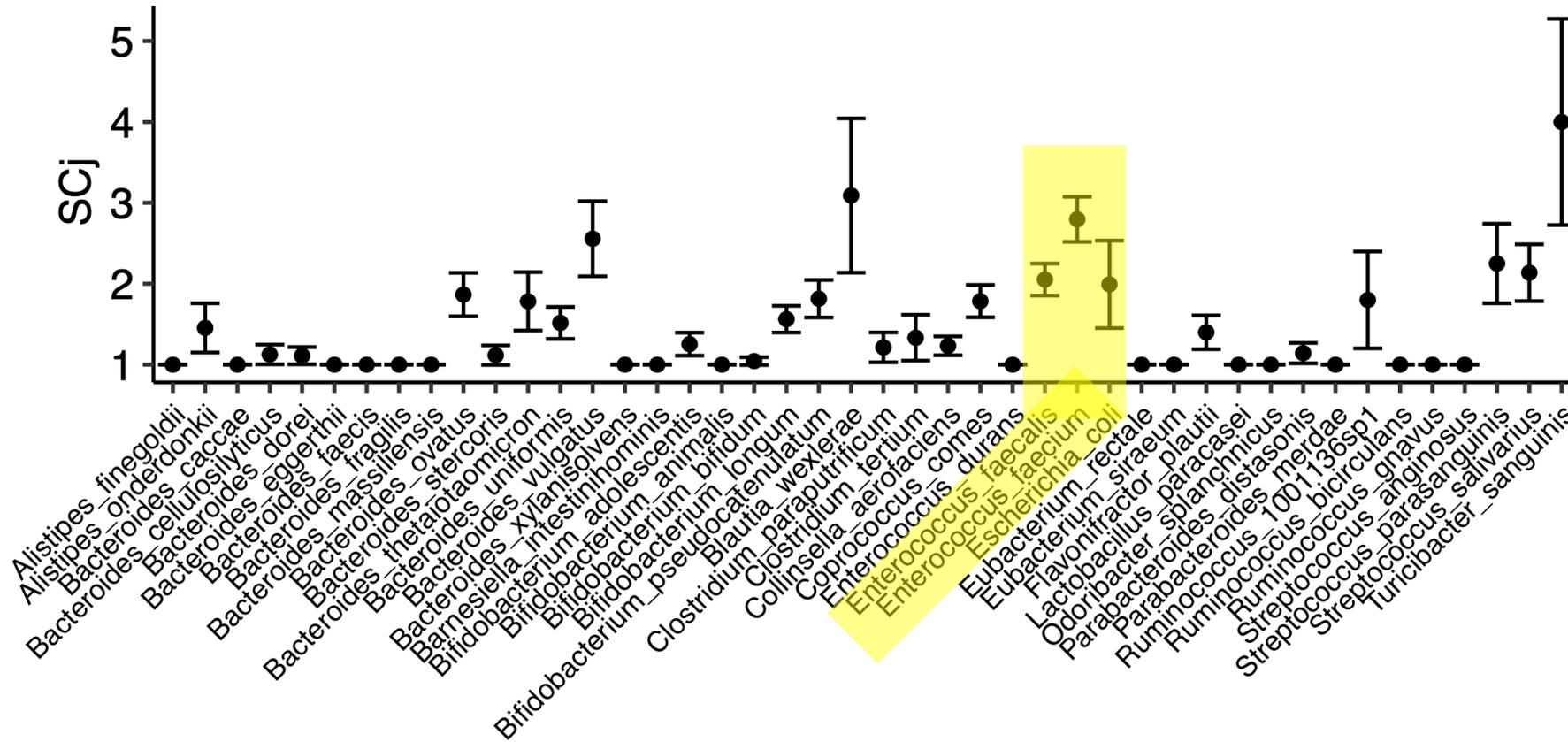# An ecological framework for strain addition and replacement

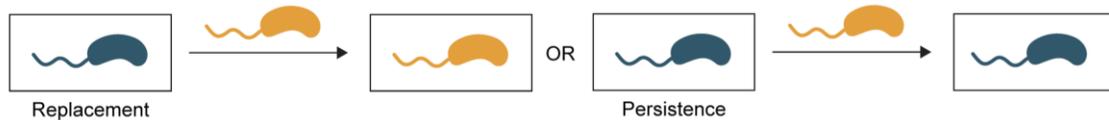**Expected outcomes**

Species $SR_j < 1.1$

Replacement — OR — Persistence

Species $SR_j > 1.2$

Addition

Proportional Occurence — Addition, Persistence, Replacement — $SR_j < 1.1$, $SR_j > 1.2$

Decolonization of antimicrobial resistant organism strategy

Species $SR_j < 1.1$

Replacement   OR   Persistence

Species $SR_j > 1.2$

Addition

if we put multiple strains per species, can we replace or suppress opportunistic pathogens from high richness species?

Thanks to

Our laboratory

Current

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Saurabh Mehandru [Mount Sinai]
Miriam Merad [Mount Sinai]
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Hazel Mitchell [U New South Wales]
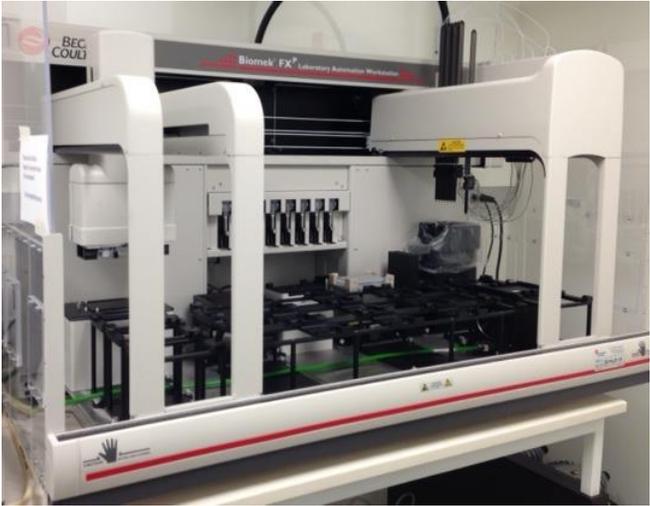Thomas Borody [Center for Dig Diseases]

Icahn School of Medicine at **Mount Sinai**

High throughput bacterial culturing facility at Mount Sinai

Anaerobic isolation

Protein extraction

Identification (MALDI-TOF)

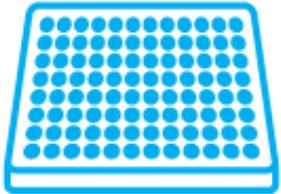Goodman et.al., PNAS 2011

Faith et.al., Science 2013

Yang et.al., Science Immunology 2022
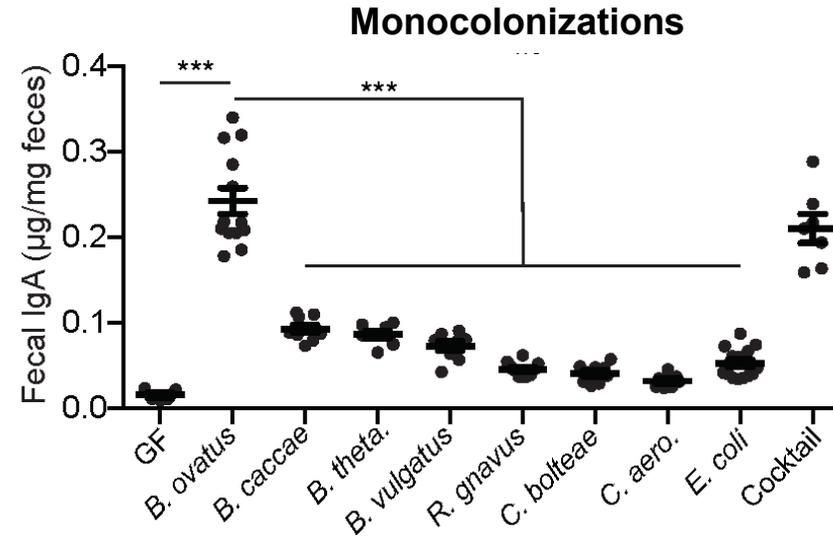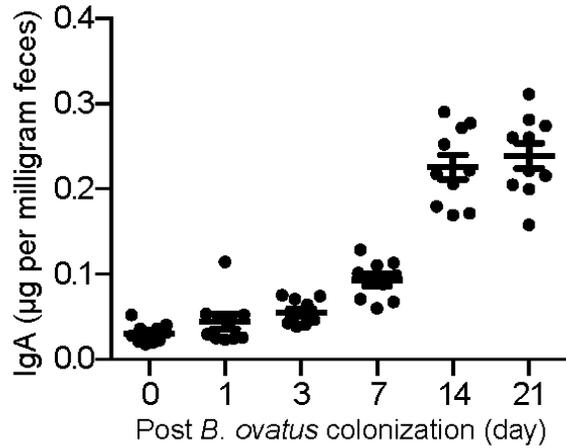
Spindler et.al., CHM 2022

Donor

1. 1 week from stool to identified bacteria in multiwell plate
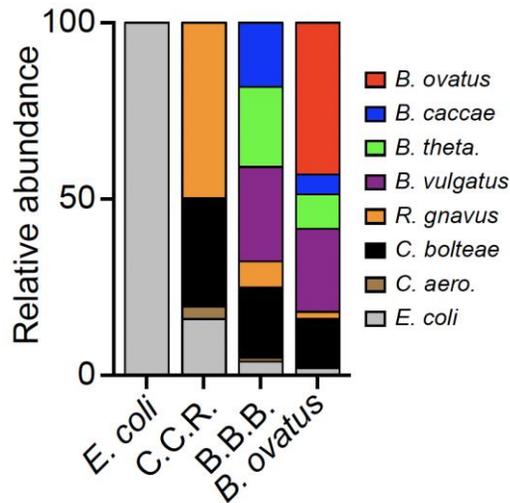2. >150 culture libraries completed
3. Up to 2 culture libraries per week

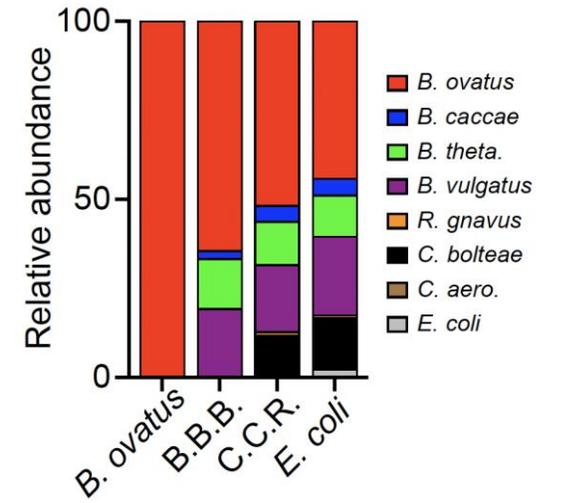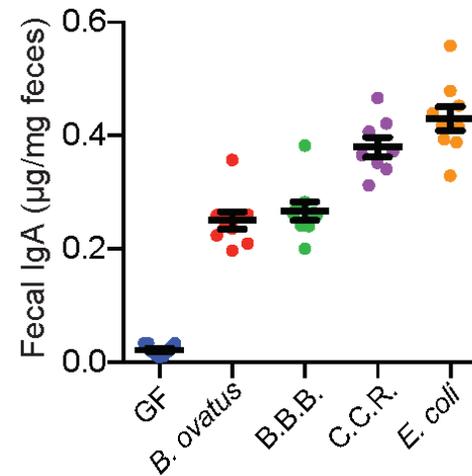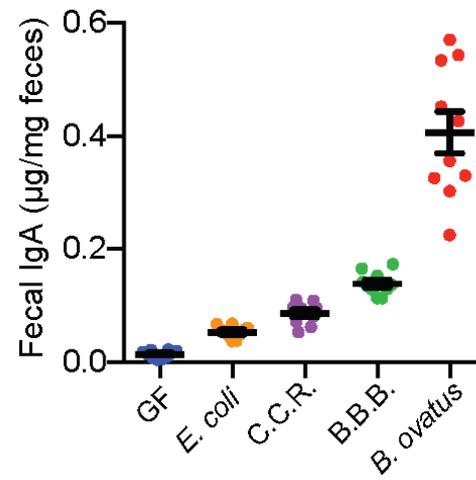Each well contains a unique bacterial strain

Bacteroides ovatus drives fecal IgA

Yang, et.al., CHM 2020

Strain richness is low in the gut relative to other environments