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Walter E. Washington
Convention Center



Society for Immunotherapy of Cancer

Homeostatic and Inflammatory Immune Responses to Human Microbiotas in Gnotobiotic Mice



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School of
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Sinai

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Presenter Disclosure Information

Graham Britton

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The funders had no role in the design, execution or analysis of experiments.

Motivating questions

- Is interpersonal variation in microbiome composition a factor that causally alters an individual's risk of developing a particular disease?



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- Can answers to either of the above questions be used clinically?

Inflammatory Bowel Diseases

- Associated with an an altered microbiome
- Some efficacy using microbiome-targeted therapy (FMT) in ulcerative colitis *Paramsothy et al., Moayyedi et al.*
- Animal models, genetic associations and human tissue studies implicate a dysregulated T cell response

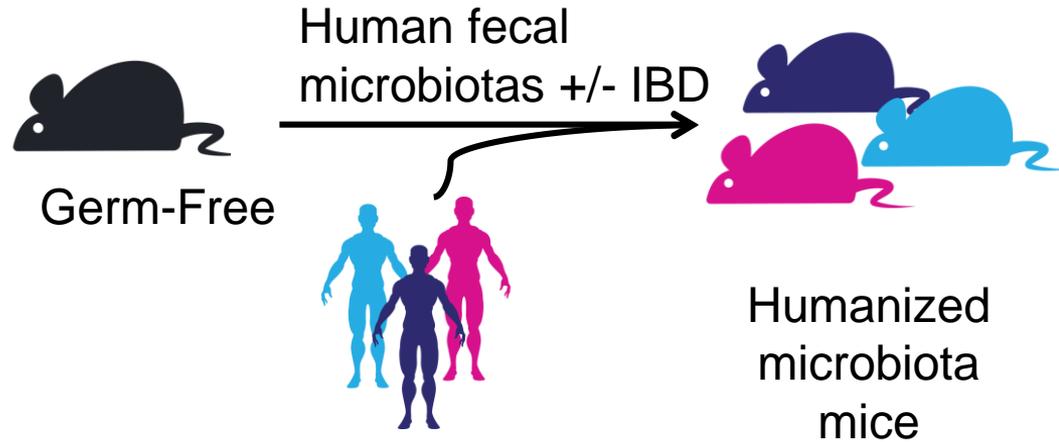


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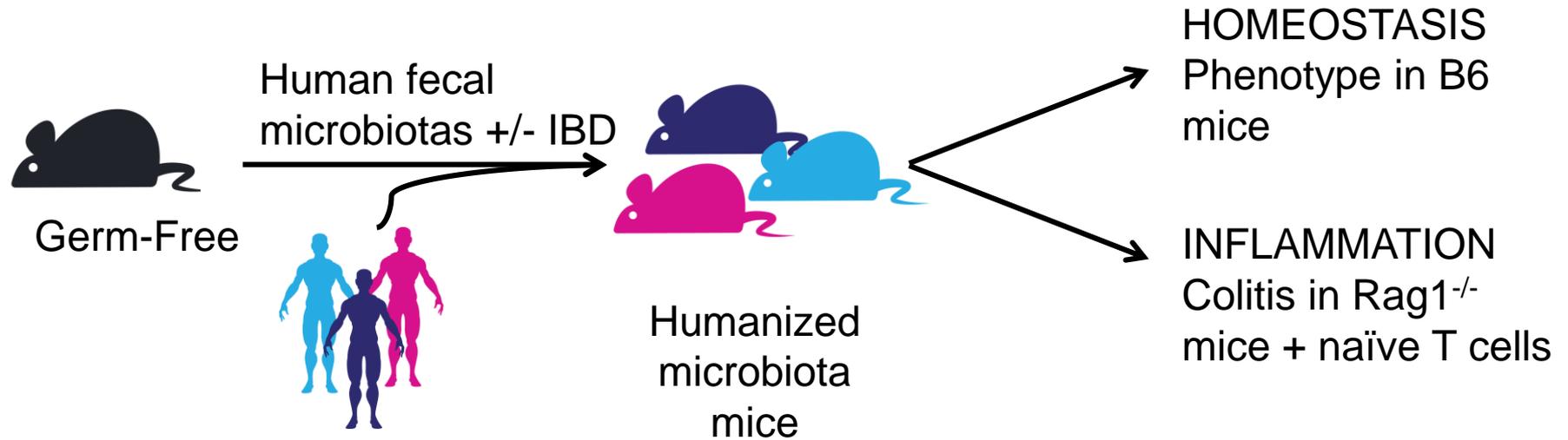
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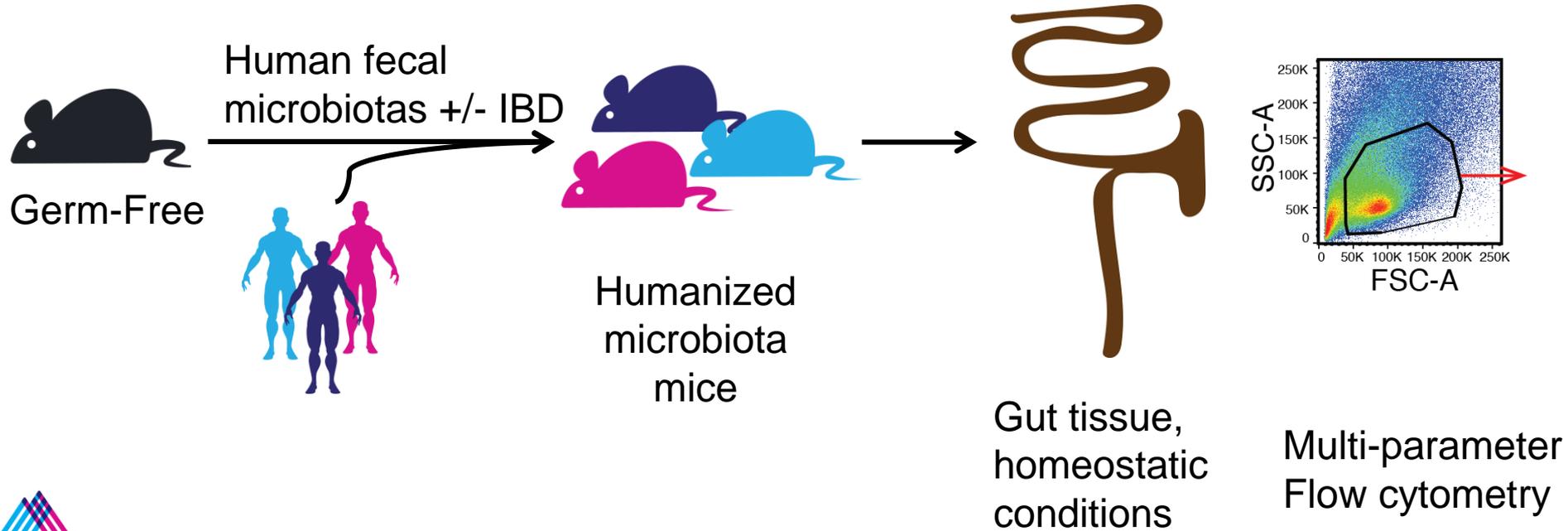
Humanized microbiome mice are a powerful model to explore microbiome-host interactions



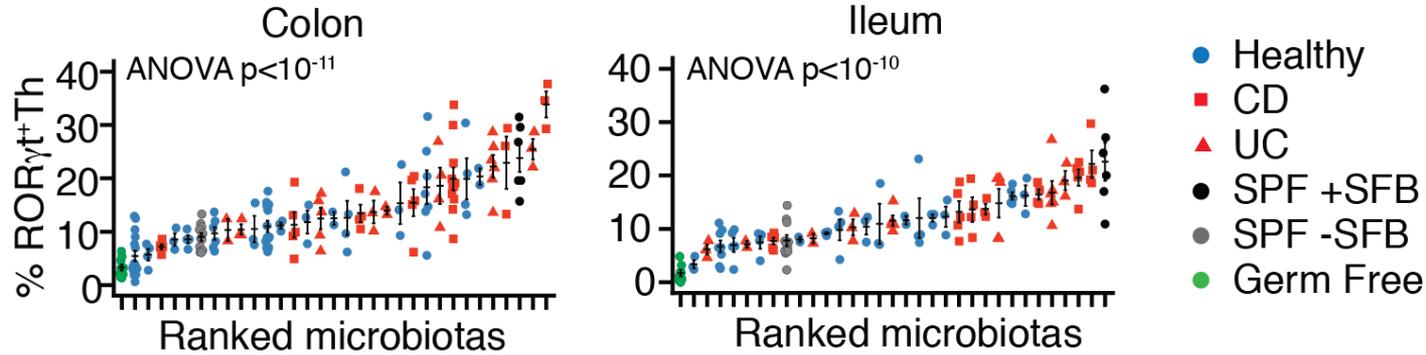
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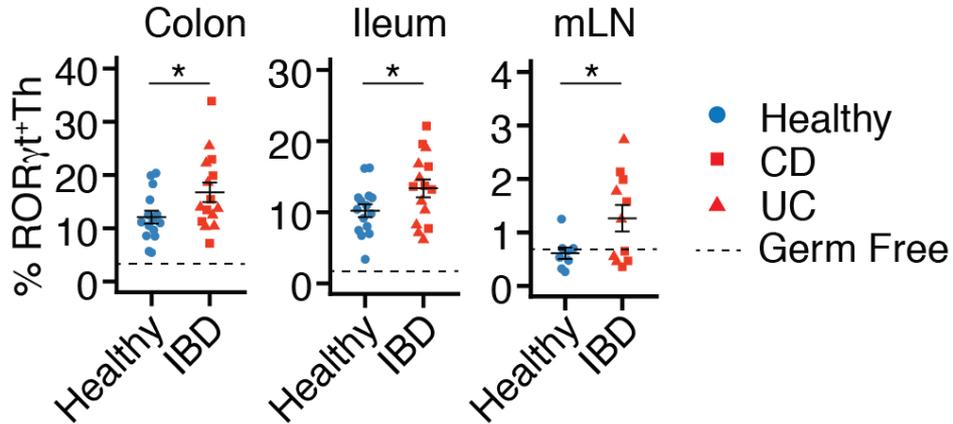
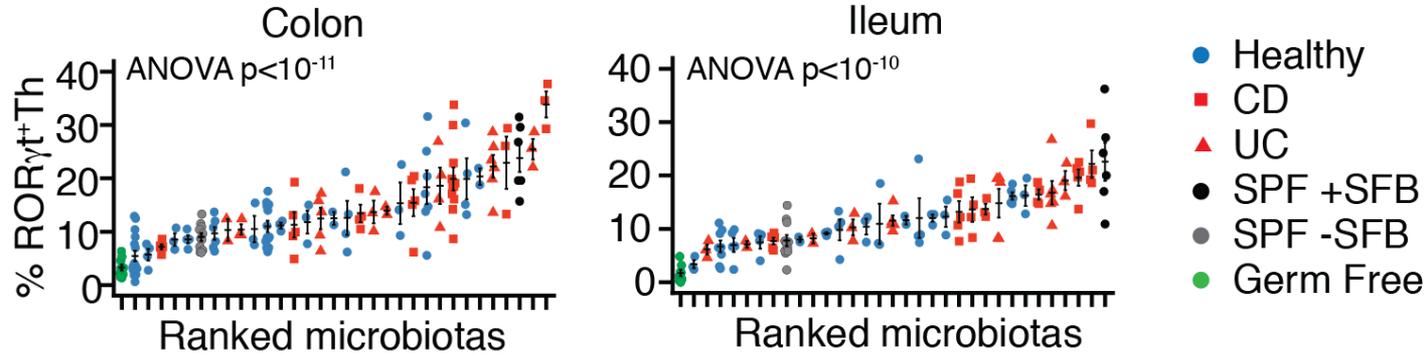
The influence of interpersonal microbiome variation on gut immune homeostasis



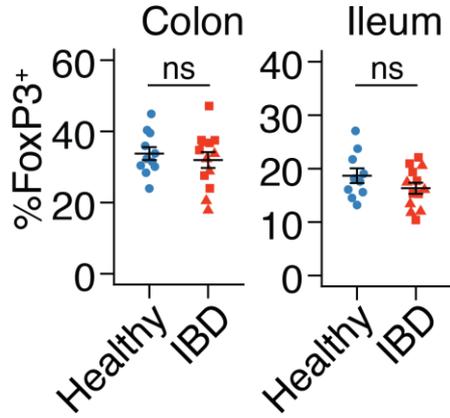
IBD microbiomes induce more ROR γ t⁺ Th17 cells than healthy donor microbiotas



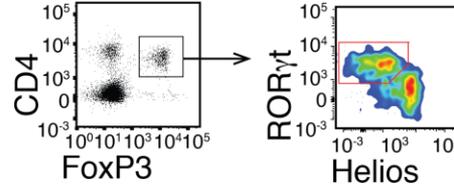
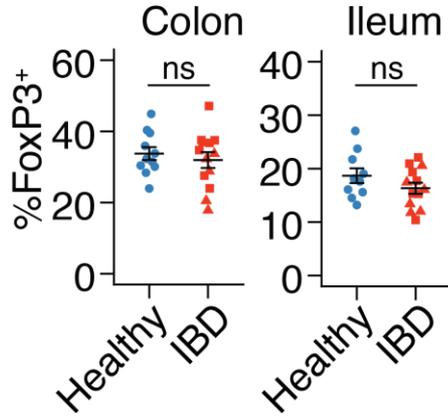
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Healthy donor microbiomes preferentially induce ROR γ t⁺ Treg



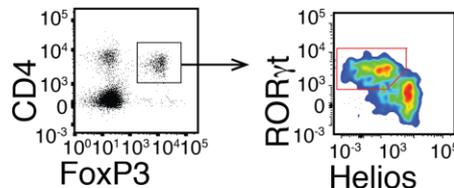
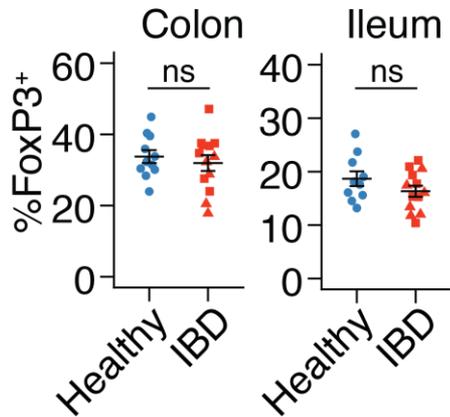
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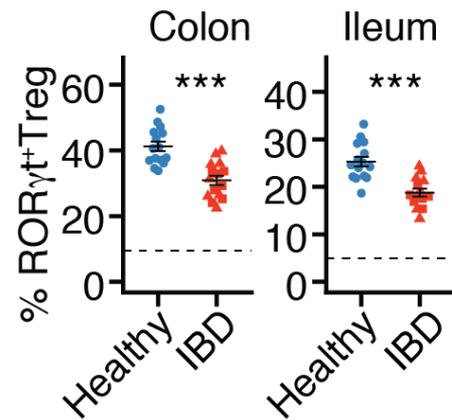
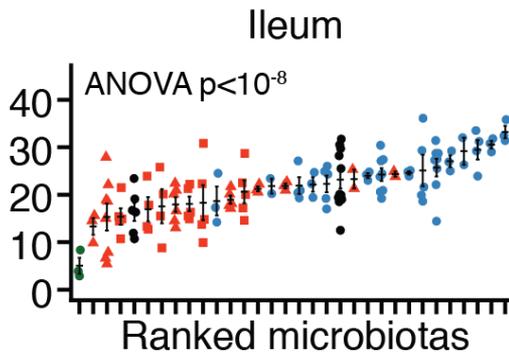
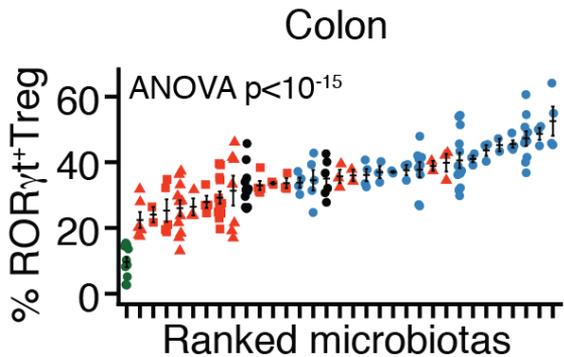
- Healthy
- CD
- ▲ UC
- SPF +SFB
- SPF -SFB
- Germ Free



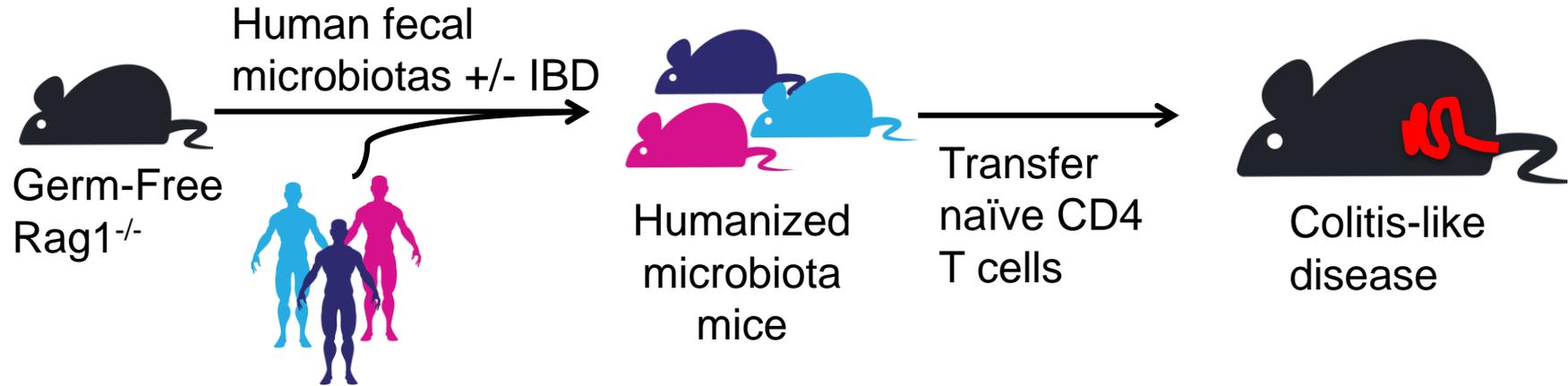
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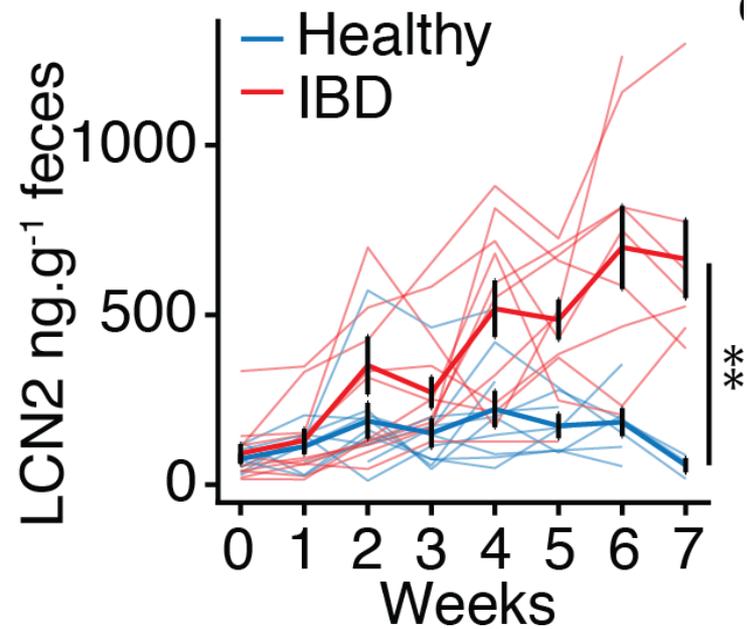
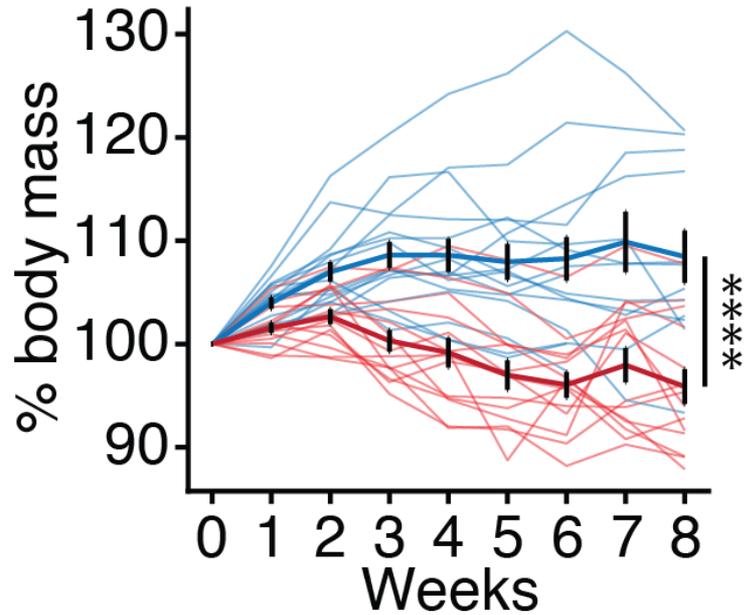
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The influence of interpersonal variation in microbiome composition on experimental colitis severity



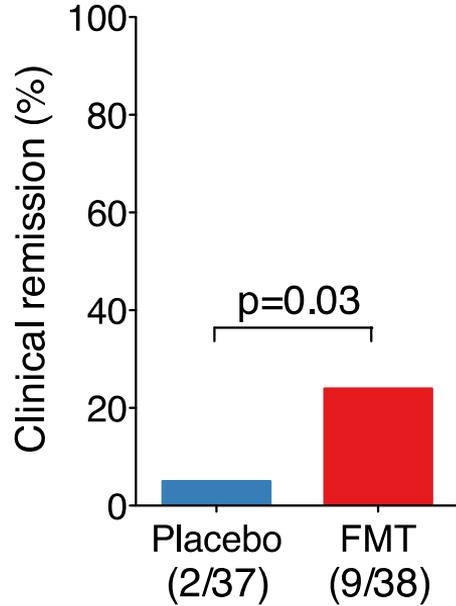
Microbiomes from donors with IBD transfer more severe colitis to susceptible mice than healthy donor microbiomes



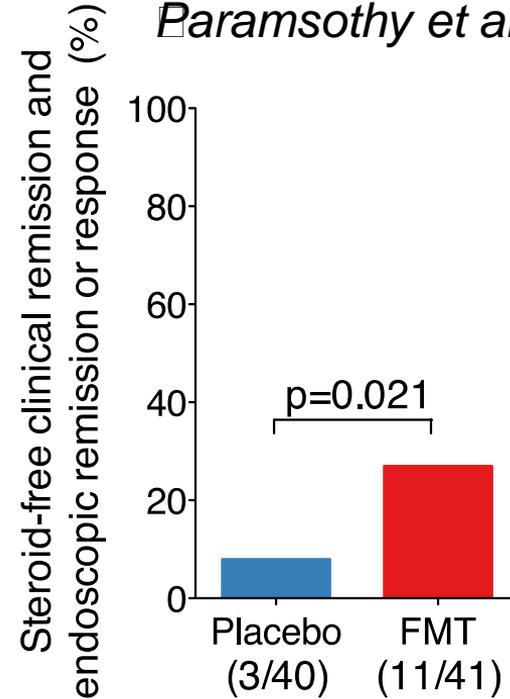
- Humanized-microbiome mice are a powerful tool to understand host responses to variation in microbiome composition
- IBD microbiotas induce an altered gut immune ‘tone’
- Induction of ROR γ ⁺Th17 cells and ROR γ ⁺Treg is altered in mice colonized with IBD microbiotas
- IBD microbiotas transfer severe colitis to susceptible mice

FMT for UC shows promise – but many experience no clinical benefit

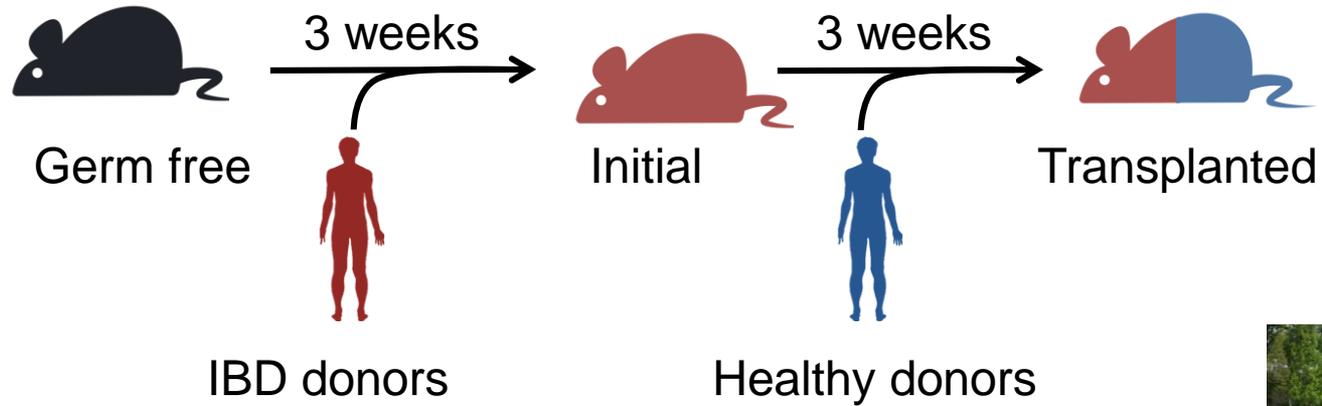
Moayyedi et al.



Paramsothy et al.



Modeling fecal transplant for IBD in mice



Eduardo Contijoch, PhD

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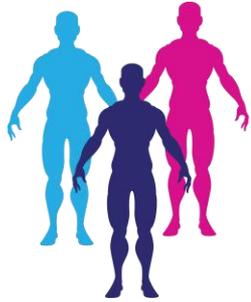
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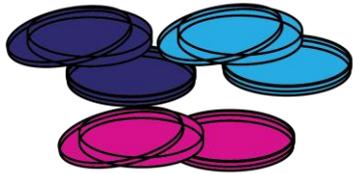
Culturing the human microbiome



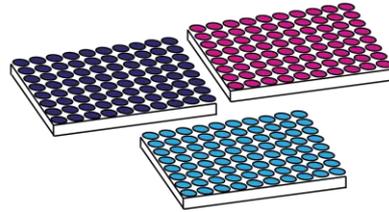
Culturing the human microbiome



Complex
microbiomes



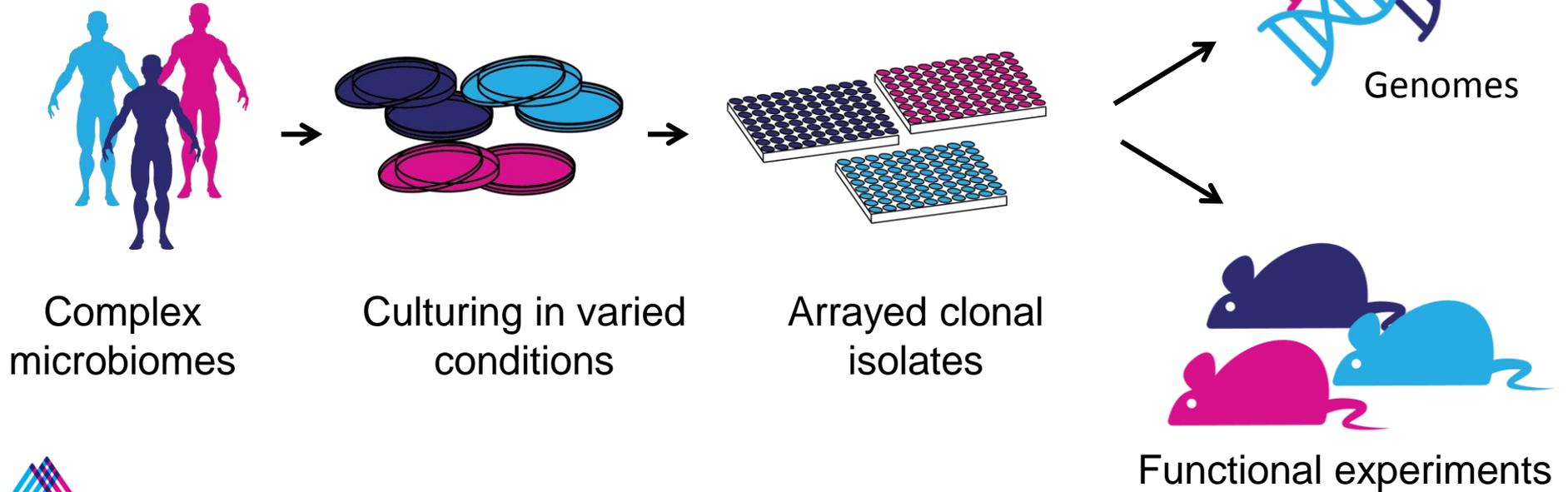
Culturing in varied
conditions



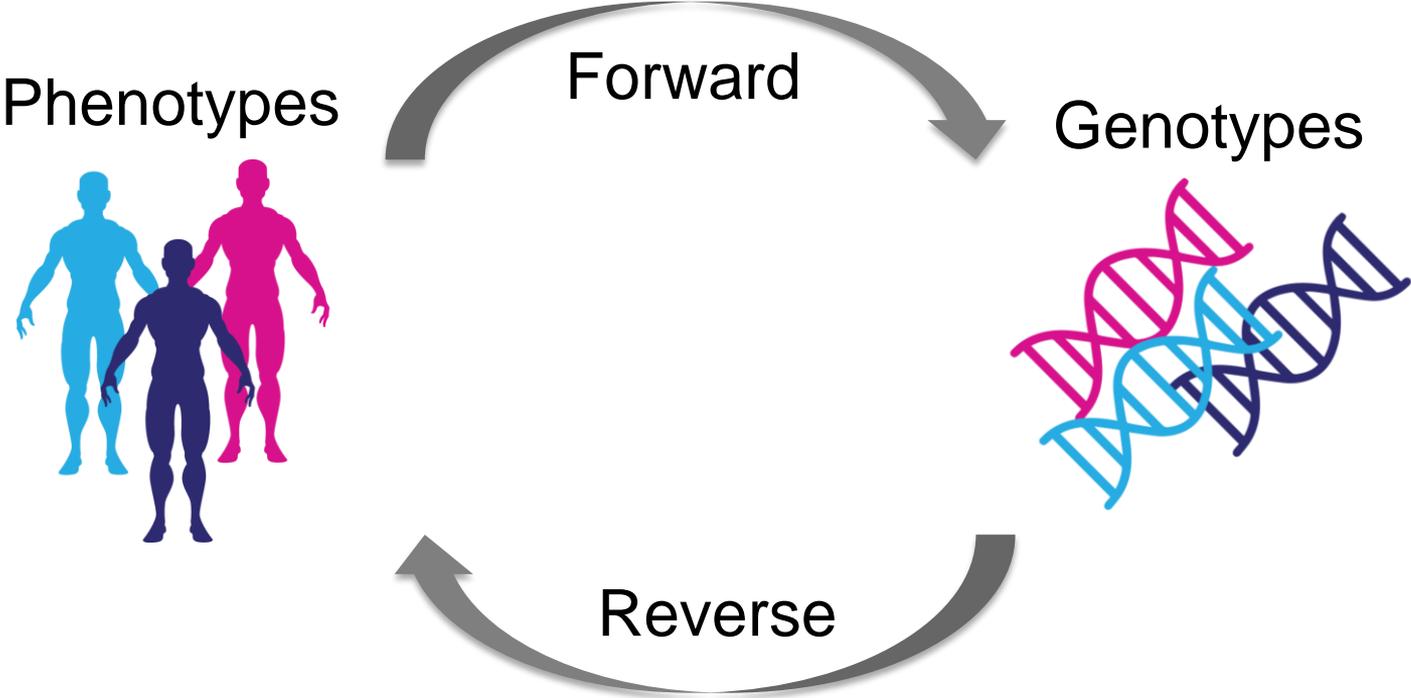
Arrayed clonal
isolates



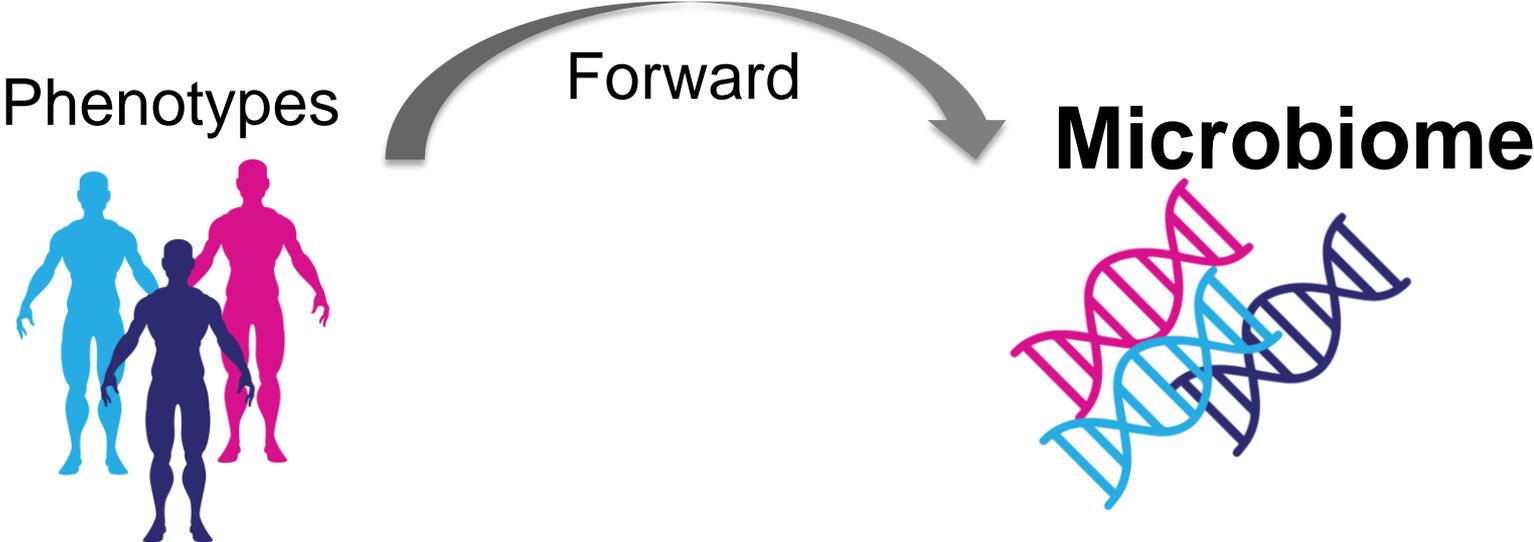
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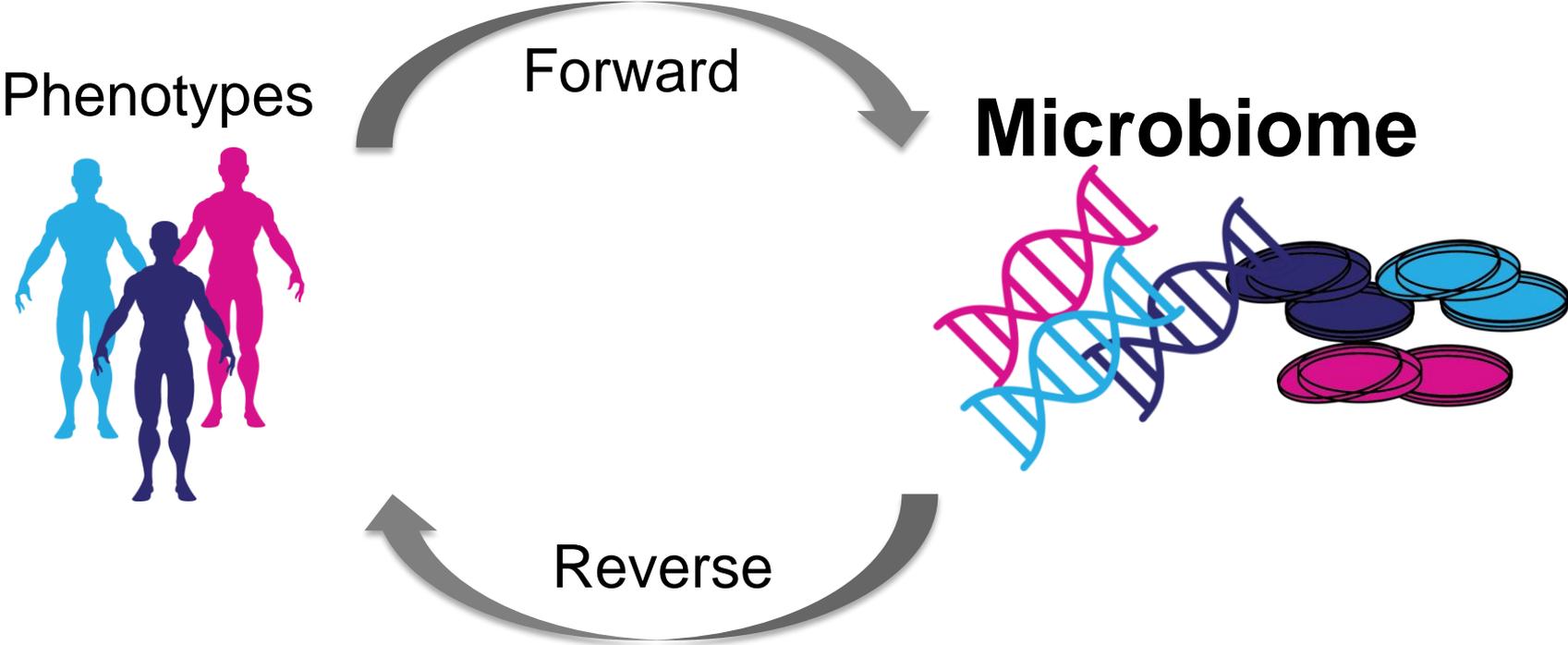
Forward vs reverse microbiome screening



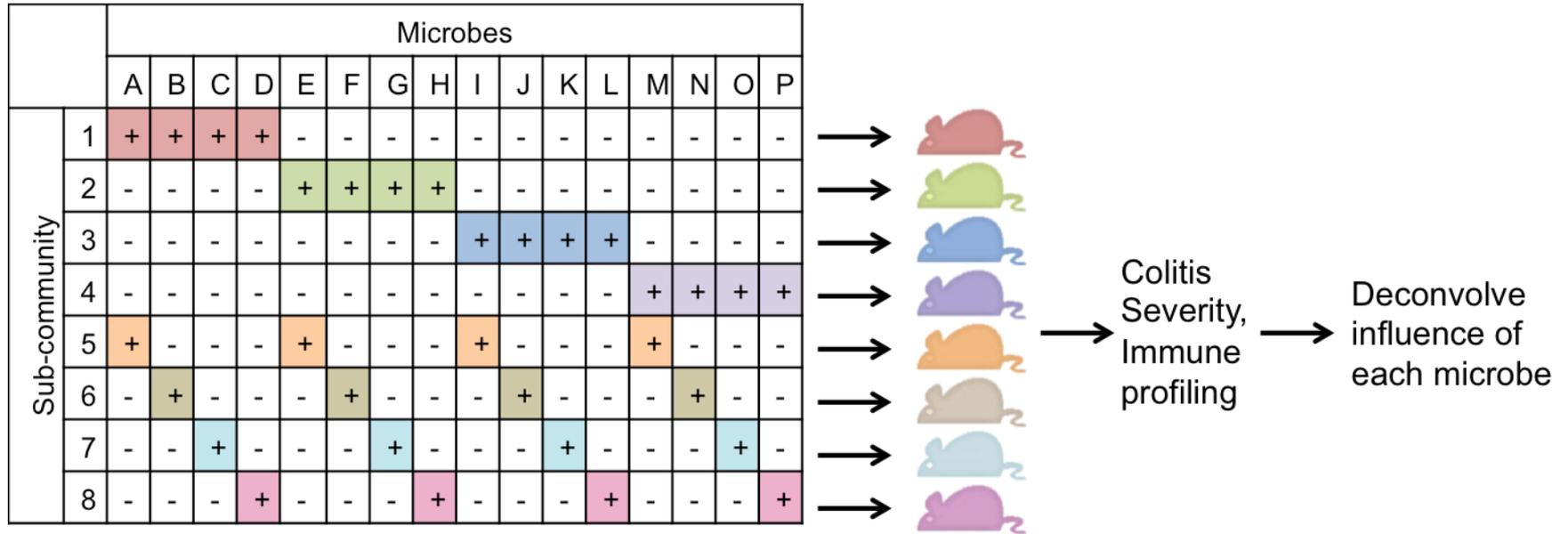
Forward vs reverse microbiome screening



Forward vs reverse microbiome screening



'Combinatorial gnotobiotics' - reverse microbiome screening



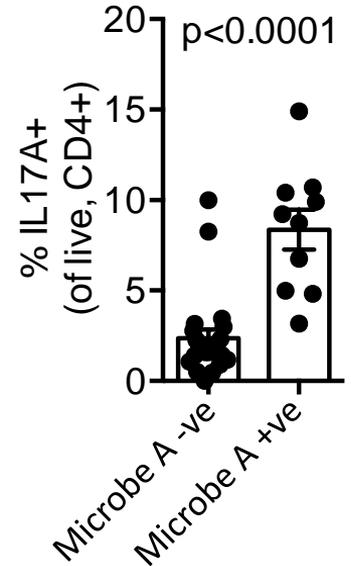
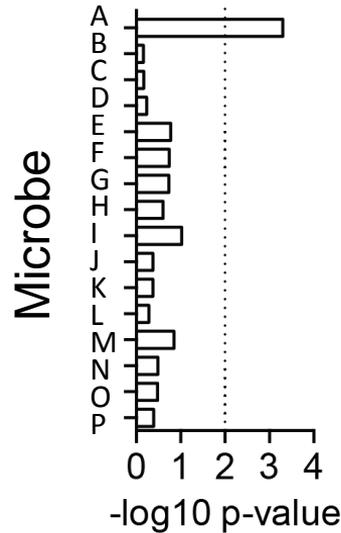
'Combinatorial gnotobiotics' can identify effector strains within complex microbiomes

A microbiome from a donor with Crohn's disease that induces IL-17⁺ T cells

Culture,
fractionate,
colonize



Association with
colon IL-17A⁺ T cells



- High-throughput culturing of the human microbiome complements sequencing methods to assess microbiome composition
- Genomes from clonal isolates can support robust metagenomic analysis
- “Combinatorial gnotobiotics” using cultured isolates can identify specific effector strains from complex human microbiomes



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