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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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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 individuals risk of developing a particular disease?

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

Inflammatory Bowel Diseases

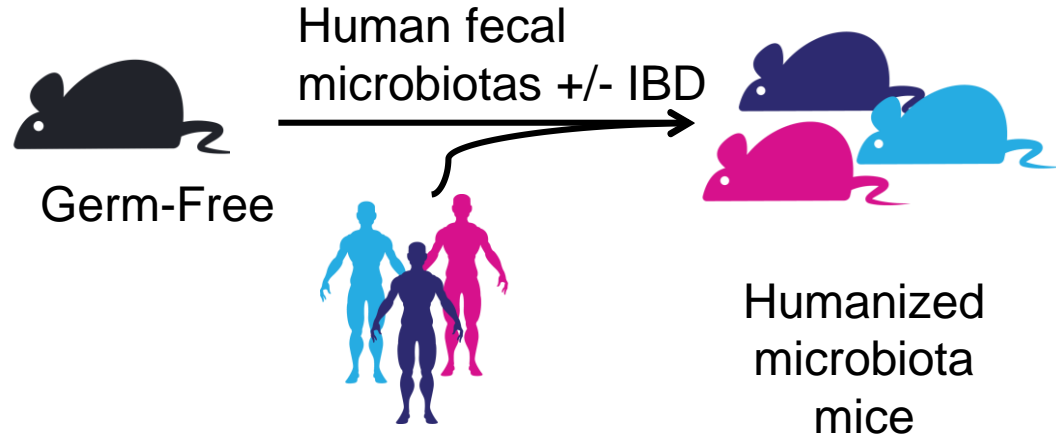
- Associated with an an altered microbiome
- Some efficacy using microbiome-targeted therapy (FMT) in ulcerative colitis *Paramsothy et al., Moayyedi et al.*
- Animal models, genetic associations and human tissue studies implicate a dysregulated T cell response

Motivating questions

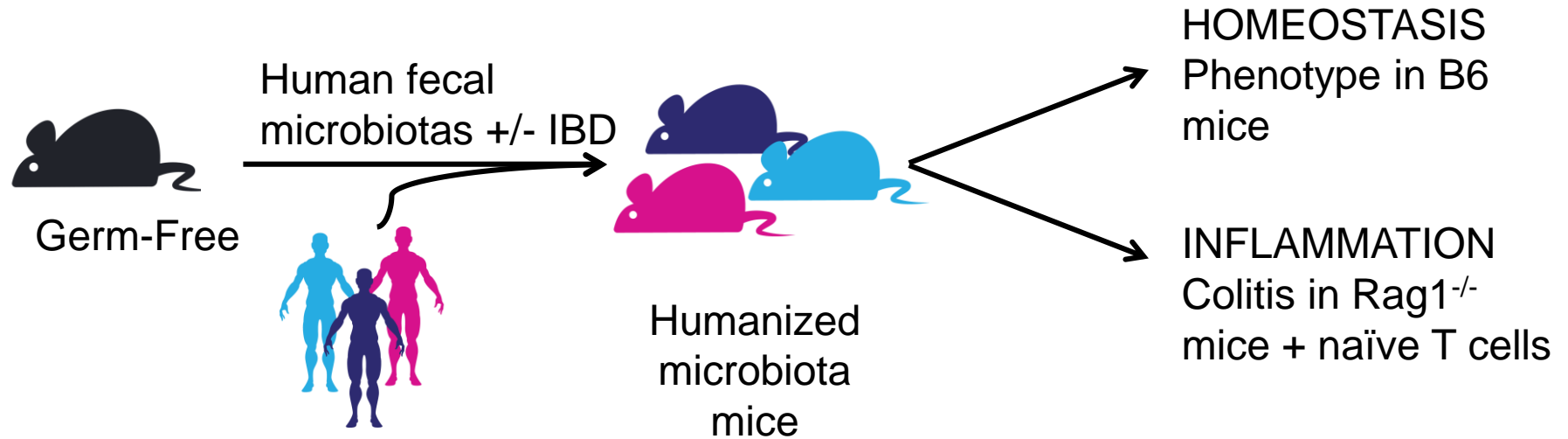
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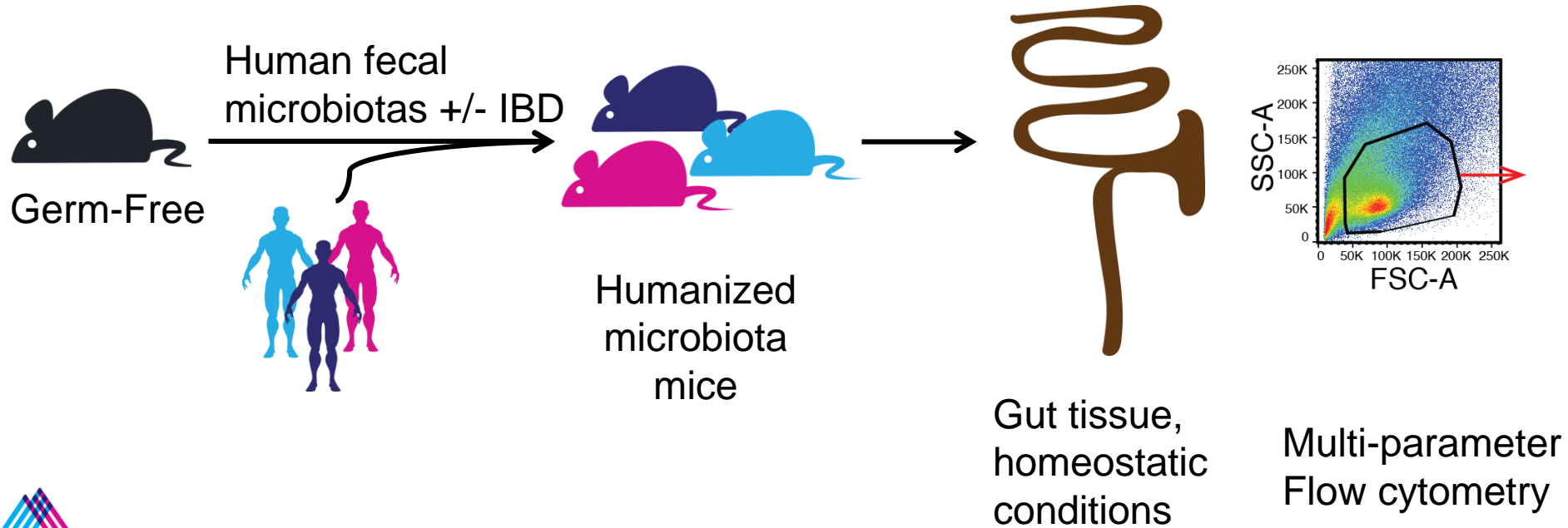
Humanized microbiome mice are a powerful model to explore microbiome-host interactions



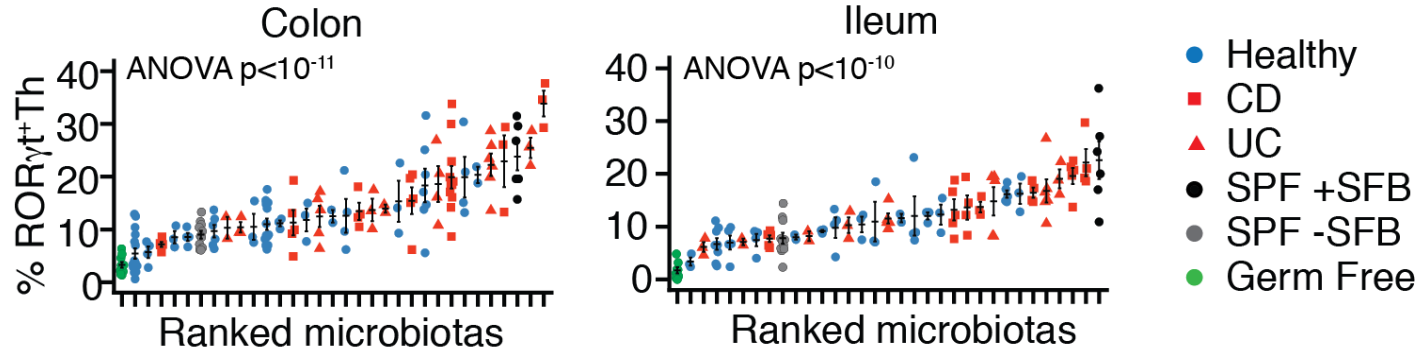
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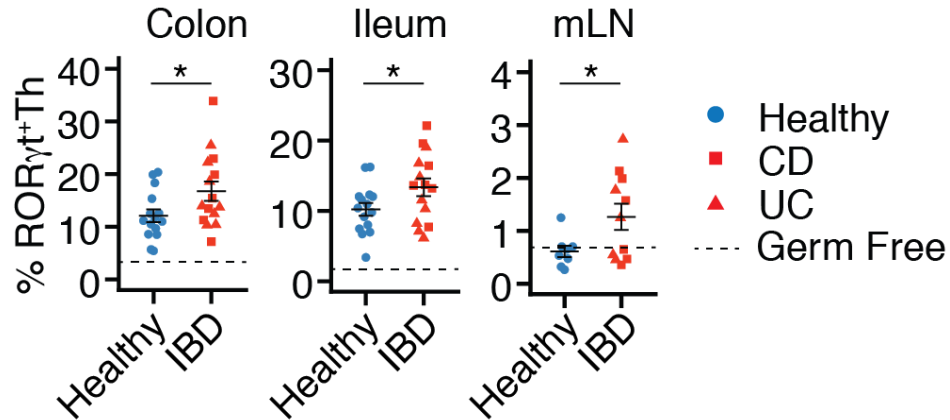
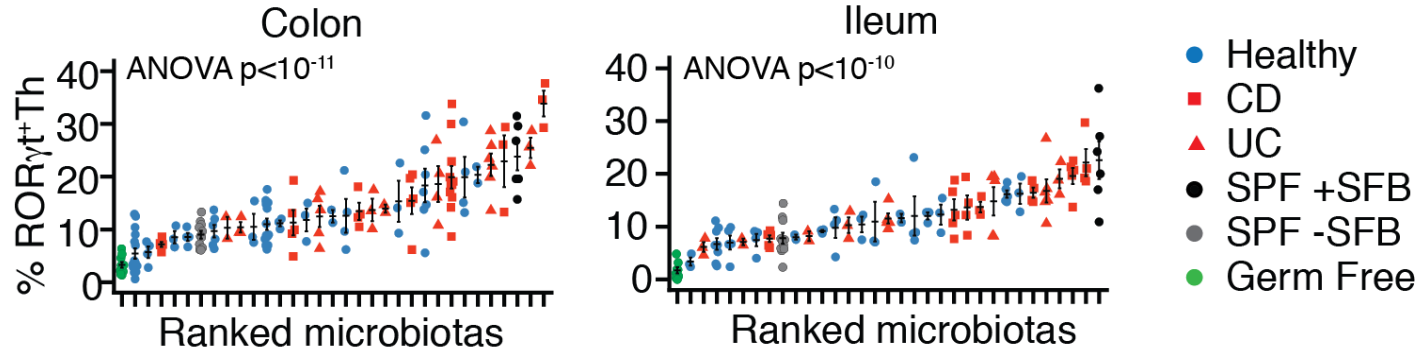
The influence of interpersonal microbiome variation on gut immune homeostasis



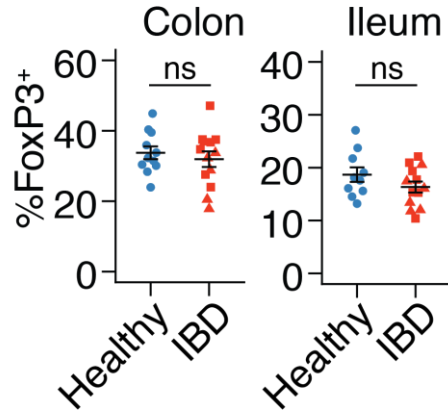
IBD microbiomes induce more ROR γ t⁺ Th17 cells than healthy donor microbiotas



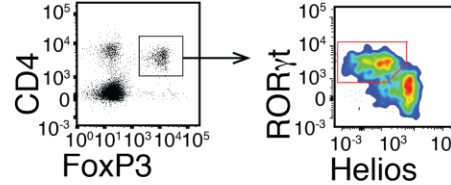
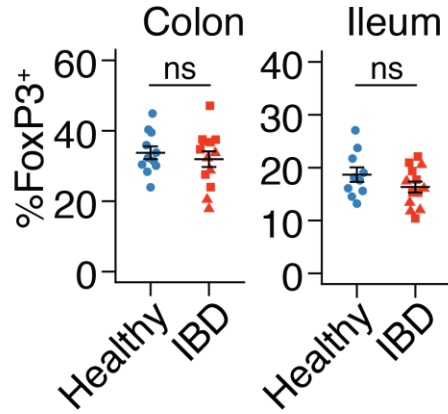
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Healthy donor microbiomes preferentially induce ROR γ t⁺ Treg

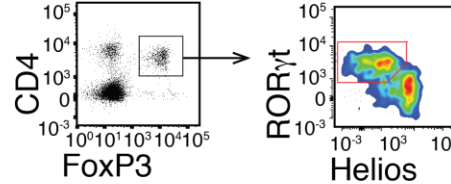
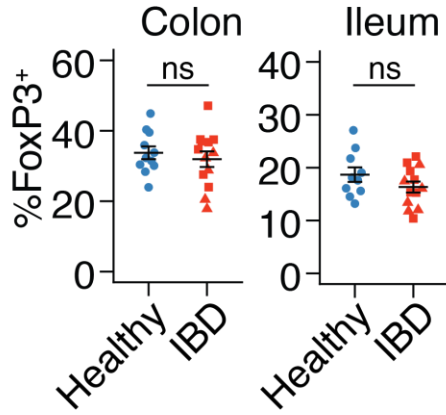


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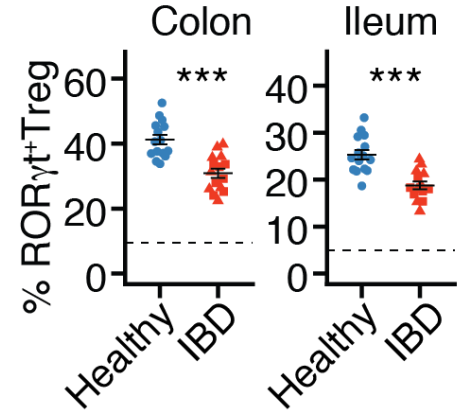
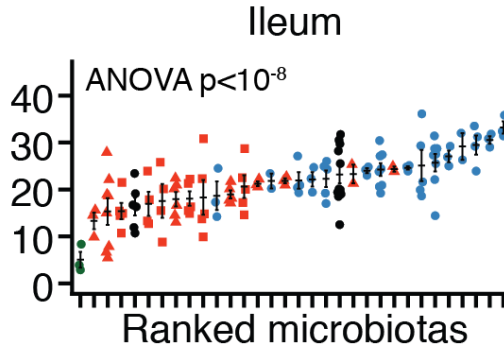
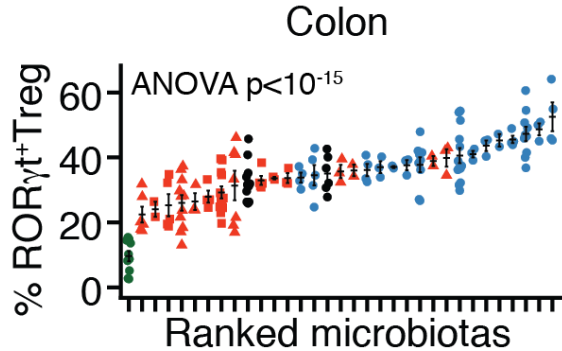


- Healthy
- CD
- ▲ UC
- SPF +SFB
- SPF -SFB
- Germ Free

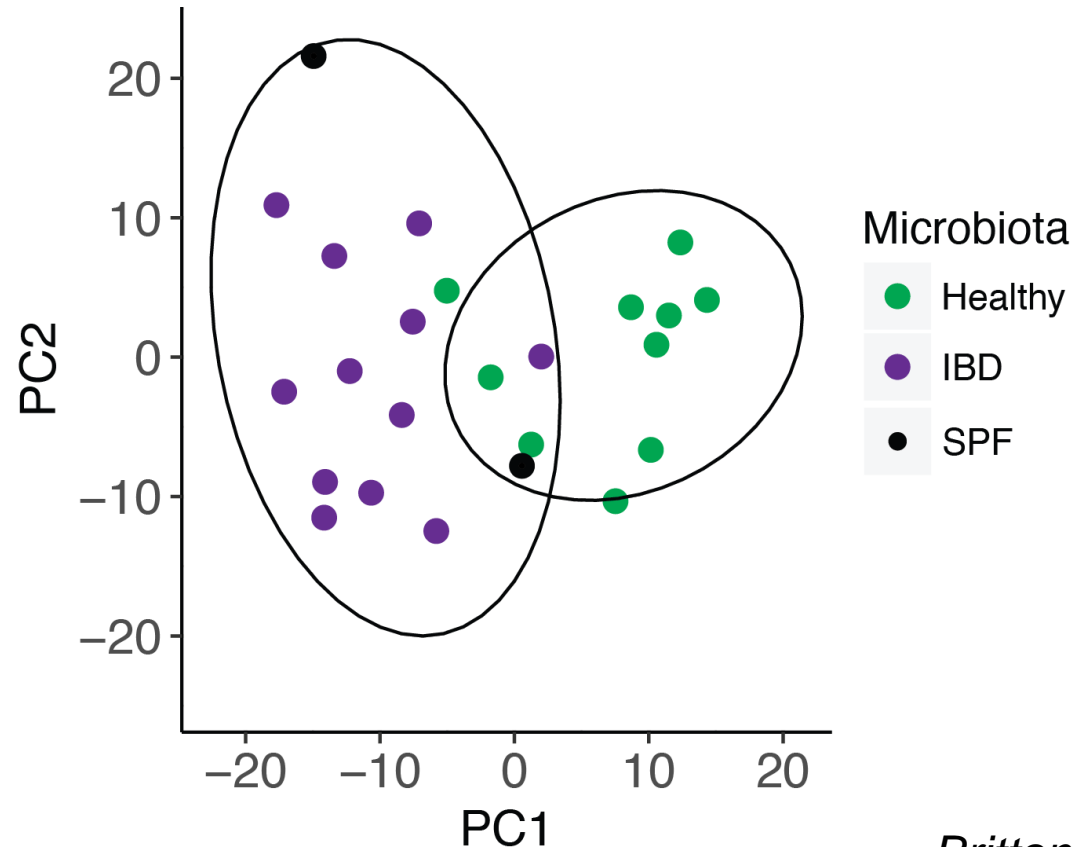
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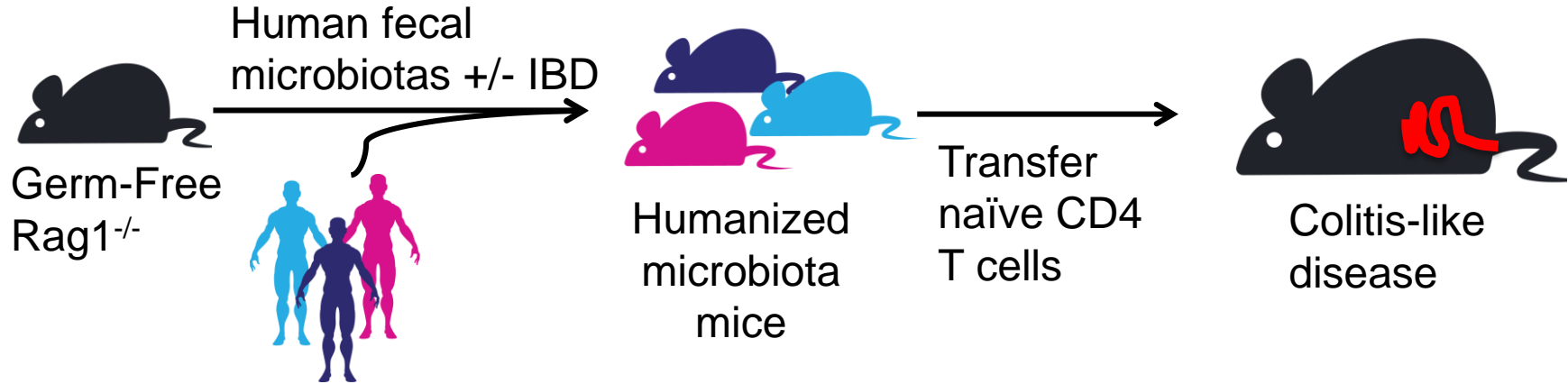
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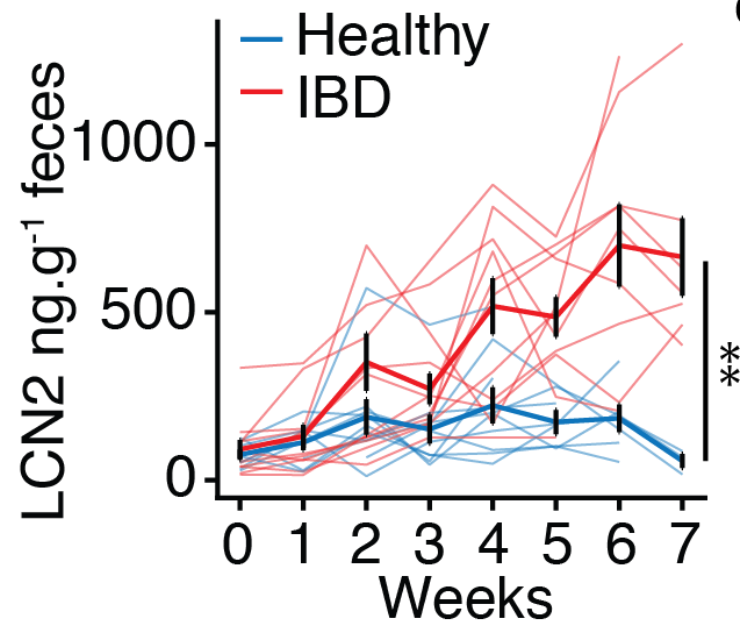
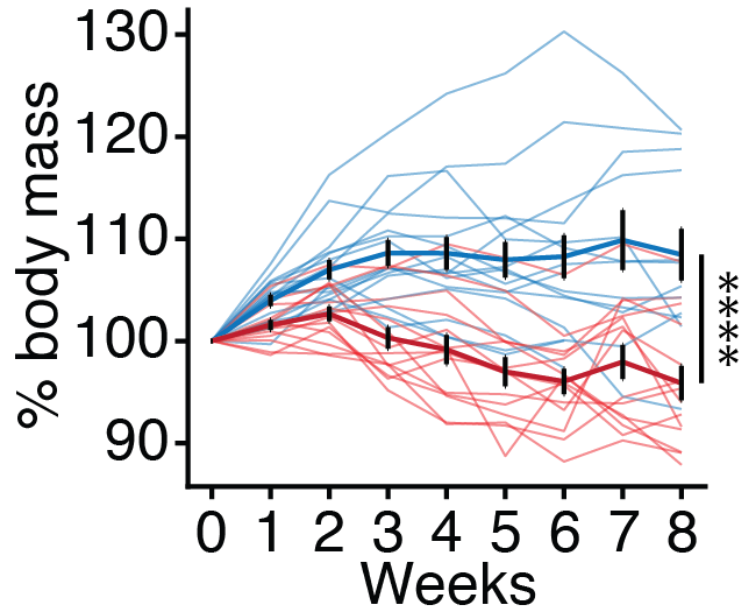
A distinct immune landscape is induced by IBD microbiomes



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



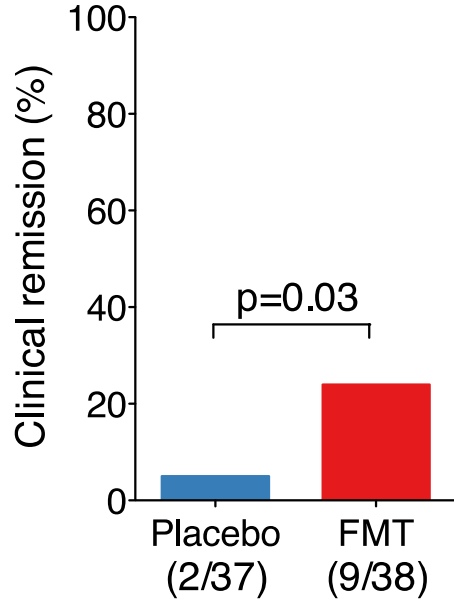
Microbiomes from donors with IBD transfer more severe colitis to susceptible mice than healthy donor microbiomes



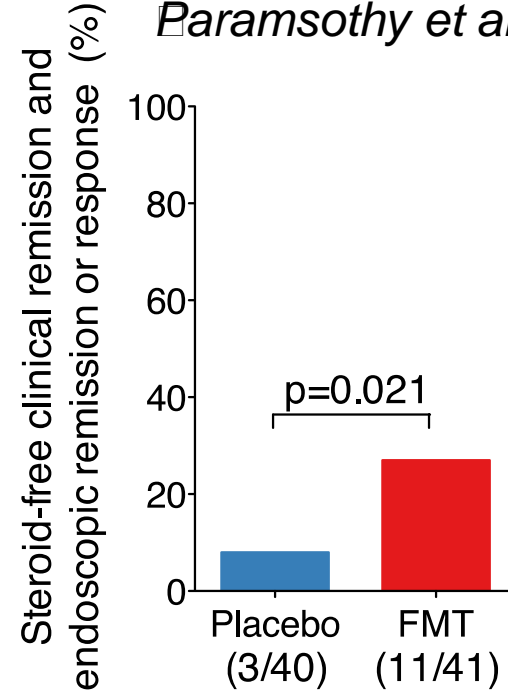
- Humanized-microbiome mice are a powerful tool to understand host responses to variation in microbiome composition
- IBD microbiotas induce an altered gut immune ‘tone’
- Induction of $\text{ROR}\gamma^+\text{Th17}$ cells and $\text{ROR}\gamma^+\text{Treg}$ is altered in mice colonized with IBD microbiotas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

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

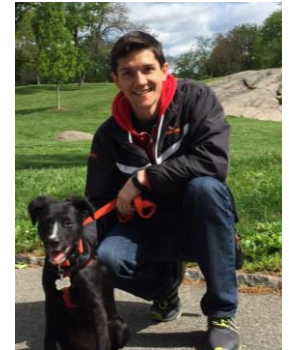
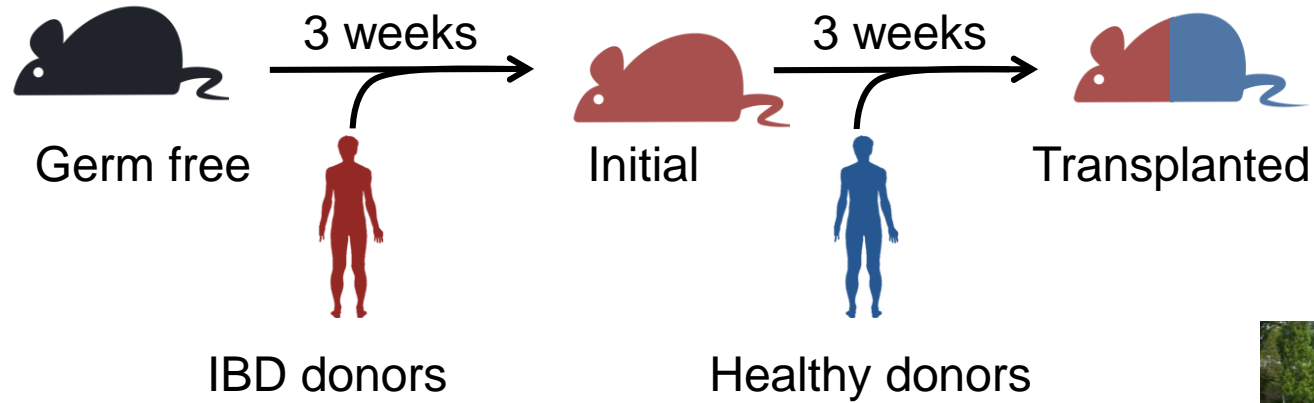
Moayyedi et al.



Paramsothy et al.

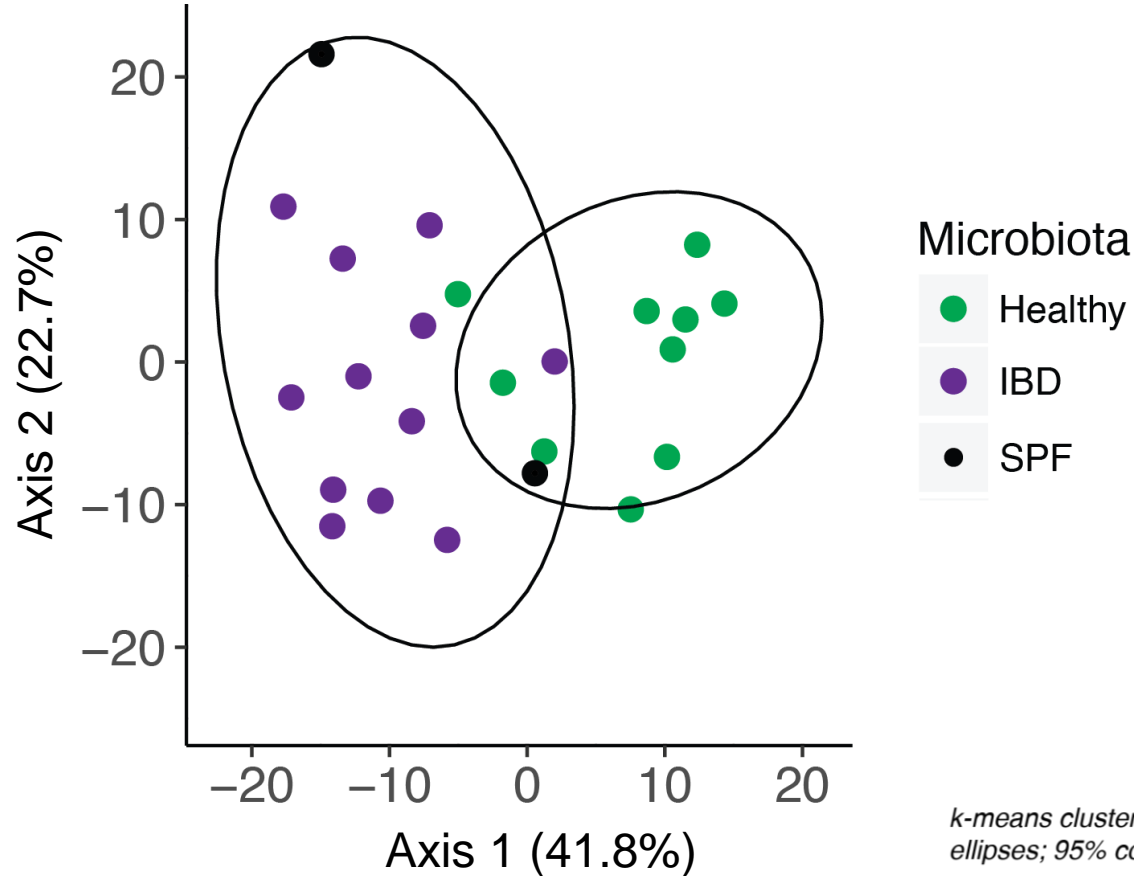


Modeling fecal transplant for IBD in mice

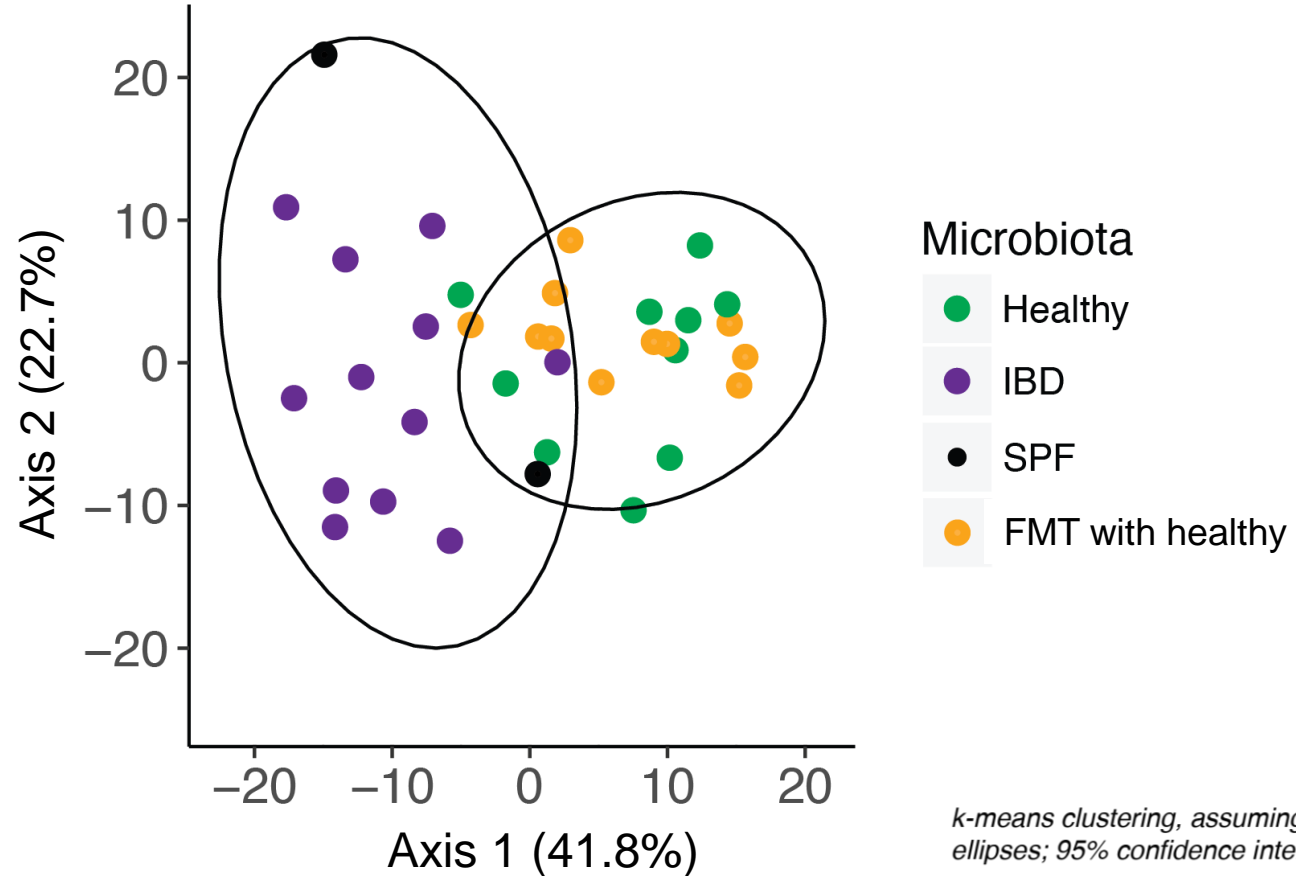


Eduardo Contijoch, PhD

Transplanting healthy microbiomes into IBD microbiome mice restores a 'healthy' immune landscape



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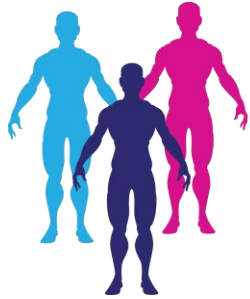
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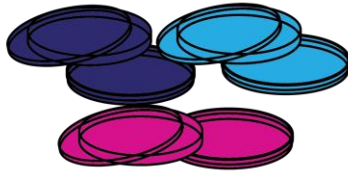
Culturing the human microbiome



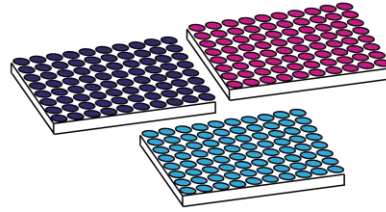
Culturing the human microbiome



Complex
microbiomes



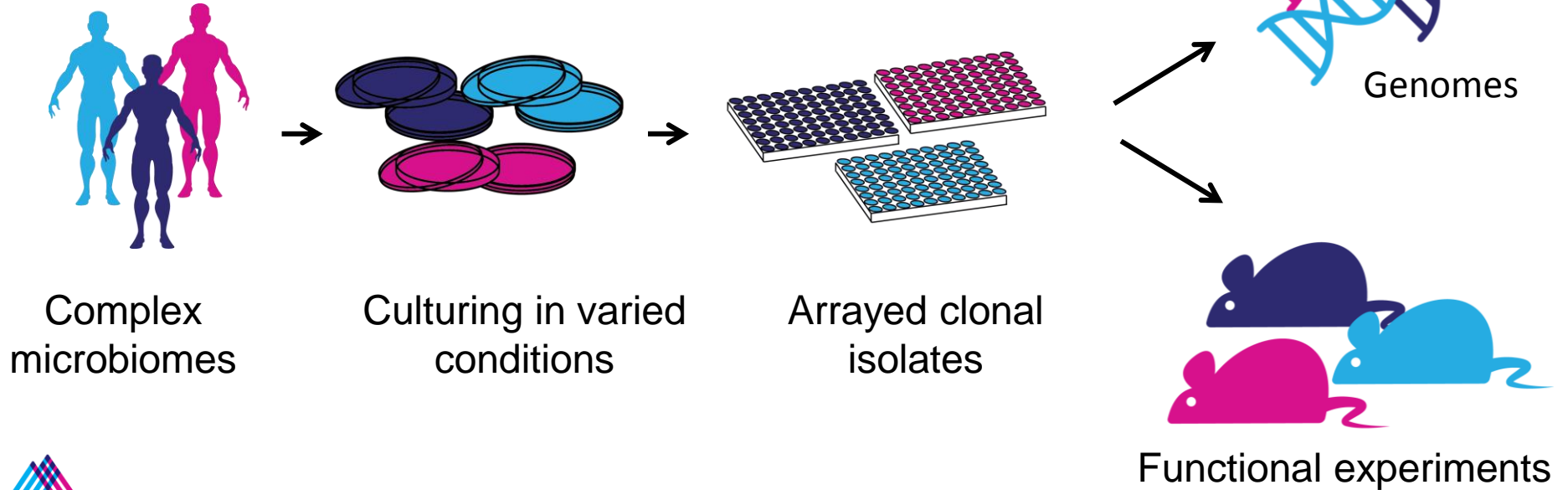
Culturing in varied
conditions



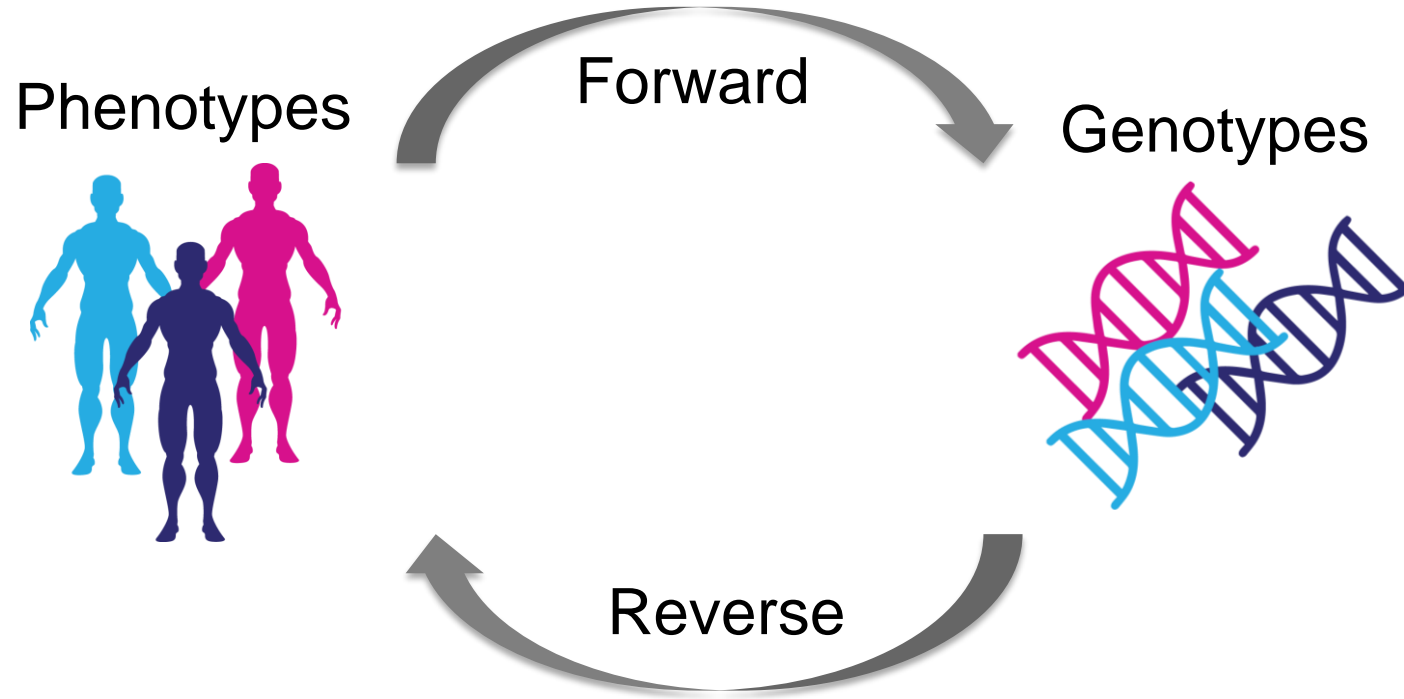
Arrayed clonal
isolates



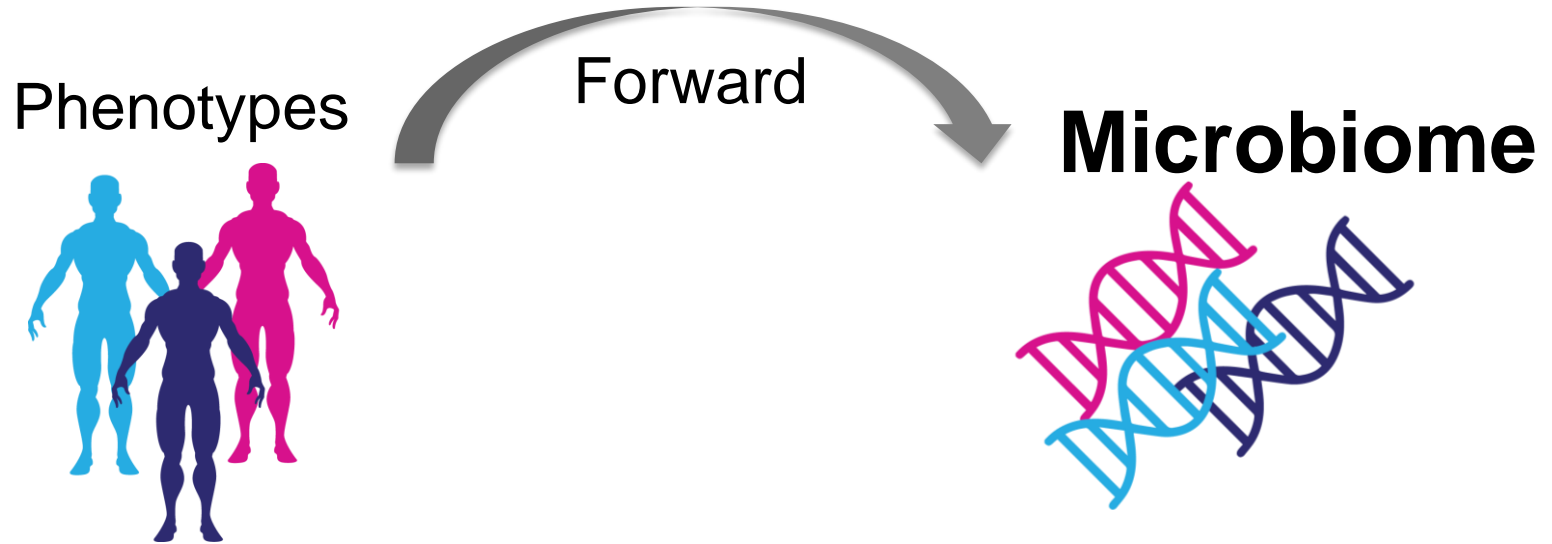
Culturing the human microbiome



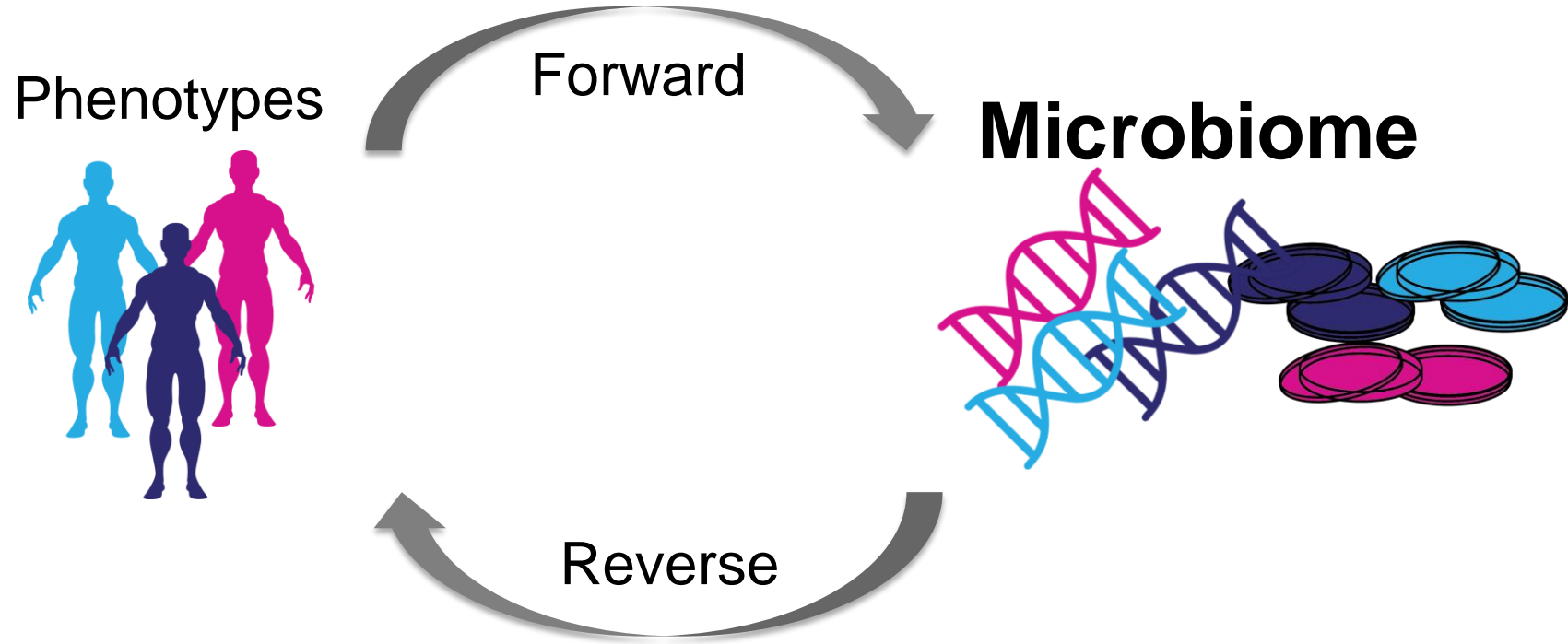
Forward vs reverse microbiome screening



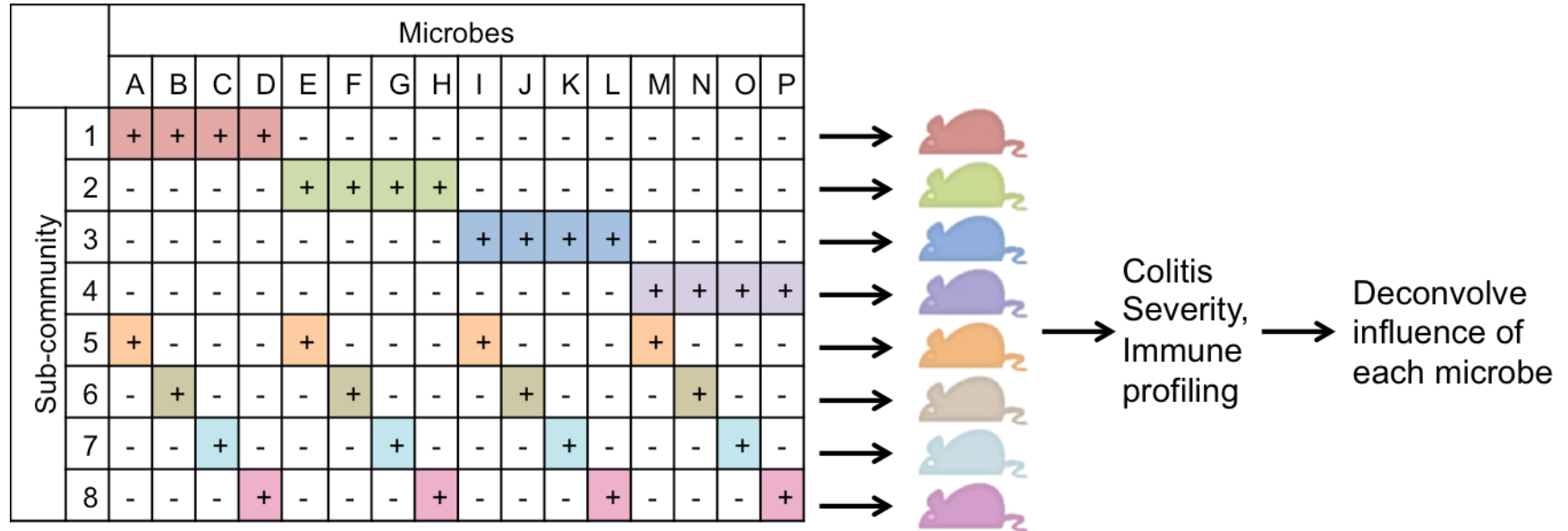
Forward vs reverse microbiome screening



Forward vs reverse microbiome screening



'Combinatorial gnotobiotics' - reverse microbiome screening

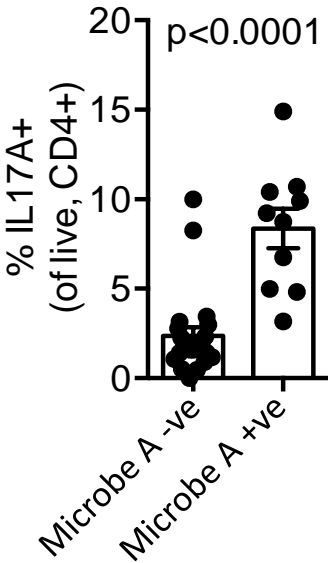
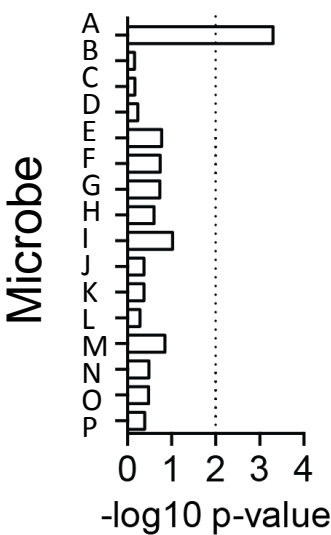


‘Combinatorial gnotobiotics’ can identify effector strains within complex microbiomes

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

With thanks.



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