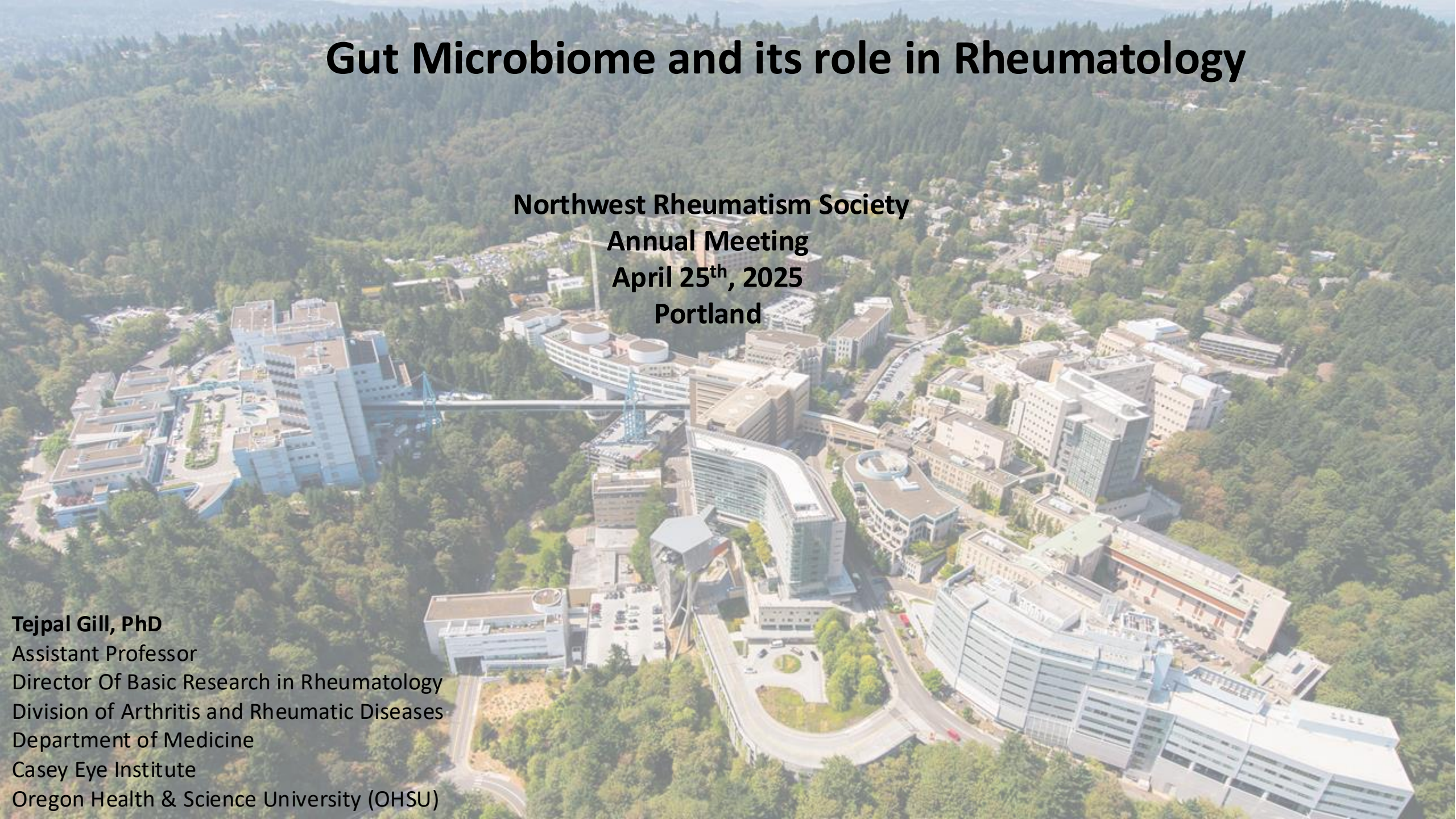
Gut Microbiome and its role in Rheumatology

Northwest Rheumatism Society
Annual Meeting
April 25th, 2025
Portland



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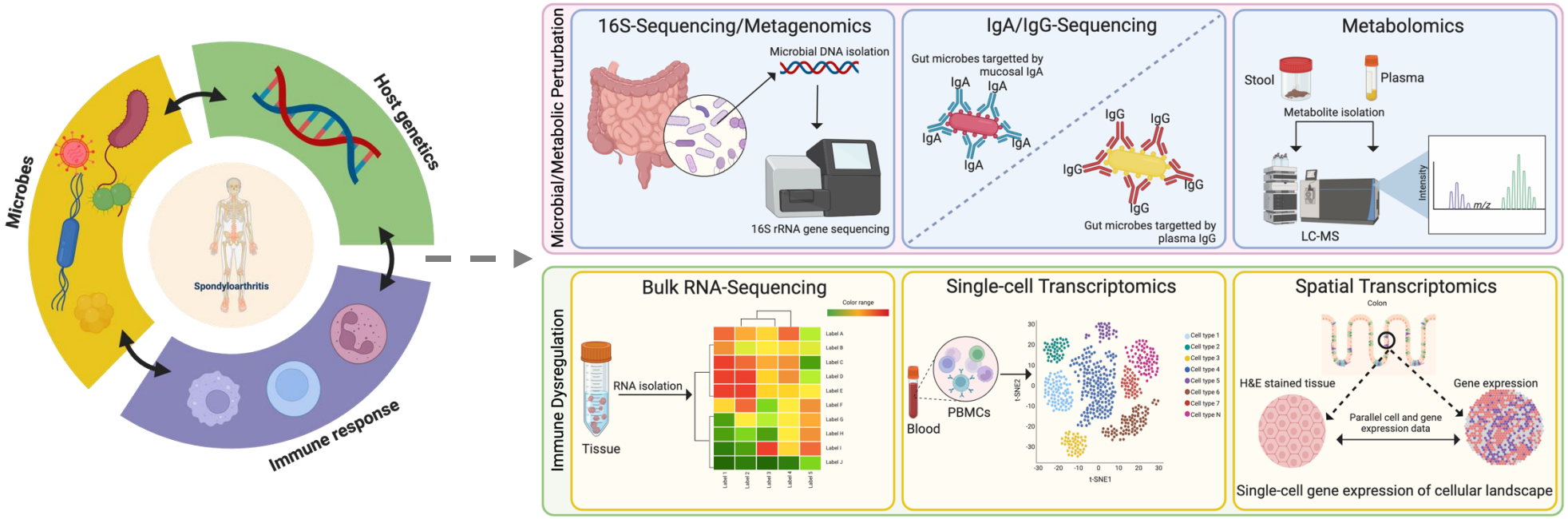
Casey Eye Institute
Oregon Health & Science University (OHSU)

No Disclosures

Determine host-microbe interactions in various spondyloarthropathies



Validation Studies

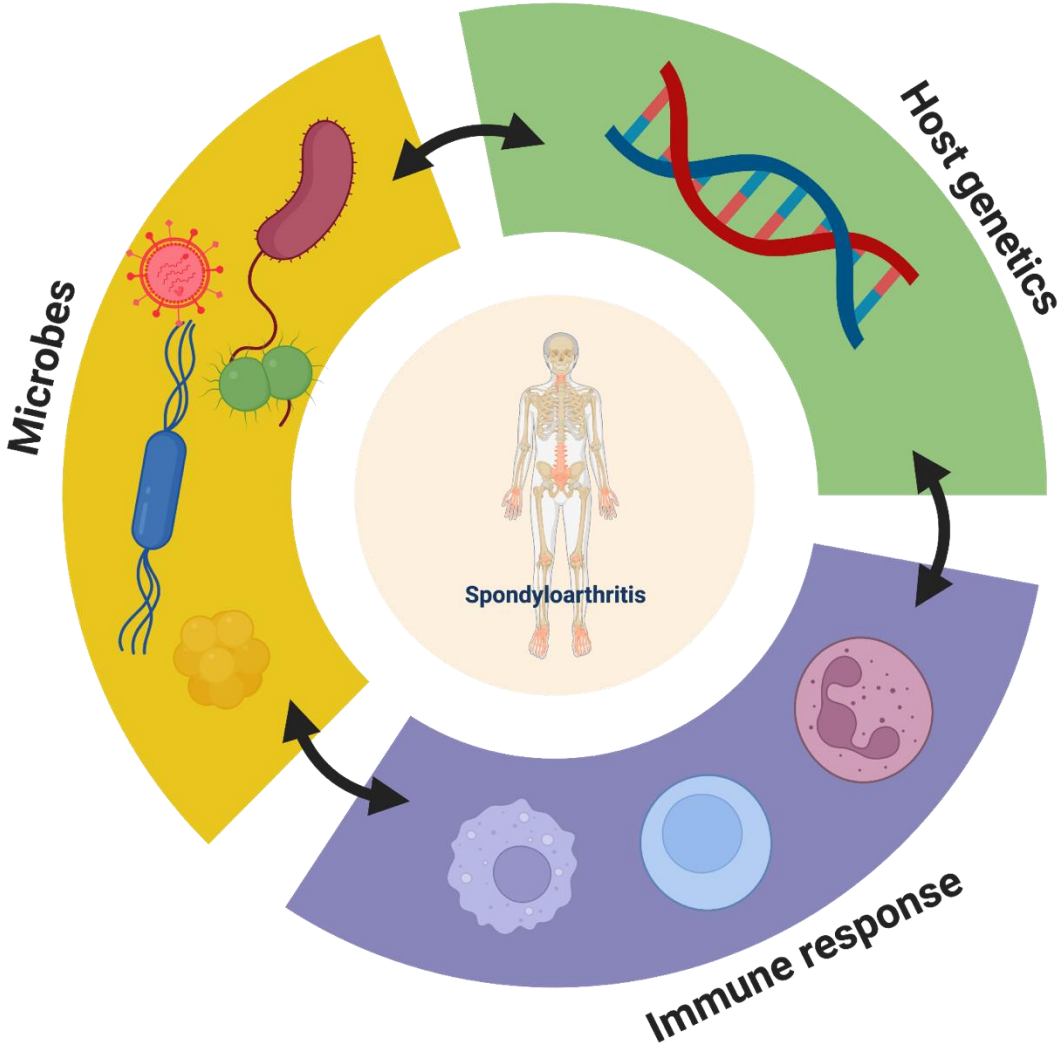
HLA-B27 Tg rat

https://www.ohsu.edu/school-of-medicine/gill-lab

Furst and Gill, Best Practice & Research Clinical Rheumatology, 2024

Figure made in Biorender

Host-Microbe Interactions in Spondyloarthritis: Focus on Axial Spondyloarthritis and Acute Anterior Uveitis



Outline

1. Spondyloarthritis

2. Effect of HLA-B27

3. Gut microbial dysbiosis and spondyloarthritis

4. Host-microbe interactions: Lessons from HLA-B27 transgenic rats

5. Host-microbe interactions in axial spondyloarthritis/acute anterior uveitis
    - Gut Microbial modulation: IgA Seq
    - Metabolic profiling of host and microbes LCMS)
    - Systemic host immune response (sc RNA-Seq and CITE Seq)

Spondyloarthritis is a group of diseases with common clinical manifestations

Group of diseases

- Axial spondyloarthritis
- Acute anterior uveitis
- Psoriatic arthritis
- Juvenile idiopathic arthritis
- Reactive arthritis
- Undifferentiated spondyloarthritis

Clinical manifestations

Articular

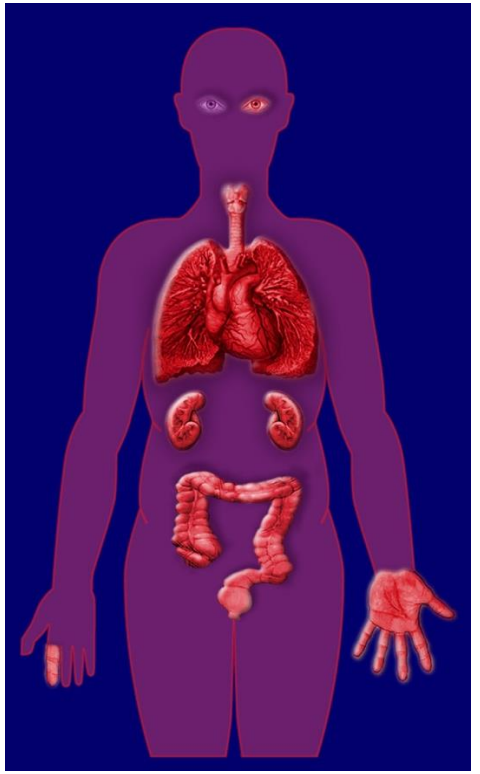
Enthesitis

Axial skeletal inflammation

Peripheral arthritis

Dactylitis

Abnormal bone formation



Extra-articular

AAU

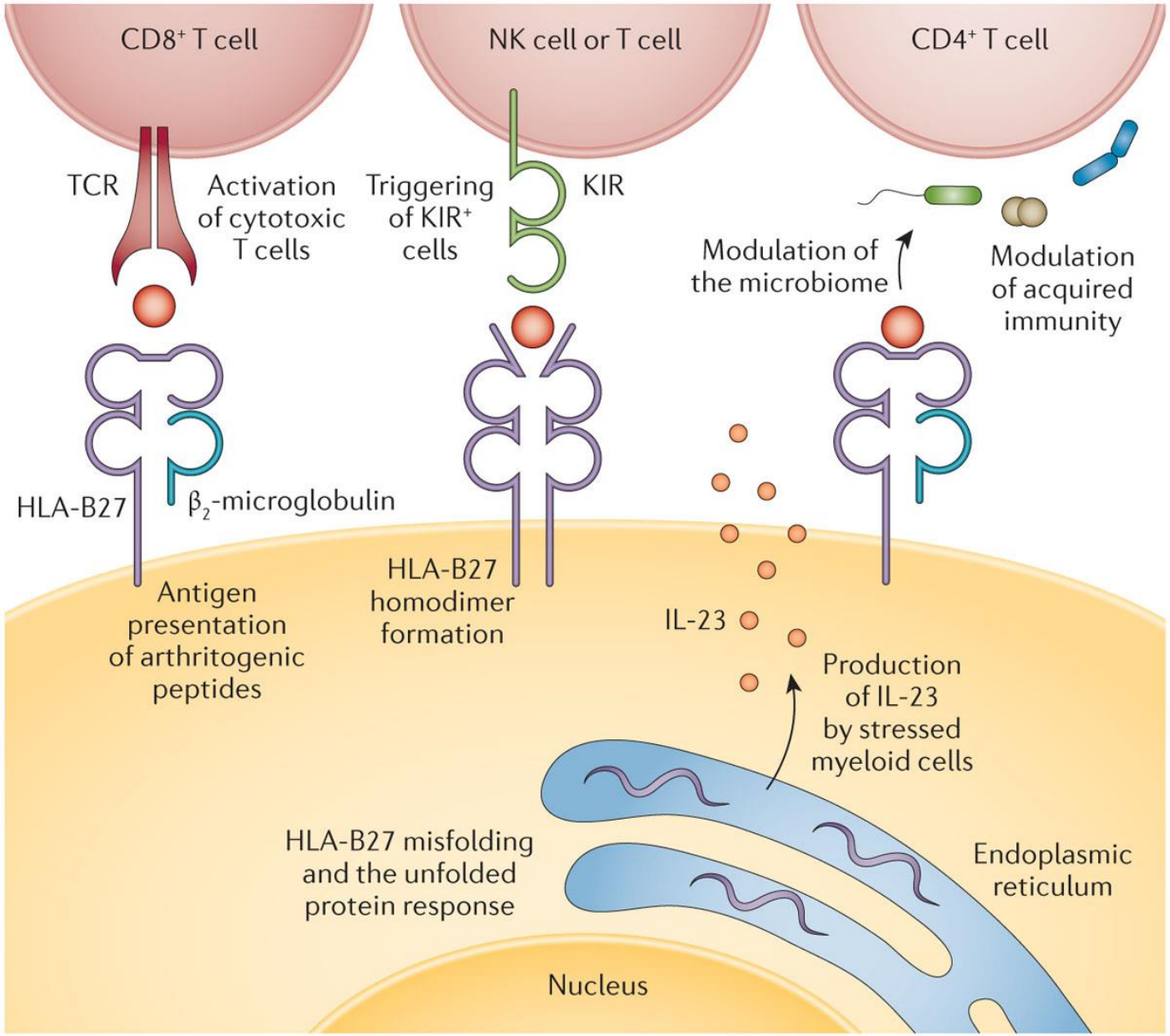
GI inflammation

Psoriasis

Cardiac and pulmonary

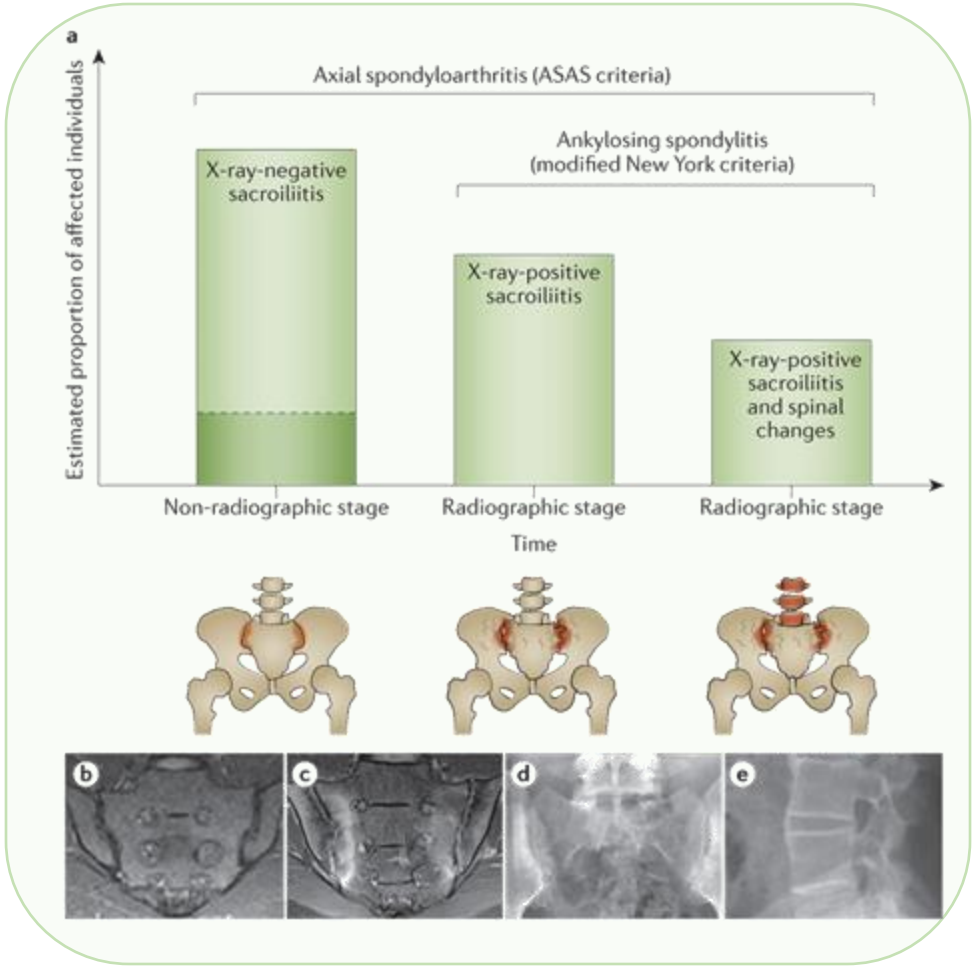
Khan: Spondyloarthropathies: *Atlas of Rheumatology* 2002.
Proft & Poddubnyy Ther Adv Musculoskelet Dis. 2018

Proposed mechanisms underlying HLA-B27 associated spondyloarthritis pathogenesis



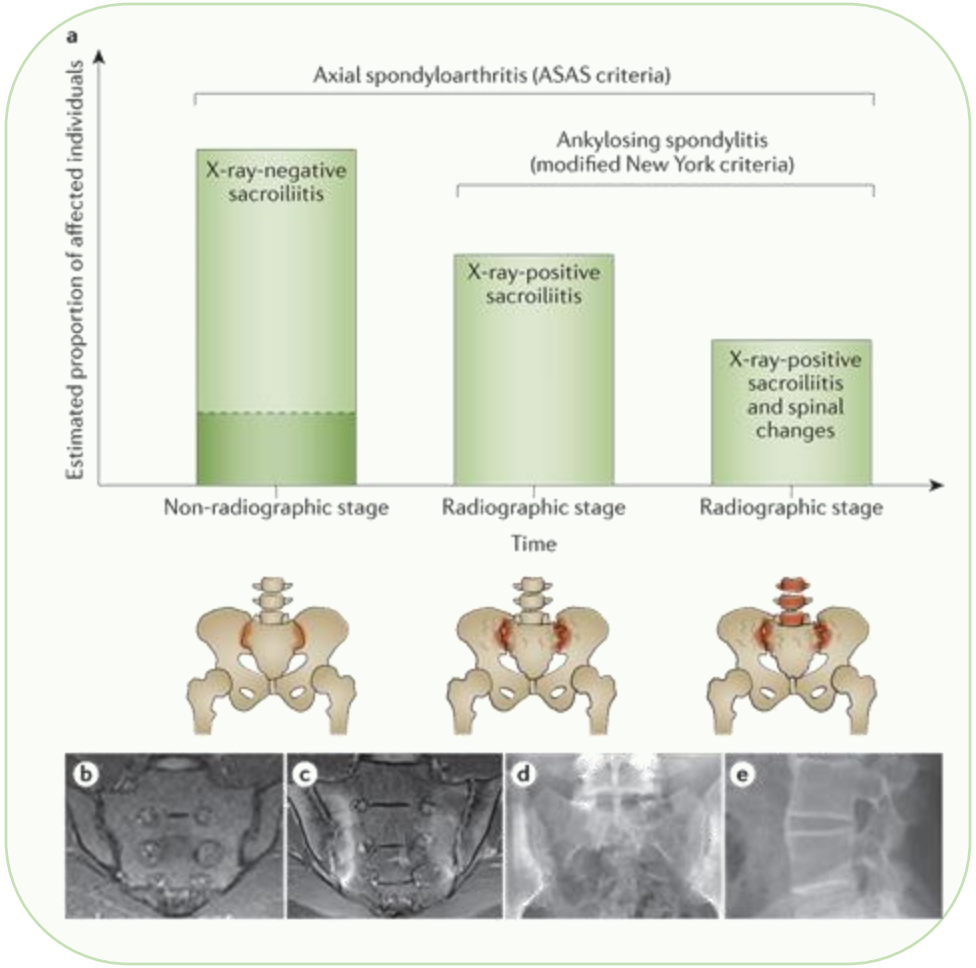
Sieper, J. *et al.* (2015) *Nat. Rev. Dis. Primers*

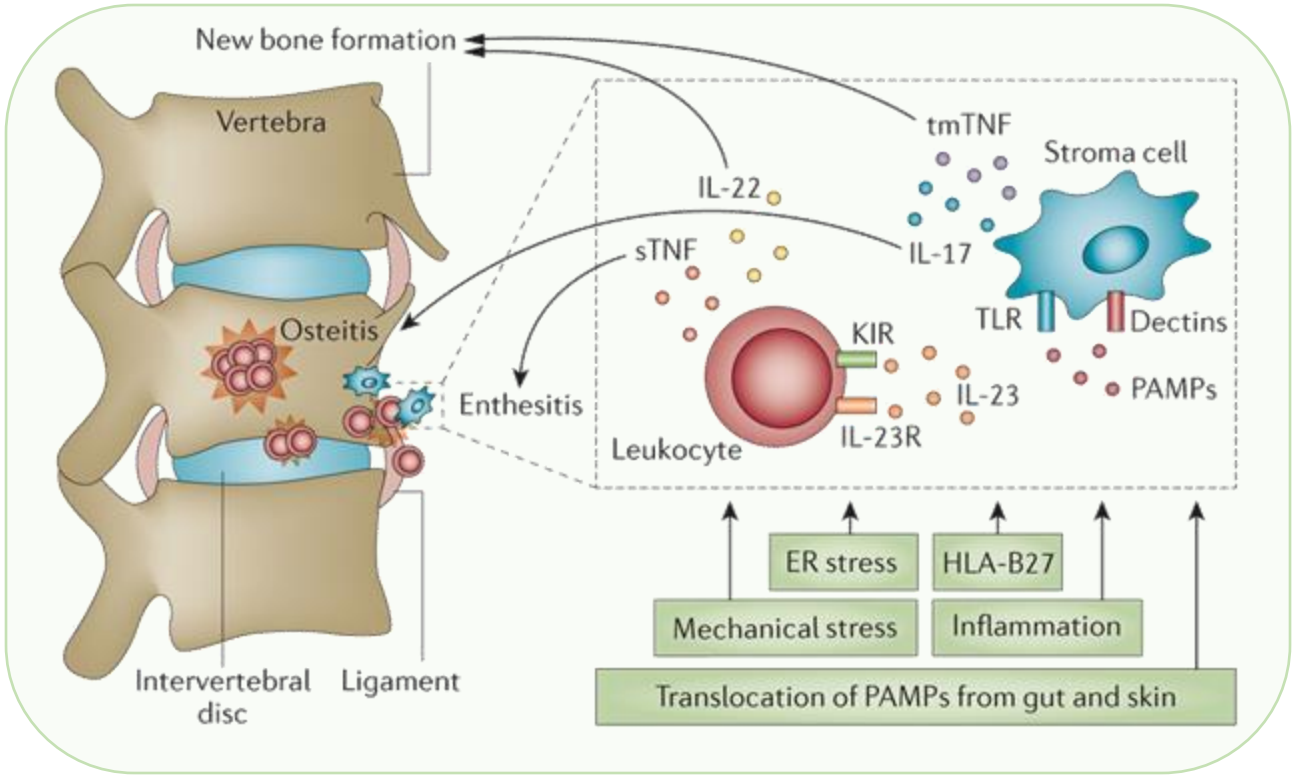
Spectrum of axial spondyloarthritis



Sieper, J. *et al.* (2015) Axial spondyloarthritis *Nat. Rev. Dis. Primers*

The pathophysiology of axial spondyloarthritis





Sieper, J. *et al.* (2015) *Nat. Rev. Dis. Primers*

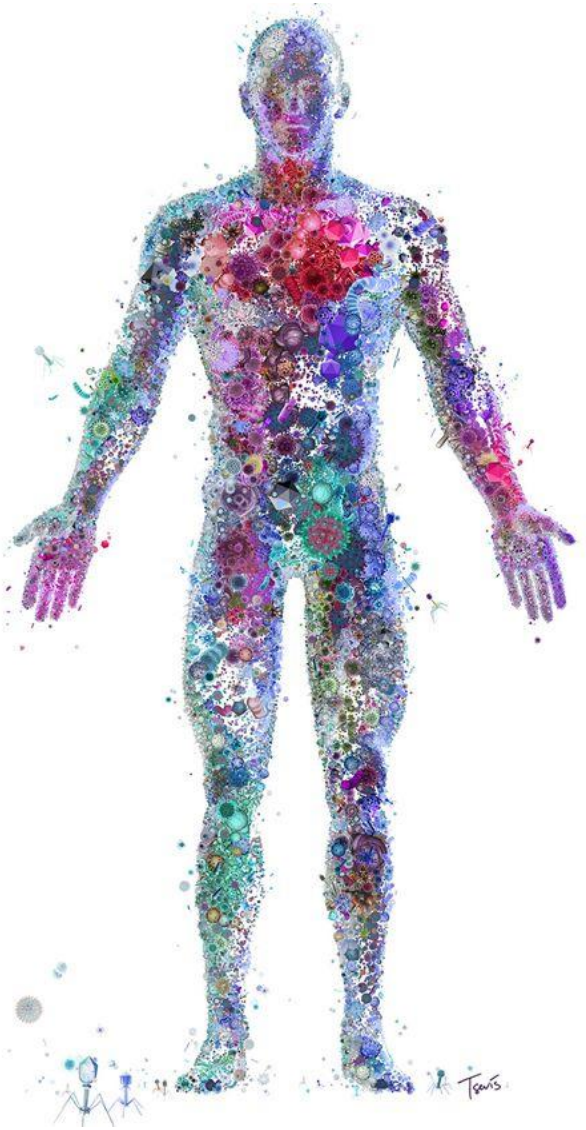
Why suspect gut microbiota in spondyloarthritis?

Gut inflammation is common in spondyloarthritis

- patients have gut inflammation
  - ~50-70% subclinical
  - ~6-10% IBD
- 50-80% of IBD patients have arthritis

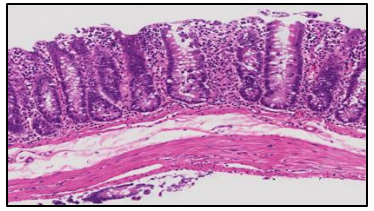
Experimental spondyloarthritis in rodents is highly dependent on gut microbiota

- Gut flora required in HLA-B27 transgenic rats
- SpA-prone (SKG) mice gut microbiota influence the incidence/severity of arthritis/ileitis



HLA-B27 Tg rat model of spondyloarthritis

peripheral joint inflammation



gastrointestinal inflammation

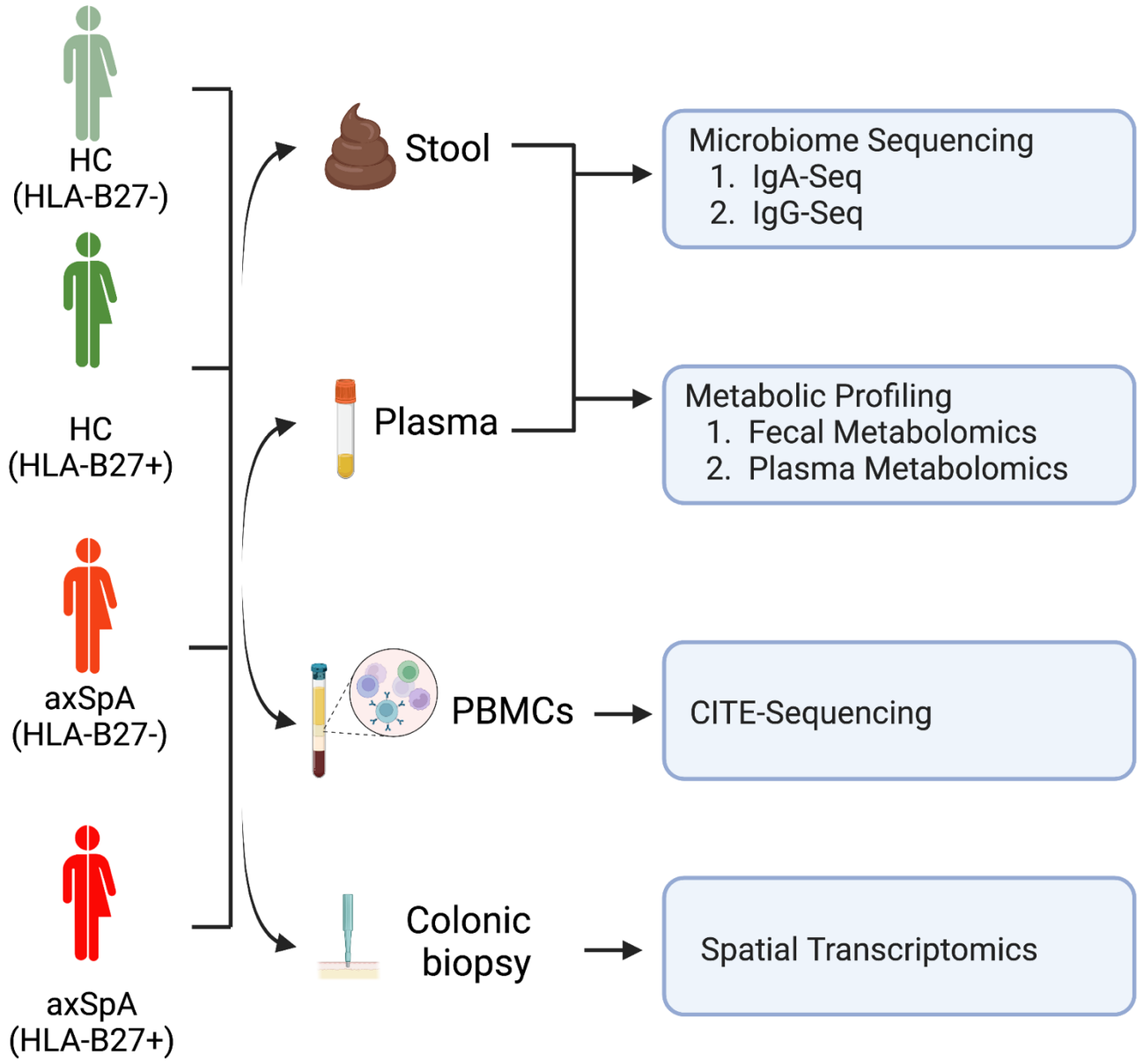
Host-microbe interactions underlying axial spondyloarthritis pathogenesis

Host-microbe interactions underlying PsA

Nominated by OHSU for Pew Biomedical

Specific Aims:

1. To investigate IgA and IgG immune response to gut microbes in axSpA
2. Functional characterization of cellular phenotypes underlying axSpA immunopathogenesis.
3. Effect of inflammatory metabolites/metabolic pathways on development of axSpA

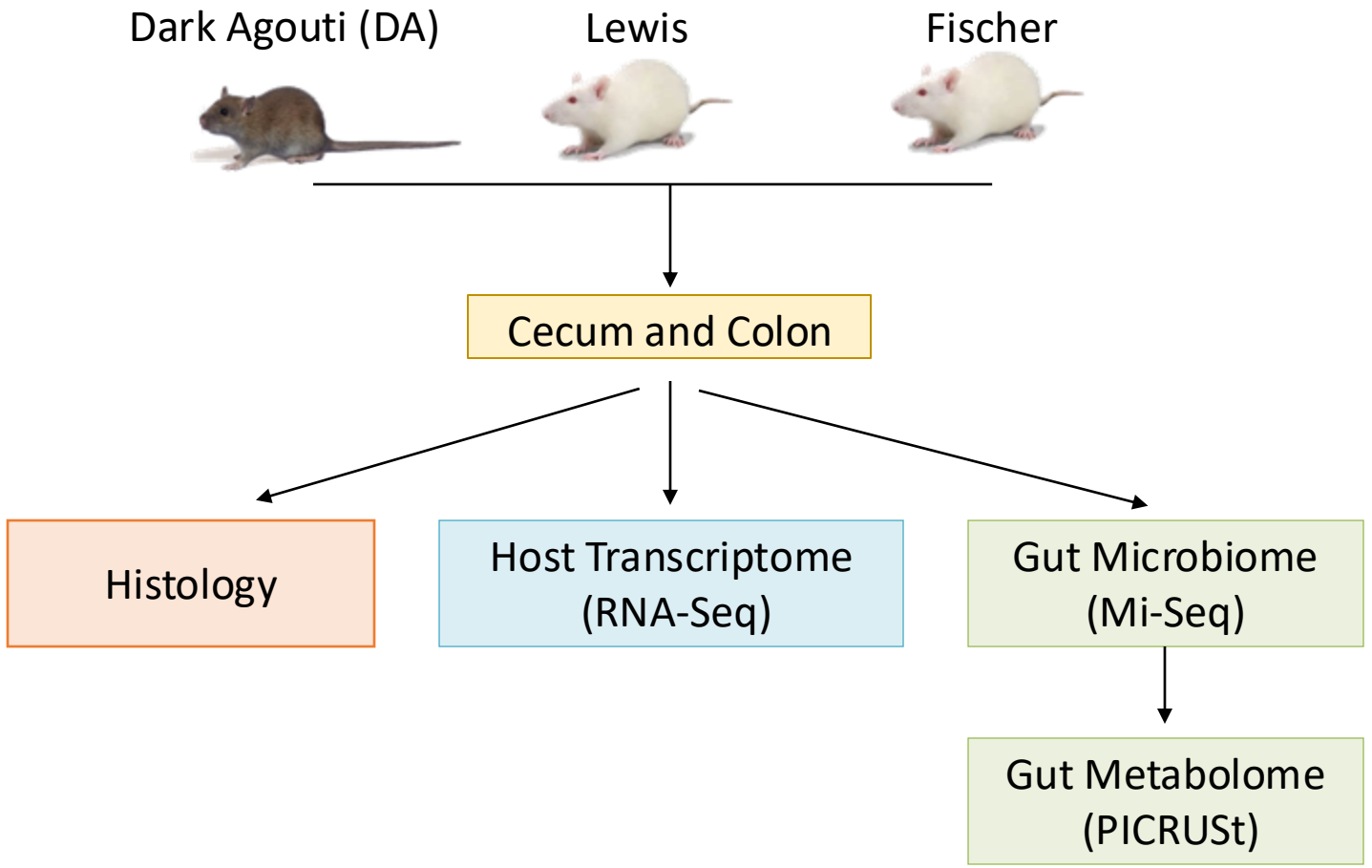


How does HLA-B27 shape the gut microbiome?

Hypothesis: By examining effects of HLA-B27 on gut microbiota in different rat backgrounds we could identify microbes that cause or promote SpA

- **HLA-B27** allele is present in 4-7% of the population
- 90% of individual carrying HLA-B27 are healthy
- 74-89% patients with axSpA carry HLA-B27

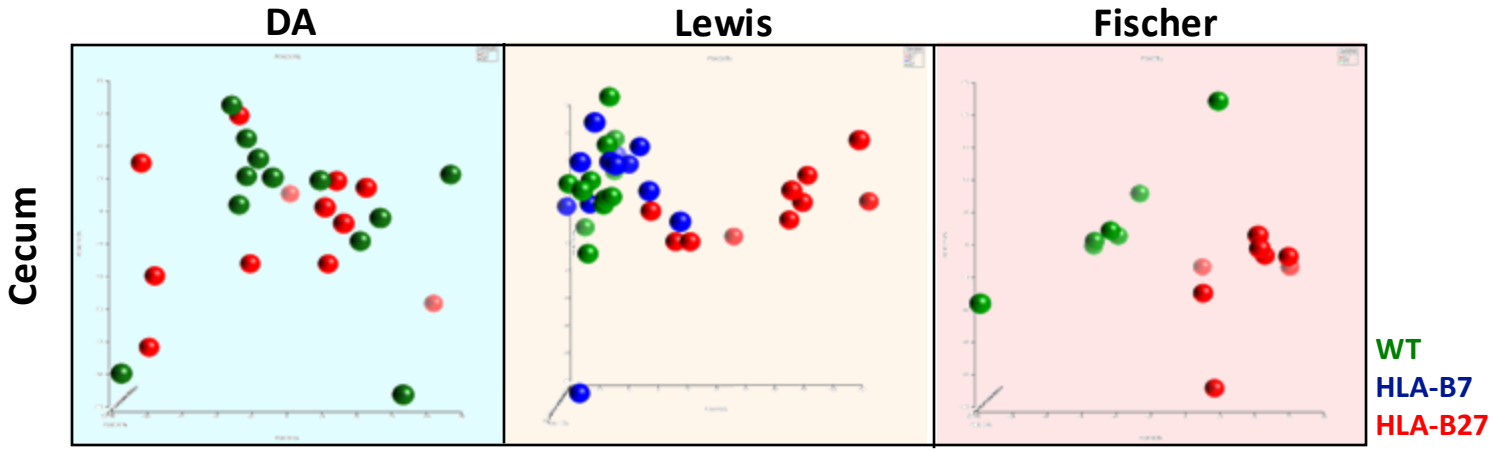
Transcriptome ?
Microbiome?



Gill *et al.*, *Arthritis & Rheumatol 2018*

N~200

HLA-B27 associated Inflammatory gene expression signature overlaps in Lewis and Fischer rats



Gill *et al.*, *Arthritis & Rheumatol 2018*

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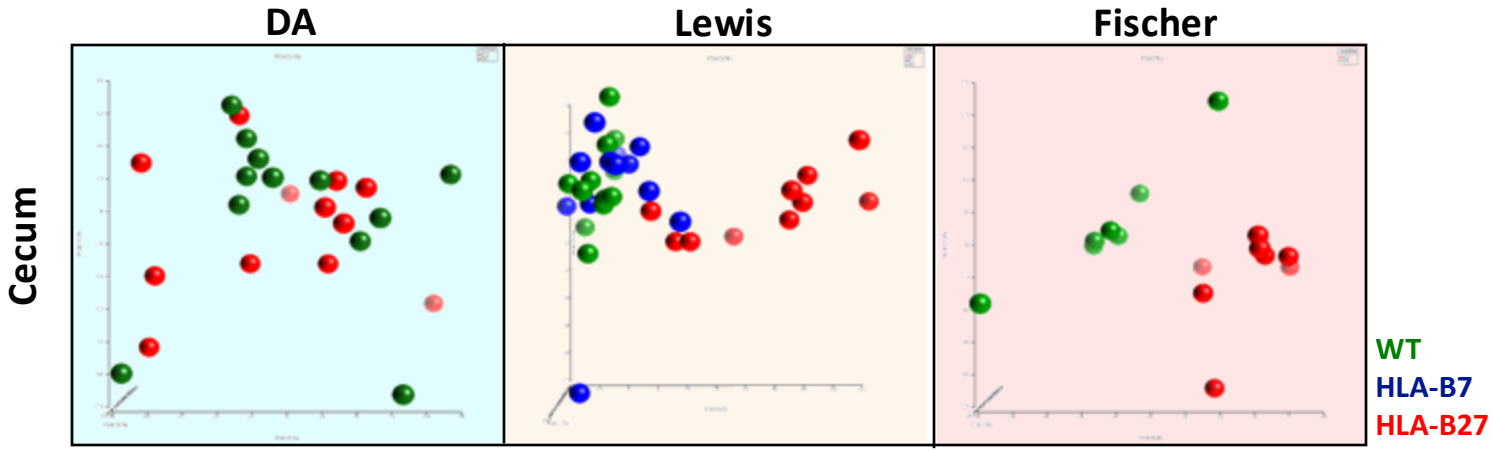
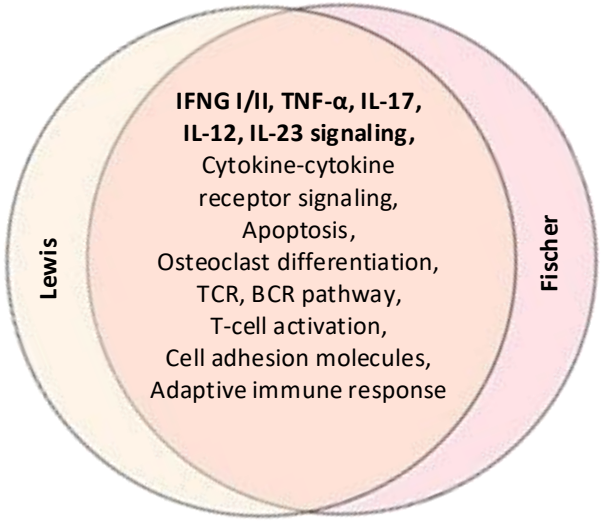
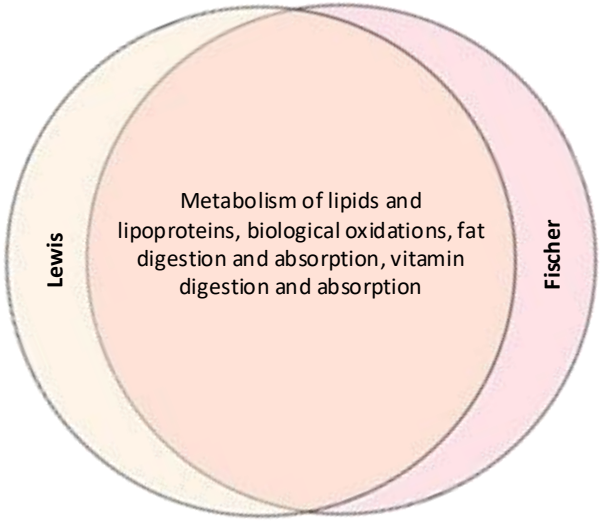




Pathways Up-regulated

Gene Expression (HLA-B27/WT) > 2 Fold Up



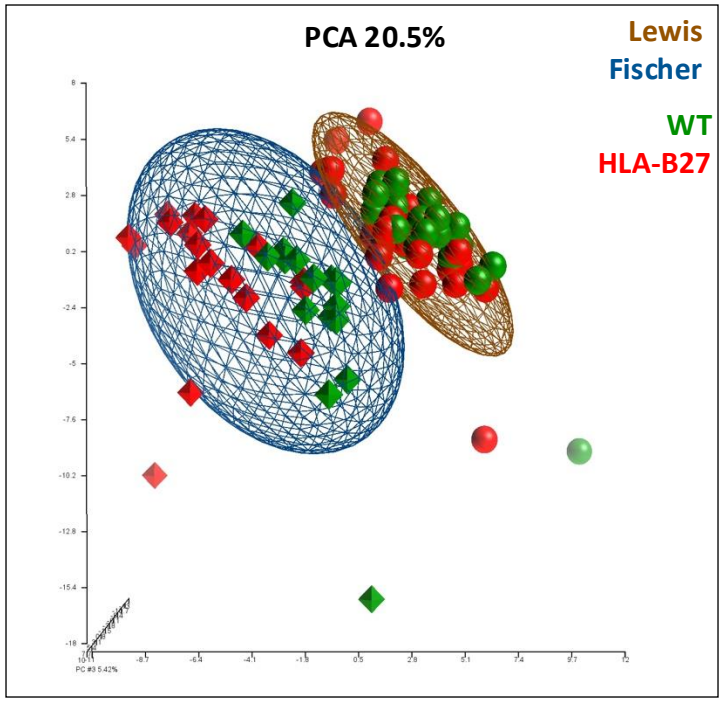
Pathways Down-regulated

Gene Expression (HLA-B27/WT) < -2 Fold Down

Gill *et al.*, *Arthritis & Rheumatol 2018*

HLA-B27 associated microbial dysbiosis is non-overlapping in Lewis and Fischer backgrounds

Principal Component Analysis

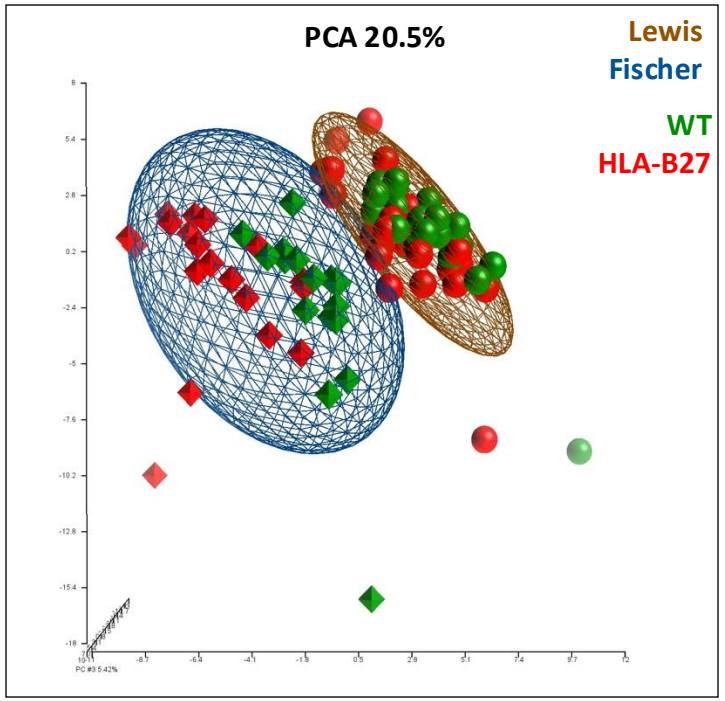


Cecum Lumen

Gill *et al.*, *Arthritis & Rheumatol 2018*

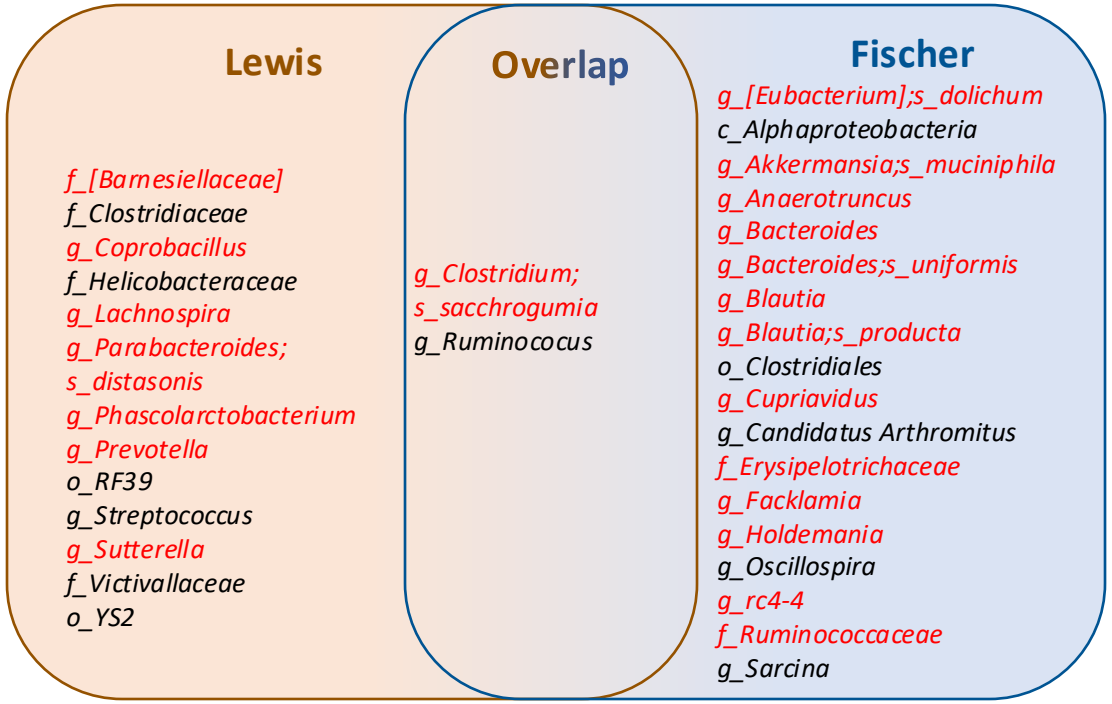
HLA-B27 associated microbial dysbiosis is non-overlapping in Lewis and Fischer backgrounds

Principal Component Analysis



Cecum Lumen

Species Level Dysbiotic Microbes

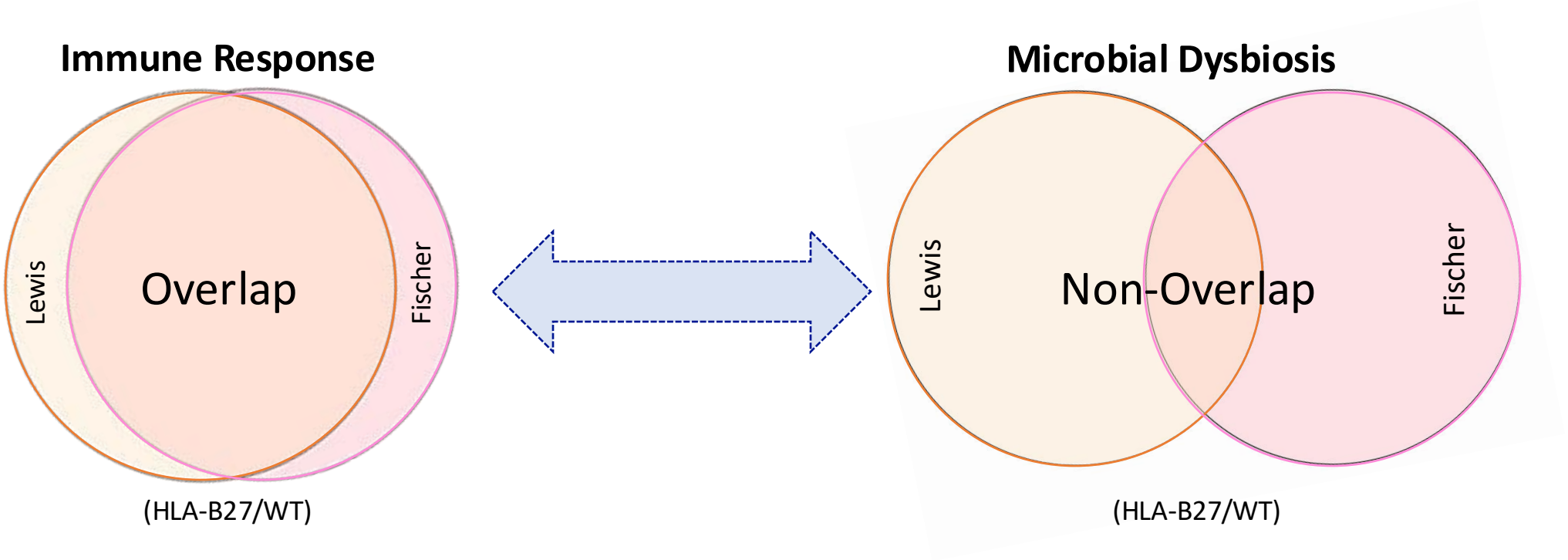


Cecum Lumen (HLA-B27/WT)

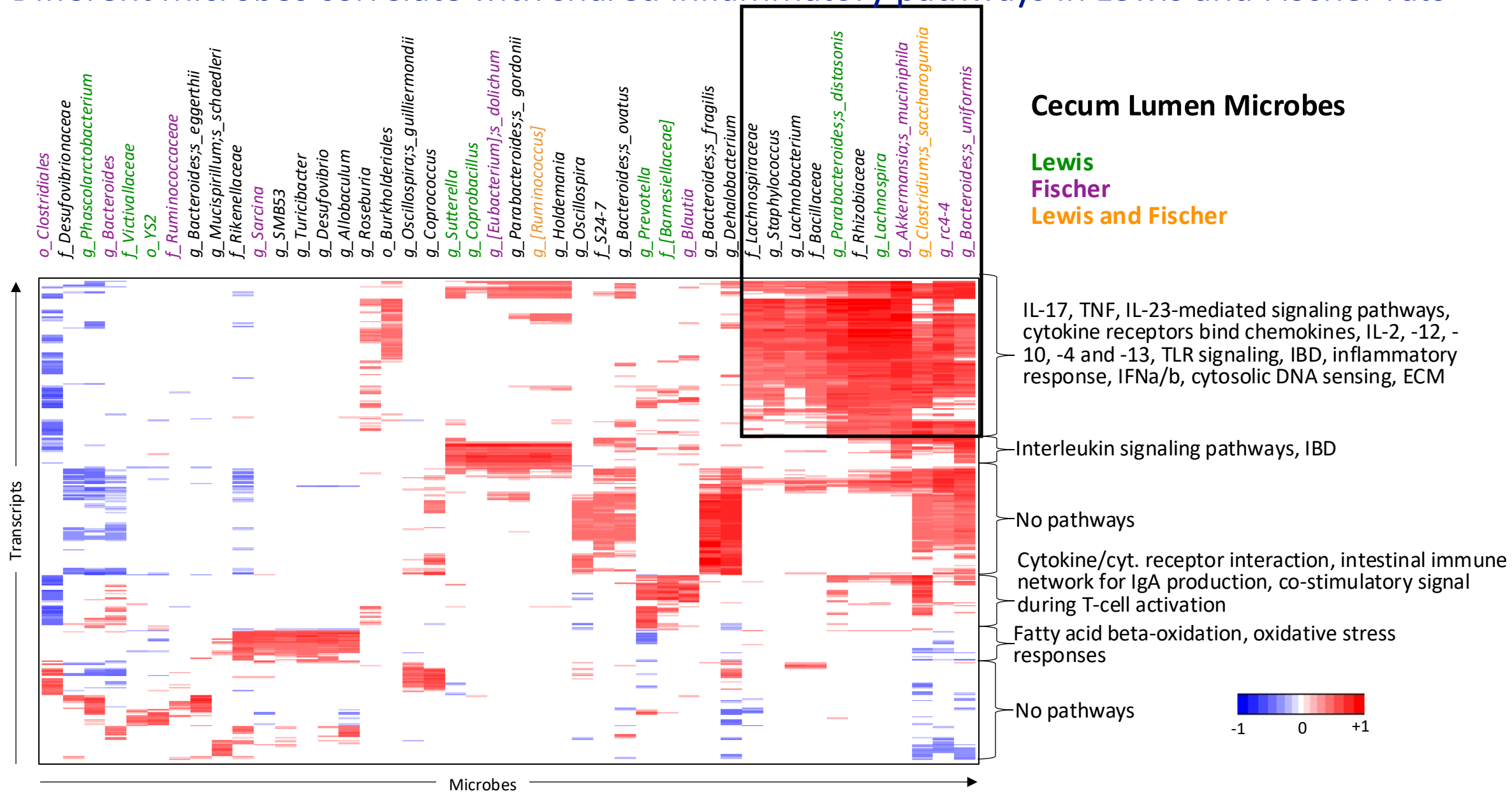
Increased/Decreased Relative Abundance

Gill *et al.*, *Arthritis & Rheumatol 2018*

What is the relation between diverse gut microbes and host immune response in SpA?

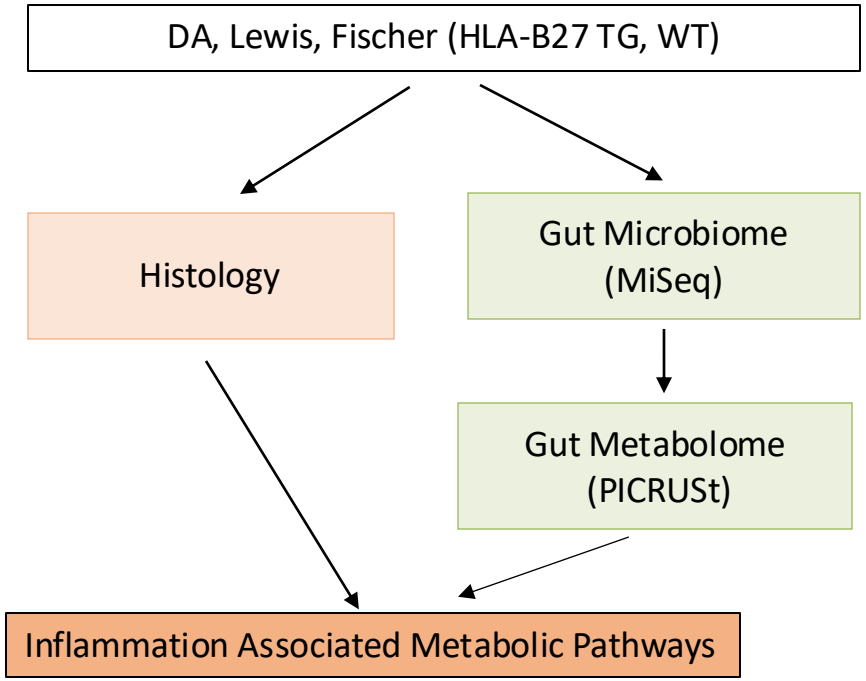


Different microbes correlate with shared inflammatory pathways in Lewis and Fischer rats



Gill *et al.*, *Arthritis & Rheumatol 2018*
Gill *et al.*, *Arthritis & Rheumatol 2019*

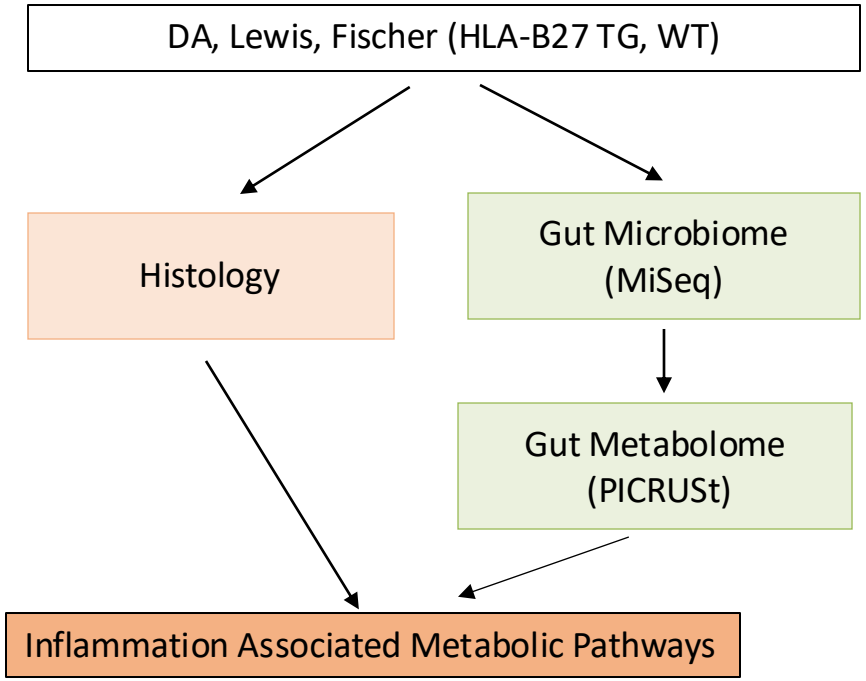
Common metabolic pathways are perturbed during gut inflammation in HLA-B27 Tg Lewis and Fischer rats



- Butanoate
- Propanoate
- LPS biosynthesis
- Steroid and steroid hormone biosynthesis
- Bacterial chemotaxis
- Flagellar assembly
- Oxidative phosphorylation

Gill *et al.*, *Arthritis & Rheumatol 2018*
Gill *et al.*, *Arthritis & Rheumatol 2019*

Common metabolic pathways are perturbed during gut inflammation in HLA-B27 Tg Lewis and Fischer rats



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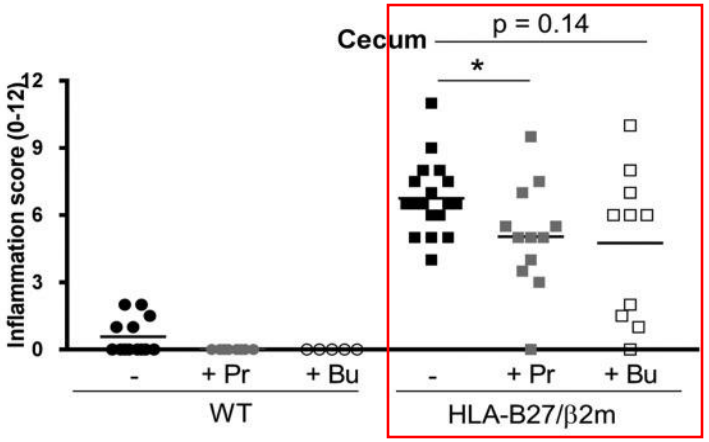


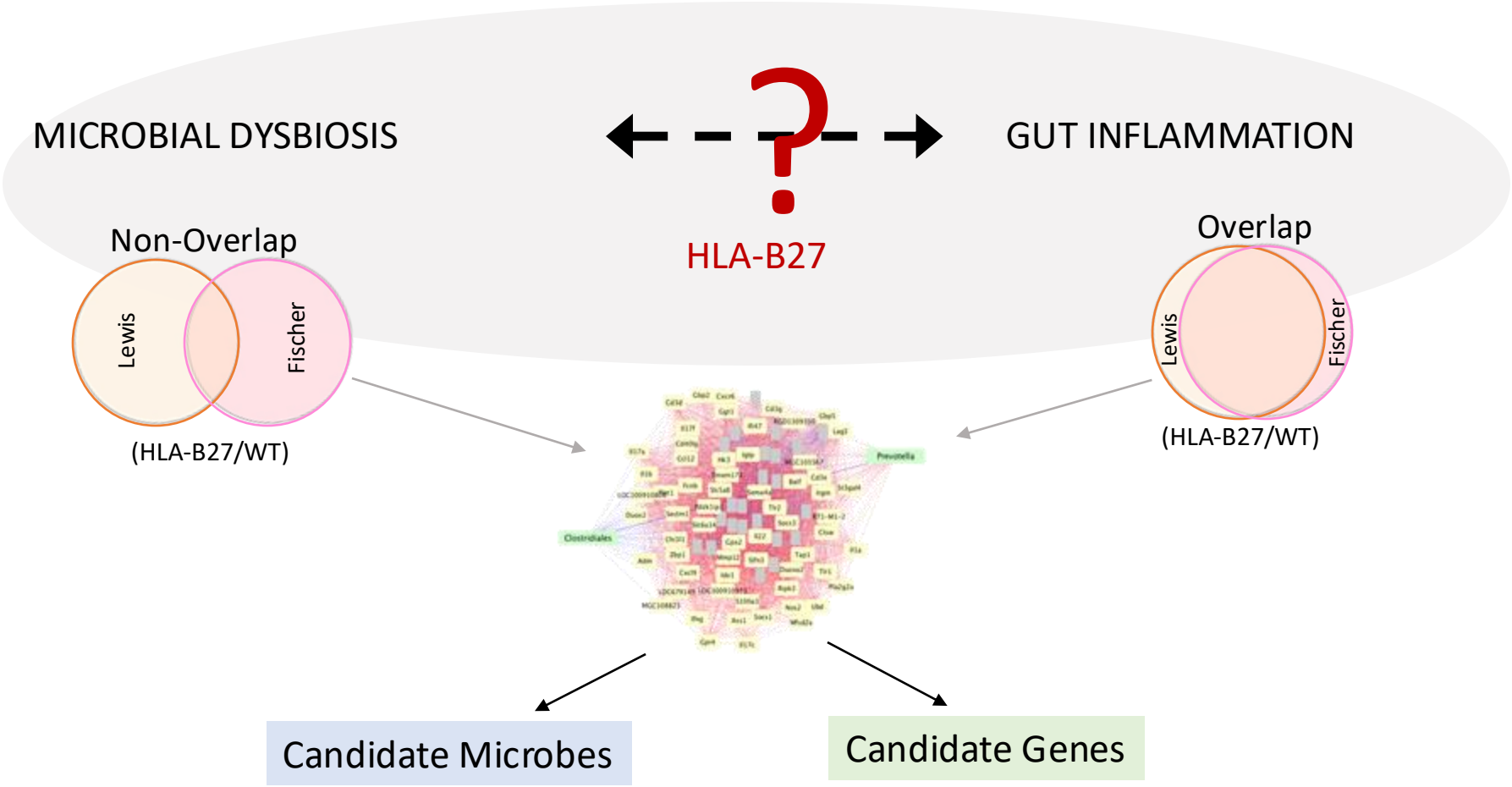
- Similar effects were seen in the colon
- Decrease in IL-1b, Il17A, IFNg expression

Gill *et al.*, *Arthritis & Rheumatol 2018*
Gill *et al.*, *Arthritis & Rheumatol 2019*

Asquith et al., Arthritis & Rheumatol, 2017

How does HLA-B27 shape the gut microbiome?

HLA-B27 is associated with gut microbial dysbiosis and host immune dysregulation



Gill *et al.*, *Arthritis & Rheumatol 2018*
Gill *et al.*, *Arthritis & Rheumatol 2019*

How does HLA-B27 alter host immune response to gut microbes?

1. **Characterize mucosal IgA response to oral and fecal microbiota in axial spondyloarthritis and acute anterior uveitis patients**

2. **Investigate host-microbe interactions in axial spondyloarthritis and acute anterior uveitis patients through**
   - Fecal and plasma metabolic profiling
   - Single cell expression signatures in PBMCs

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Fecal and plasma metabolic profiling of axSpA and AAU patients

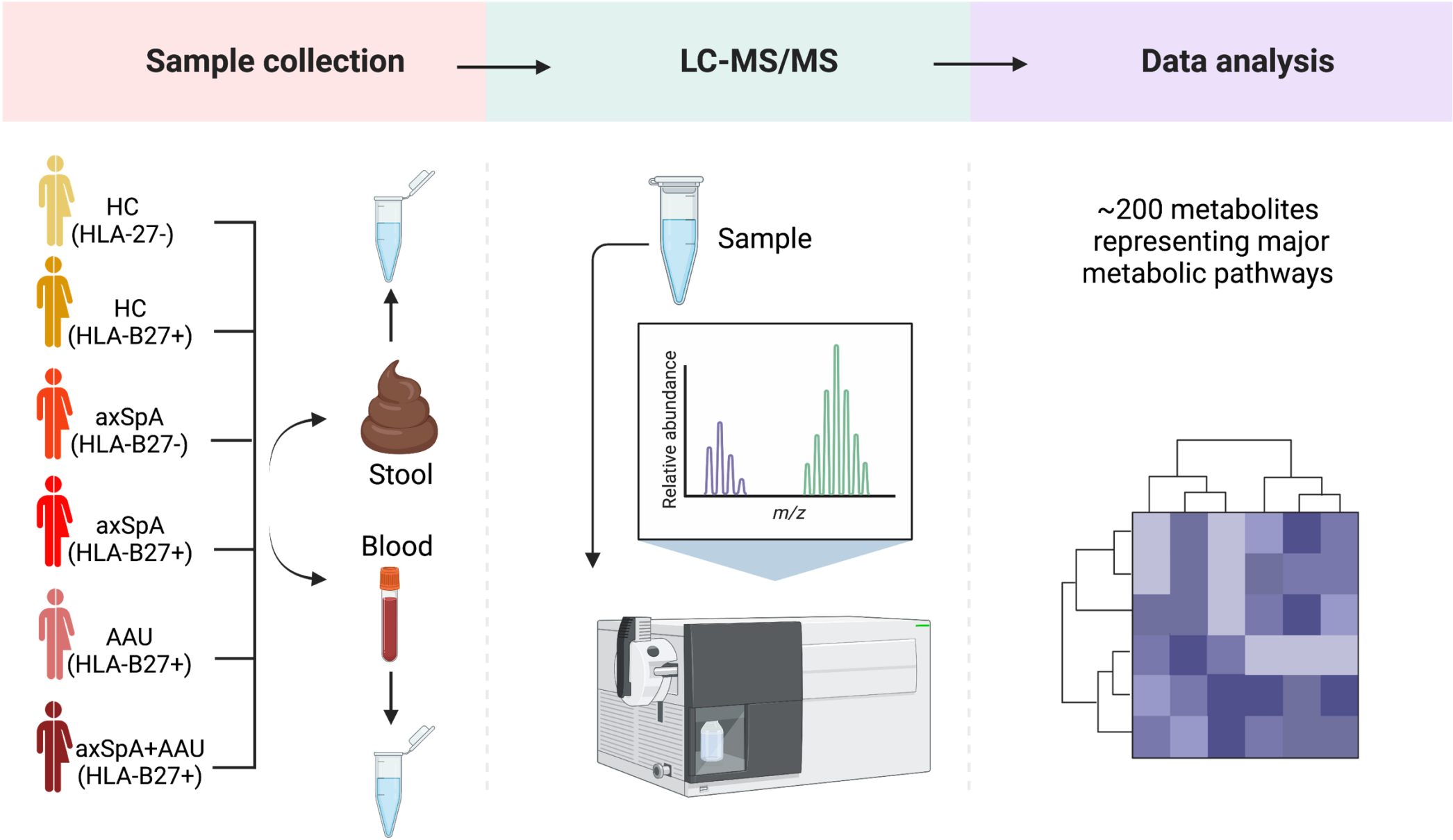
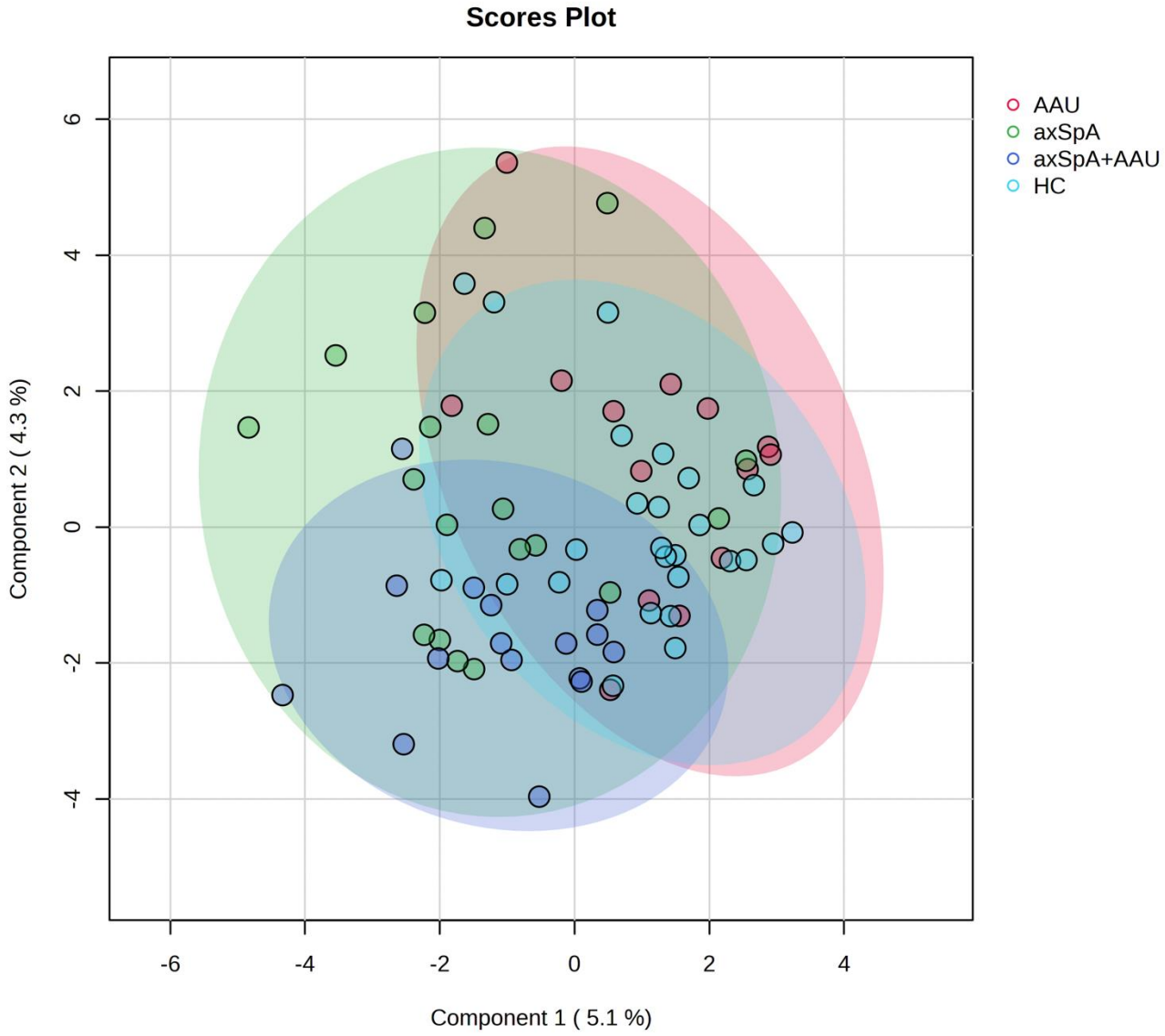


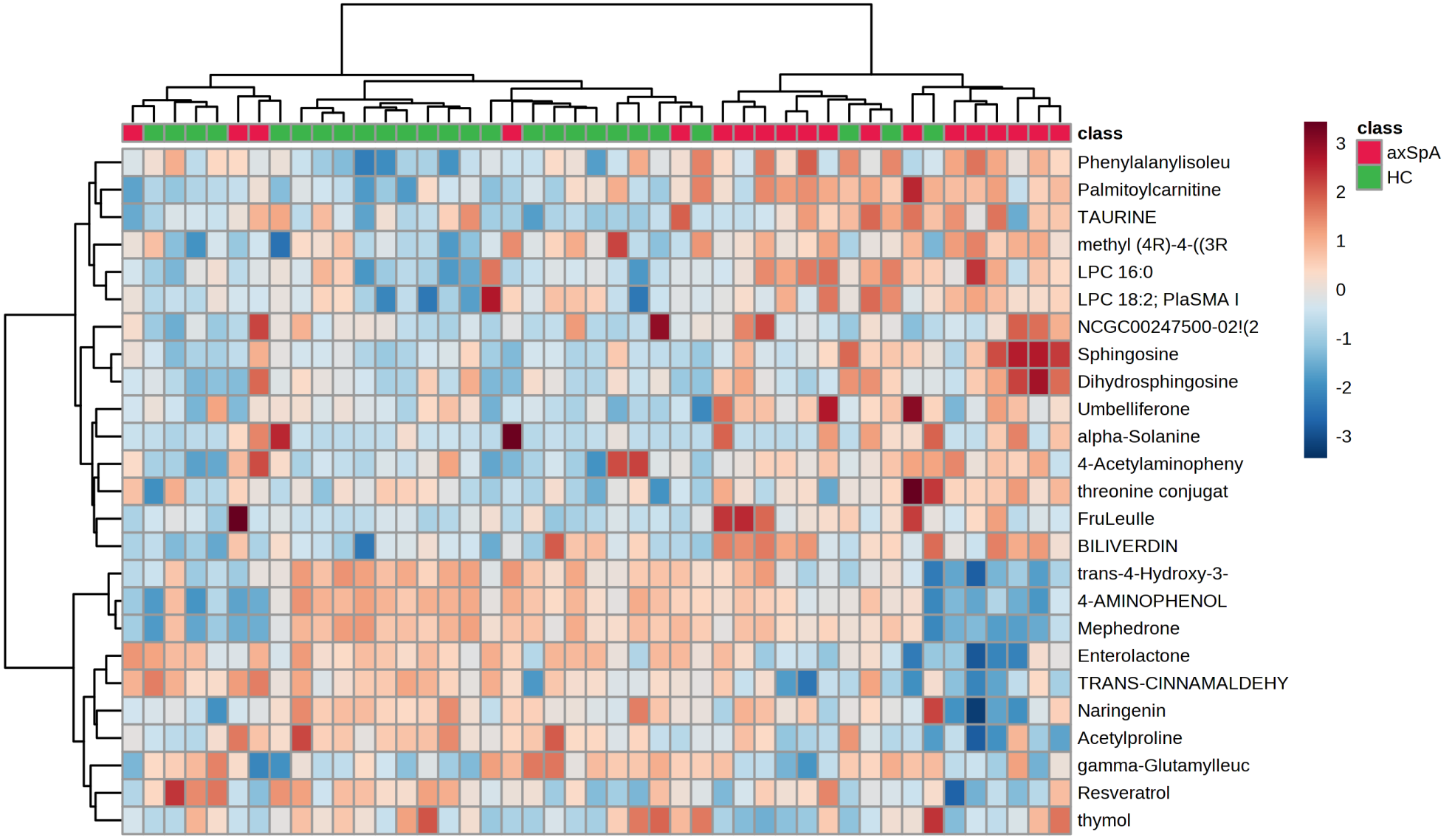
Figure made by using Biorender.com

Altered fecal metabolites in patients with axSpA, AAU and axSpA+AAU



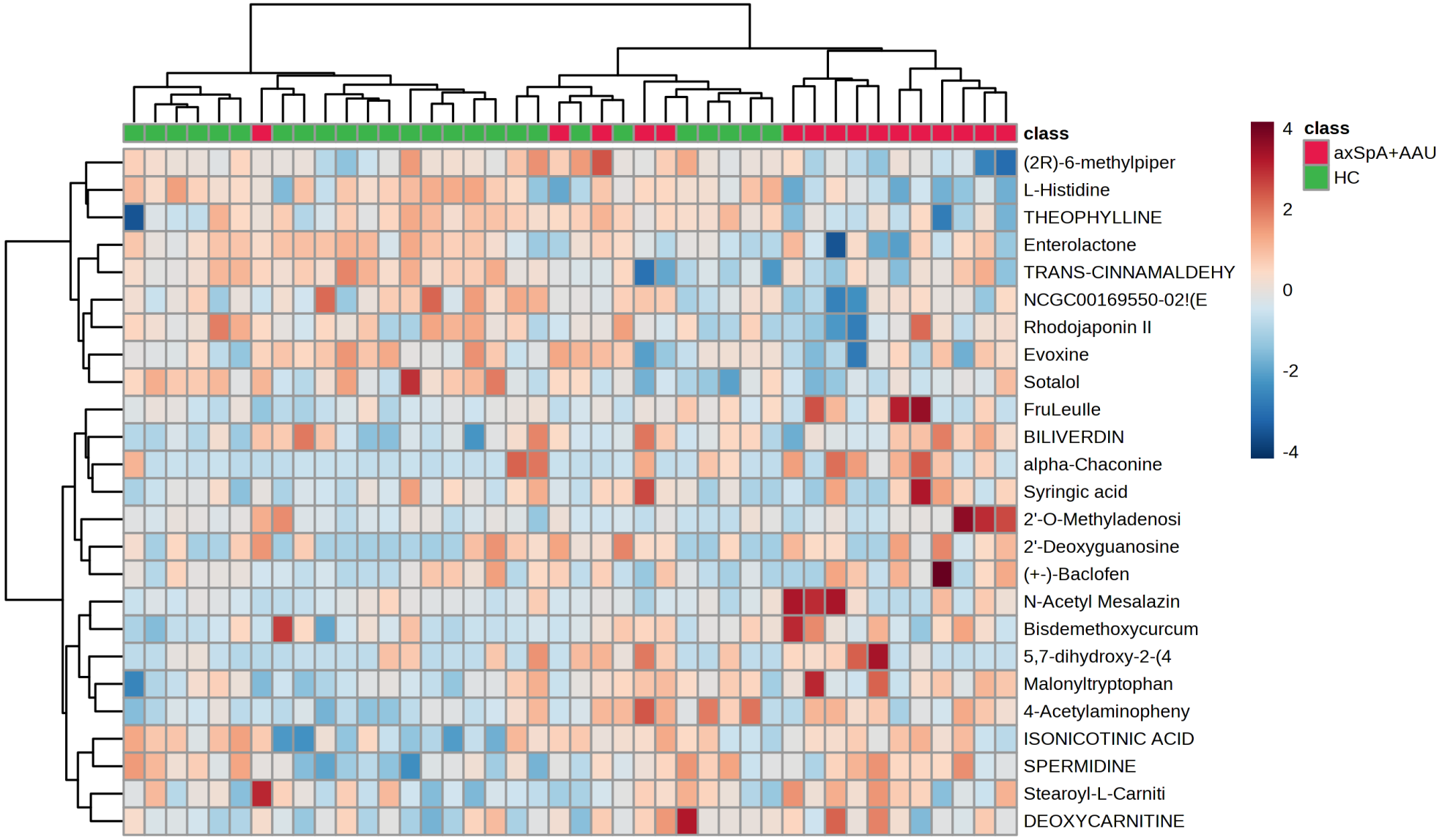
Gill-Unpublished data

Fecal metabolic profile is altered in axSpA patients in comparison with healthy controls



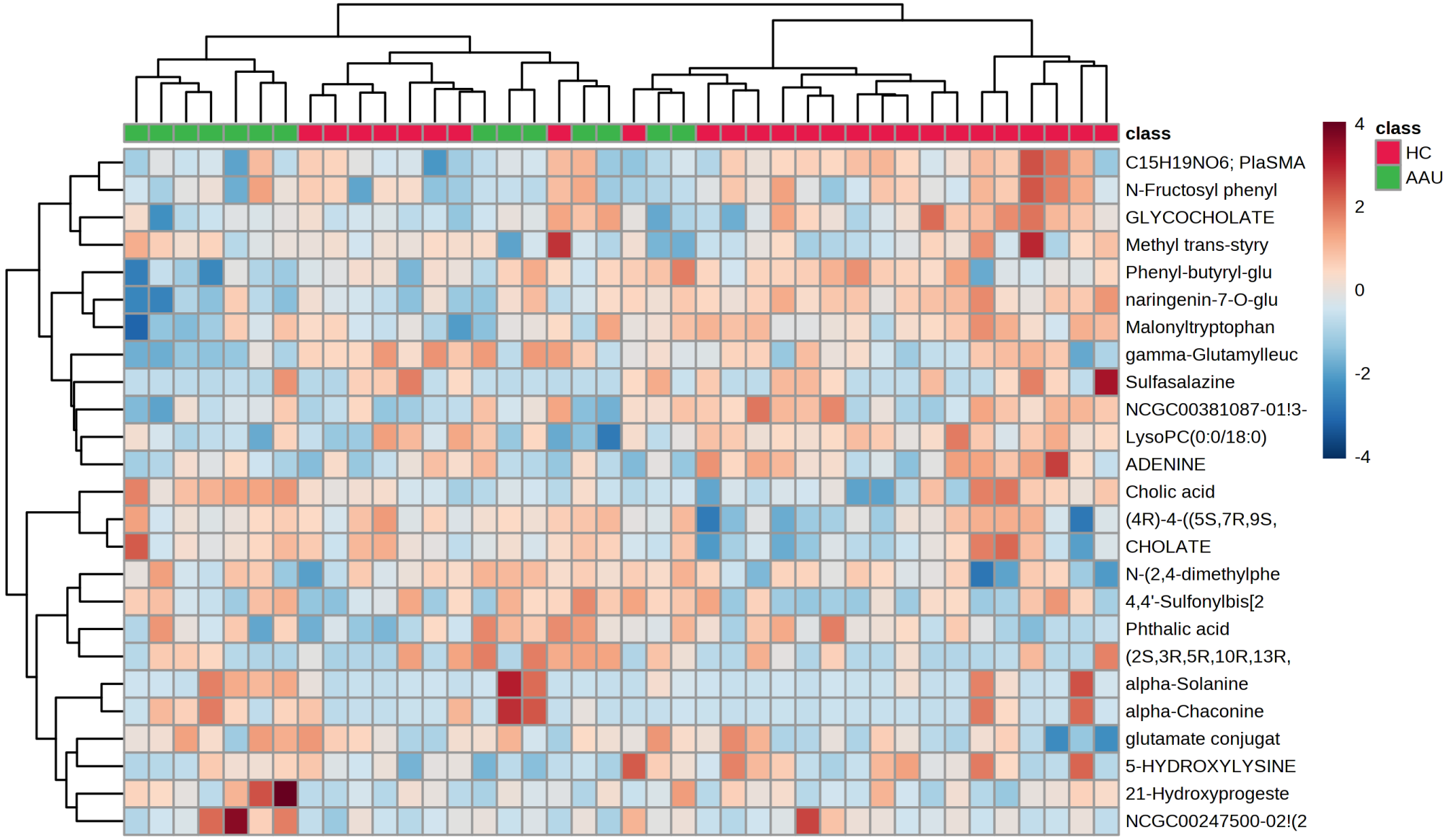
Gill-Unpublished data

Fecal metabolic profile is altered in axSpA+AAU patients in comparison with healthy controls



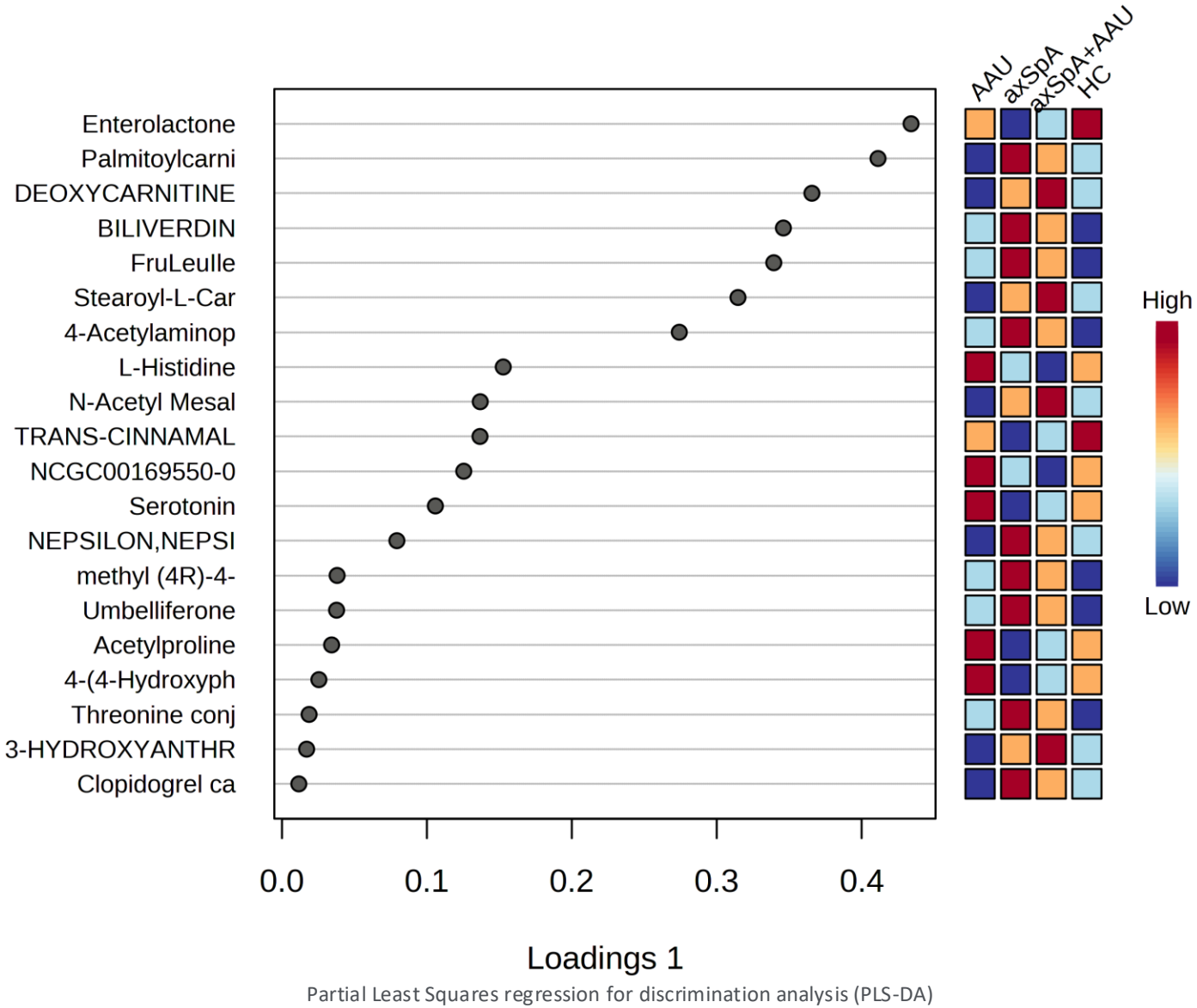
Gill-Unpublished data

Fecal metabolic profile is altered in AAU patients in comparison with healthy controls



Gill-Unpublished data

Distinct fecal metabolic profiles in patients with AxSpA and AAU

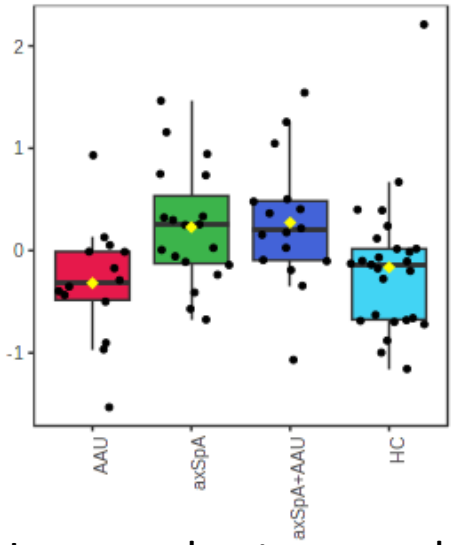


Partial Least Squares regression for discrimination analysis (PLS-DA)

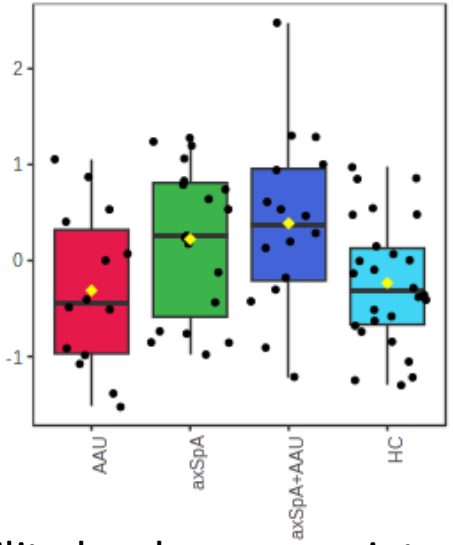
Gill-Unpublished data

Distinct fecal metabolic profiles in patients with AxSpA and AAU

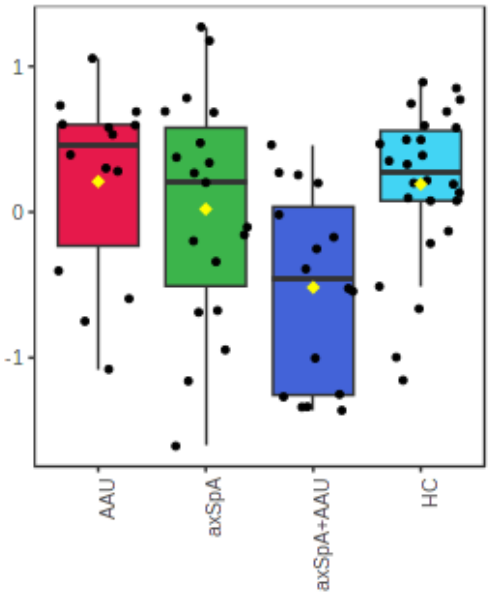
Deoxycarnitine



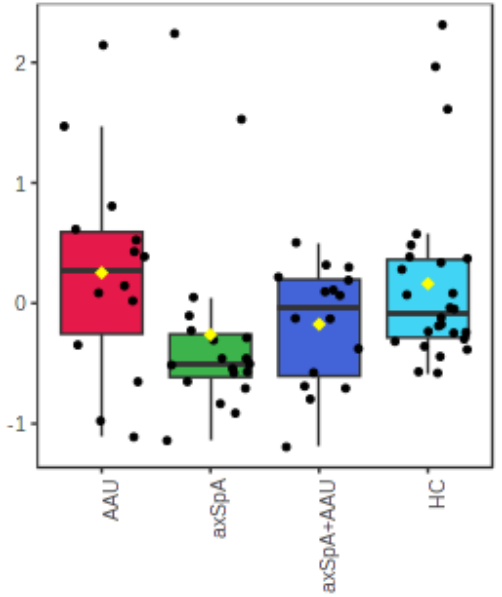
Stearoyl-L-Carnitine



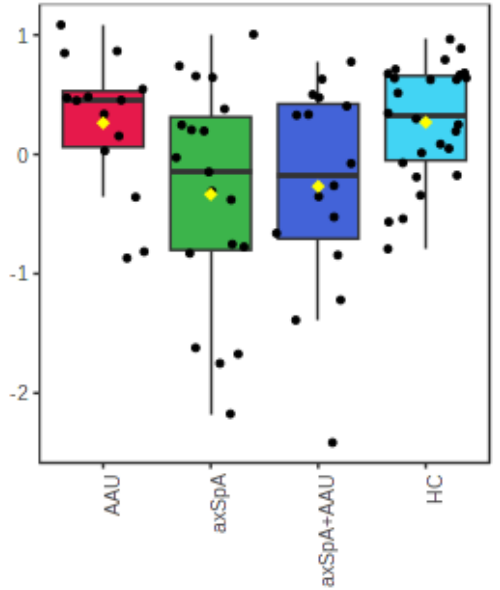
L-Histidine



Serotonin



Enterolactone

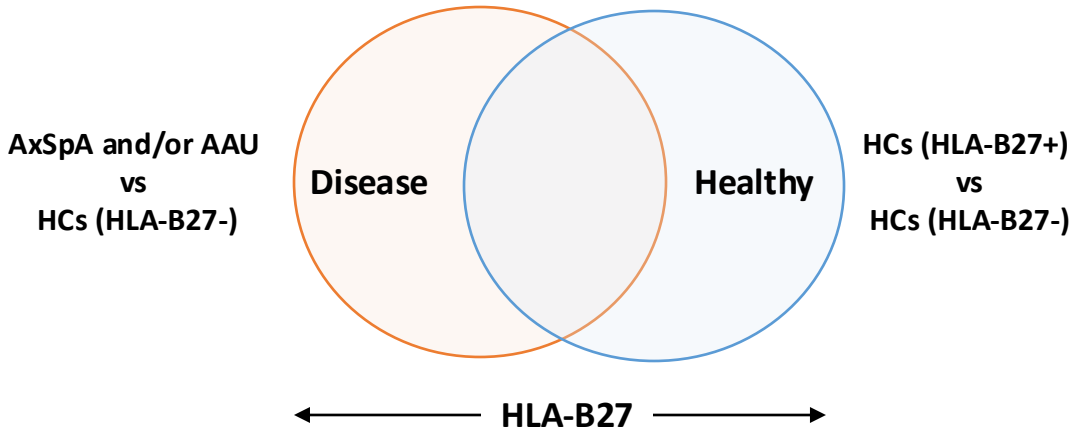


Increased gut permeability has been associated with elevated acylcarnitine and deoxycarnitine.

Semba RD, et al., EBioMedicine. 2017

Enterolactone is a anti-inflammatory gut microbial metabolite

Metabolic profiling may reveal disease and HLA-B27 associated perturbation in axSpA and AAU



HC- healthy controls
AxSpA- axial spondyloarthritis
AAU- acute anterior uveitis

- Both host genetics (HLA-B27) and disease status may affect the metabolic profile.
- Expected overlap in metabolic markers of disease in patients from diverse location/host genetic backgrounds.
- Host-microbe interactions and disease pathogenesis of candidate metabolites will be dissected using HLA-B27 Tg rats

How does HLA-B27 alter host immune response to gut microbes?

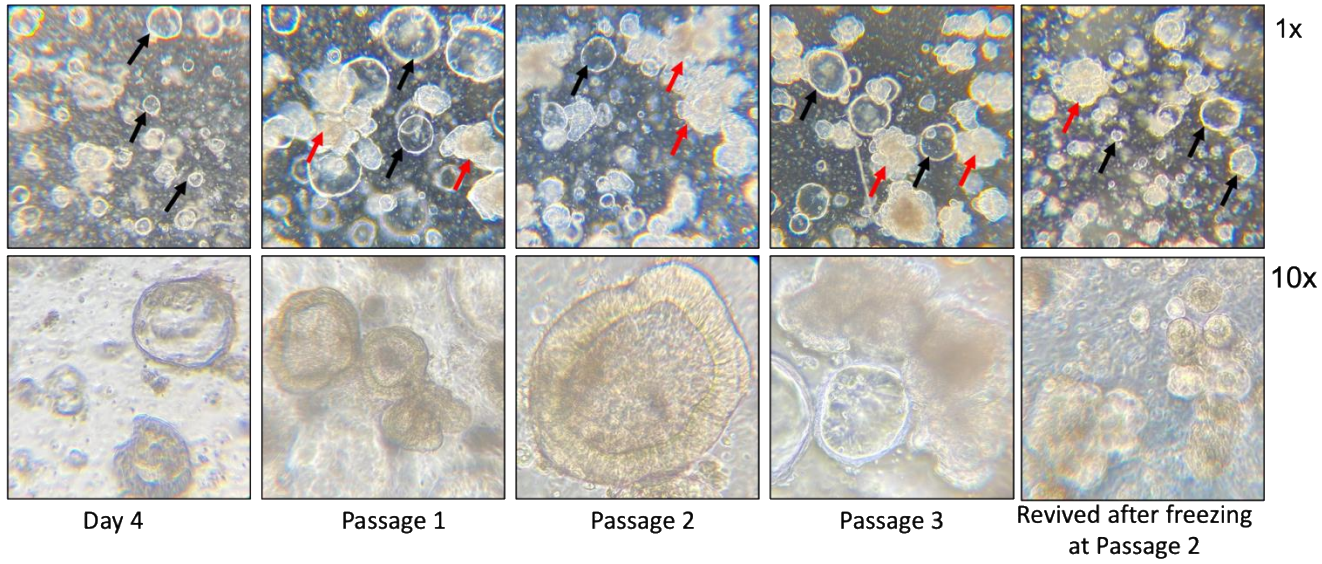
1. Characterize mucosal IgA response to oral and fecal microbiota in axial spondyloarthritis patients

2. **Investigate host-microbe interactions in axial spondyloarthritis patients through**
   - Fecal and plasma metabolic profiling
   - Single cell expression signatures in PBMCs

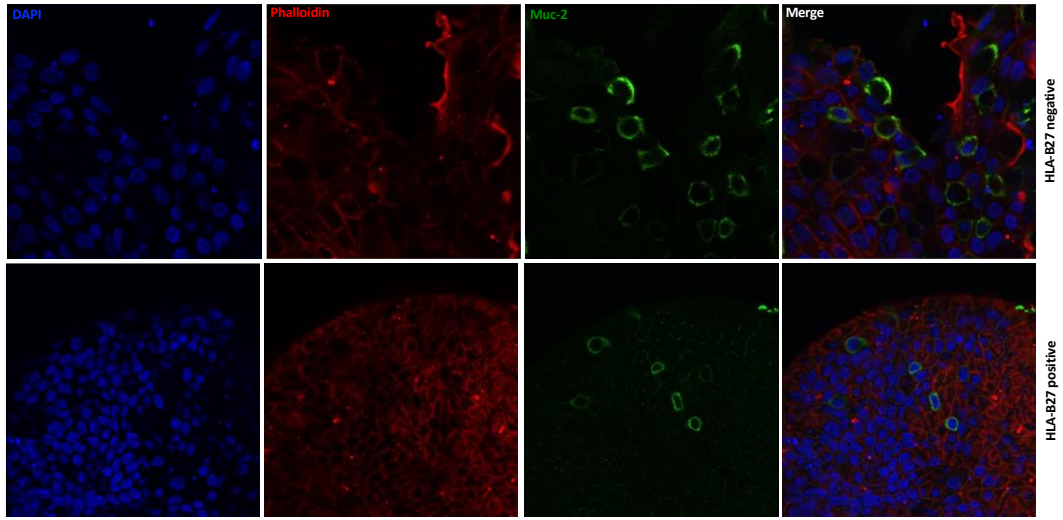
Thank You !!

Colonic organoids to characterize HLA-B27 associated perturbation of intestinal epithelial cell biology

1. Establishment of human colonic organoids from frozen biopsy



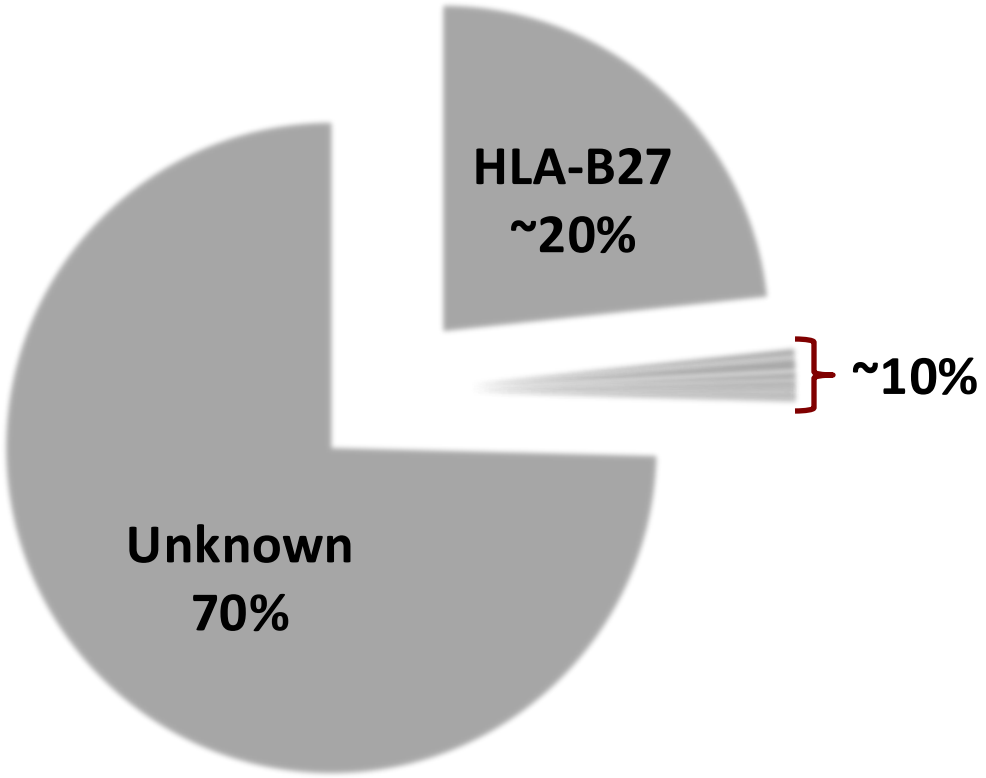
Representative images from an HLA-B27 negative organoid line (HC3). Organoids are shown after establishment of cultures (day 4), after passage 1, 2 and 3 at 1x (top panel) or 10x (bottom panel) magnification. The organoid culture represents a mix of early-stage organoids (spheroids, black arrows) and mature organoids (lobular, red arrows) are shown. Each passage is after 4-6 days. Organoids on far right represent organoids revived after freezing them at passage 2.



Decreased mucus production in goblet cells in colonic organoids from HLA-B27+ healthy individuals

RNA Seq is just done. Now gene expression analysis for LPS treated organoids from axSpA patients and controls

HLA-B27– a genetic risk factor for axial spondyloarthritis – does not explain disease heritability

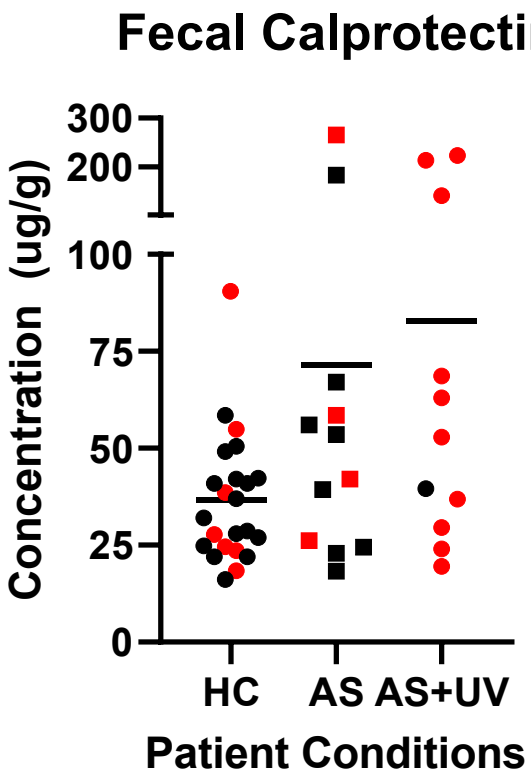


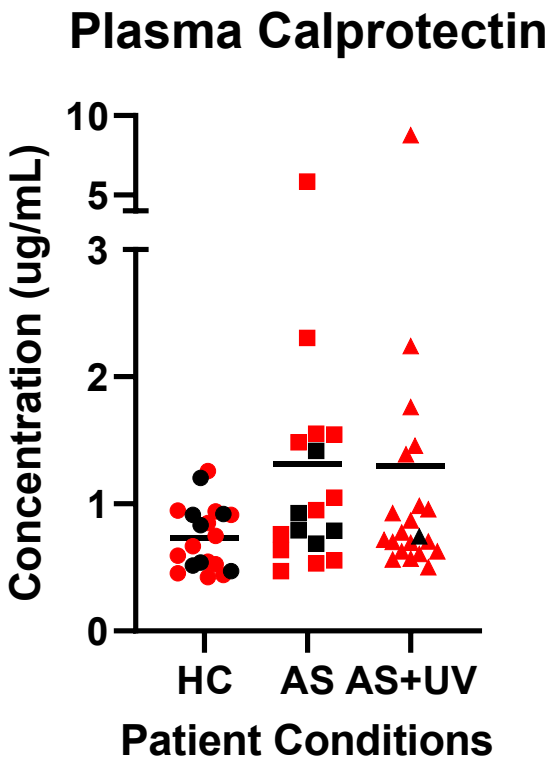
> 110 genes or genomic regions

IL23R
IL23R–IL12RB2
ERAP1-ERAP2
IL12B
CARD9
IL17R
JAK2
TYK2
STAT3

- **HLA-B27** allele is present in 4-7% of the population
- 90% of individual carrying HLA-B27 are healthy
- 74-89% patients with axSpA carry HLA-B27

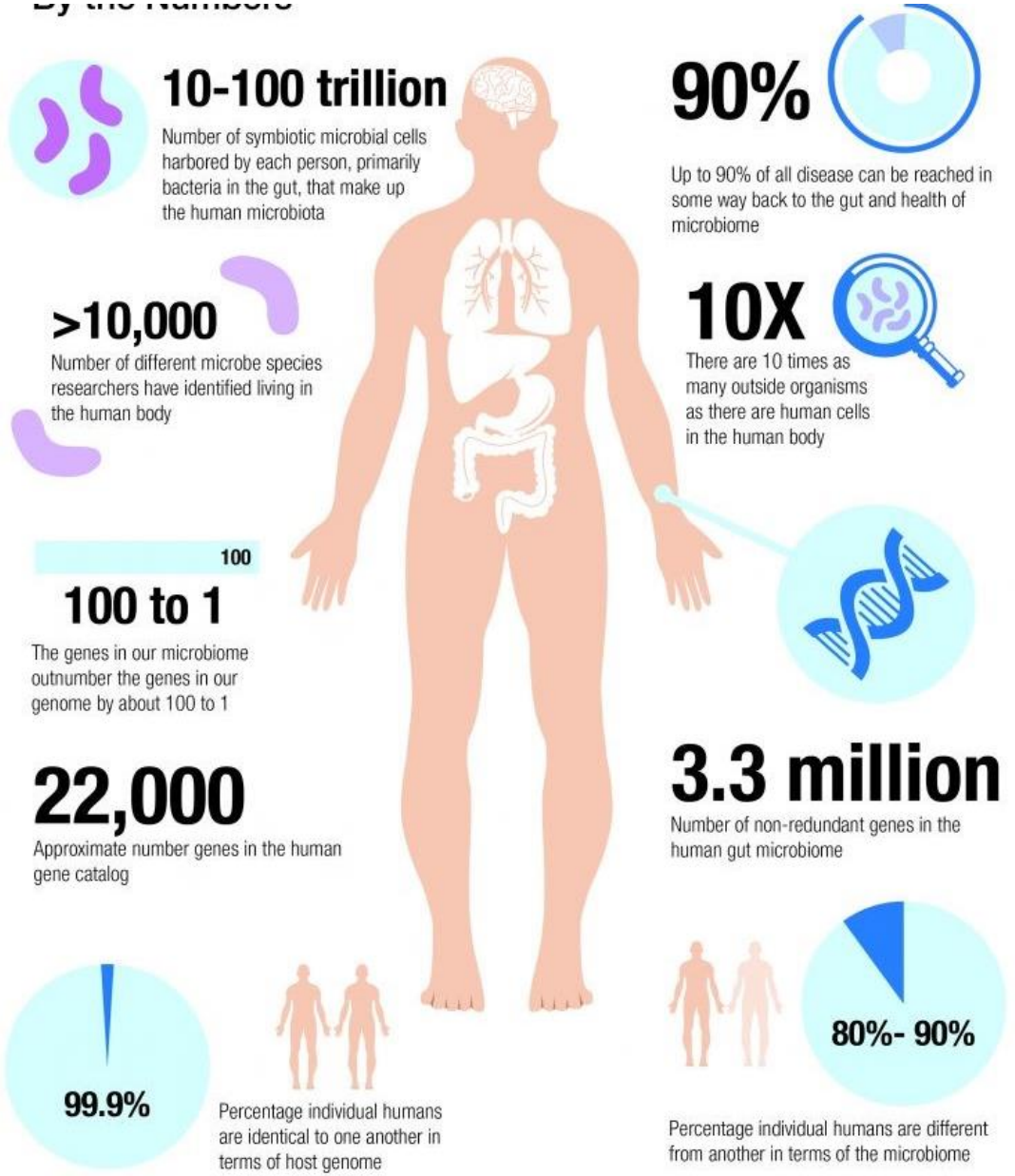
P value for HC vs AS+UV: 0.0072





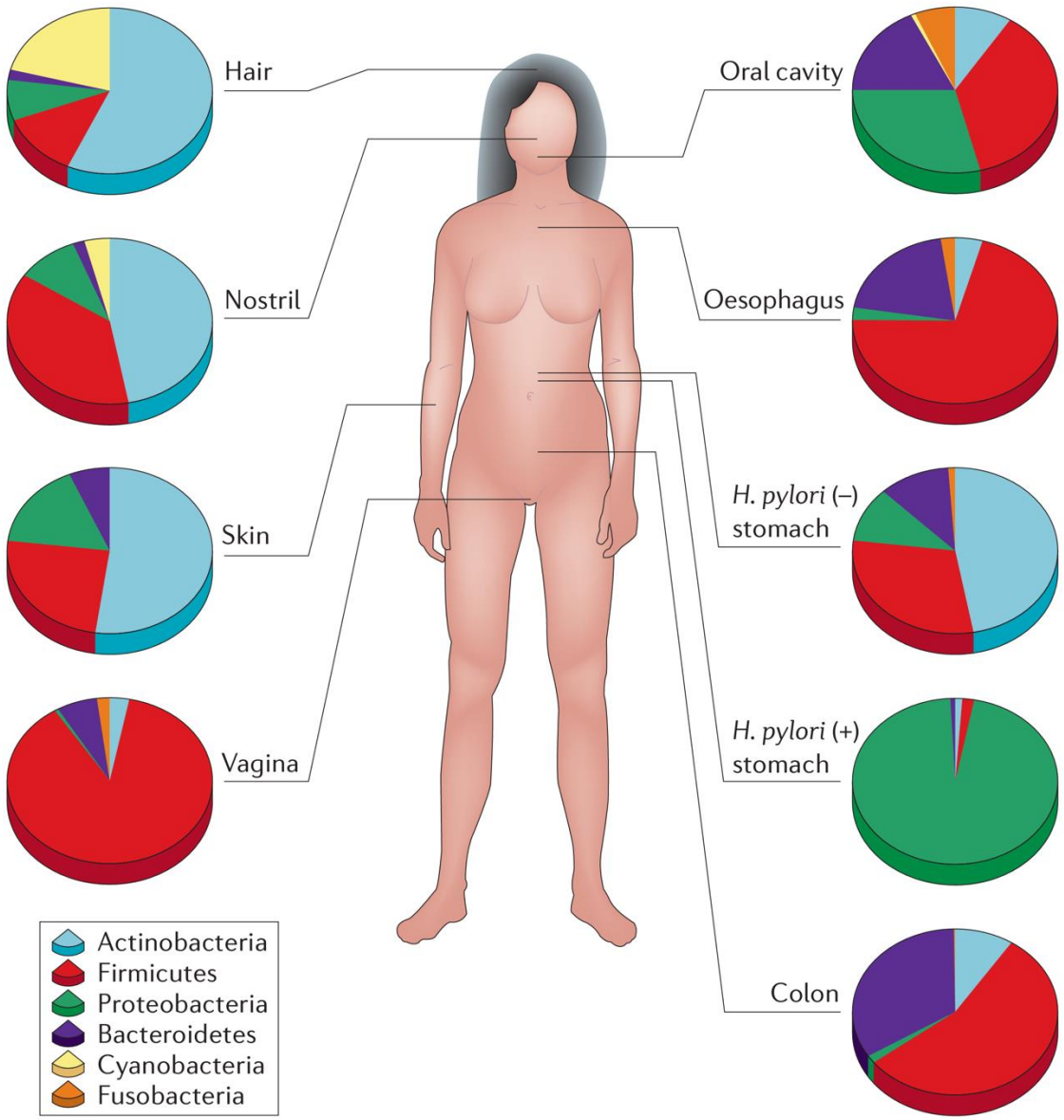
Microbiome: implications in health and disease

- 10X more microbial cells than human cells
- 3.3 million microbial genes v/s 22K genes in human gene
- 99.9 % similarity between host genome v/s 80-90% individuals have different microbiome
- More than 10,000 microbial species live in/on human body
- Immune education
- Vitamins and SCFAs production
- Drug metabolism /efficacy
- IBD, diabetes, hypertension, fatty liver, many cancers, spondyloarthropathies, multiple sclerosis



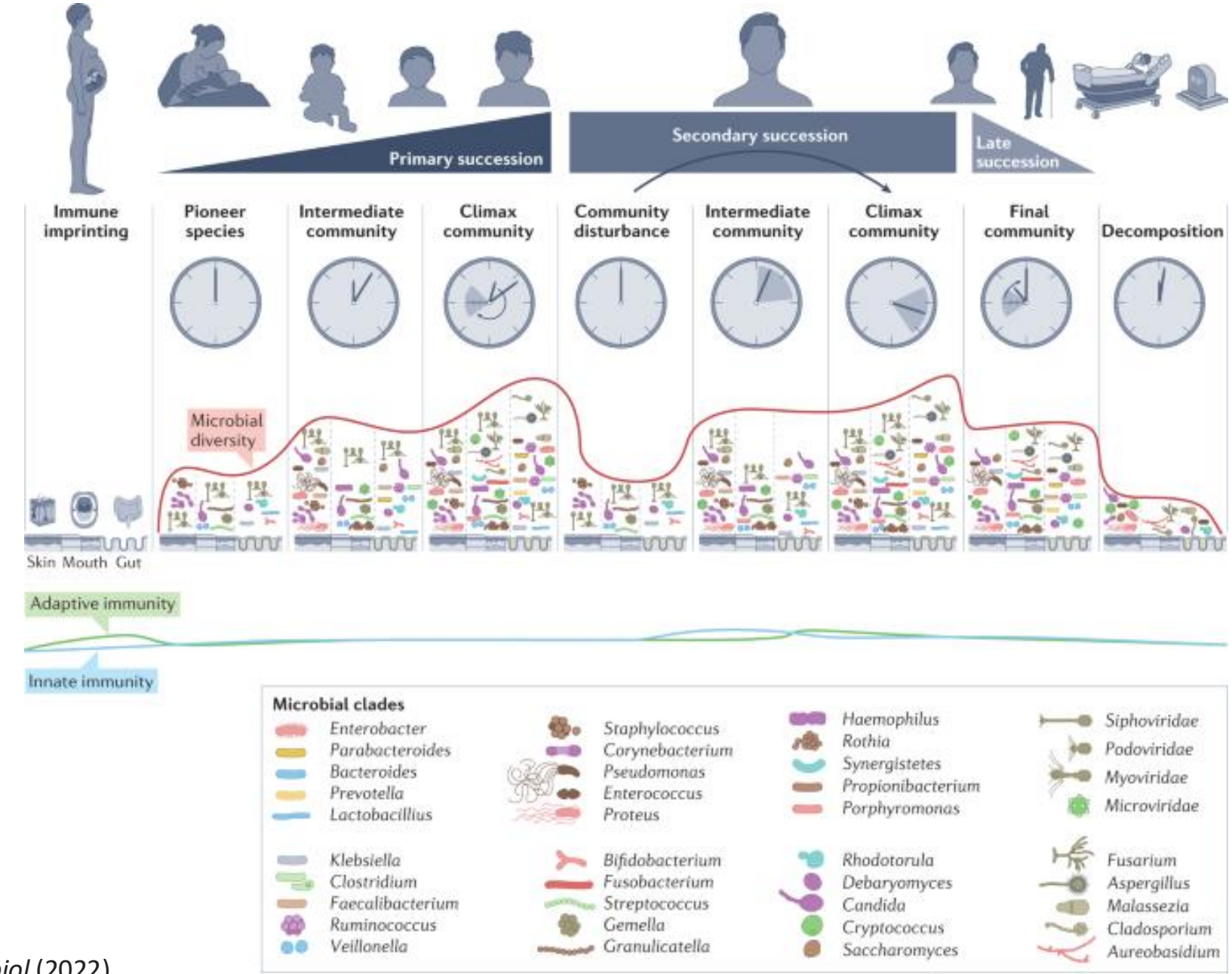
Turnbaugh et al., *Nature* 2007
Qin et al., *Nature* 2010
Hill and Artis, *Annual Rev Immunol* 2010
Schmidt et al., *Cell* 2019

Compositional differences in the microbiome by anatomical site.



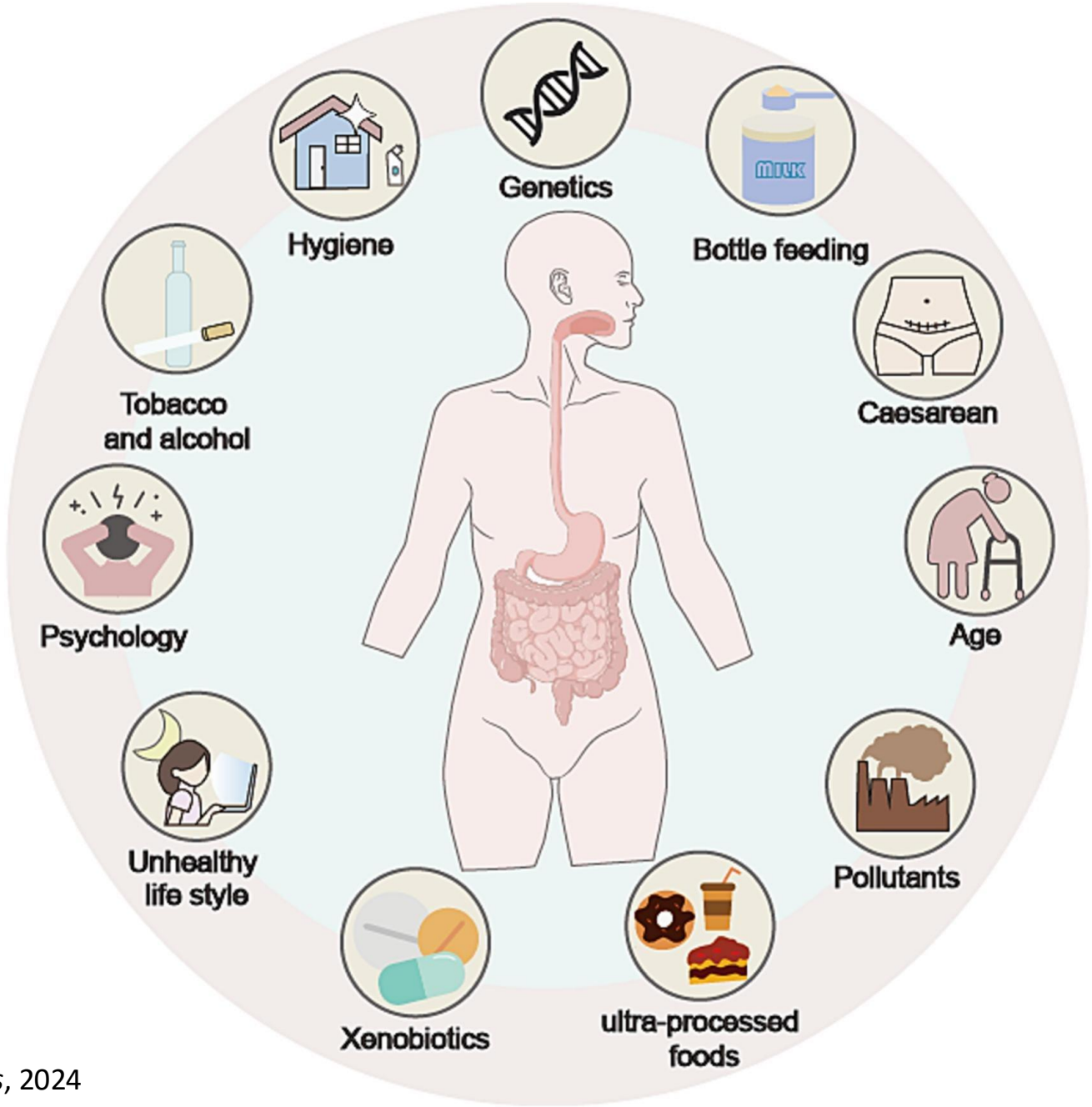
Cho, I., Blaser, M. *Nat Rev Genet* 2012

Microbiota succession throughout life from the cradle to the grave



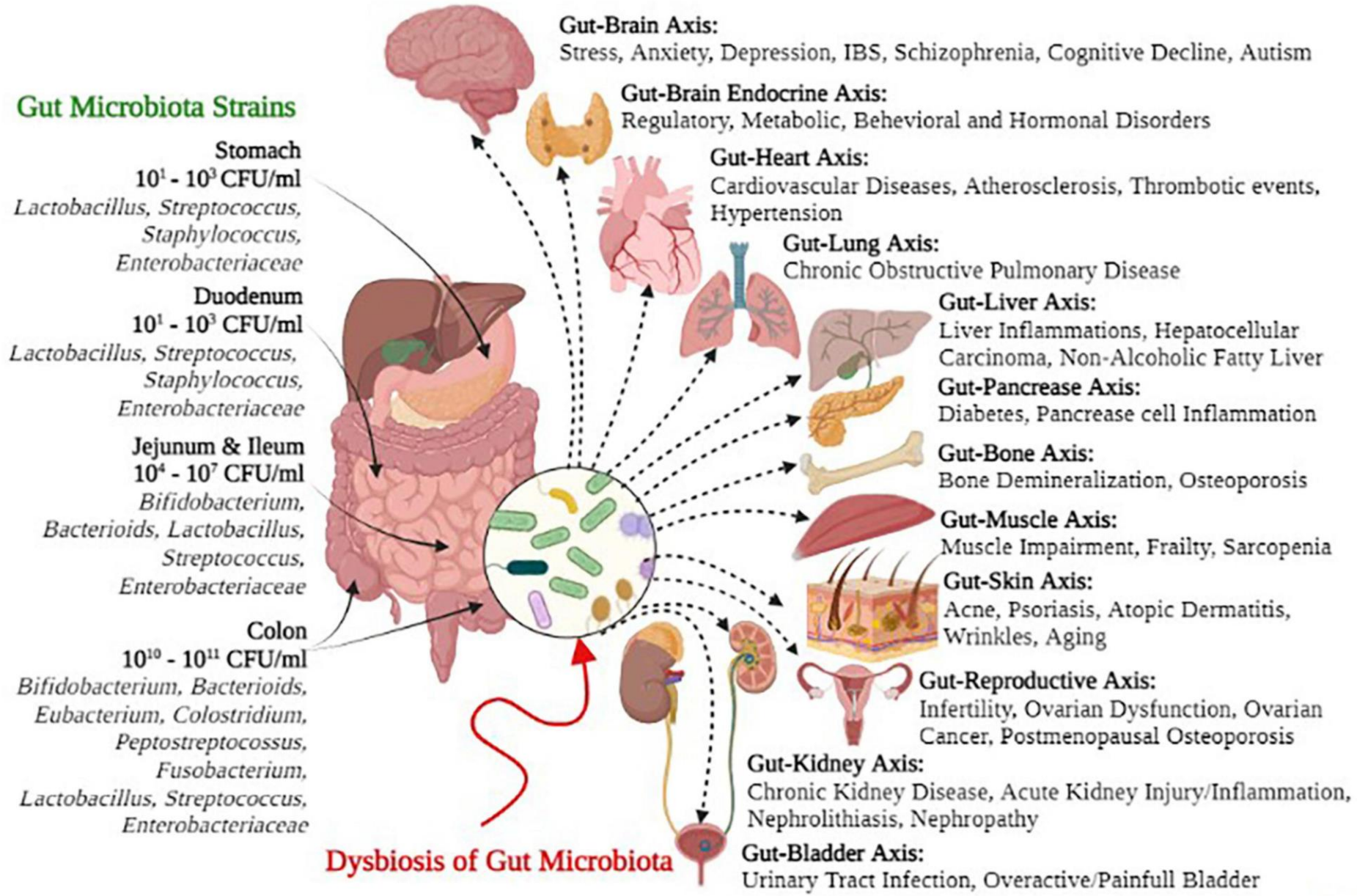
Martino, *Nat Rev Microbiol* (2022).

Environmental/genetic factors influencing the gut microbiome.



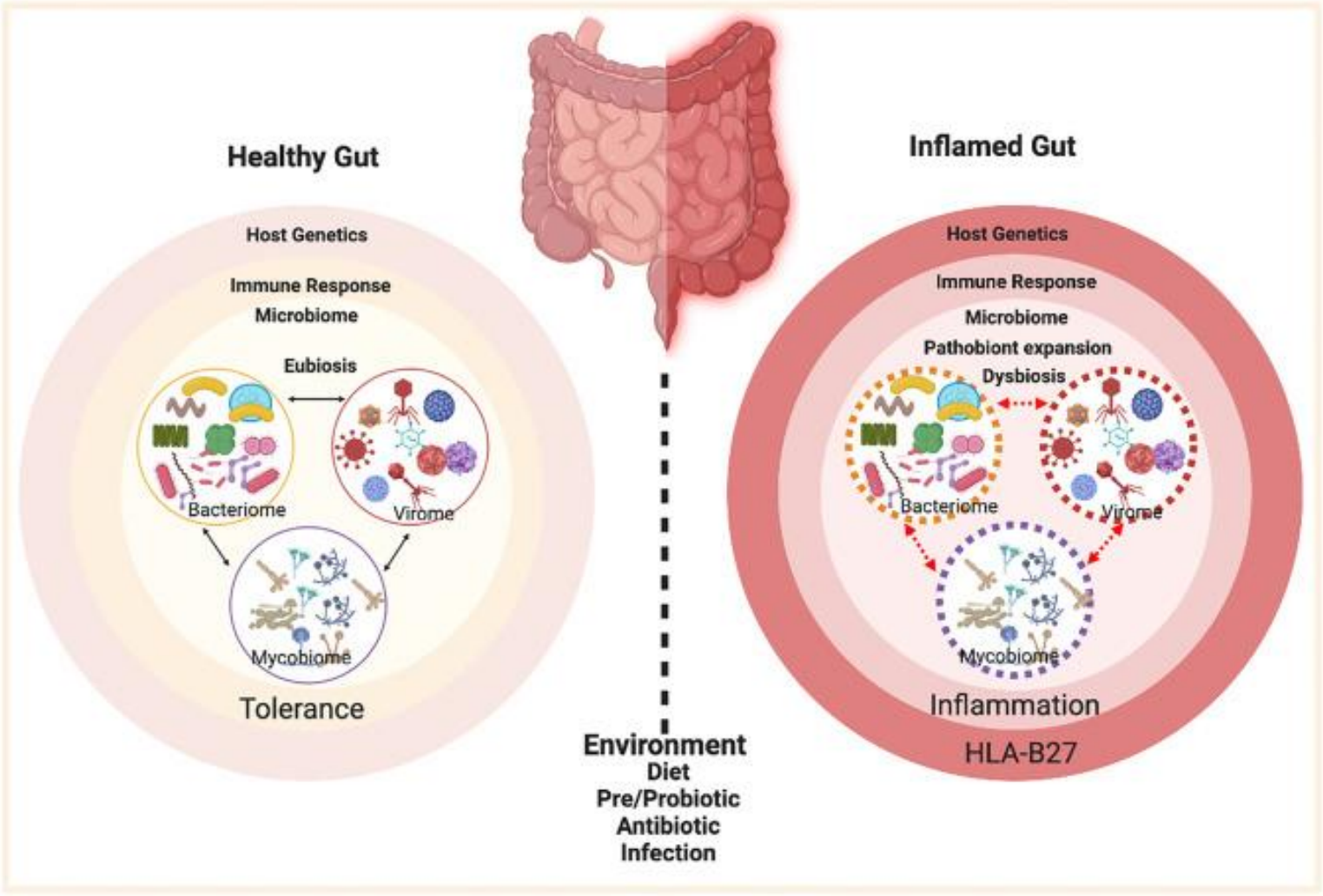
Wang et al., *Autoimmunity Reviews*, 2024

Gut microbial perturbations are linked with various diseases



Afzaal et al., *Front. Microbiol.,* 2022

Gut microbial and metabolic perturbations in axial spondyloarthritis



Gill and Rosenbaum, Frontiers Immunol, 2021

Microbiome and gut-joint axis in spondyloarthritis

Strong association with HLA-B27

Gut inflammation is common in spondyloarthritis

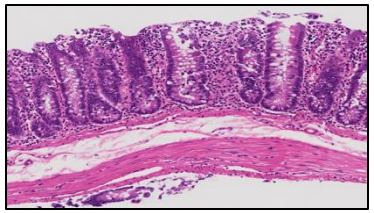
- AS patients have gut inflammation
  - ~50% subclinical
  - ~6-10% IBD
- 50-80% of IBD patients have arthritis

Experimental spondyloarthritis in rodents is highly dependent on gut microbiota

- Gut microbiota is required in HLA-B27 transgenic rats
- SpA-prone (SKG) mice gut microbiota influence the incidence/severity of arthritis/ileitis

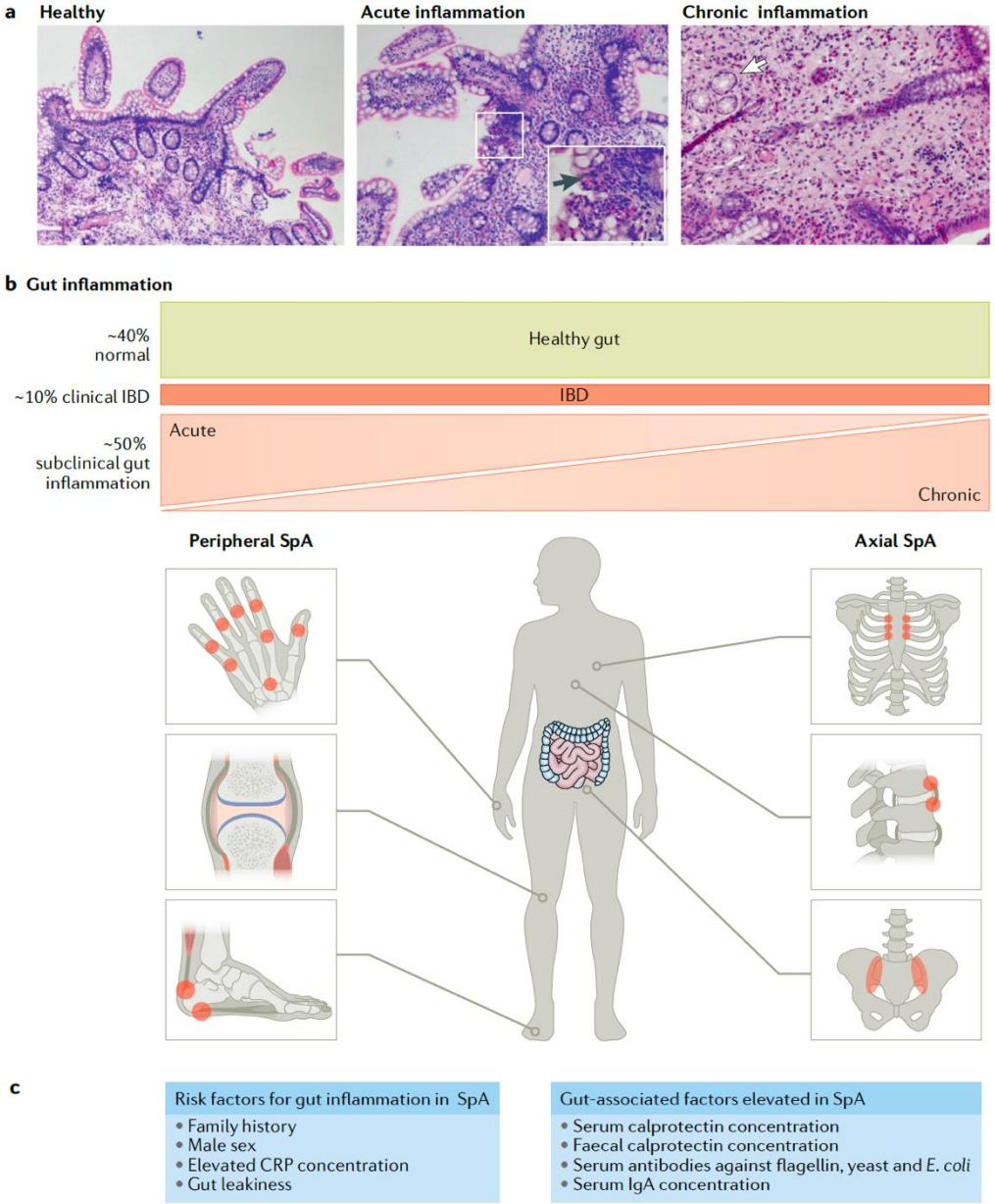
HLA-B27 Tg rat model of spondyloarthritis

peripheral joint inflammation



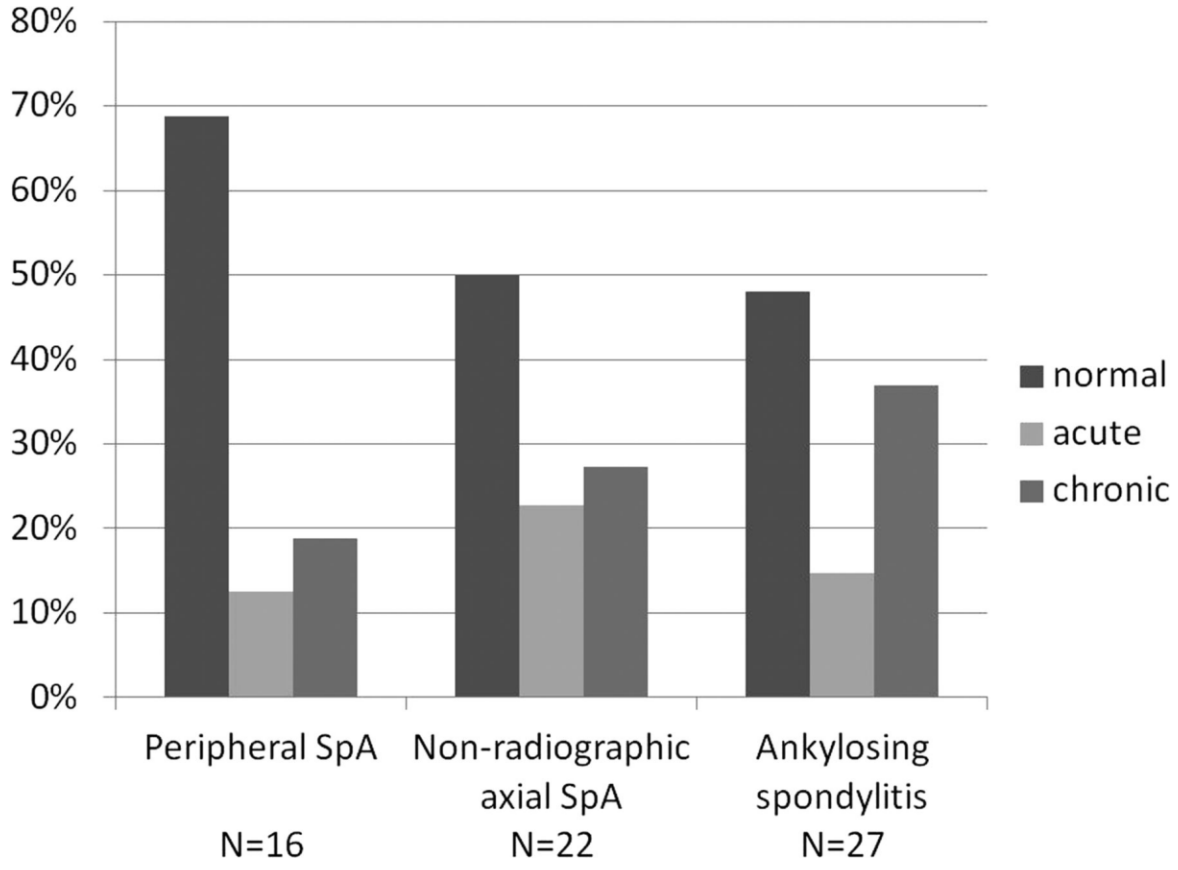
gastrointestinal inflammation

Taurog, *J Expt Med*, 1994
Rehaume, *Arthritis Rheumatol* 2014

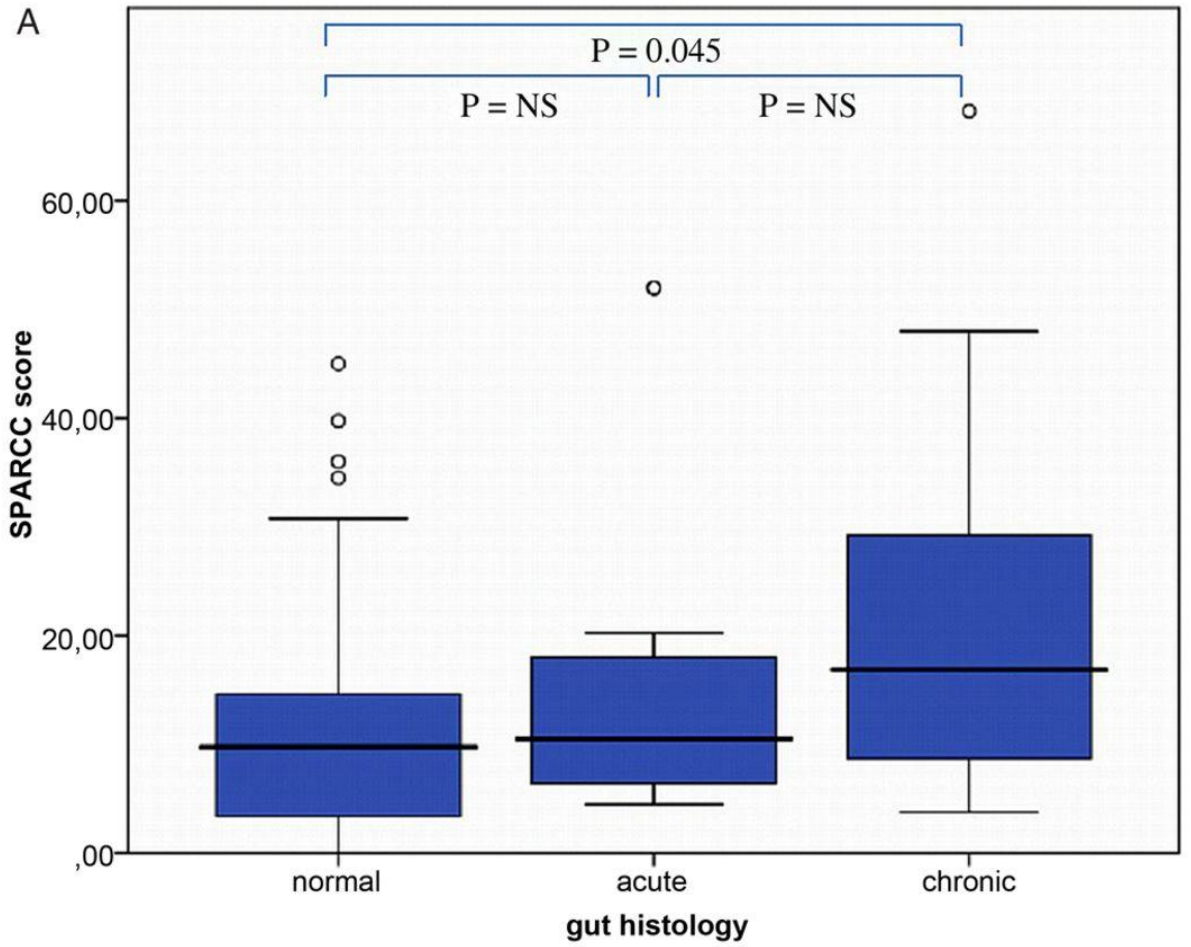


Clinical manifestations of the gut–joint axis of inflammation in SpA
Gracey, *Nature Rev Rheum*, 2020

Inflammation of the epithelial mucosa is a key feature in axSpA pathophysiology



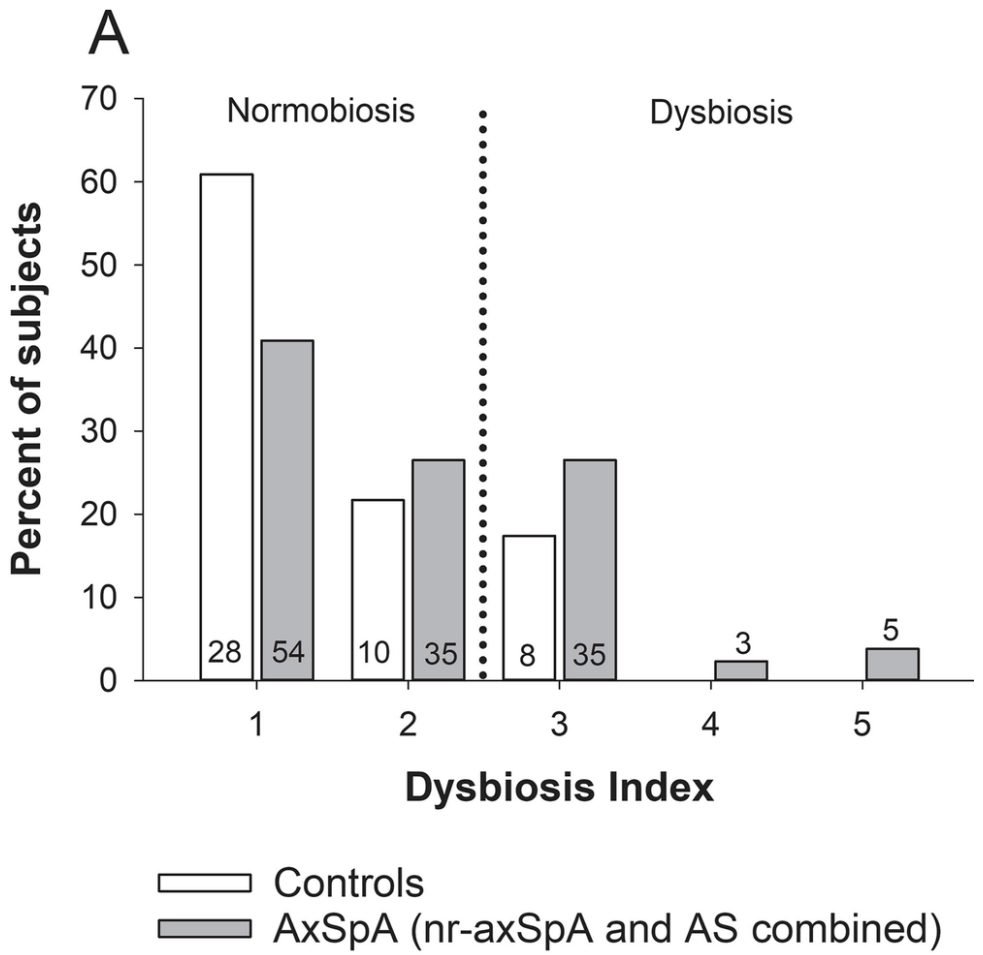
Ileocolonoscopy analysis

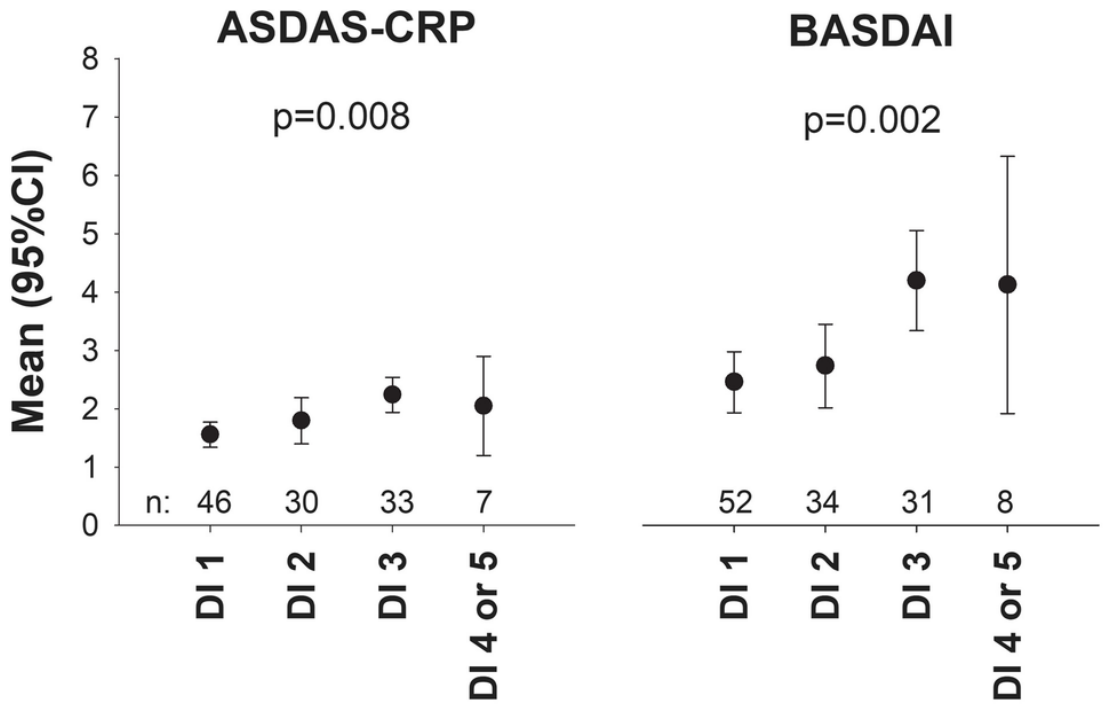


The SPARCC score is a method for assessing inflammatory lesions (bone marrow edema) in the sacroiliac (SI) joints using MRI

Van Praet, et. al., Ann Rheum Dis. 2013
Van Praet, et. al., Ann Rheum Dis. 2014

Gut dysbiosis associated with worse disease activity and physical function in axSpA



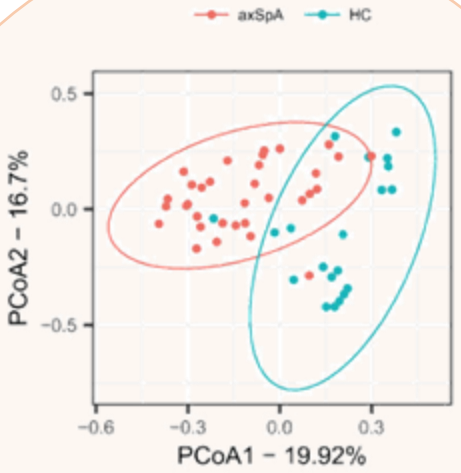


Sagard, J., Olofsson, T., Mogard, E. *et al*. *Arthritis Res Ther* **24,** 42 (2022).

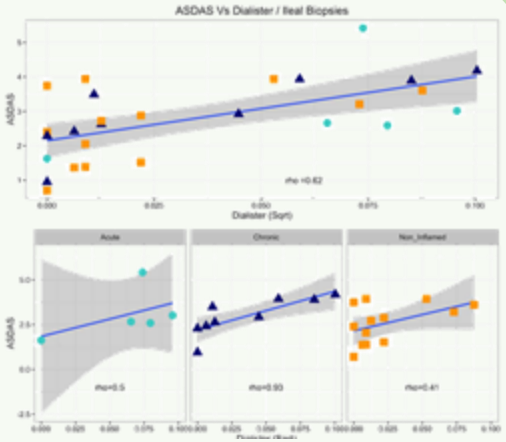
Relationship of gut microbial dysbiosis with spondyloarthritis

1. General Microbial Dysbiosis

- **Costello**, Intestinal Dysbiosis in Ankylosing Spondylitis. Arthritis Rheumatol. 2015.
- **Min,** Identification of gut dysbiosis in axial spondyloarthritis patients and improvement of experimental ankylosing spondyloarthritis by microbiome-derived butyrate with immune-modulating function. Front Immunol. 2023.
- **Manasson,** Gut microbiota perturbations in reactive arthritis and postinfectious spondyloarthritis. Arthritis Rheumatol. 2018.



Min, *Front. Immunol*, 2023



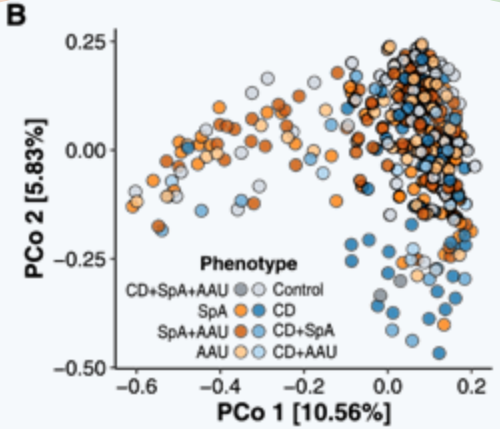
Tito, *Arthritis Rheumatol*, 2017

2. Disease Biomarkers

- **Breban,** ARD, 2016 (*R. gnavus*)
- **Chen**, Variations in gut microbial profiles in ankylosing spondylitis: disease phenotype-related dysbiosis. Ann Transl Med. 2019.
- **Tito**, Dialister as a Microbial Marker of Disease Activity in Spondyloarthritis. Arthritis Rheumatol. 2017.
- **Sagard**, Gut dysbiosis associated with worse disease activity and physical function in axial spondyloarthritis. *Arthritis Research & Therapy, 2020.*

3. Overlap with Inflammatory Diseases

- **Scher**, Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol*, 2015.
- **Essex,** Shared and distinct gut microbiota in spondyloarthritis, acute anterior uveitis, and Crohn's disease. Arthritis Rheumatol. 2024



Essex, *Arthritis Rheumatol*, 2024

Non-Overlap with IBD

- **Sternes**, Distinctive gut microbiomes of ankylosing spondylitis and inflammatory bowel disease patients suggest differing roles in pathogenesis and correlate with disease activity. Arthritis Research & Therapy. 2022

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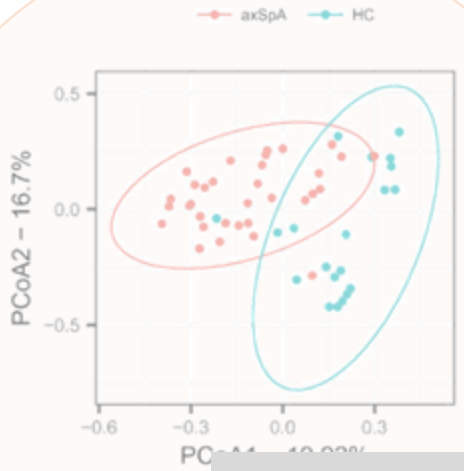

Min, *Front*

Arthritis Rheumatol, 2017

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What about HLA-B27?

3. Overlap with Inflammatory Diseases

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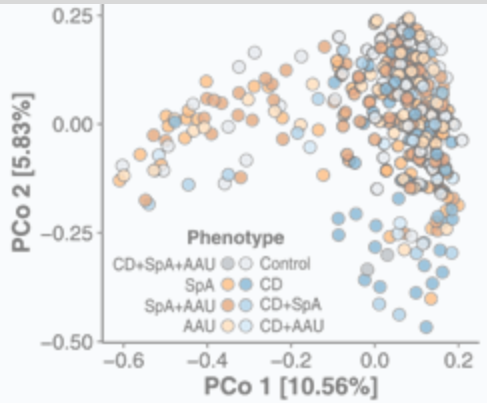
- **Essex,** Shared and distinct gut microbiota in spondyloarthritis, acute anterior uveitis, and Crohn's disease. Arthritis Rheumatol. 2024

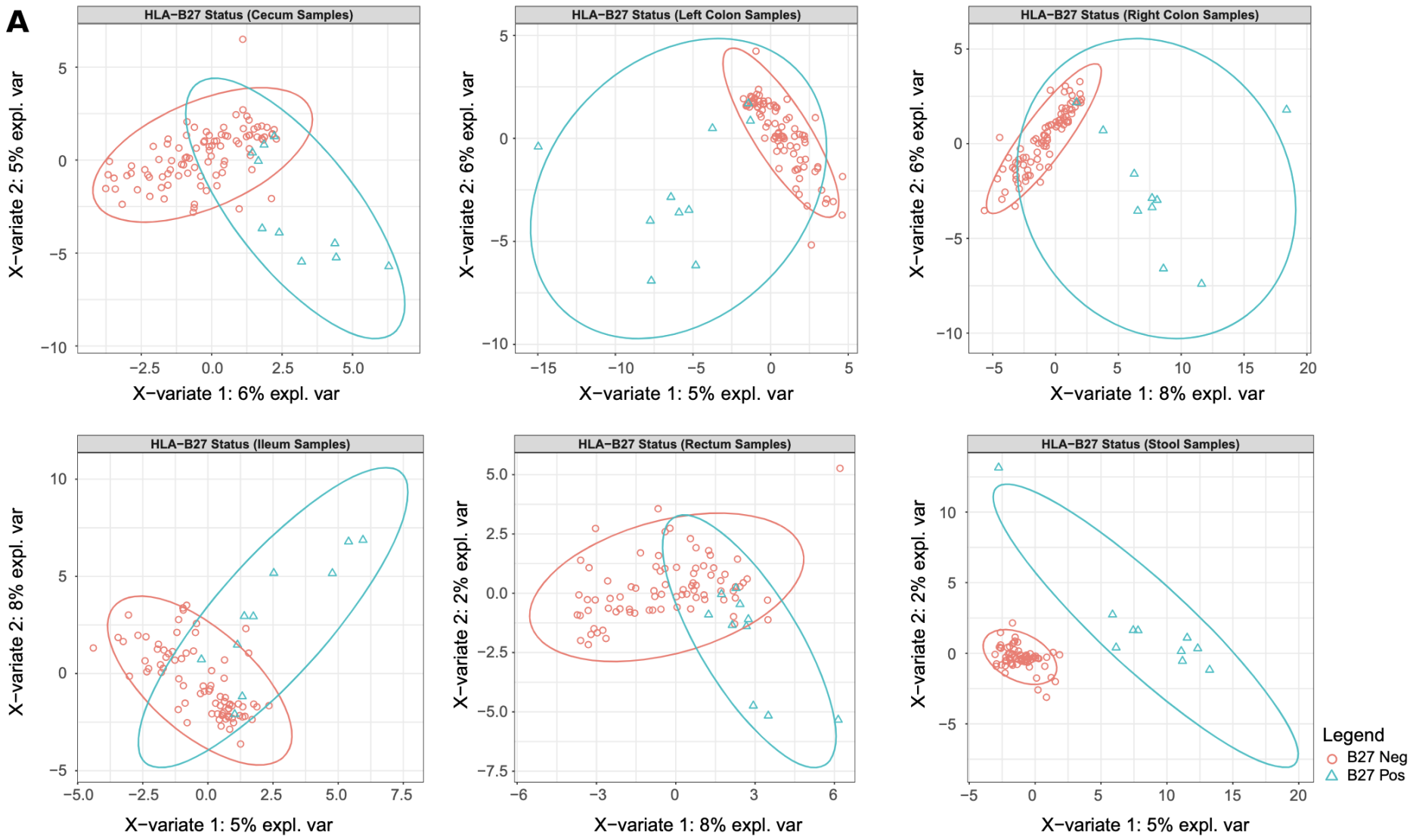


Essex, *Arthritis Rheumatol*, 2024

Non-Overlap with IBD

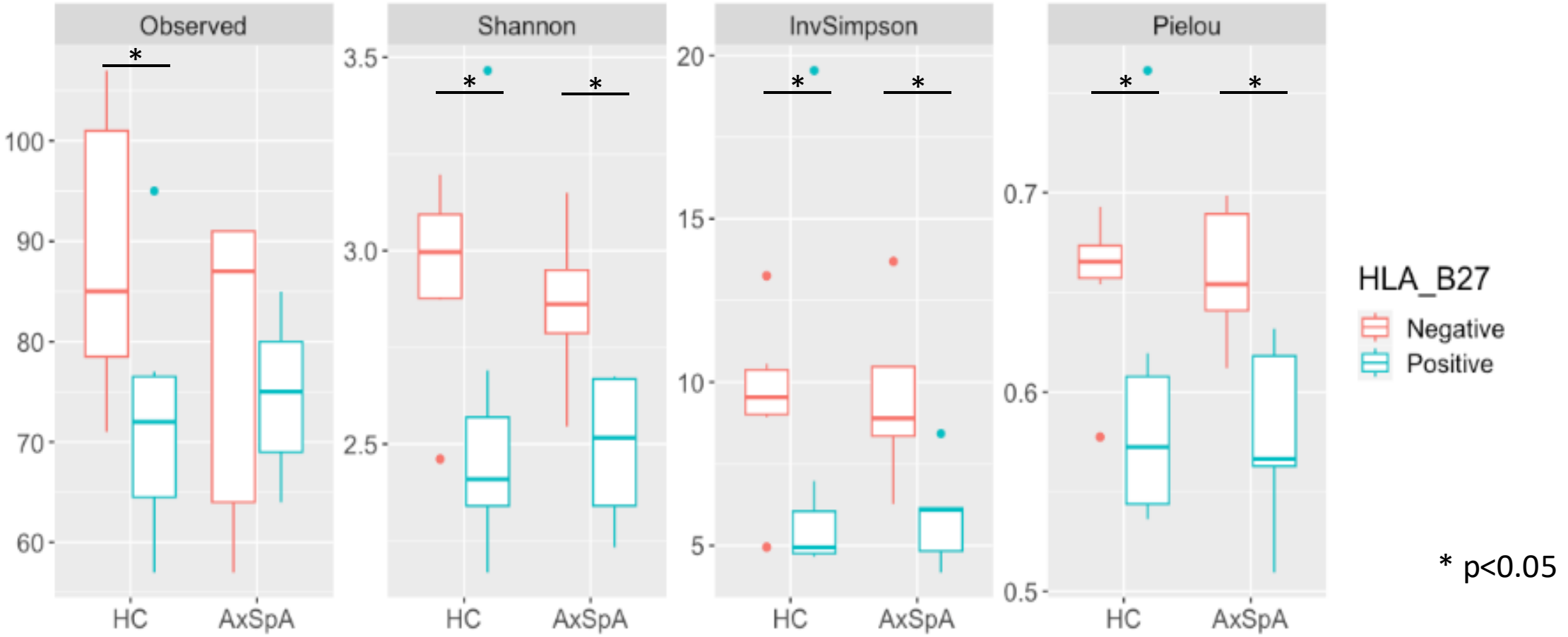
- **Sternes**, Distinctive gut microbiomes of ankylosing spondylitis and inflammatory bowel disease patients suggest differing roles in pathogenesis and correlate with disease activity. Arthritis Research & Therapy. 2022

HLA-B27 associated with risk of ankylosing spondylitis influences the gut microbiome



Asquith *et al.*, *Arthritis & Rheumatol 2019*

HLA-B27 is associated with decreased alpha diversity in healthy controls and axSpA subjects

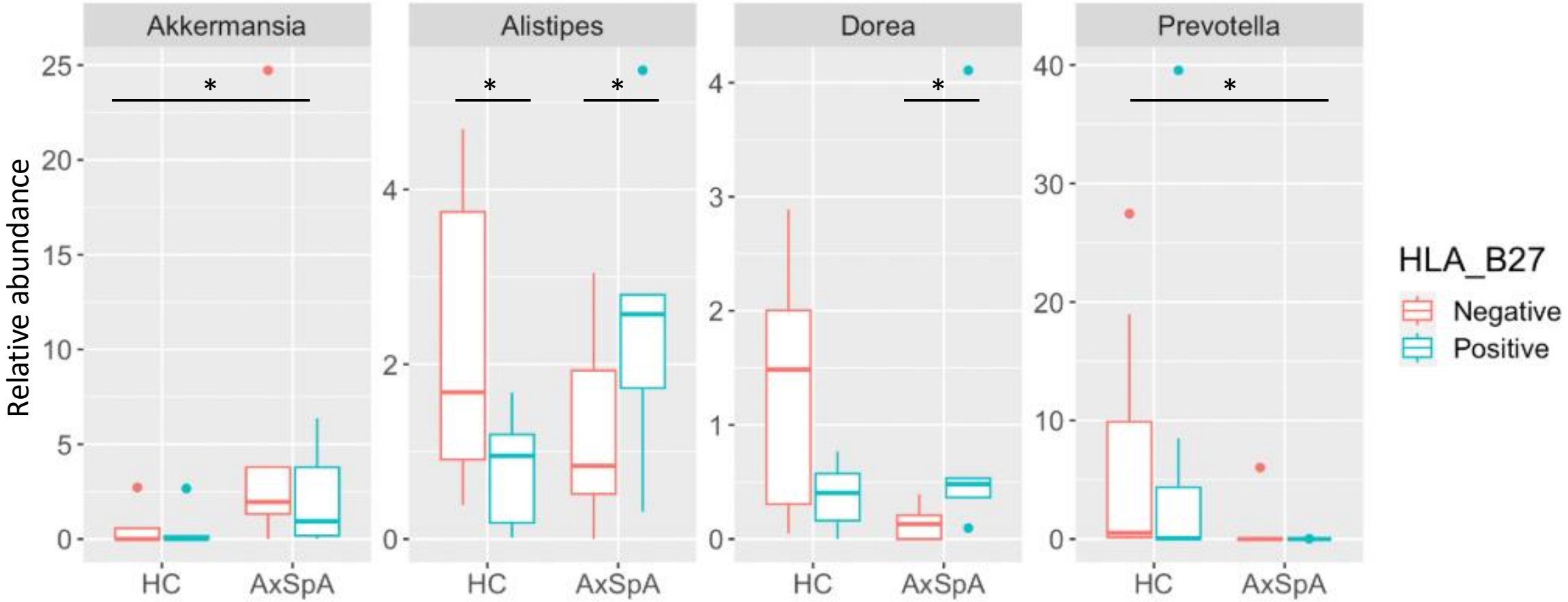


* p<0.05

Deodhar, Gill, Magrey. ACR Open Rheumatol. 2023

Gill, *unpublished data*

Gut microbial abundance is affected by axSpA as well as HLA-B27 status

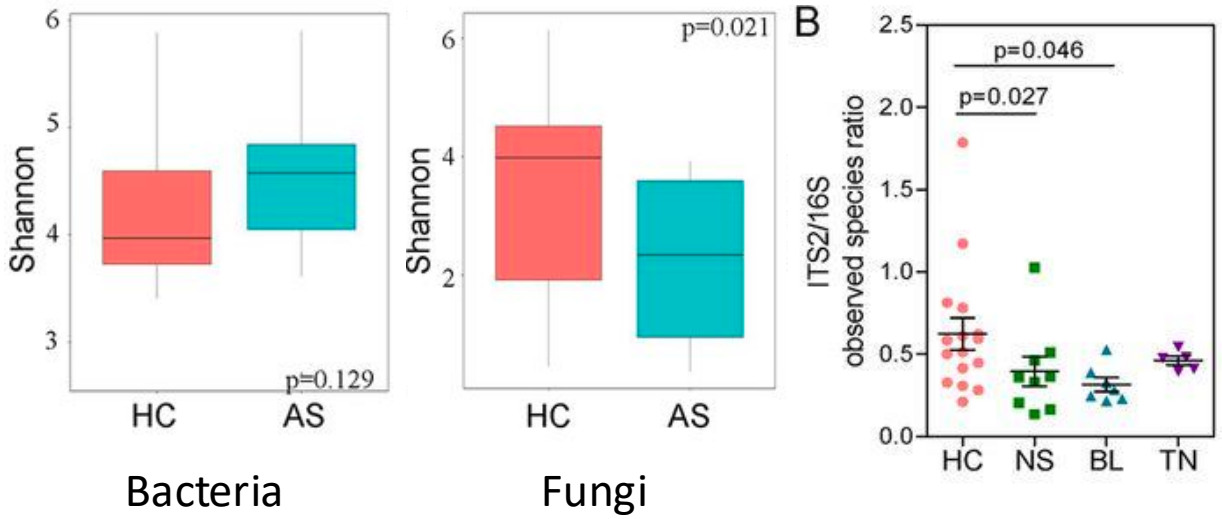


Gill, *unpublished data*

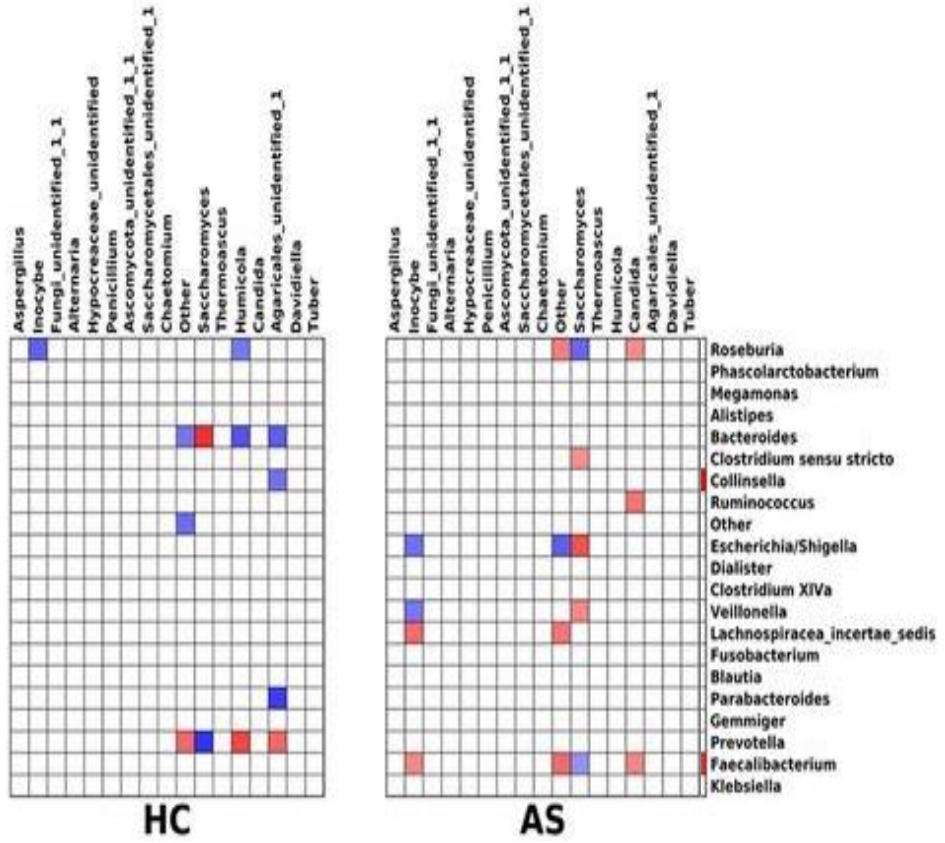
Role of Mycobiome (fungal community) in the pathogenesis of SpA

Altered bacterial-fungal Interkingdom networks in the guts of AS patients

- Altered bacterial and fungal communities in AS patients receiving different therapeutic regimens
- Alpha Diversity of bacteria increased, while the alpha diversity of intestinal fungi was decreased in AS patients



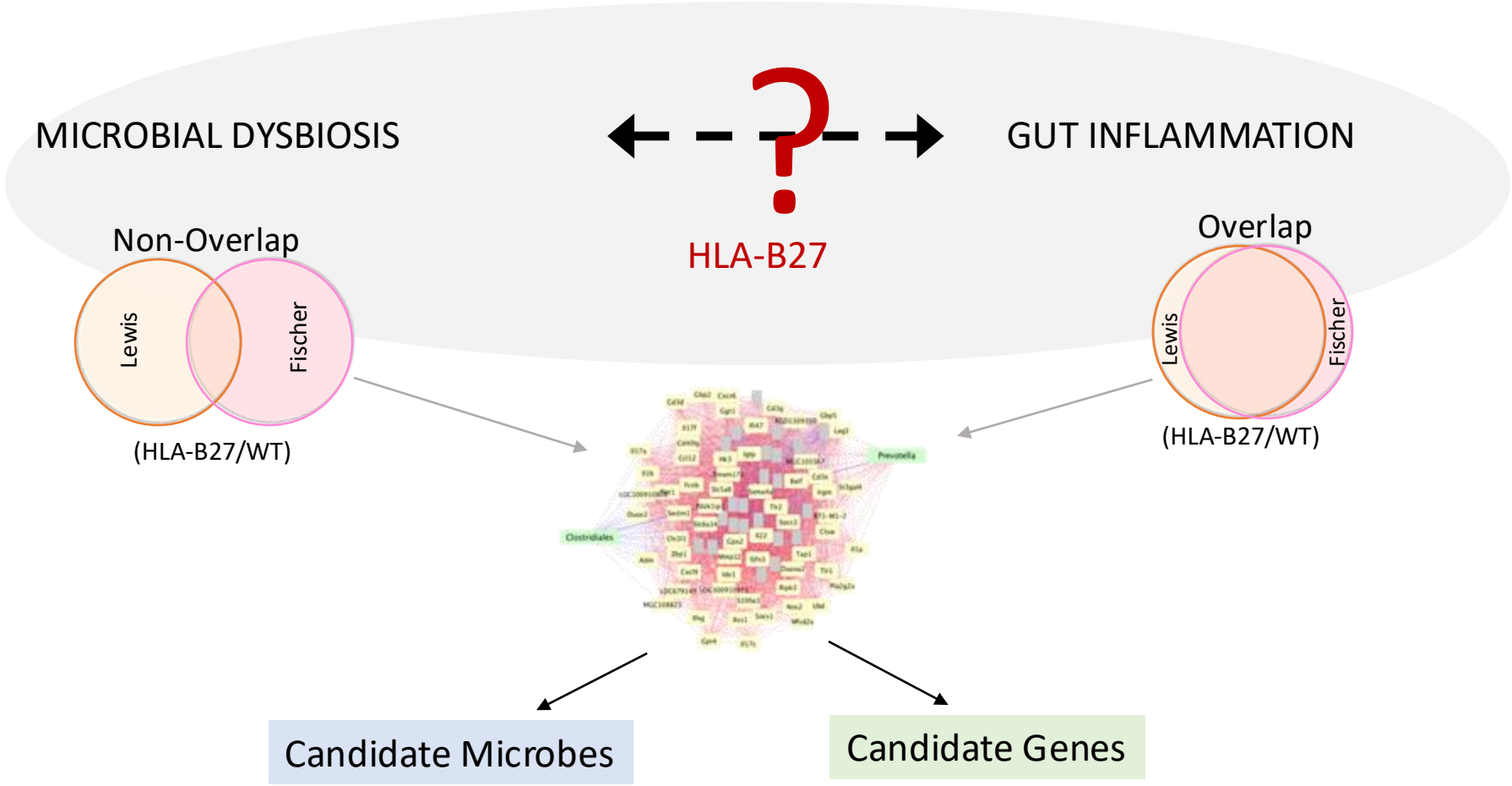
- Altered bacterial-fungal networks in AS patients



Li et al., *mSystems* 2019

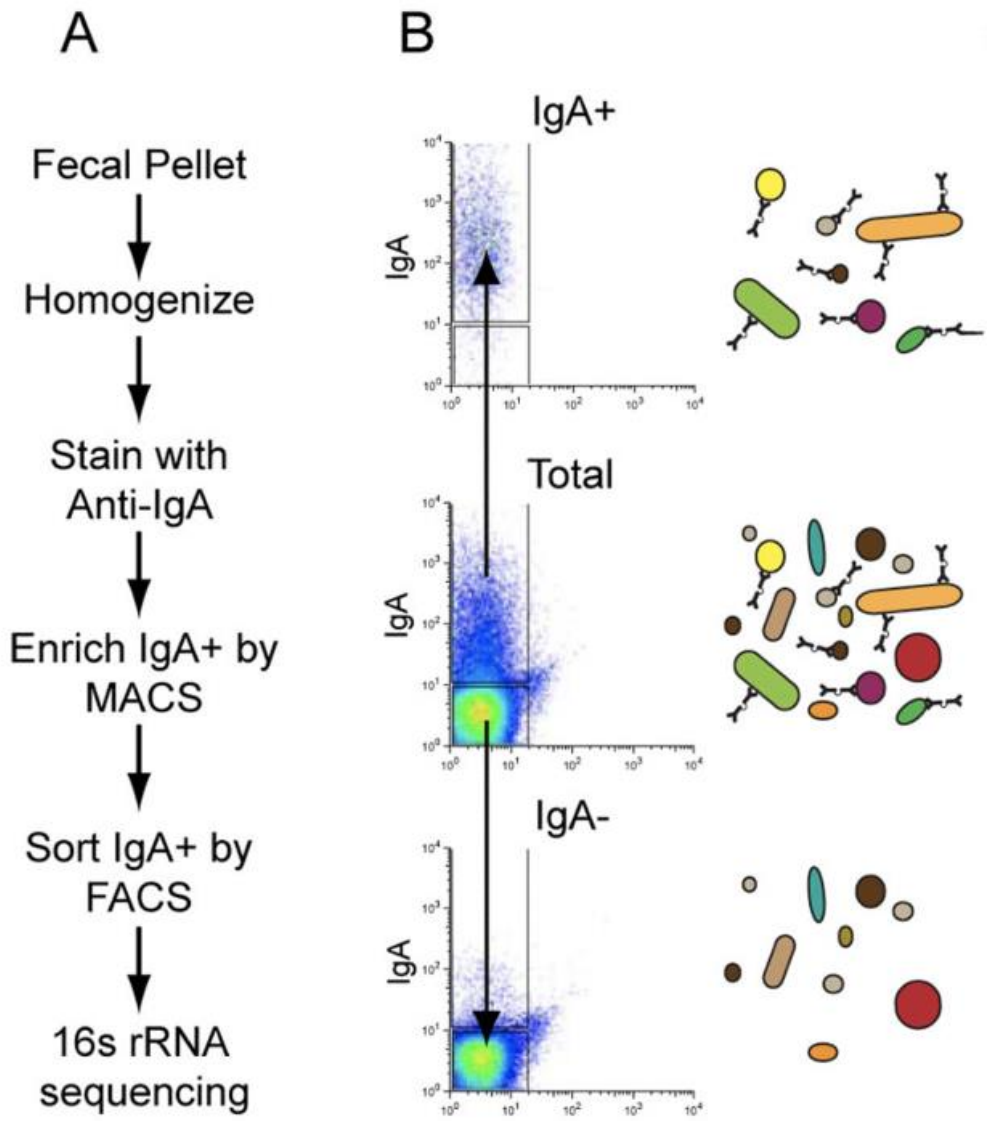
How does HLA-B27 shape the gut microbiome?

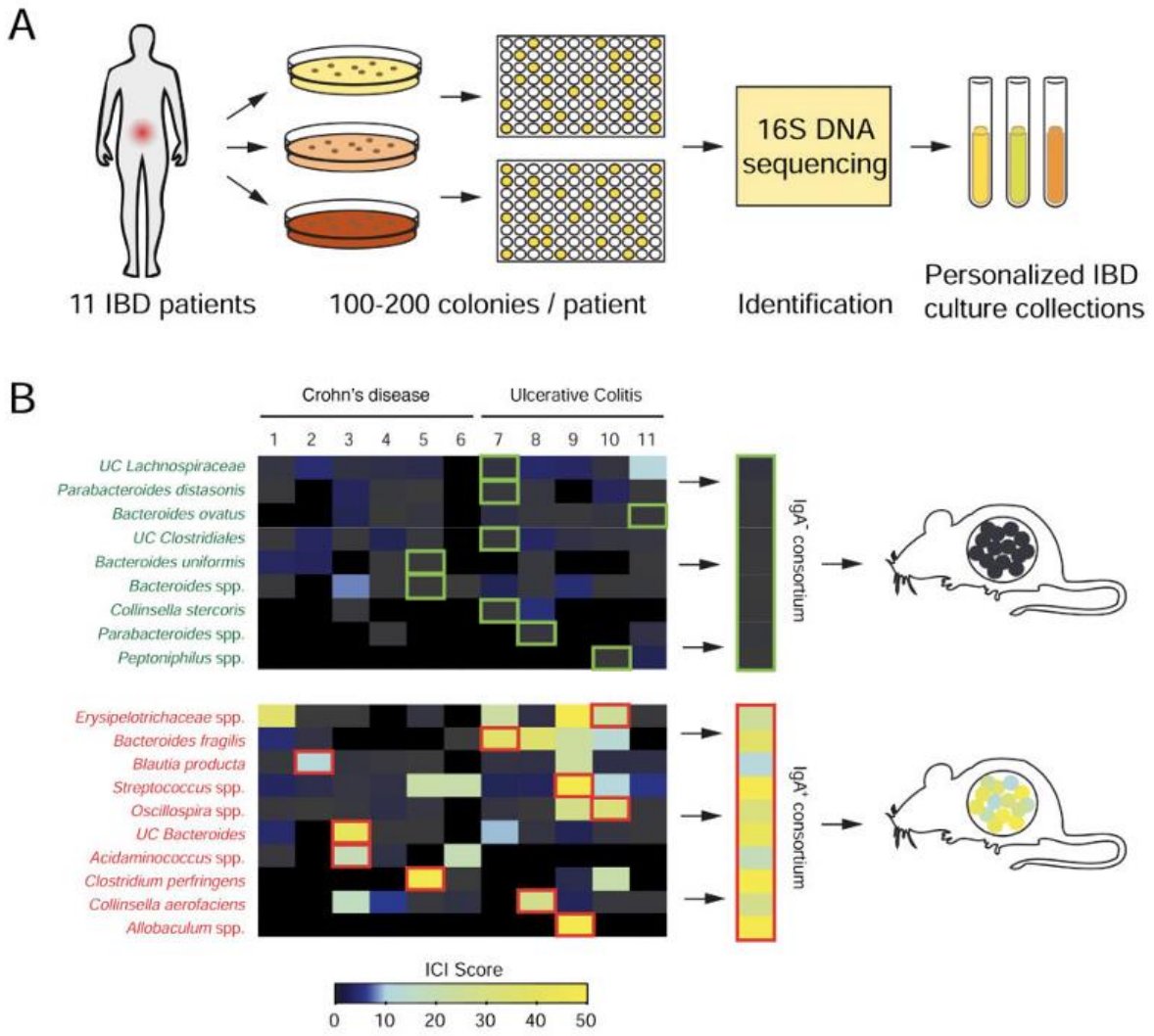
HLA-B27 is associated with gut microbial dysbiosis and host immune dysregulation



Gill *et al.*, *Arthritis & Rheumatol 2018*
Gill *et al.*, *Arthritis & Rheumatol 2019*

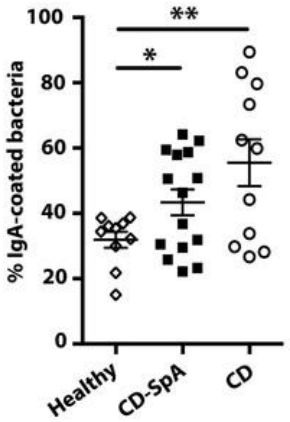
Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease

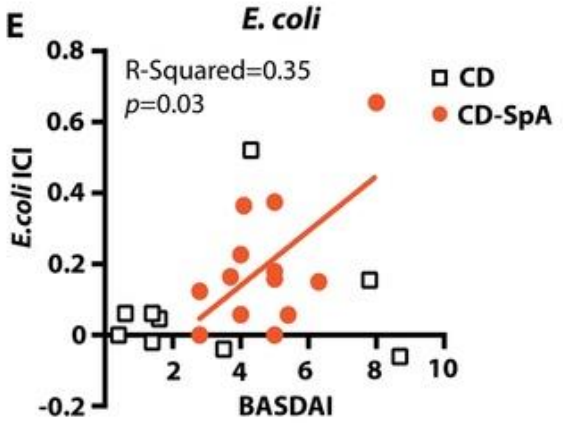


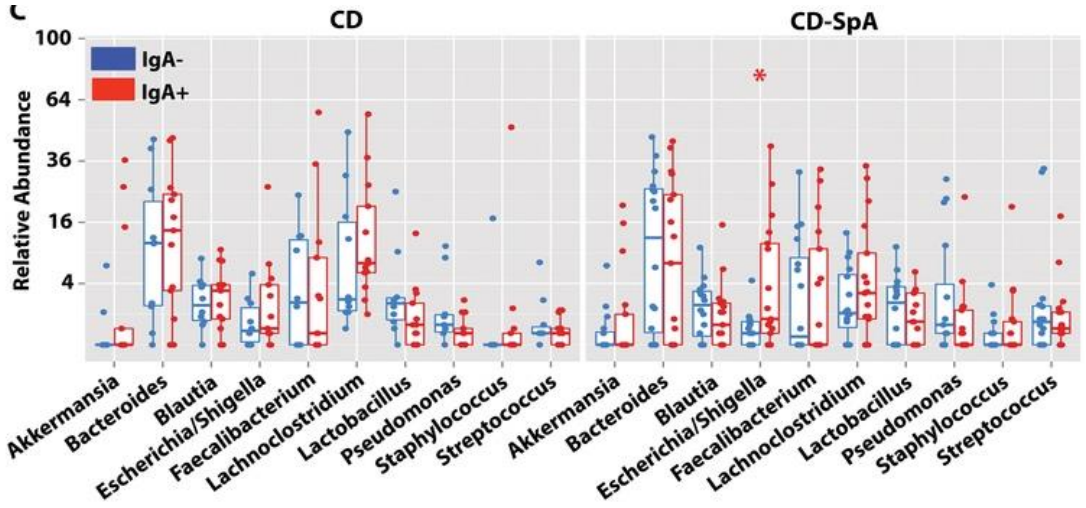


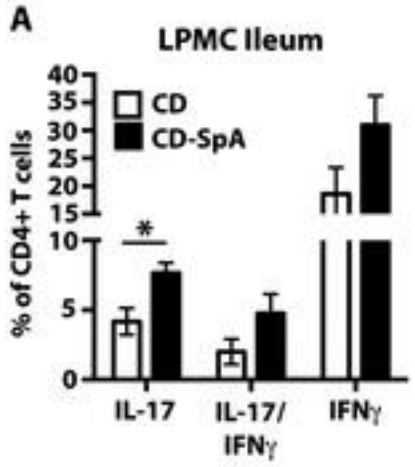
Palm, et al., Cell 2014

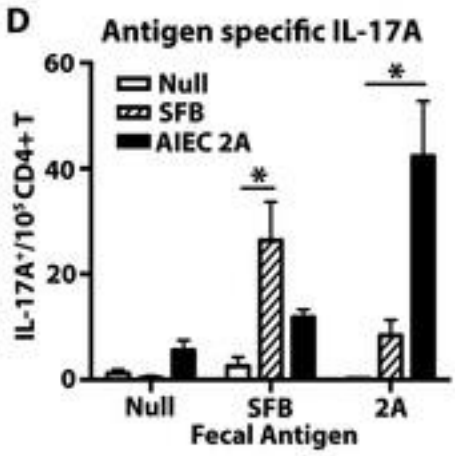
IgA-coated *E. coli* in Crohn's disease SpA promote T_H 17-dependent inflammation





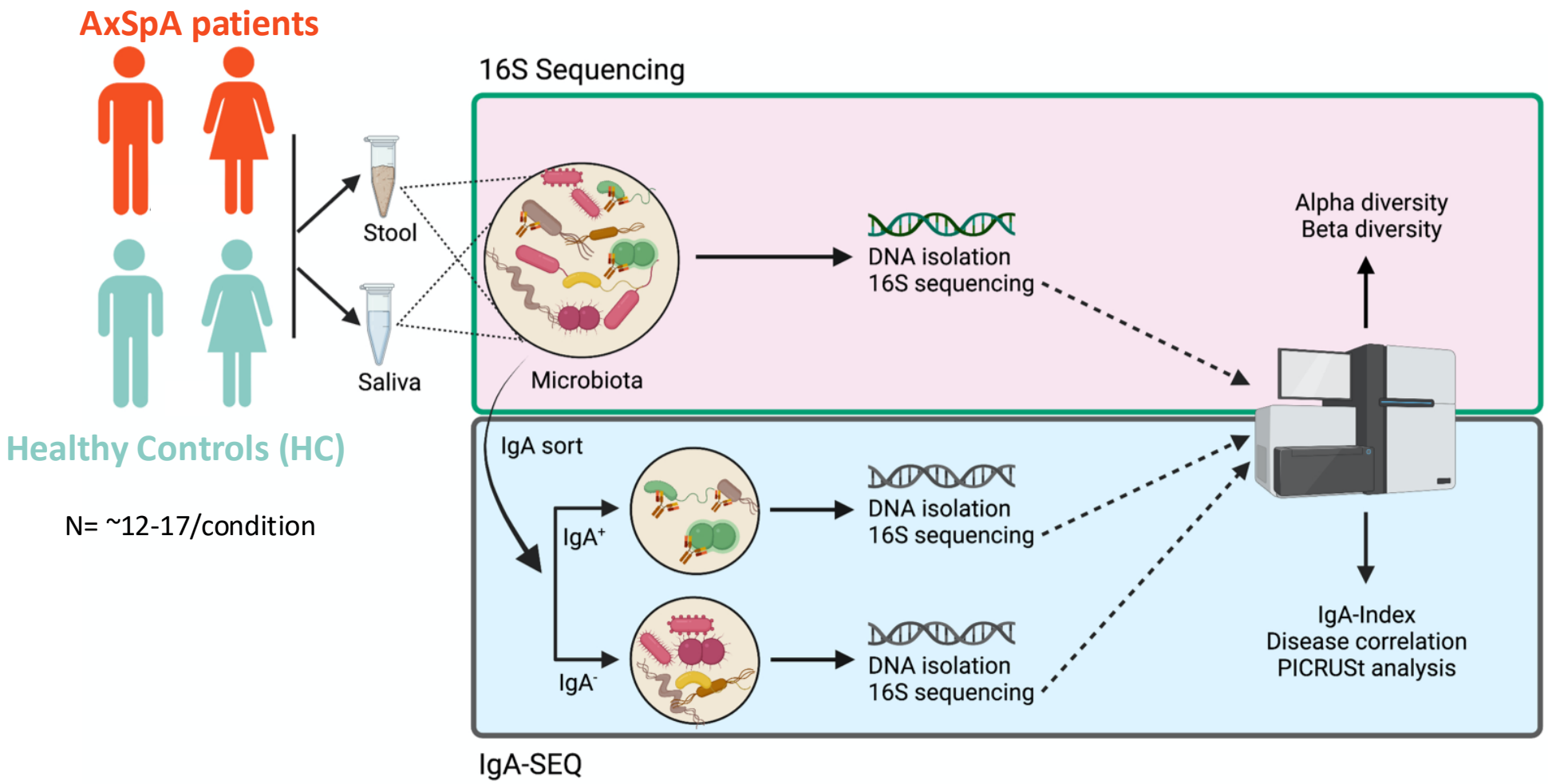






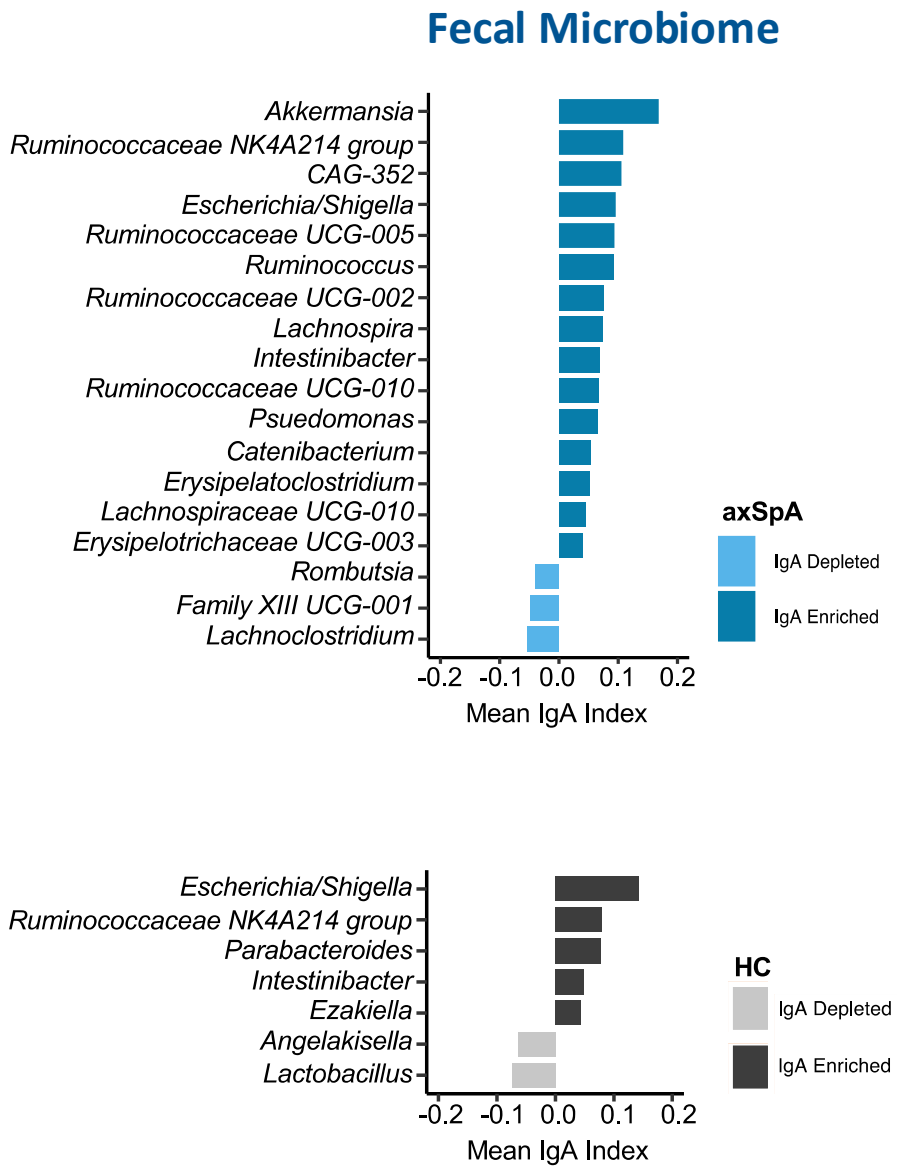
Viladomiu. *Sci Transl Med*. 2017

IgA coating defines a subset of bacteria that selectively stimulates intestinal immunity



Gill et al, *Frontiers in Immunology* 2022

AxSpA patients exhibit IgA enrichment of inflammation associated fecal microbiota



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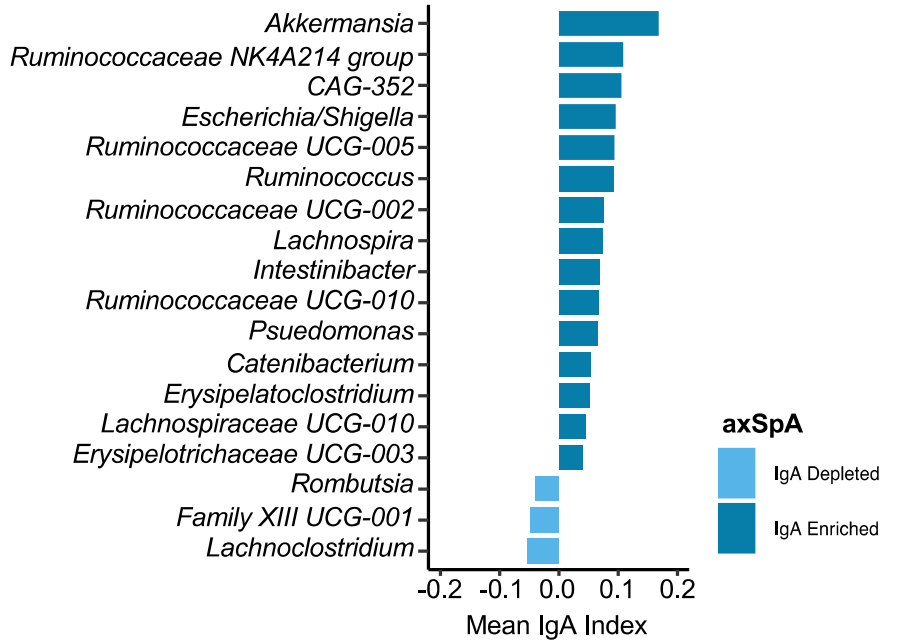
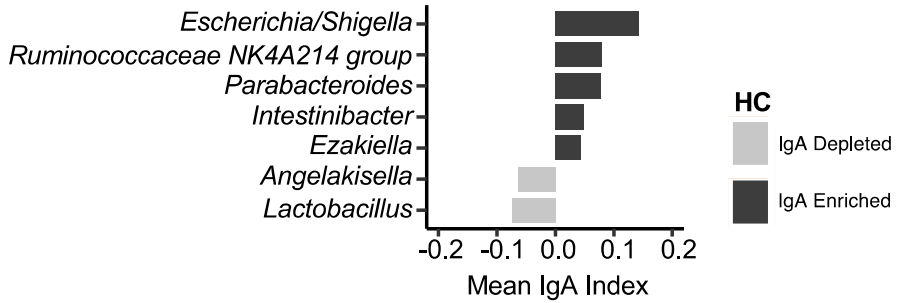
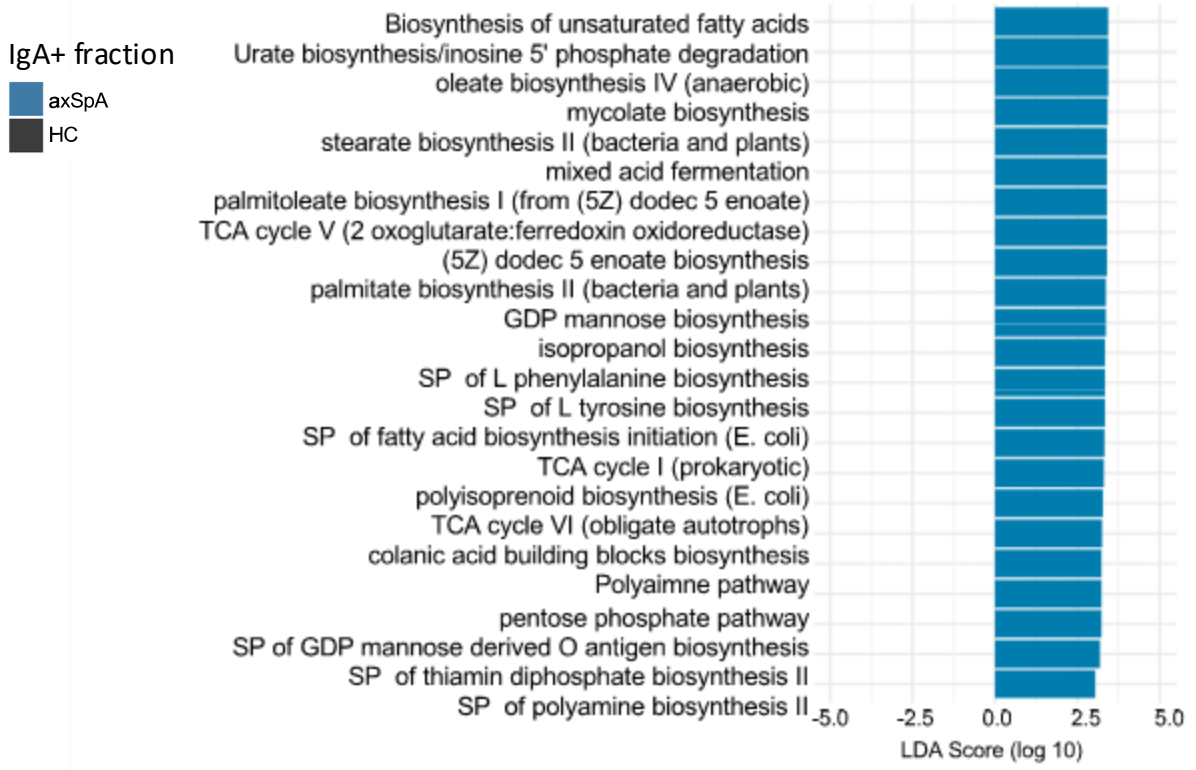
AxSpA patients exhibit IgA enrichment of inflammation associated fecal metabolome

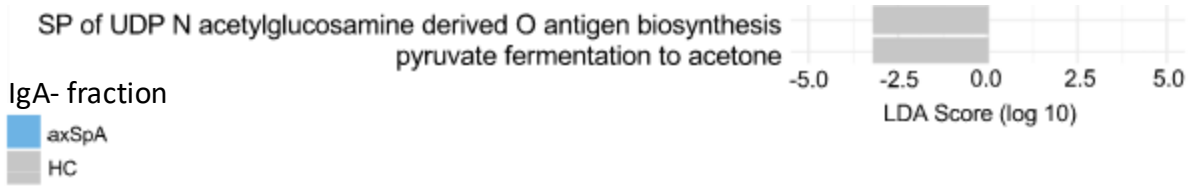
Fecal Microbiome





Fecal Metabolome





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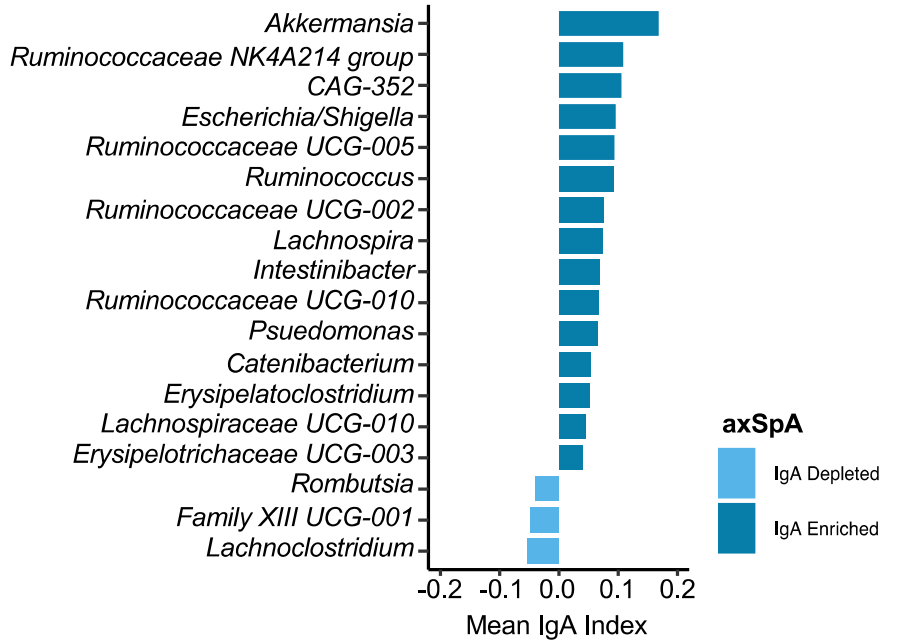

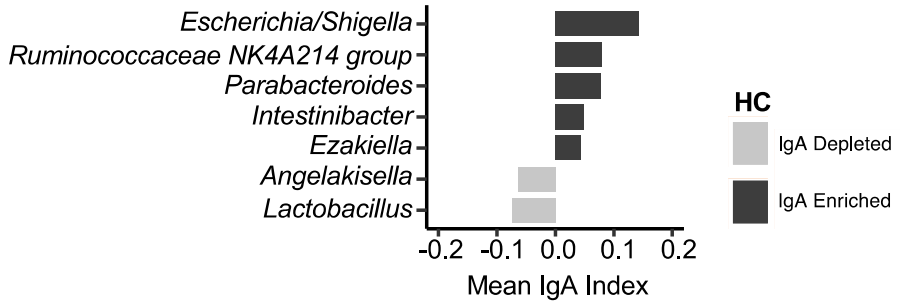

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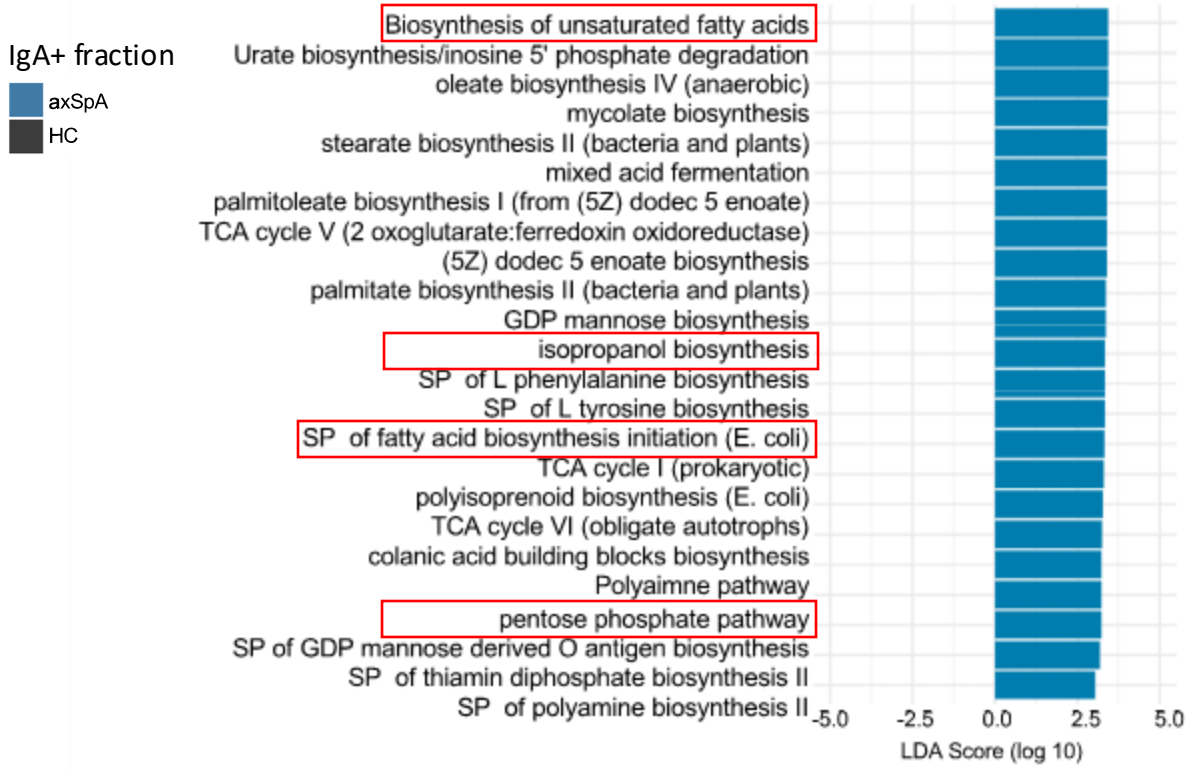
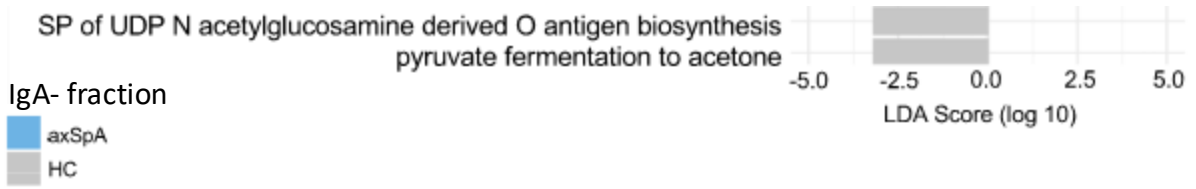
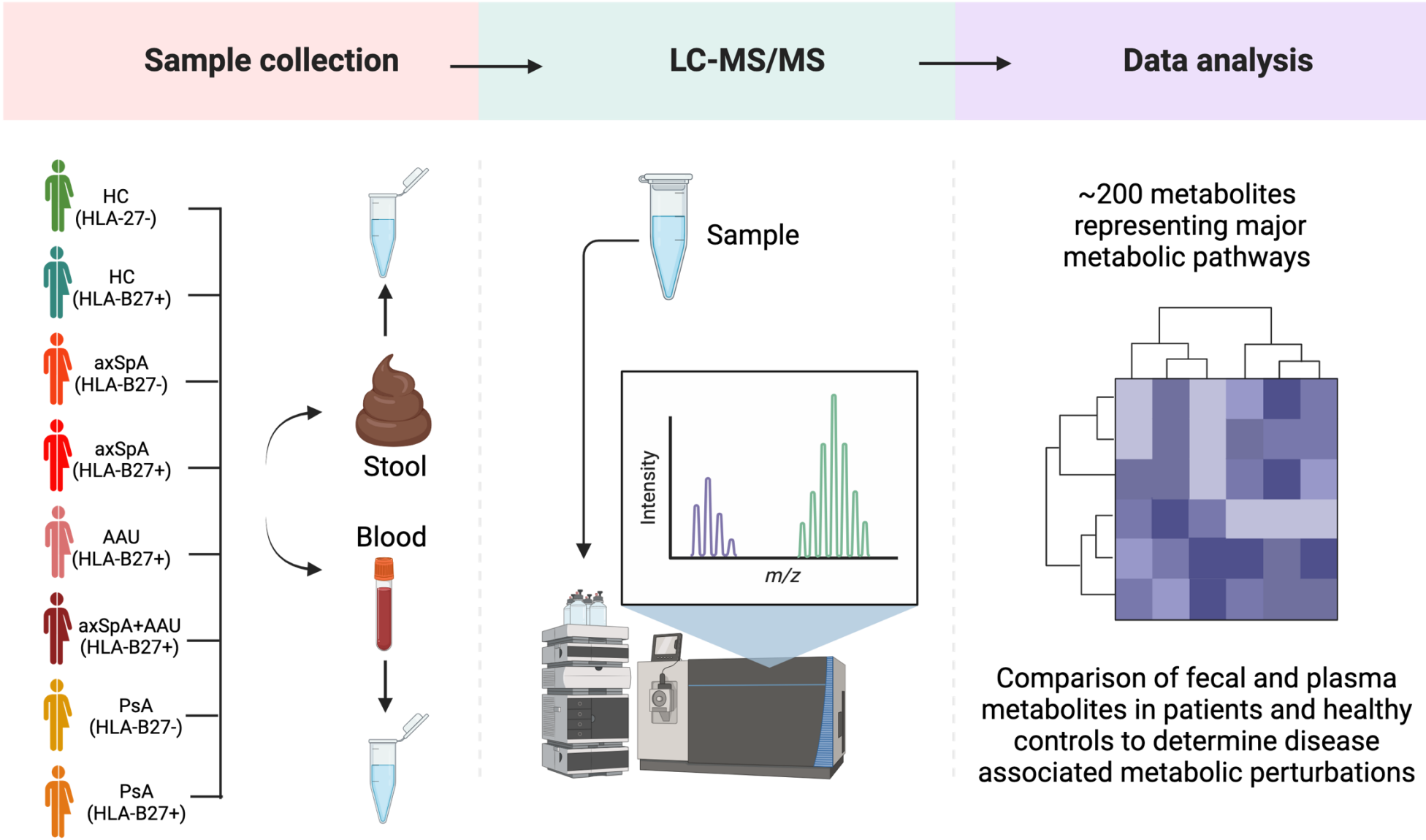




Gill et al, *Frontiers in Immunology* 2022

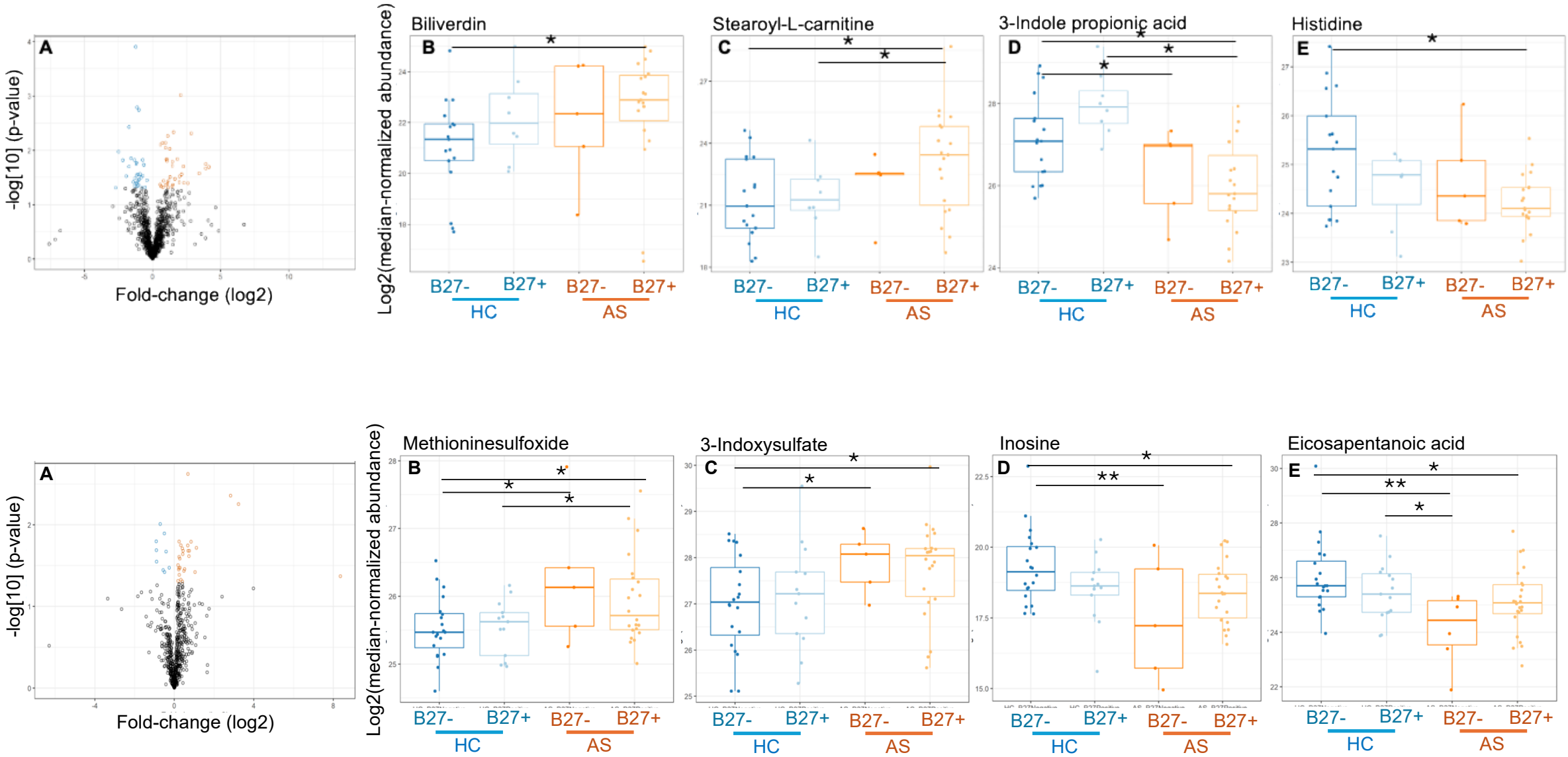
Fecal and plasma metabolic profiling of spondyloarthritis patients



Gill, *unpublished data*

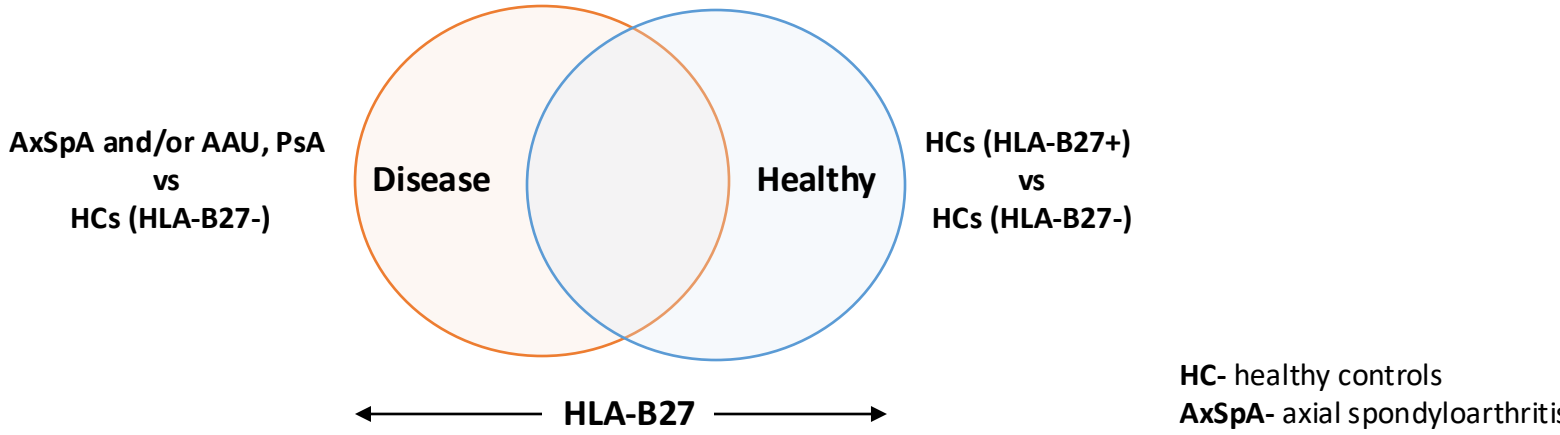
Figure made by using Biorender.com

Plasma metabolites altered in radiographic axial spondyloarthritis patients



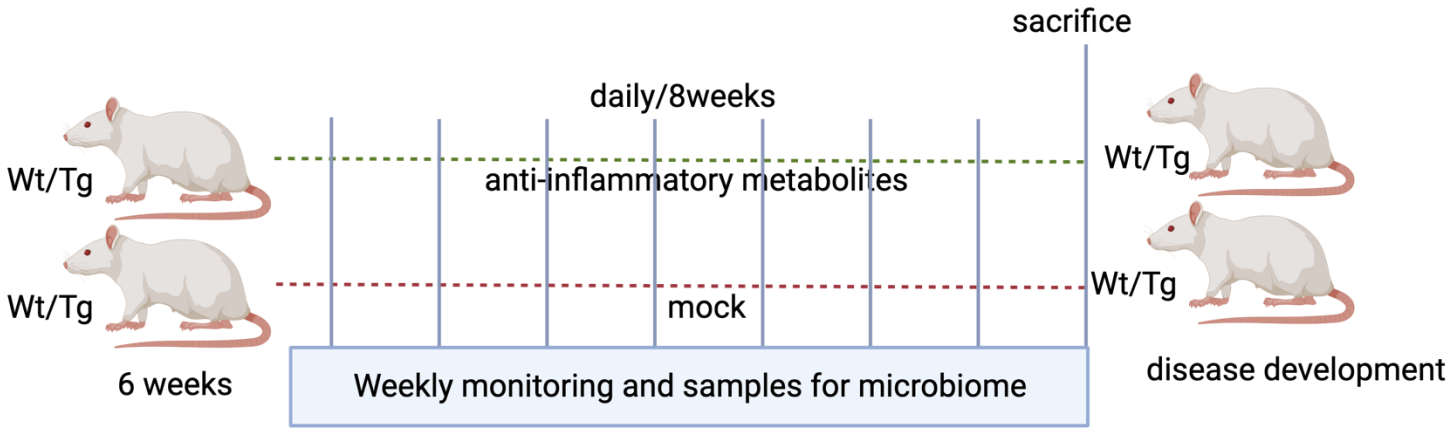
Gill, *unpublished data*

Metabolic profiling may reveal disease and HLA-B27 associated perturbation in spondyloarthritis



HC- healthy controls
AxSpA- axial spondyloarthritis
AAU- acute anterior uveitis

- Host-microbe interactions and disease pathogenesis of candidate metabolites will be dissected using HLA-B27 Tg rats

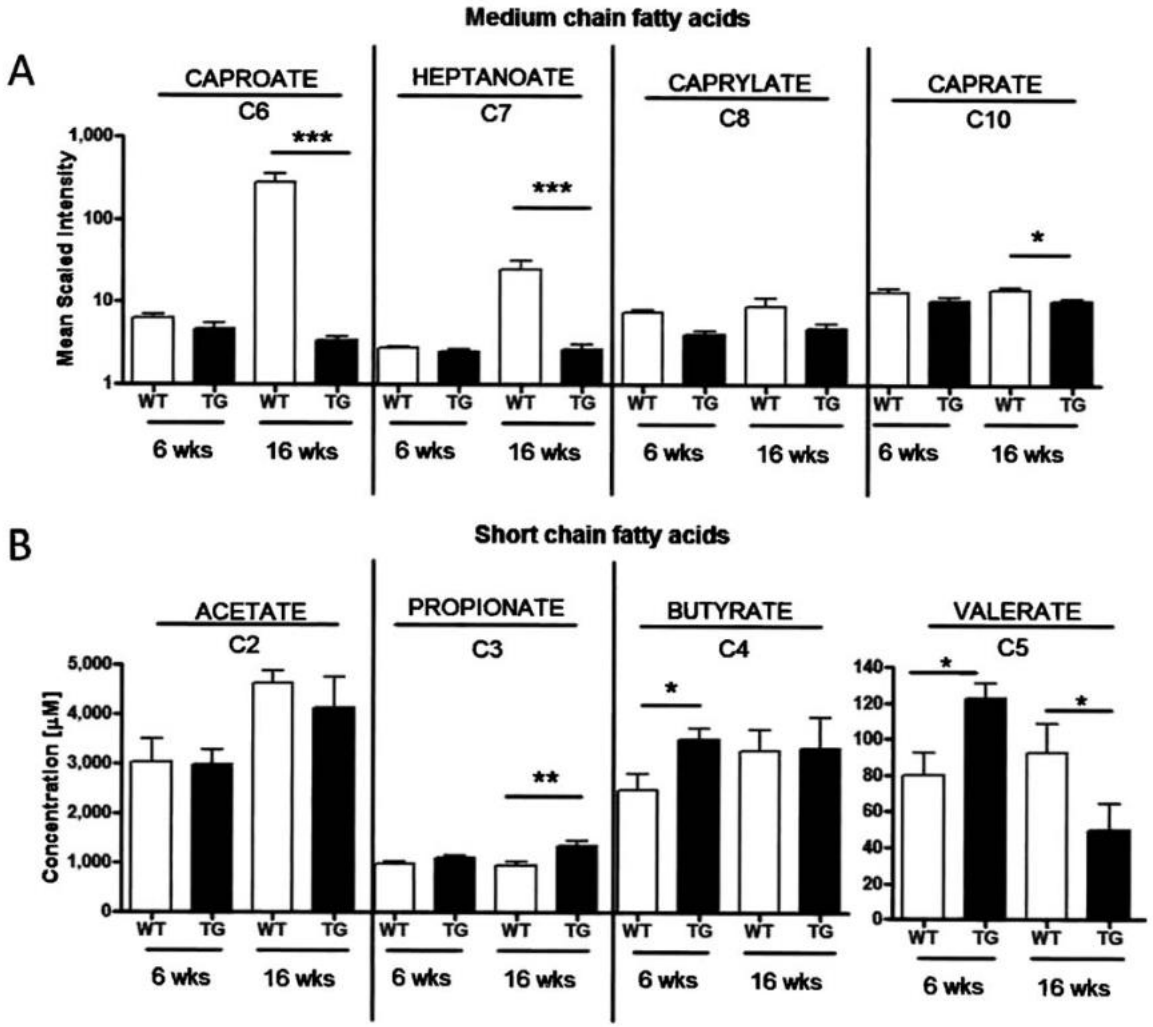


Gill, *unpublished data*

Gill, *unpublished data*

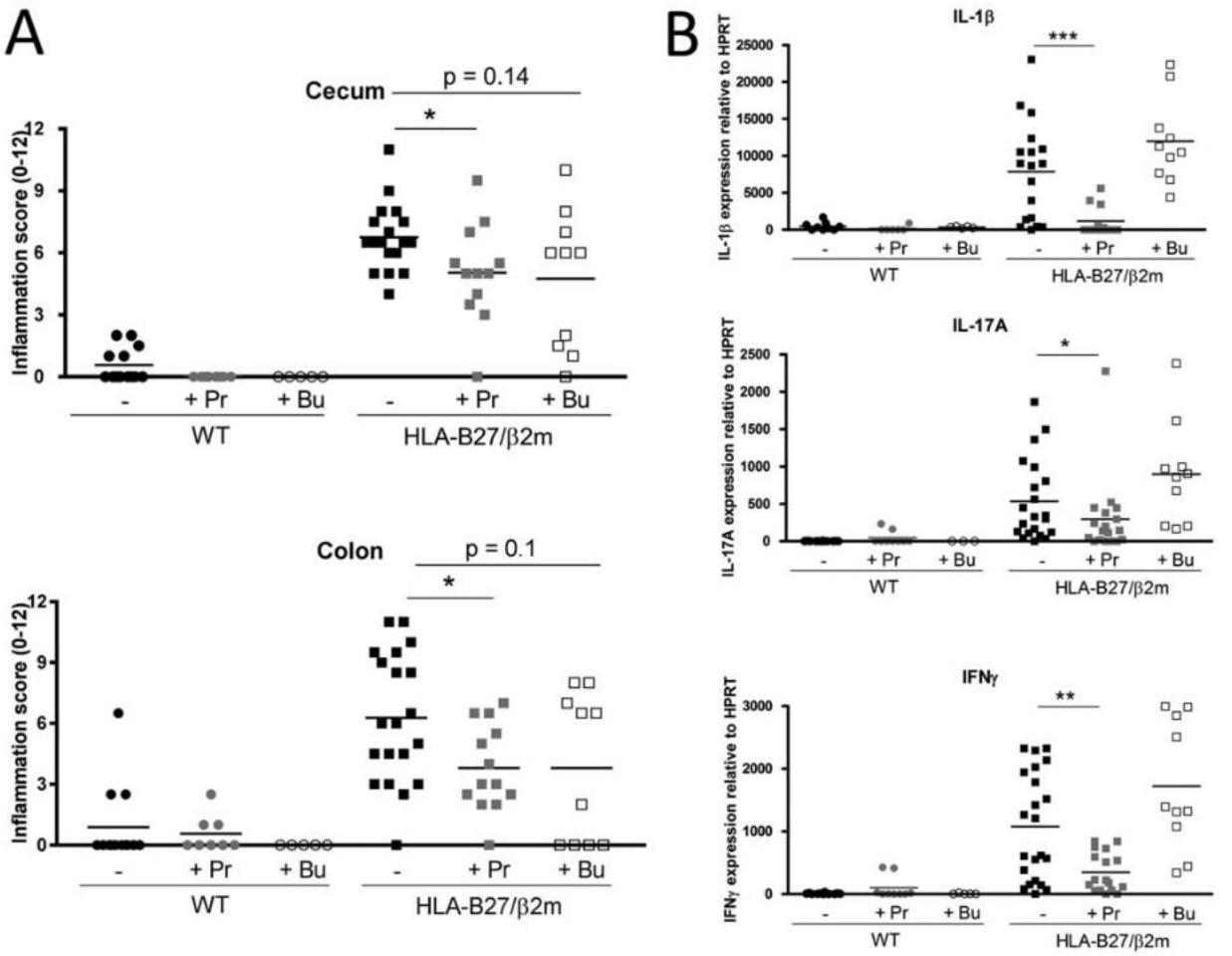
SCFA ameliorates disease in HLA-B27 transgenic model of spondyloarthritis

HLA–B27 expression alters intestinal levels of medium-chain fatty acids (MCFAs) and short-chain fatty acids(SCFAs)



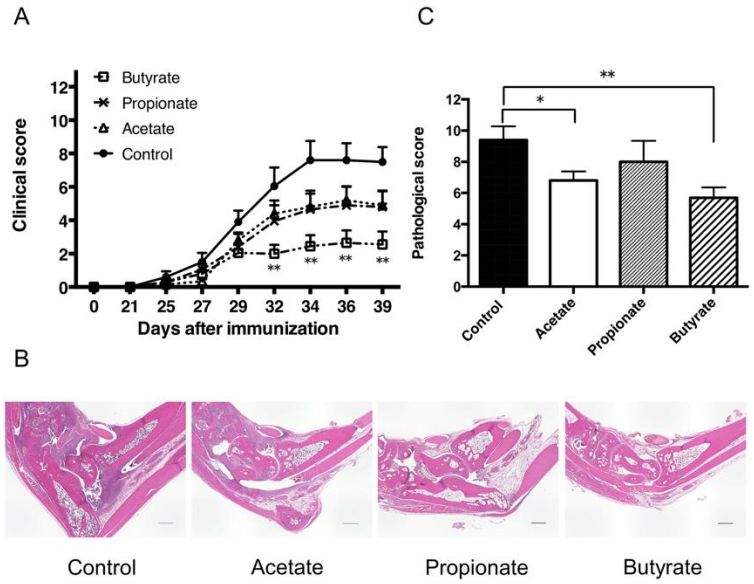
Asquith, *Arthritis Rheumatol*, 2017

Administration of the short-chain fatty acid sodium propionate (Pr) significantly attenuates HLA–B27–associated immune pathology.

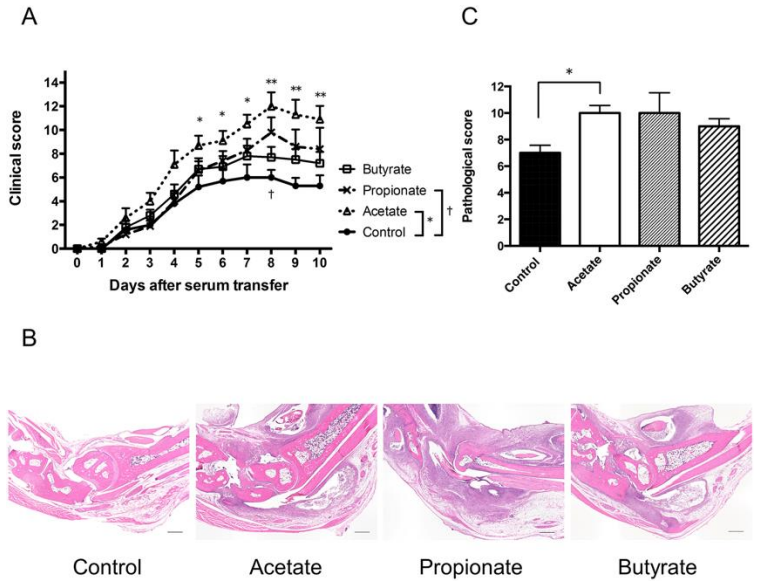


SCFA and high fiber diet ameliorates disease in mouse models of arthritis

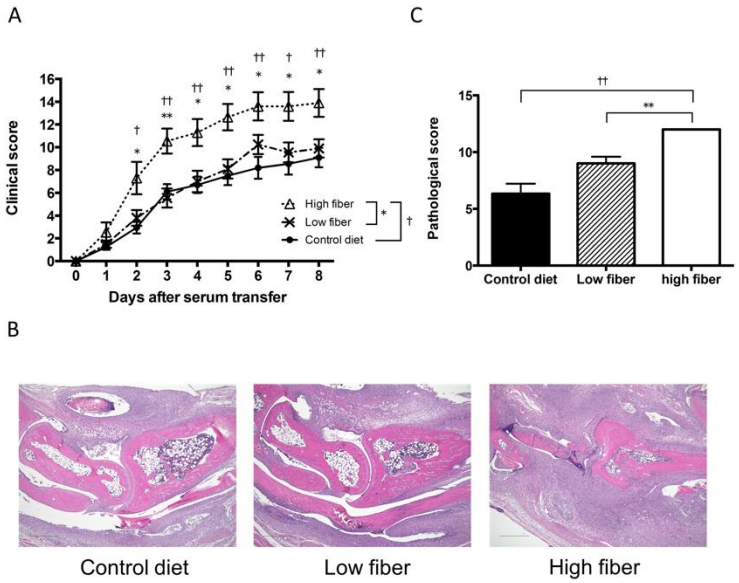
SCFA ameliorates collagen induced arthritis (CIA)



SCFAs onK/BxN mouse serum–induced arthritis.



High-fiber diet on K/BxN mouse serum–induced arthritis.

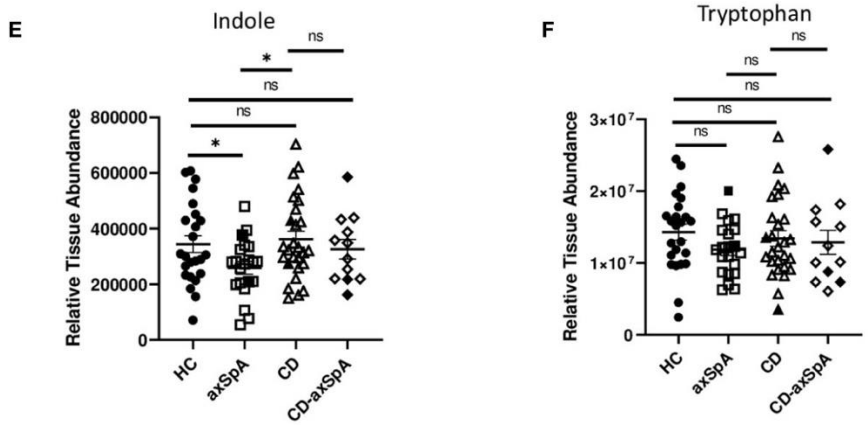


Mizuno M, Noto D, Kaga N, Chiba A, Miyake S . *PLOS ONE* 2017

Altered metabolic profile in axial spondyloarthritis patients

Multi ‘Omics Analysis of Intestinal Tissue in Ankylosing Spondylitis Identifies Alterations in the Tryptophan Metabolism Pathway

Berlinberg, *Front. Immunol*, 2021

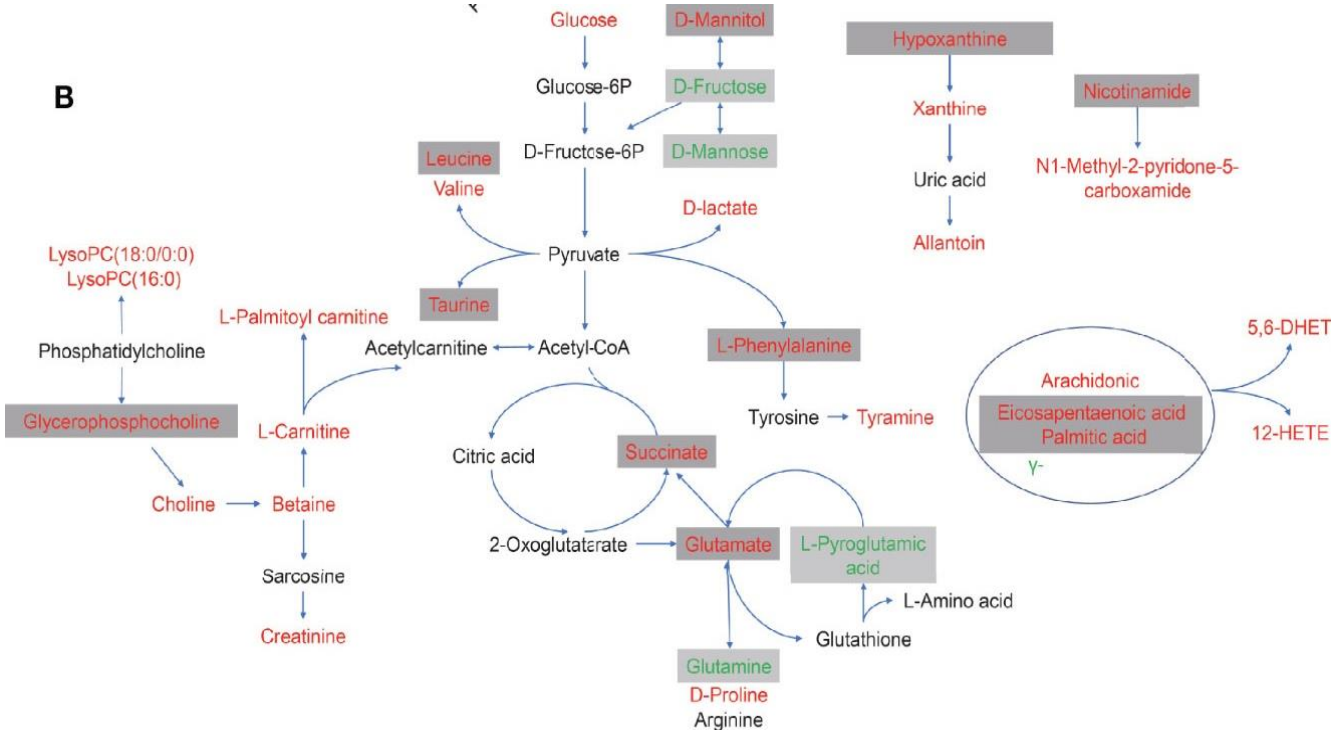


Fecal metabolomics in pediatric spondyloarthritis implicate decreased metabolic diversity and altered tryptophan metabolism as pathogenic factors.

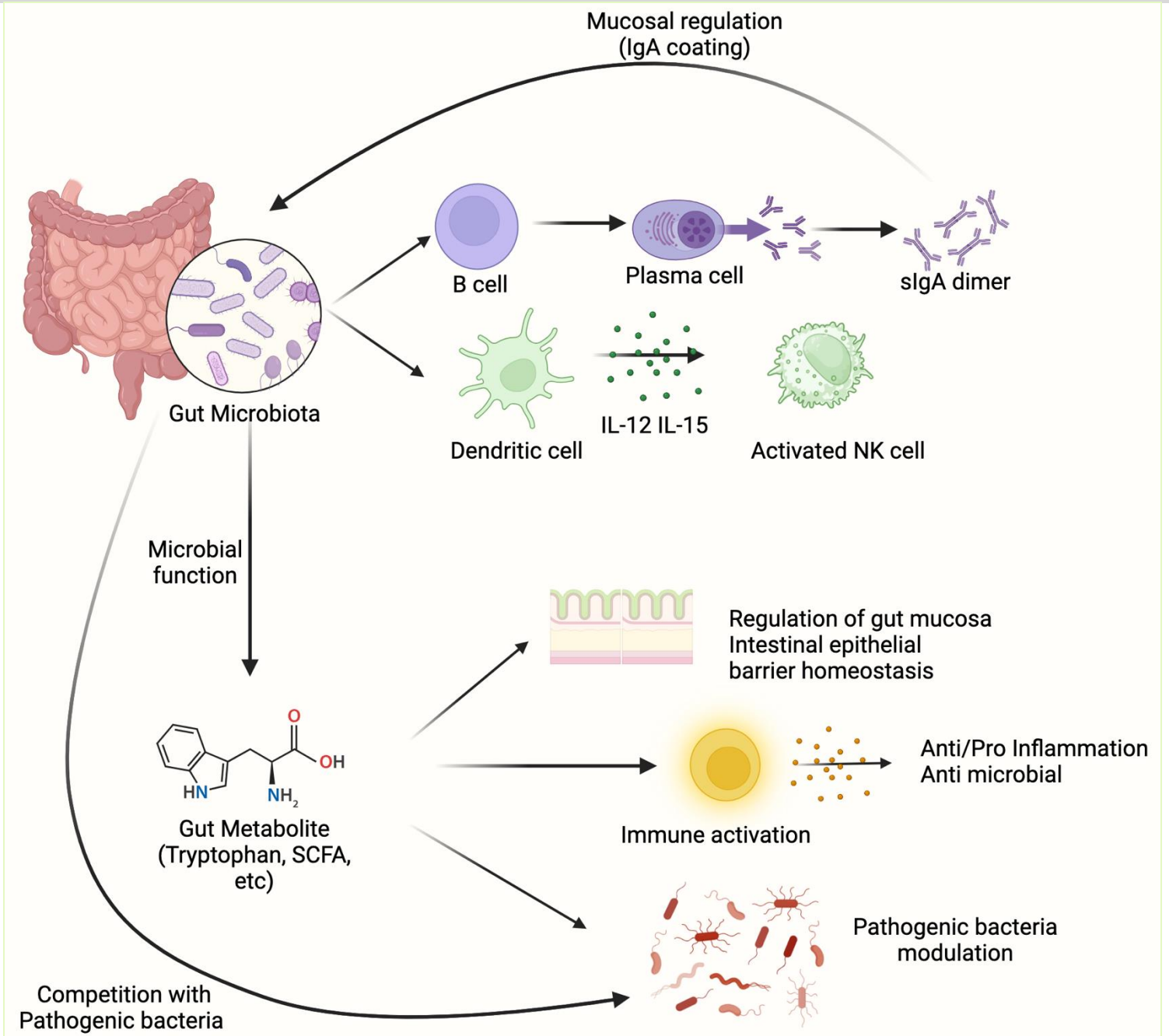
Stoll, Genes Immun. 2016.

Serum Metabolomics Signatures Associated With Ankylosing Spondylitis

Ou, *Front Immunol*, *2021*



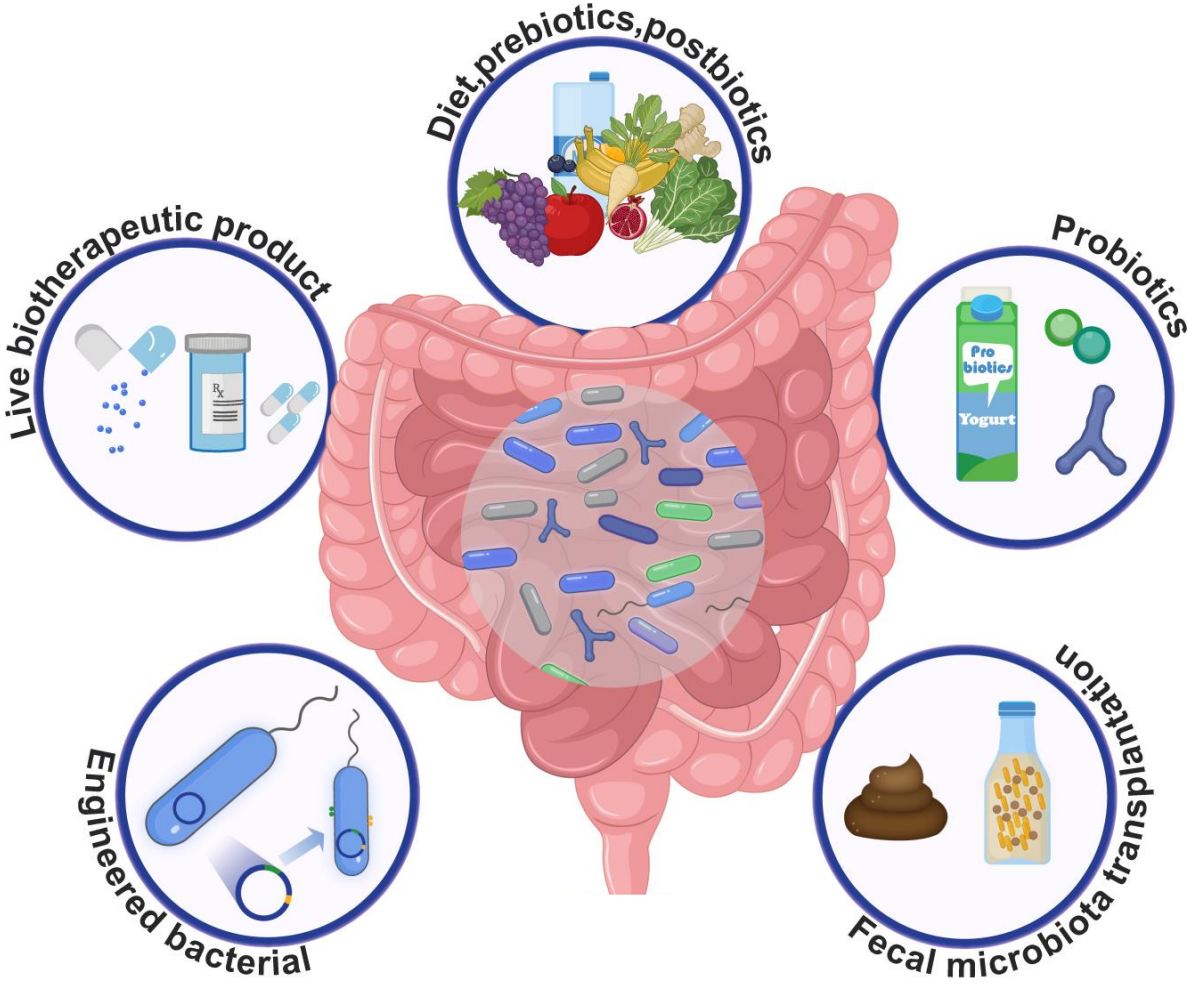
Role of gut microbial dysbiosis in the pathophysiology of spondyloarthritis



Gill, Unpublished

Figure made in Biorender

Strategies to modify gut microbiota for disease treatment



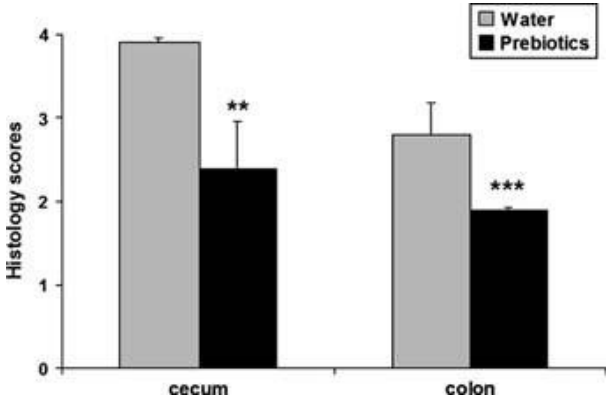
Hou, K., *et al. Sig Transduct Target Ther* 2022

Clinical implications of microbial modulation as therapeutic target

1. Prebiotics and Probiotics

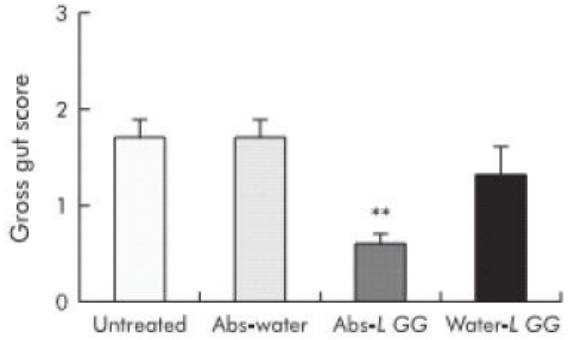
Reduction of Colitis by Prebiotics in HLA-B27 Transgenic Rats Is Associated with Microflora Changes and Immunomodulation

Hoentjen, *Inflammatory Bowel Diseases*, 2005



Lactobacillus GG prevents recurrence of colitis in HLA-B27 transgenic rats after antibiotic treatment

Dieleman, *Gut* 2003



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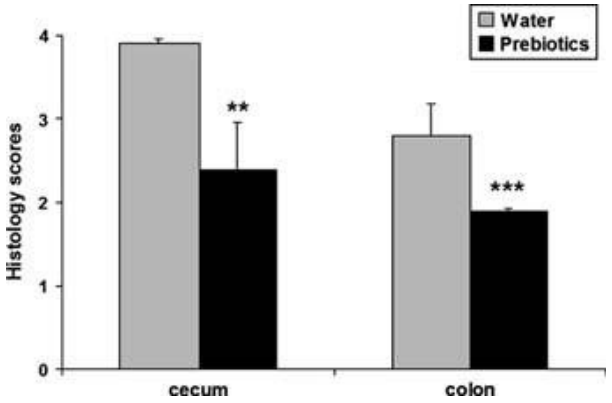

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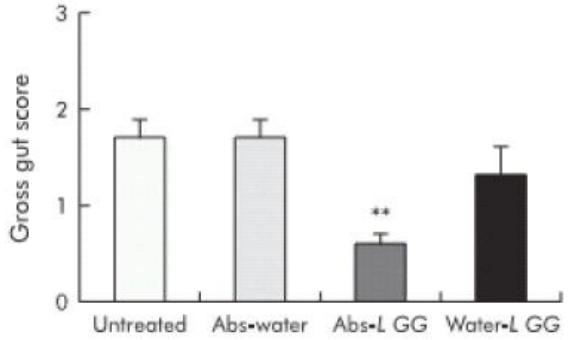

Probiotic Therapy for the Treatment of Spondyloarthritis: A Randomized Controlled Trial

Jenks, *J Rheumatol* 2010

Did not observe disease modulation with probiotics

Spore-Based/Mineralized Probiotics

- resistant to stomach acid, bile acids, and digestive enzymes.
- reach the large intestine alive, transform and colonize gut.

Future implications of microbial modulation as therapeutic targets

Spore-Based Probiotics

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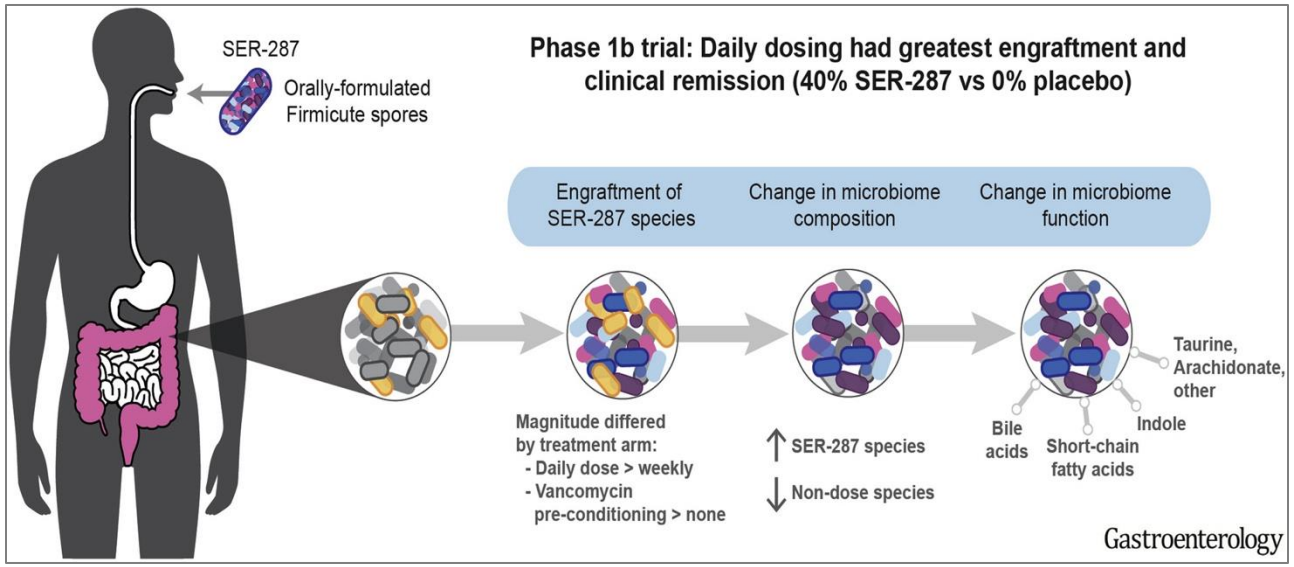
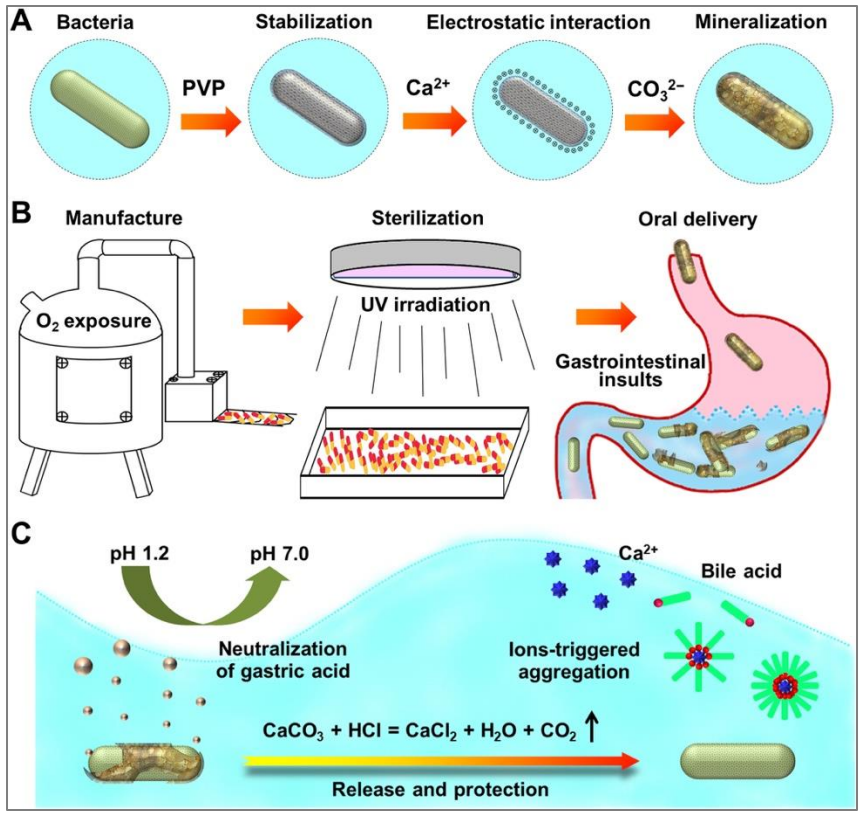


Henn, *Gastroenterology,* 2021

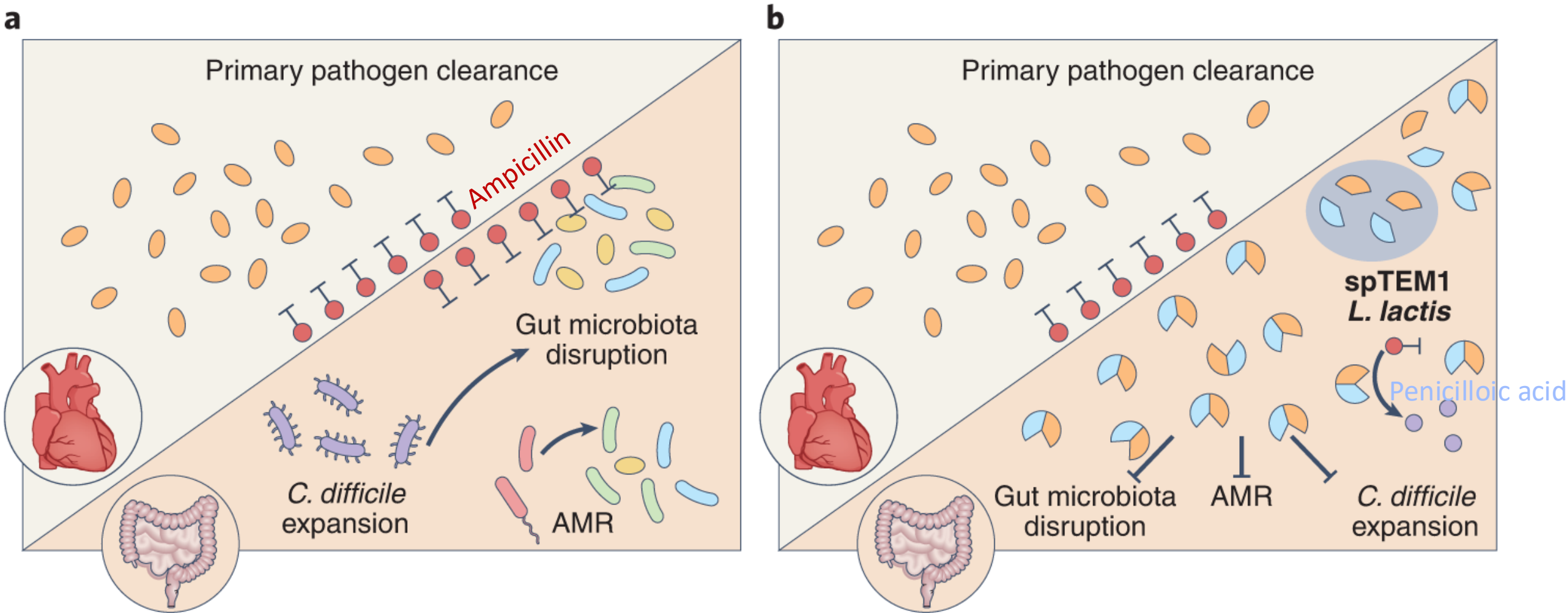
Mineralized Probiotics

- Mineral coating on the surface
- Neutralization of gastric acid, adaptable release of coated bacteria,
- double-decomposition reaction of mineral coating in the gastrointestinal tract following oral ingestion.



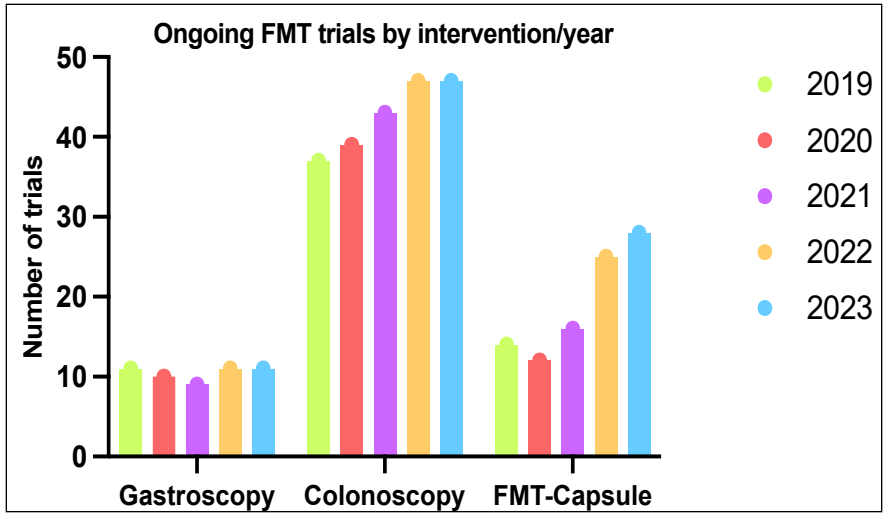
Zhongmin, *Sci. Adv* 2023

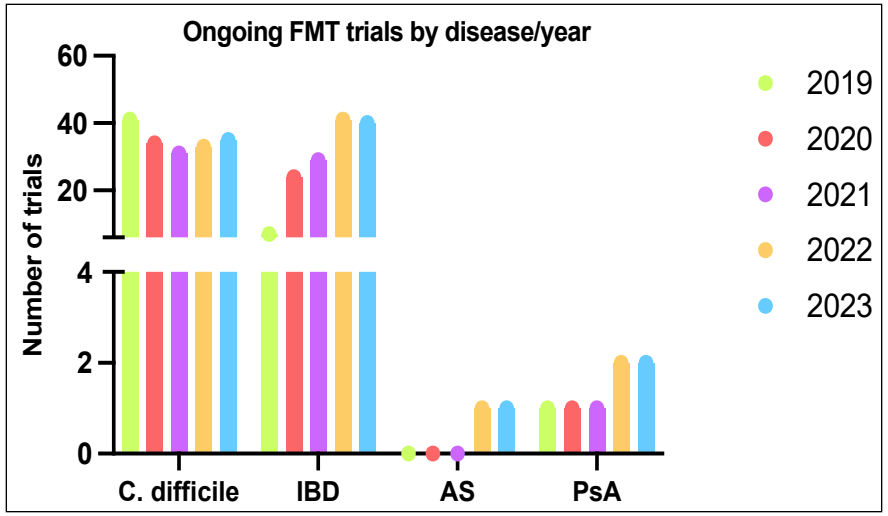
Engineered live biotherapeutic for the prevention of antibiotic-induced dysbiosis

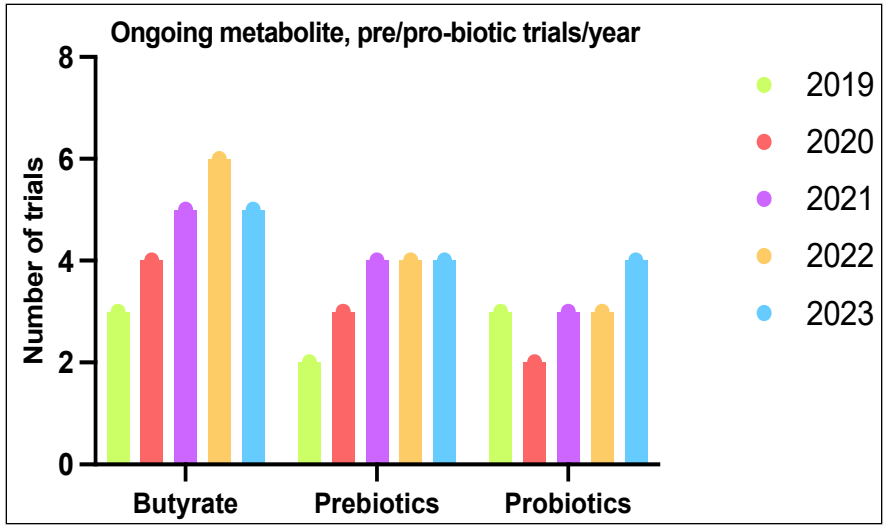


Cubillos-Ruiz, *et al*. *Nat. Biomed. Eng* 2022.
Olson & Turnbaugh. *Nat Microbiol* 2022.

Fecal microbiota transfer: lessons from clinical trials







Gill, *unpublished data*

Fecal microbiota transfer: lessons from clinical trials

- **Refined Fecal Microbiota Transplantation (FMT) for Ulcerative Colitis (UC) (REFOCUS):** NCT04968951
  To determine whether FMT delivered via oral capsules can induce clinical remission in patients with mild to moderate ulcerative colitis.

- **Fecal Microbial Transplantation for Rheumatoid Arthritis Trial (FeMiTRA):** NCT05790356
  Investigate the effects of capsules containing stool from healthy donors, in rheumatoid arthritis patients.

- **FMT for Remission of Active Ulcerative Colitis in Adults:** NCT04202211
  To establish the safety and effectiveness of lyophilized FMT for treating ulcerative colitis (UC) in adults.

- **Efficacy and Safety of Fecal Microbiota Transplantation in Peripheral Psoriatic Arthritis (FLORA):** NCT03058900
  To explore clinical aspects associated with modifying the intestinal microbiota by infusing fecal donor microbiota into the small intestine of psoriatic arthritis patients.

- **Early FMT for C. difficile:** NCT02465463
  Patients in the experimental arm underwent a fecal microbiota transplant (FMT) after finishing a course of antibiotics.

- **Safety and Efficacy of Faecal Microbiota Transplantation in Treatment-naïve Patients With Newly Diagnosed Chronic Inflammatory Diseases (FRONT)-Denmark:** NCT04924270
  - To explore clinical efficacy aspects, safety, and patient acceptability associated with capsule FMT performed in newly diagnosed, untreated patients with chronic inflammatory rheumatic-, dermatological-, gastrointestinal- and pulmonary diseases.

Clinical implications of microbial modulation as therapeutic target

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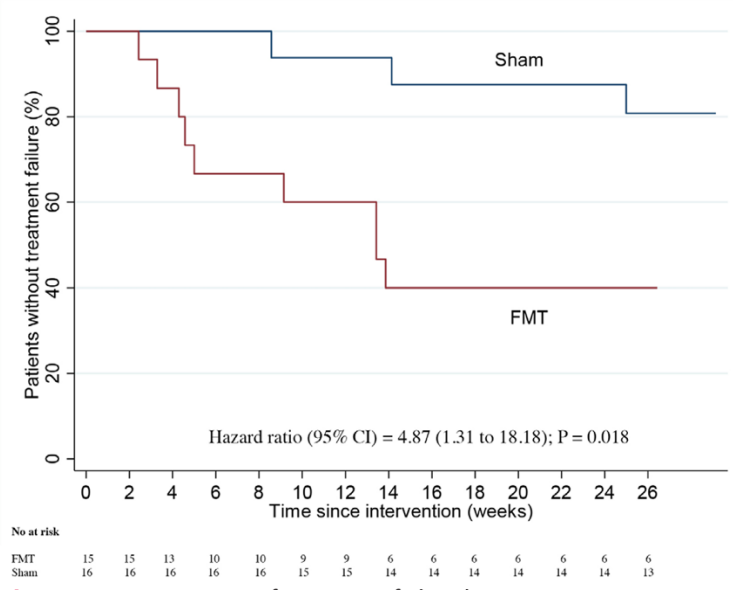
  Kragsnaes, Ann Rheum Dis, 2021



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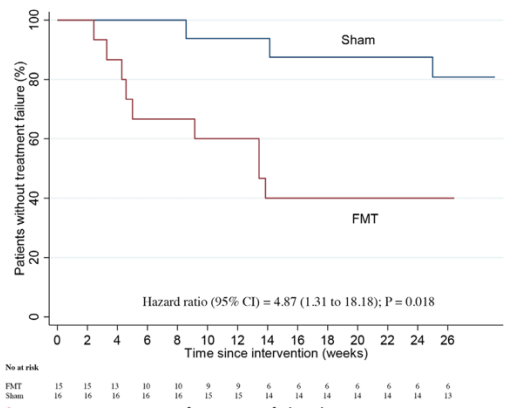
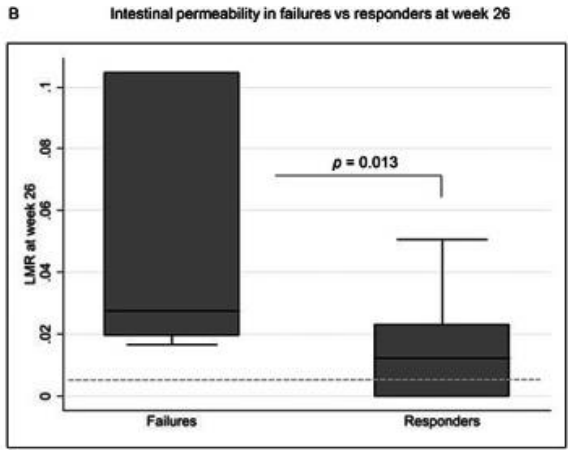
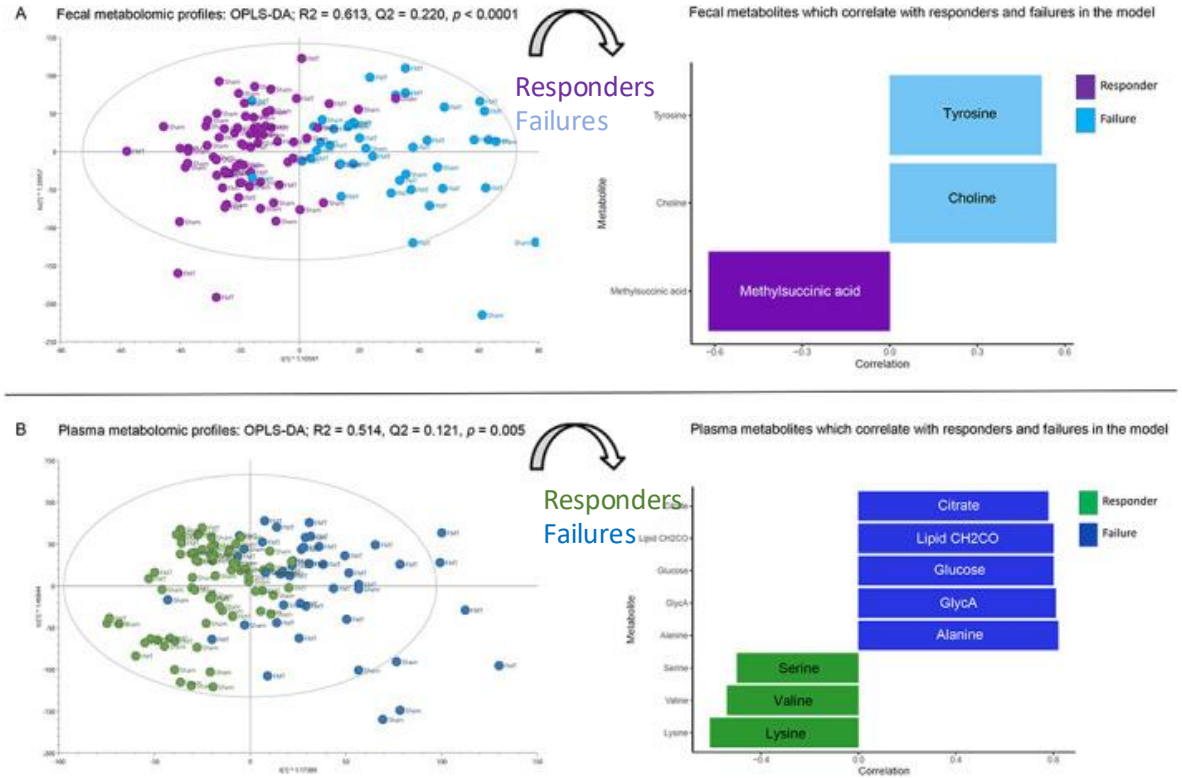


Small intestinal permeability and metabolomic profiles associate with clinical response in psoriatic arthritis patients

Kragsnaes, *ACR Open*, 2023





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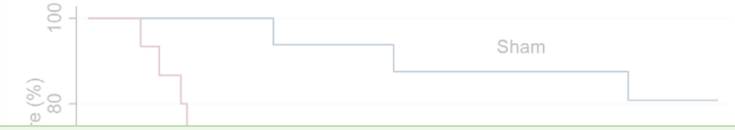

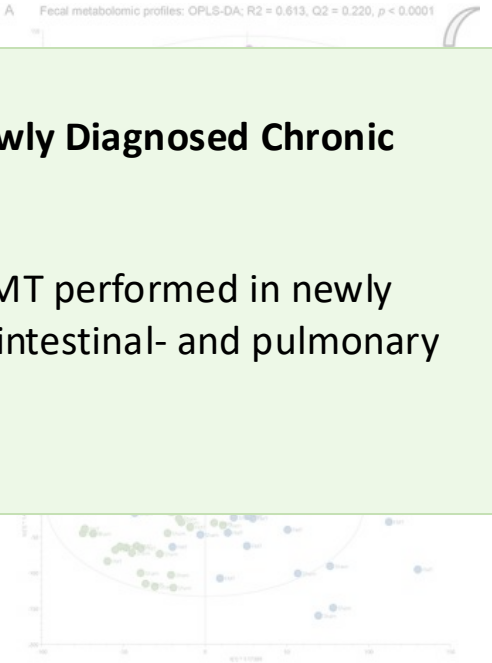

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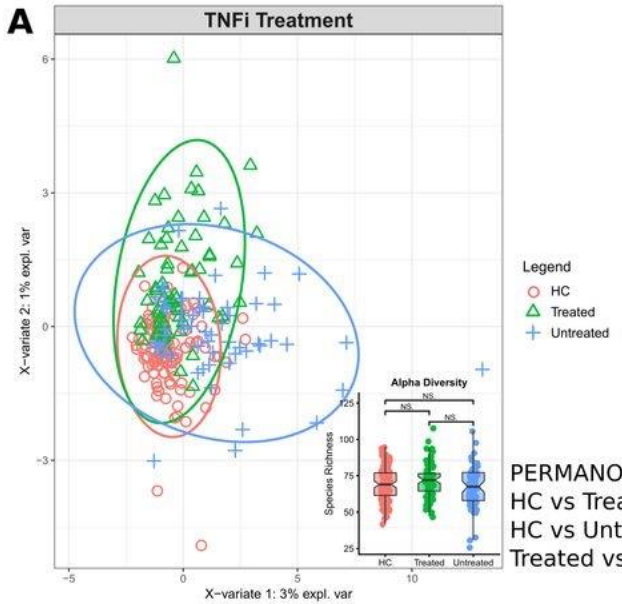
Maja Kragsnaes and Torkell Ellingsen

Clinical implications of microbial modulation as therapeutic target

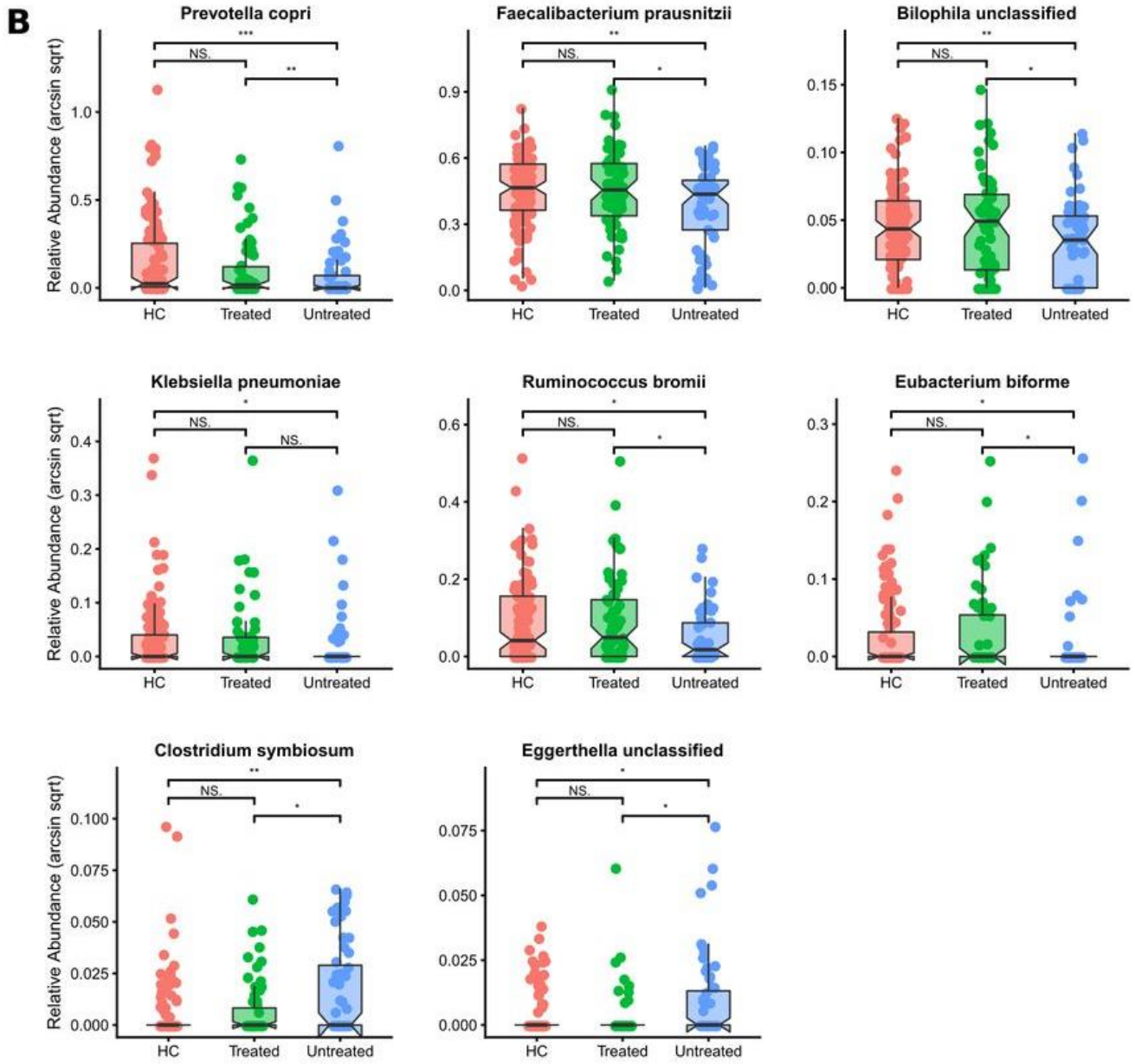
3. Biologics

TNFi therapy in AS patients was correlated with restoration of the perturbed microbiome, highlighting a potential mechanism of action



PERMANOVA
HC vs Treated: P = 0.069
HC vs Untreated: P = 0.0002
Treated vs Untreated: P = 0.0215

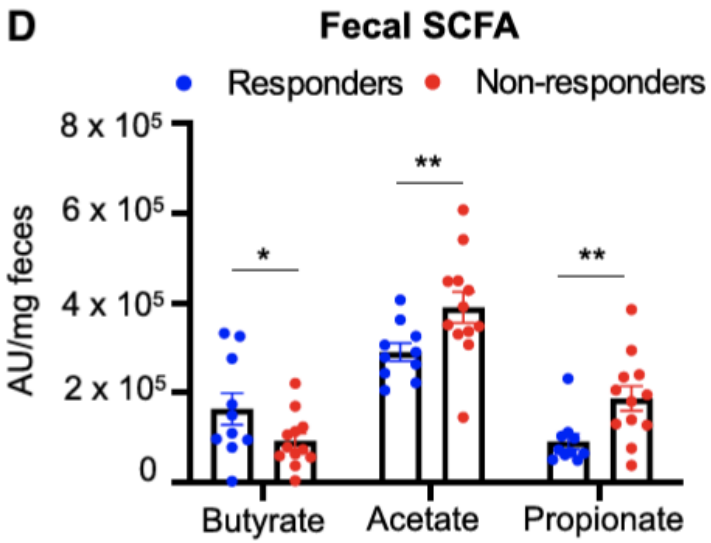
Metagenomic analysis

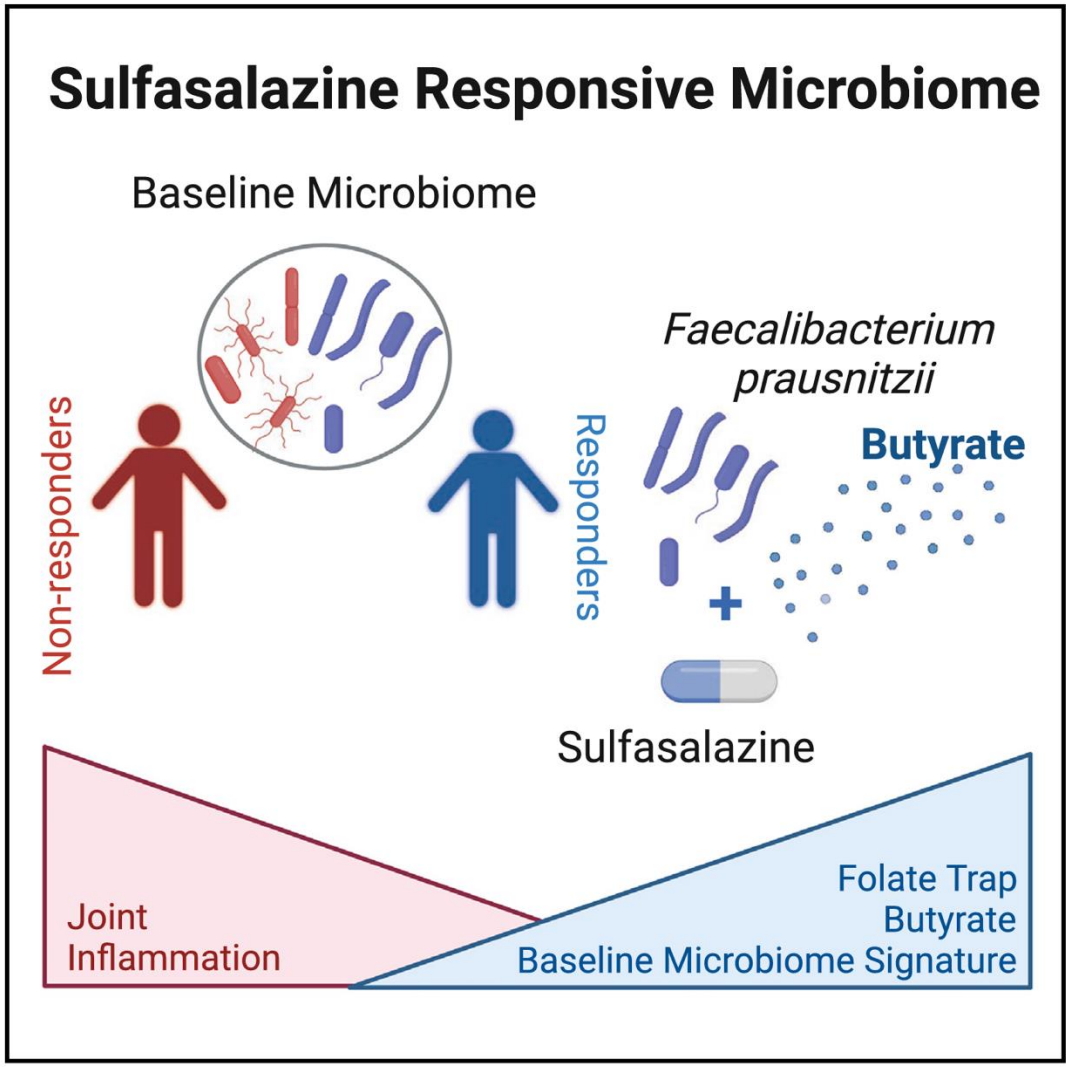


Yin, Arth Rheum Disease 2020

The gut microbiome regulates the efficacy of sulfasalazine therapy for IBD-associated SpA

- IBD-SpA subjects that respond to sulfasalazine therapy have a distinct gut microbiome
- The responder microbiome is enriched in *F. prausnitzii* and butyrate
- Sulfapyridine promotes butyrate production by F. prausnitzii, which limits colitis
- F. prausnitzii restores response in mice with non-responder microbiomes

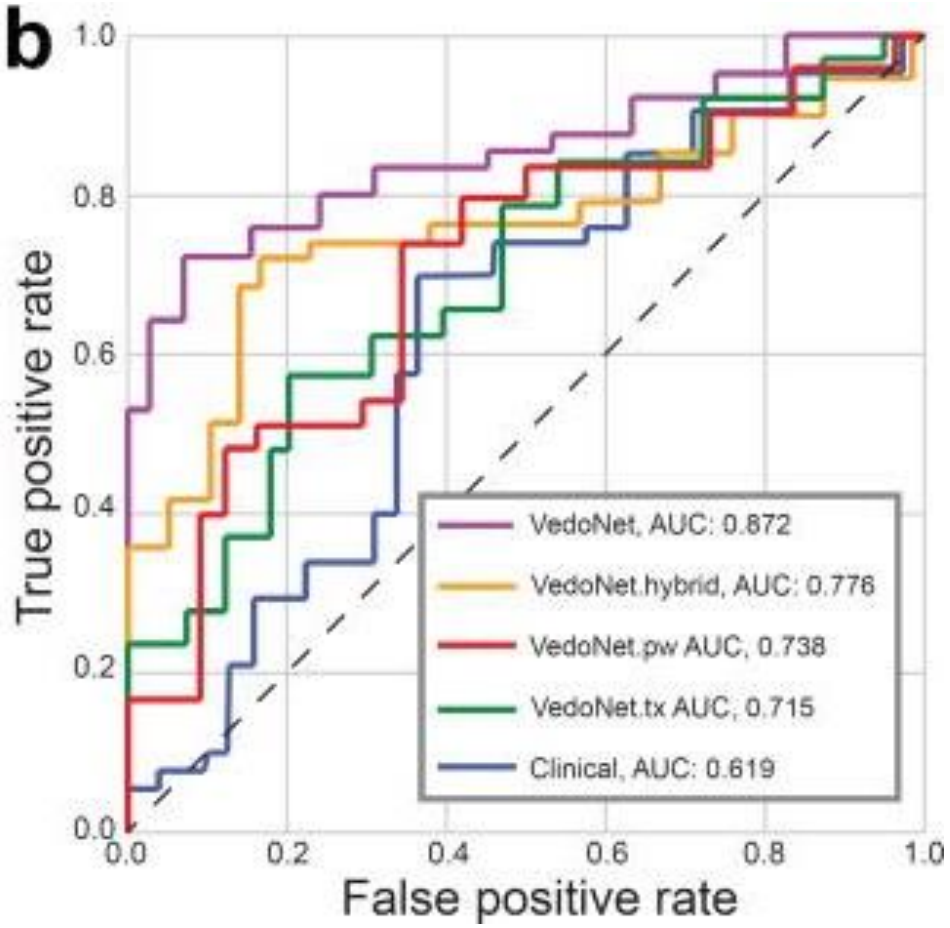




Lima, *Cell Reports Medicine*, 2024

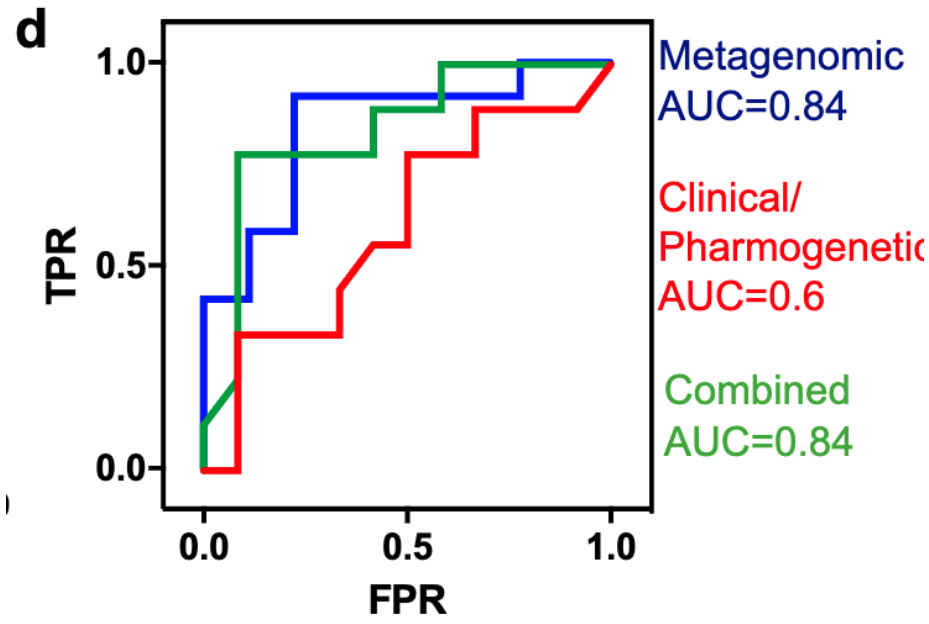
Future implications of microbial modulation as therapeutic target

1. Gut microbiome function as a predictor of treatment response



Vedolizumab in IBD

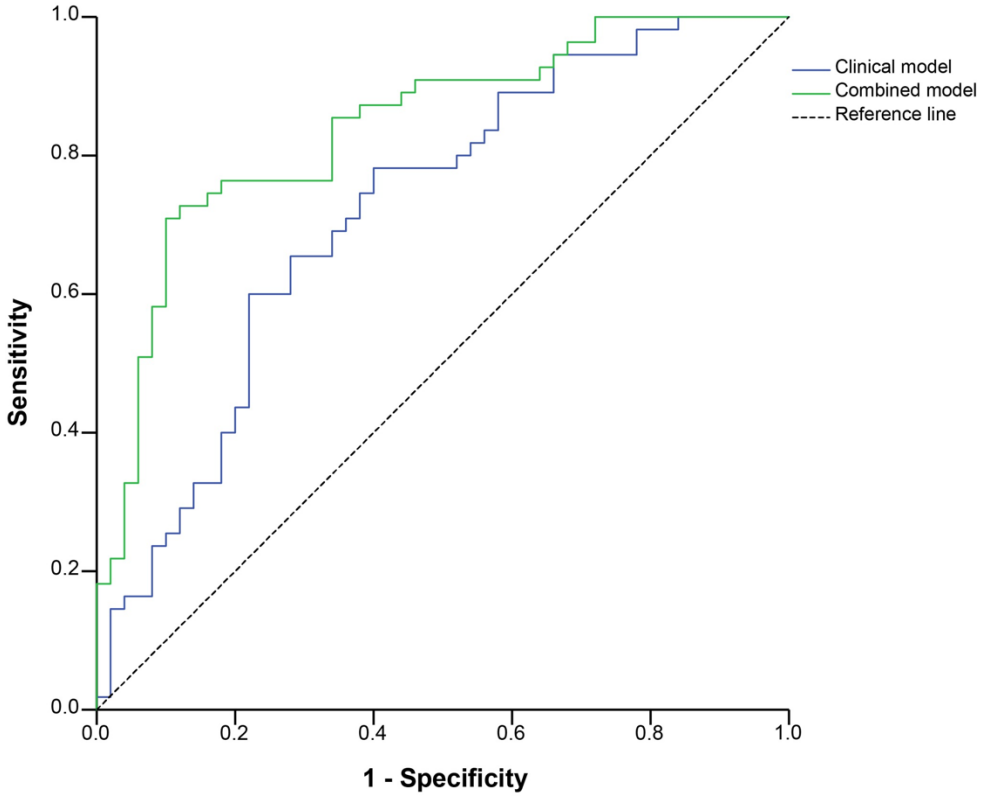
Ananthkrishnan, Cell Host & Microbe, 2017



Methotrexate in RA

Artacho et al., *Arthritis Rheumatol.* 2021

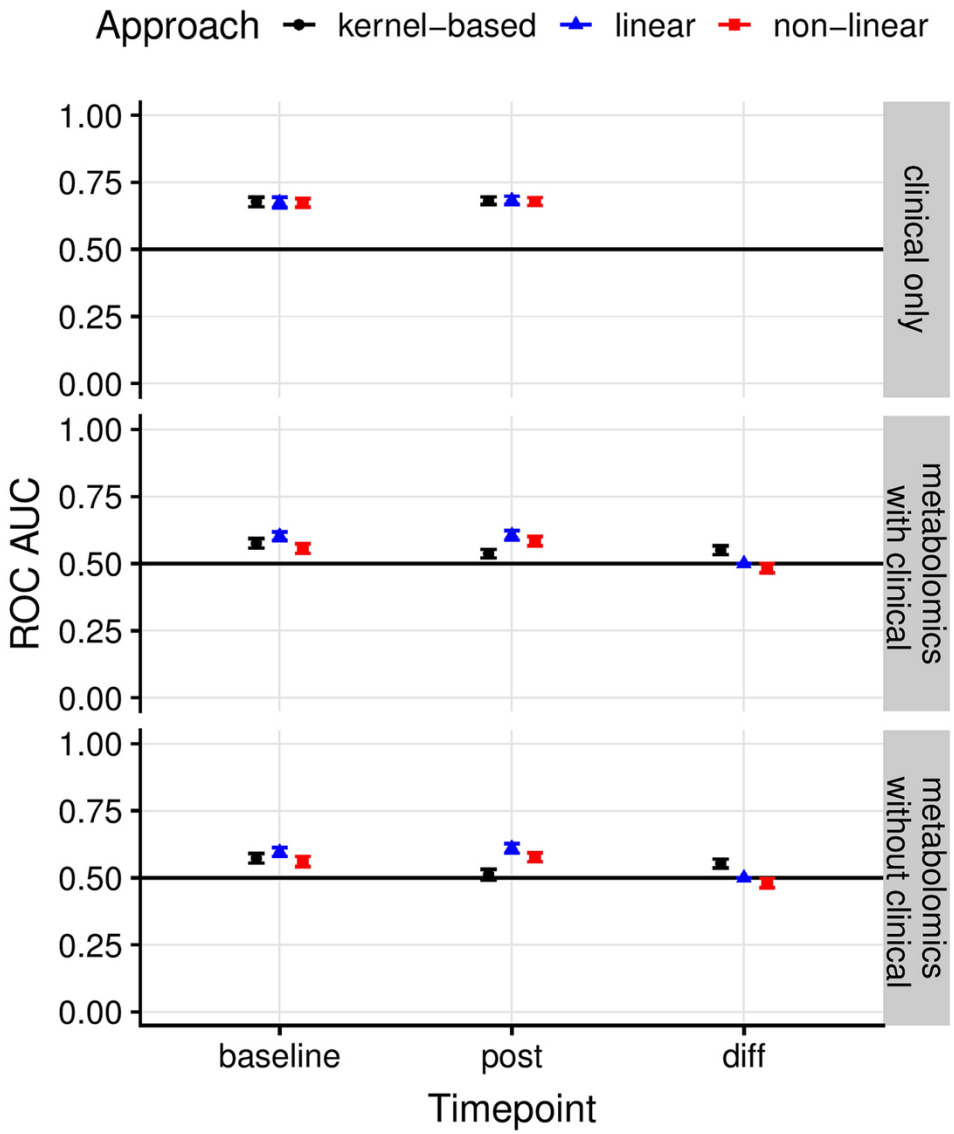
Inflammatory metabolomic profile to predict response to TNF-α inhibitors in RA



ROC curves of clinical and combined model between good- and non-responder to TNFi.

Cuppen, 2016 *Plos ONE*

Prediction of response of methotrexate in RA patients using serum lipidomics



Maciejewski, 2021 *Sci Reps*

Limitations in implicating gut microbial dysbiosis as driver in SpA pathogenesis

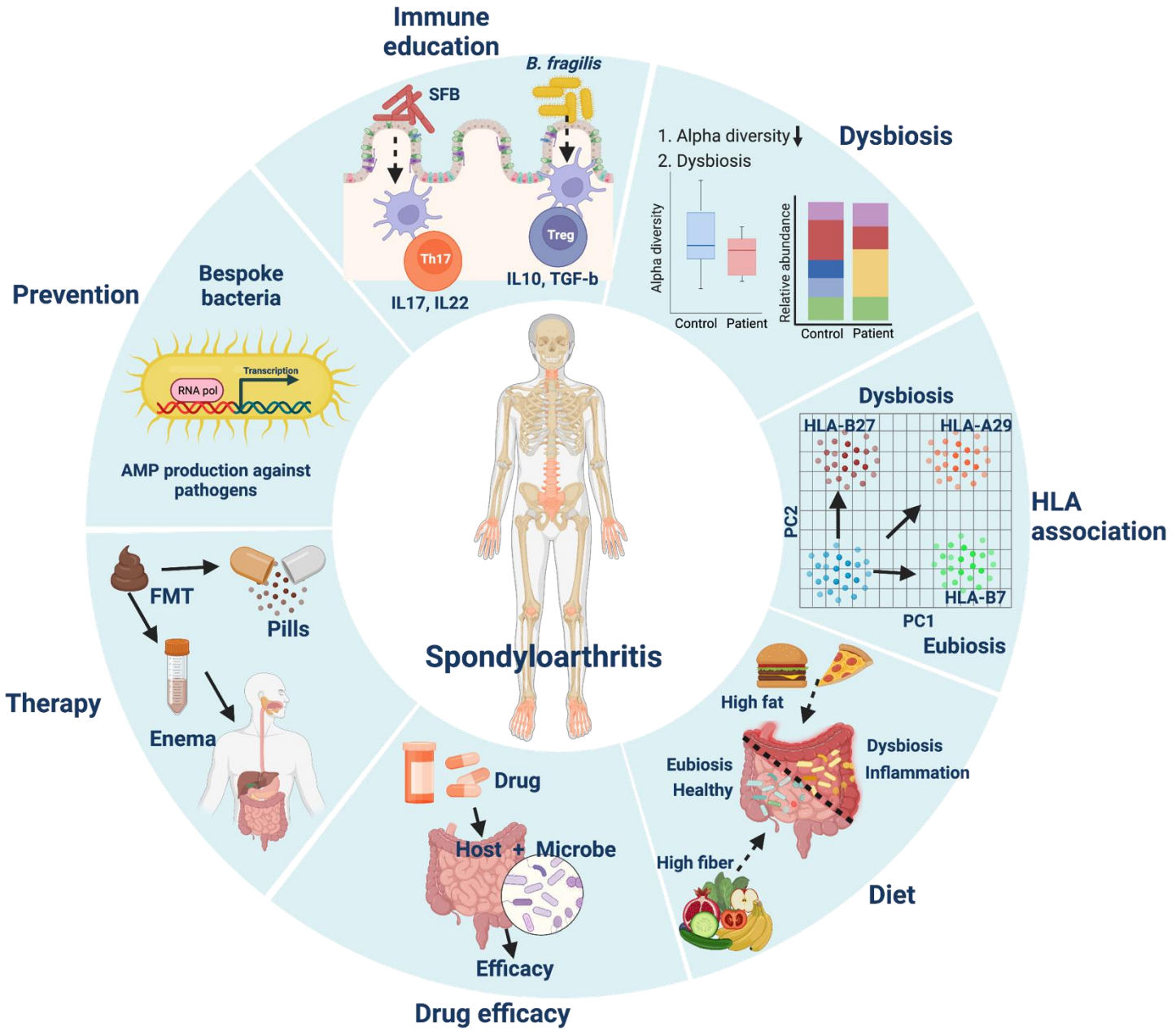
- *Gut microbiota is difficult to characterize*
  We know about bacteria, what about fungi and viruses and their interactions?

- *Definition of a healthy gut microbiota*
  Gut microbiome varies in all individuals (diet, environment, genetics etc.), thus it is hard to define

- *Hard to establish causal links*
  Cause and effect is difficult to establish (e.g. microbial function redundancy)

- *Therapies and complex and outcomes are hard to measure*
  FMT (complex microbial community) establishment in recipient is dependent on diet, host genetics, gut microenvironment etc.

Microbial implication in spondyloarthritis pathogenesis and treatment



Adapted from Rosenbaum

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Kimberly Ogle

Past members
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Manuel Rodriguez
Henry Bringenberg
Claire Ramirez
John Davis
Emma Faye-Olsen

Spondylitis Association of America™

SPARTAN
Spondyloarthritis Research and Treatment Network

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

OHSU

Pacific Northwest National Laboratory

The Collins Foundation

Medical Research Foundation

Thank You !!