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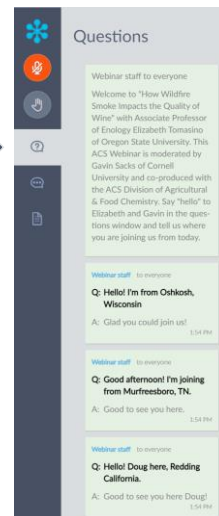
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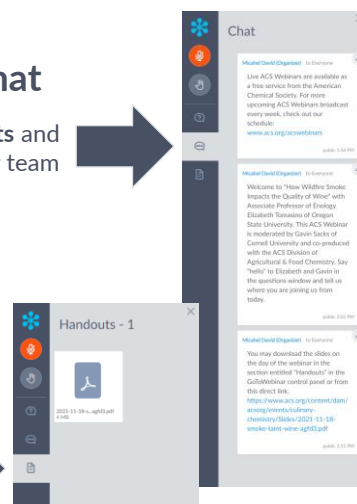


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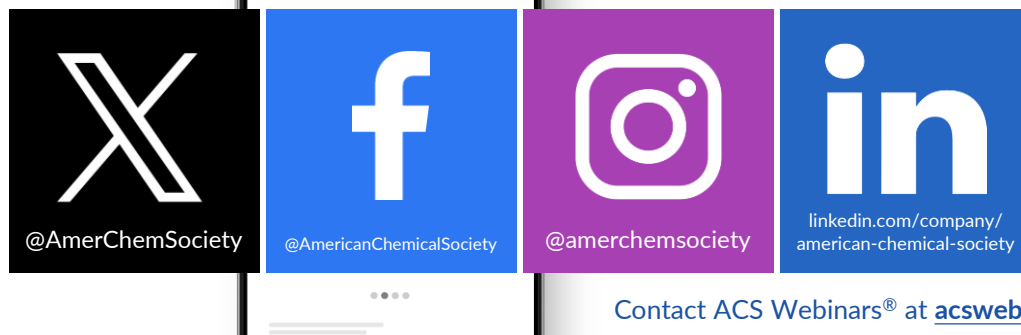


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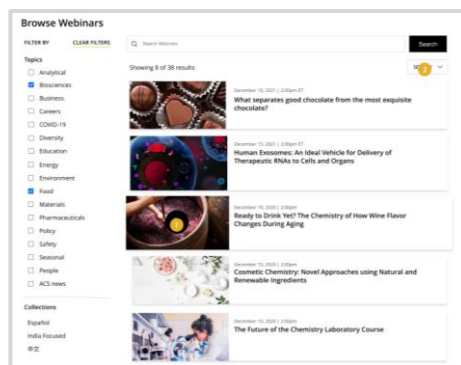
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Hanin Sarhan, Bridge Fellow at Indiana University

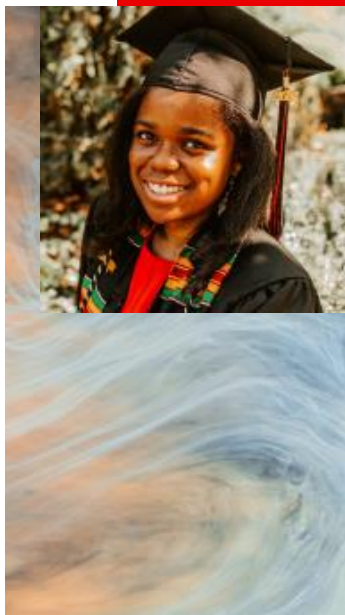
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ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
(Chemical-biological Engineering, Computer Science & Molecular Biology)



“The ACS Scholars Program provided me with monetary support as well as a valuable network of peers and mentors who have transformed my life and will help me in my future endeavors. The program enabled me to achieve more than I could have ever dreamed. Thank you so much!”

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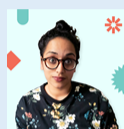
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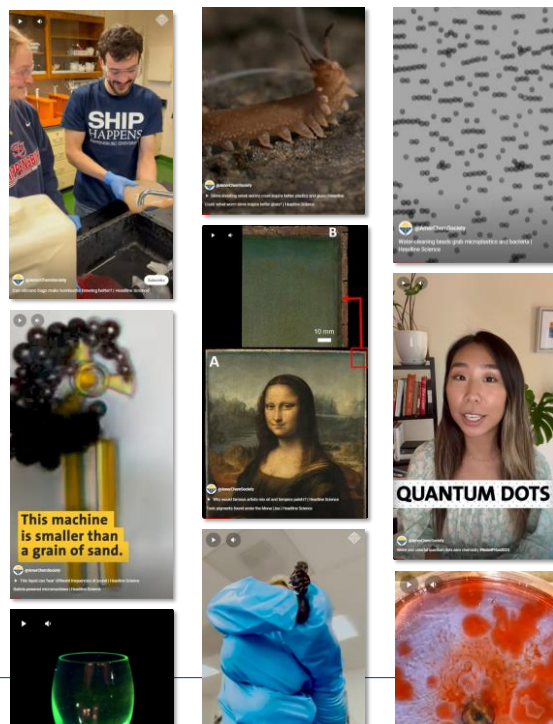
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Personal Career Consultations

Jim Tung
 Consulting
 Lacamas Laboratories
 S.S., Biochemistry, University of Oregon
 Ph.D., Organic Chemistry, University of Notre Dame

Jim Tung works at Lacamas Laboratories in Portland, OR, currently as a business development manager. He has been with Lacamas for 10 years, working on developing new chemical manufacturing projects. Before that, he was a senior research chemist at Glaber Research in Champaign, IL, performing kilo-scale organic chemistry.

An Oregon native, Jim got his B.S. in biochemistry from the University of Oregon, his Ph.D. in organic chemistry from the University of Notre Dame, with postdoctoral experience at Pfizer's laboratories in La Jolla, CA. He is past chair of the Portland Section of the American Chemical Society and was 2019 general co-chair of NORM 2019. He has interests in process chemistry, labor economics, social media outreach and encouraging career exploration and development for younger chemists.

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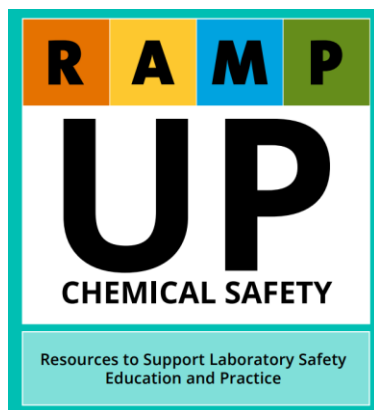
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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect



Resources

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ACS Publications DEIR Hub See what ACS Publications is doing for fostering inclusivity in scholarly publishing →	ACS Volunteer and ACS Meetings Code of Conduct Fostering a positive and welcoming environment for attendees, volunteers and staff. →
C&EN Trailblazers C&EN highlights scientists from different backgrounds who are making an impact in chemistry. →	NEW! Download DEIR Educational Resources Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics. →
Quick Guide: Inclusion Moments Learn more about what Inclusion Moments are and see ideas to host them during your meetings. →	Quick Guide: How to host inclusive in-person events Recommendations and best practices to ensure that your events can accommodate everyone. →

Diversity, Equity, Inclusion, and Respect

**Adapted from definitions from the Ford Foundation Center for Social Justice:

Equity**

Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**

The representation of varied identities and differences (race, ethnicity, gender, disability, sexual orientation, gender identity, national origin, tribe, caste, socio-economic status, thinking, and communication styles, etc.) collectively and as individuals. ACS seeks to proactively engage, understand, and draw on a variety of perspectives.

Inclusion**

Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect

Ensures that each person is treated with professionalism, integrity, and ethics underpinning all interpersonal interactions.

<https://www.acs.org/diversity>

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Microbiome Mechanics: Building a Healthier Gut



JORDAN BISANZ, PhD

Assistant Professor, Biochemistry and
Molecular Biology, Pennsylvania State
University and the One Health
Microbiome Center



MARCOS PIRES, PhD

Director of Graduate Studies and
Associate Professor, Chemistry,
University of Virginia



JAN CLAESEN, PhD

Assistant Professor, Lerner Research
Institute, Cleveland Clinic and Assistant
Professor, Molecular Medicine, Case
Western Reserve University



CATHERINE LEIMKUHLER
GRIMES, PhD

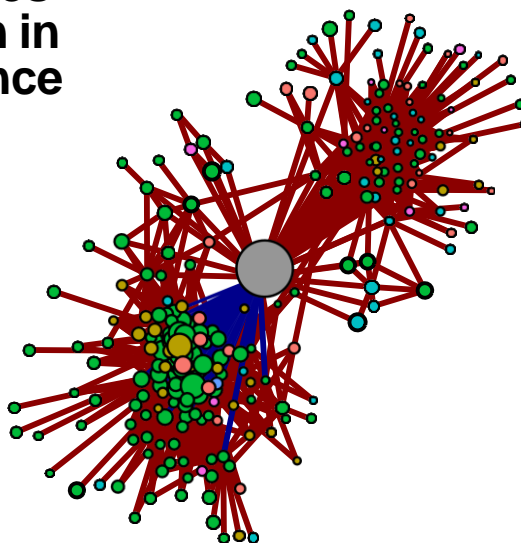
Co-Director, Chemistry Biology
Interface Graduate Program and
Professor, Department of Chemistry &
Biochemistry, University of Delaware

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A synthetic microbiota designed through meta-analysis provides insight to community function in *Clostridioides difficile* resistance



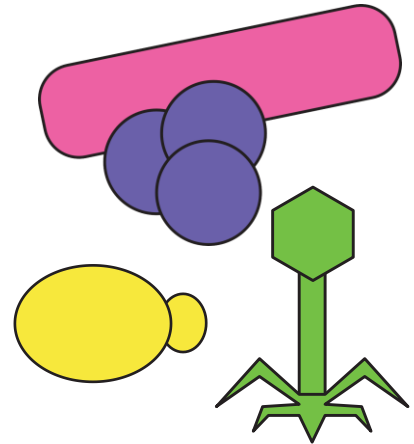
Jordan Bisanz PhD
Biochemistry and Molecular Biology
One Health Microbiome Center
Pennsylvania State University

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Challenges in translating microbiome science

1. What defines a healthy microbial community?
2. Does a singular healthy microbiota exist?
3. What are the mechanisms that drive health?
4. How can we design functional microbial communities?

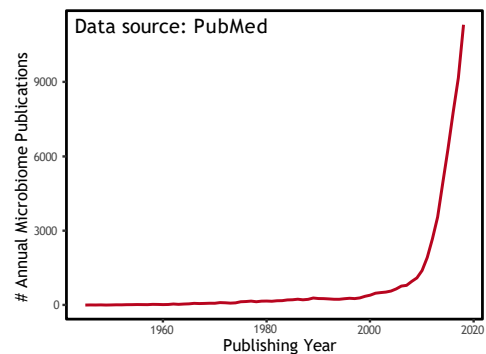
Proposed solution: meta-analysis



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Microbiome meta-analysis

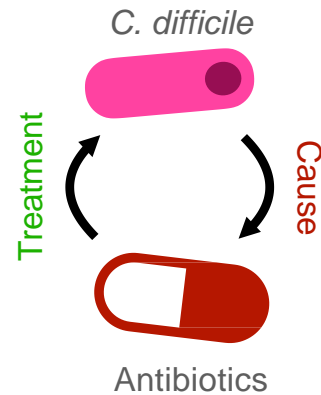
- >10 years of high throughput microbiome data in public repositories
- Not all of it is useful, but it allows for studying the human microbiome across populations and disease states
- MAGs have become an incredibly powerful tool for microbiome research
- Is there more we can learn from this data in aggregate?



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Clostridioides difficile

- Opportunistic pathogen causing spectrum of disease
- Normally suppressed by healthy gut microbiome and triggered by antibiotics
- Treatment frequently followed by recurrent infection
- ~1/2 million annual infections in US and on the rise costing billions
- Fecal transplant has proven effective but has limitations



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Fecal transplant alternatives

- Fecal transplants are highly efficacious but:
 - May carry MDR pathogens
 - May have undesirable off-target effects
 - Rely on human donors -> intrinsically irreproducible composition
- Can we rationally design a synthetic fecal microbiome transplant (sFMT) alternative?
 - **But what organism(s) should we put in it?**

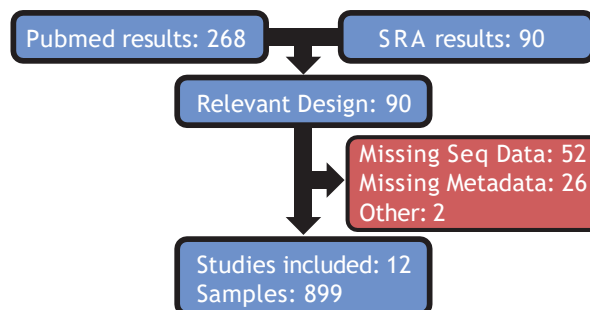


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I. Design of Synthetic Communities

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C. difficile meta-analysis

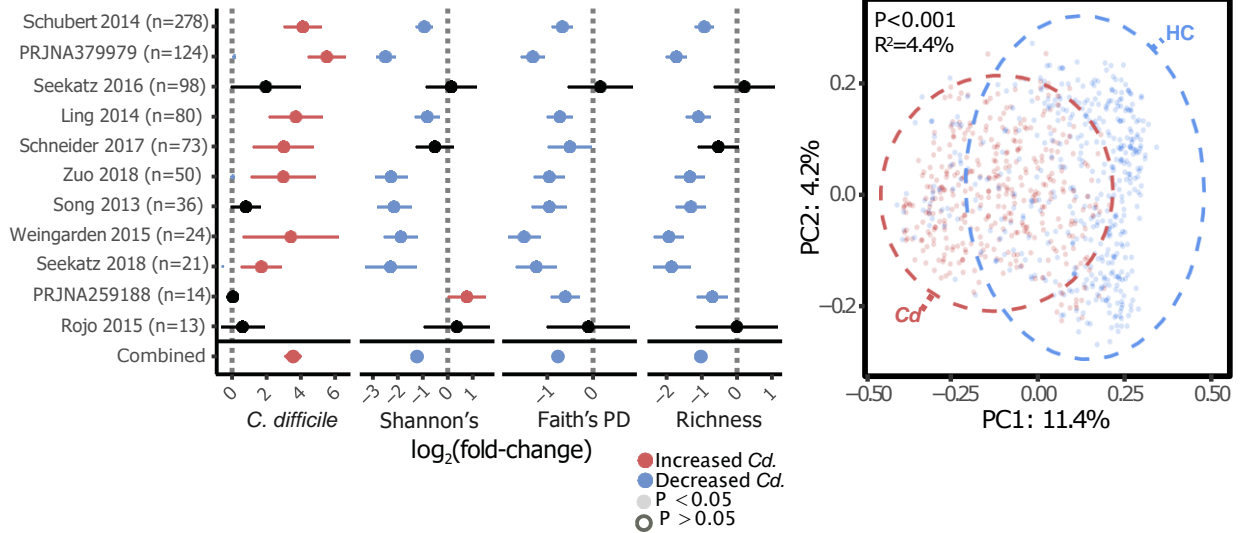


Susan Tian
BMMB Grad Student

Goal: Identify the organisms most robustly anti-correlated with *C. difficile* colonization

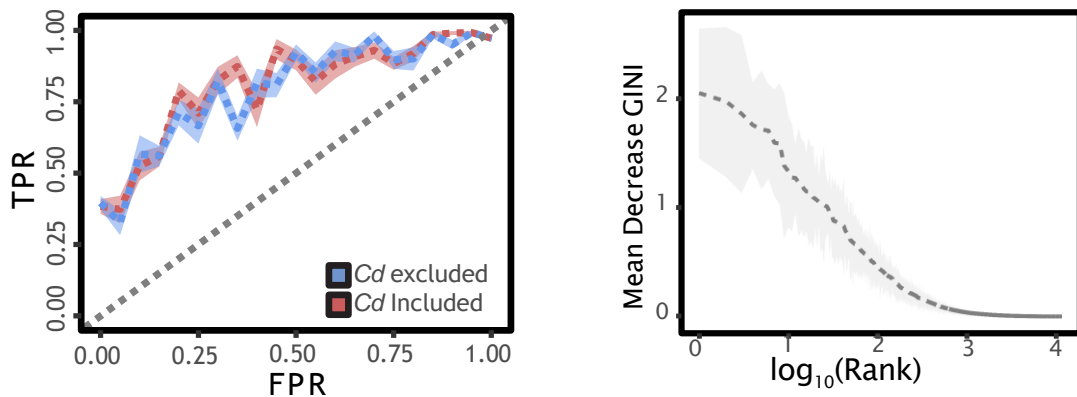
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Altered community composition with *C. difficile*



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Random Forest model training

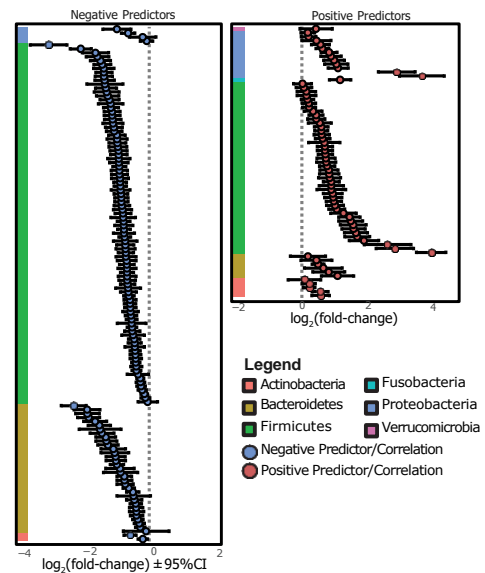


- Accurate predictions of *C. difficile* colonization in external validation studies (AUROC=0.81±0.2)
- ~200 features (organisms) with predictive ability

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Predictive taxa

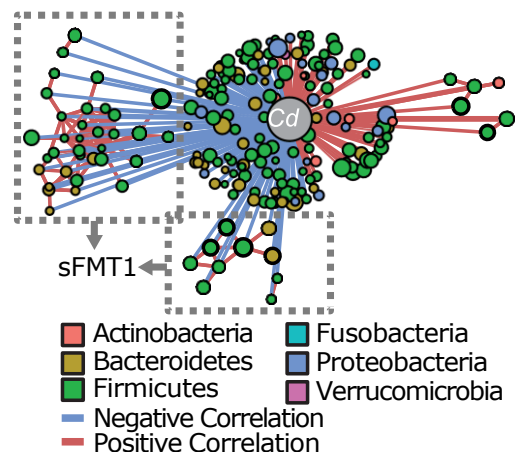
- Predictive taxa are enriched for negative predictors
- Predictive taxa cover a broad phylogenetic range
- *Clostridium scindens*, a known inhibitor of *C. difficile* is not predictive of *C. difficile* colonization *in vivo*



35

Identifying taxa for synthetic community

- Features anti-correlated with *C. difficile* are correlated with each other:
 - Evidence that they will form a stable community?
- We constructed:
 - **sFMT1**: 37 pure culture strains anti correlated with *C. difficile*
 - **sFMT1+Cd**: sFMT1 with *C. scindens*
 - **ProCd**: 25 pure culture strains positively associated with *C. difficile*

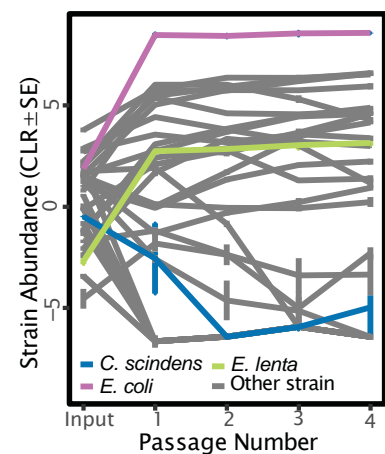
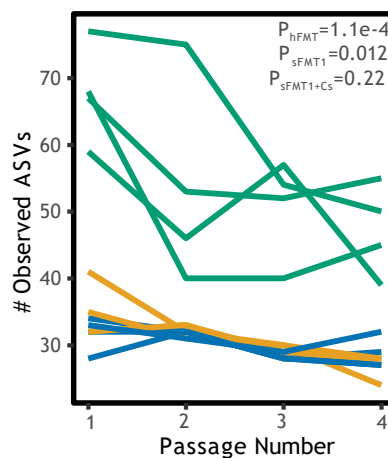
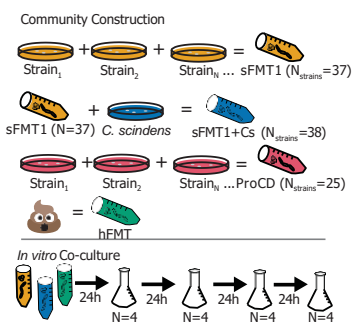


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II. Characterizing Community Assembly and Function

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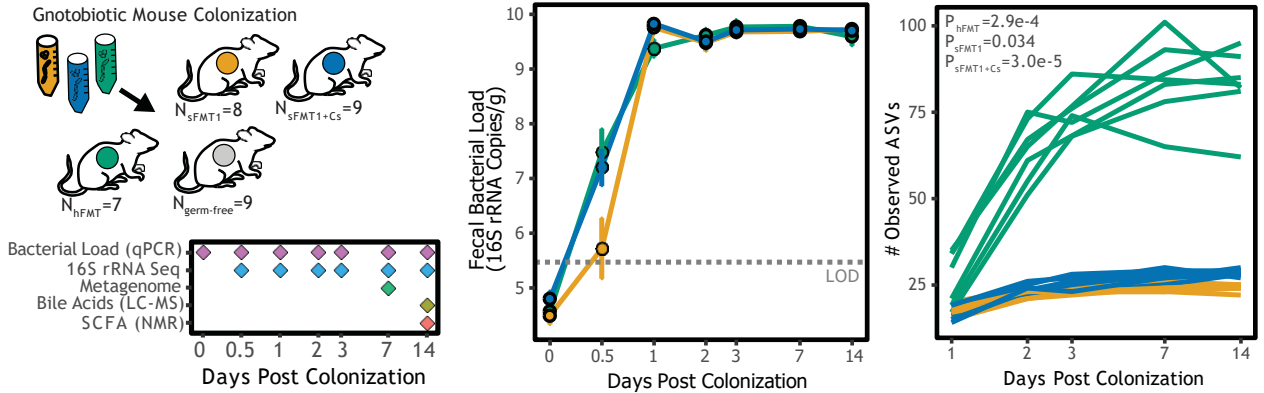
Characterization in serial culture



- sFMT forms a stable community *in vitro*

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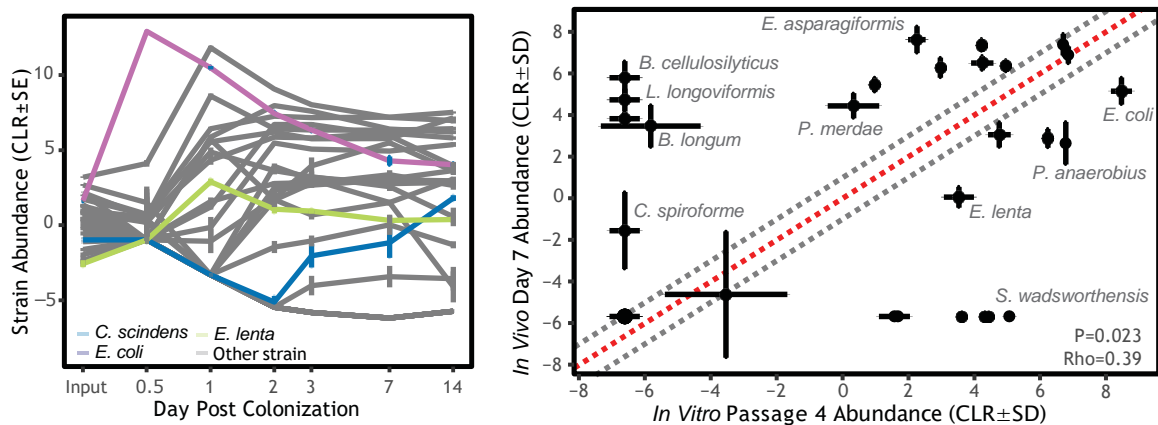
Composition *in vivo*



- sFMT colonization kinetics mimic a human fecal transplant

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In vivo vs *in vitro*



- There are “waves” of succession during colonization similar to humans
- *In vivo* community composition and temporal dynamics are distinct from *in vitro*

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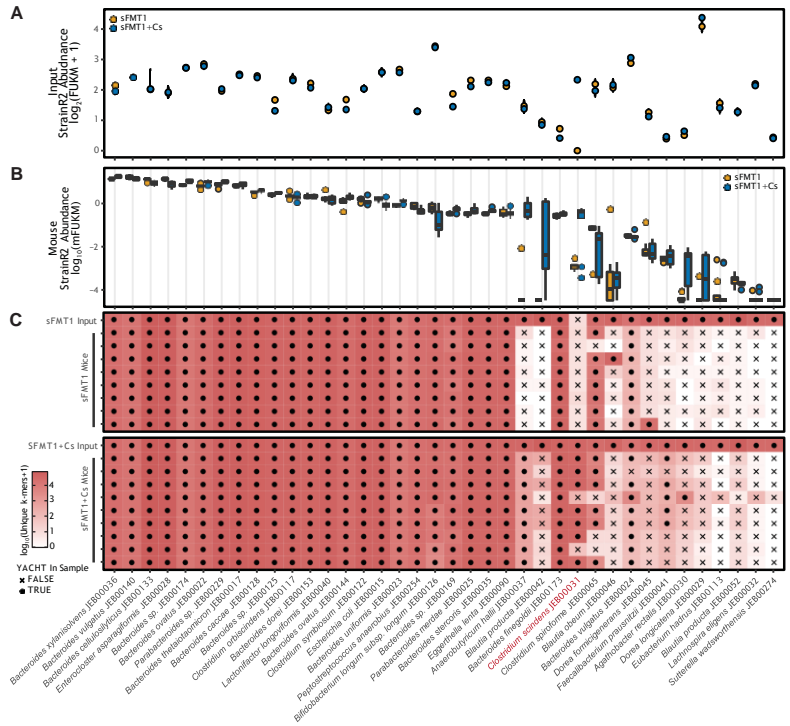
- Metagenomic methods needed to differentiate strains for higher sensitivity and specificity
- Developed StrainR2: normalization based on effective unique genome size
- FPKM (Fragments per kilobase per million reads mapped)
- FUKM (Fragments per unique thousand hashed k-mers per million reads mapped)



Kerim Heber
CS/BMB Undergrad

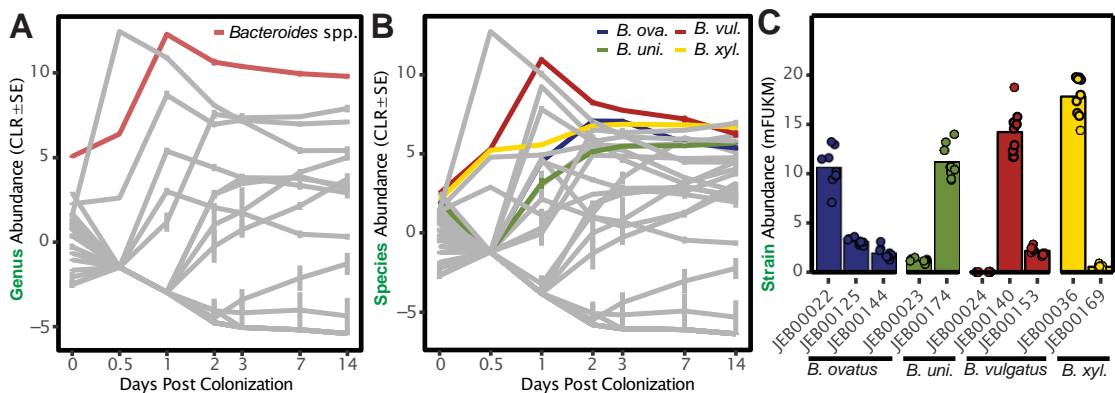


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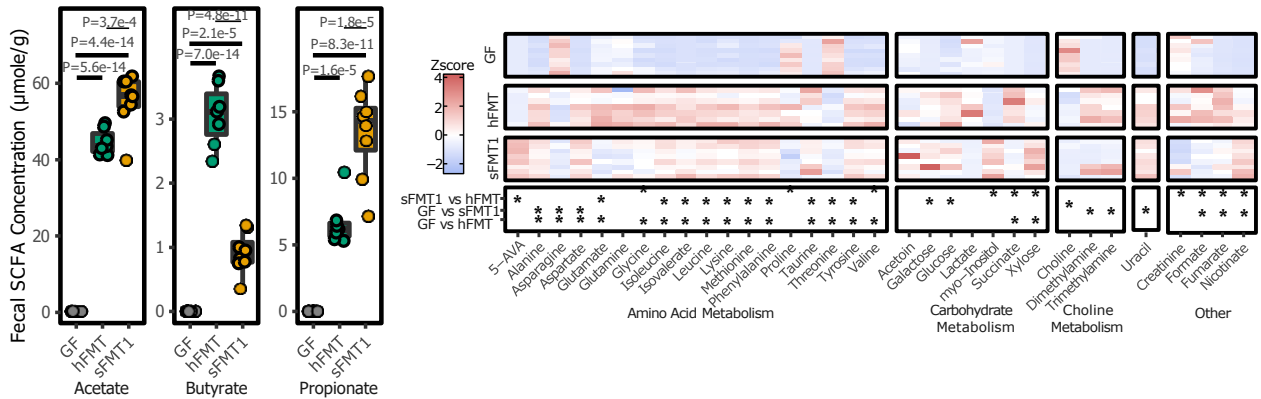
Intraspecies competition



- What are the determinants of competitive exclusion *in vivo*?

42

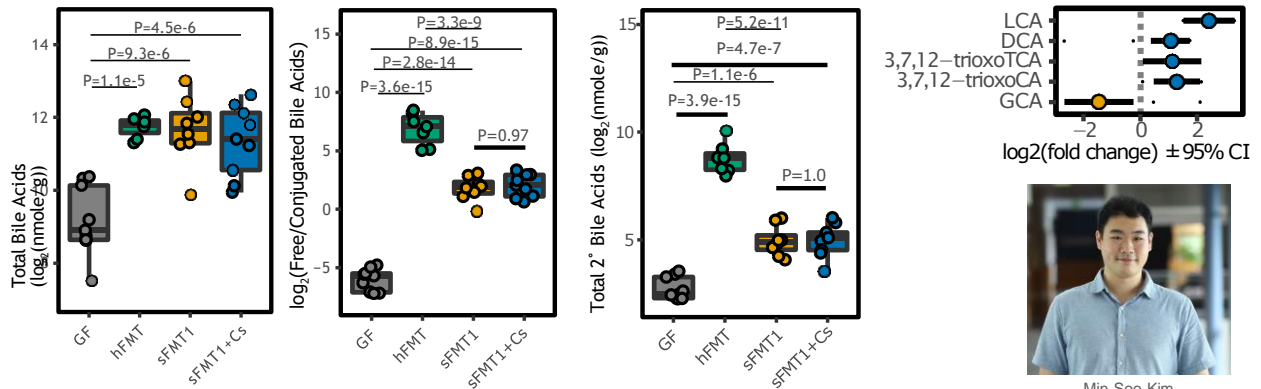
sFMT metabolism *in vivo*



- SCFAs are derived from bacterial metabolism of non-digestible carbohydrates among other sources
- sFMT1 replicates metabolism of human-derived fecal transplant (hFMT)

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sFMT bile acid transformation

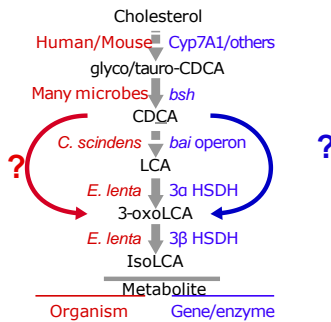
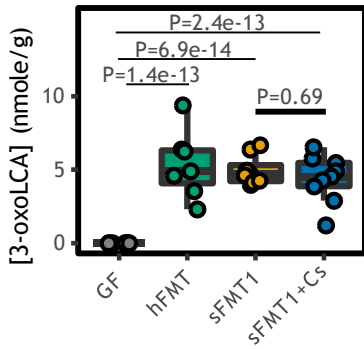


Min Soo Kim
BMMB Graduate Student

- sFMT1 replicates many biotransformations observed in a complex human sample and addition of *C. scindens* leads to 7a-dehydroxylation

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An unexpected observation



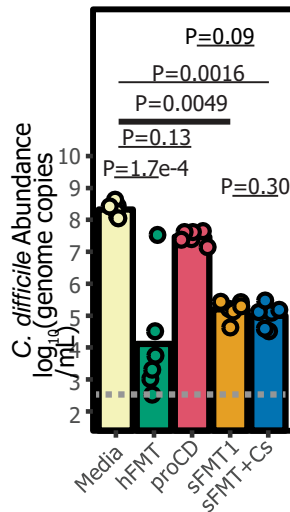
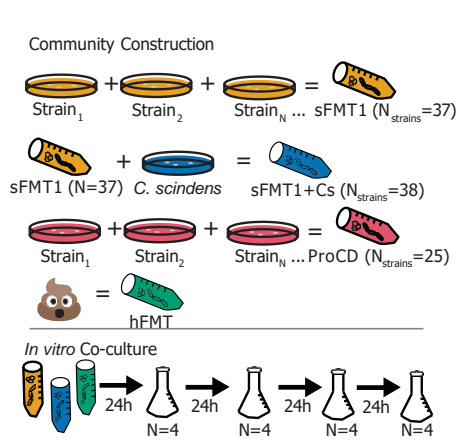
- 3-oxoLCA is a potent anti-inflammatory molecule acting on Th17 cells
- 3-oxoLCA is also an inhibitor of *C. difficile*
- How could 3-oxoLCA be produced in the absence of *C. scindens*?

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III. Measuring resistance to *C. difficile* infection

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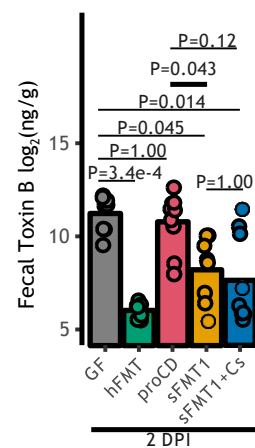
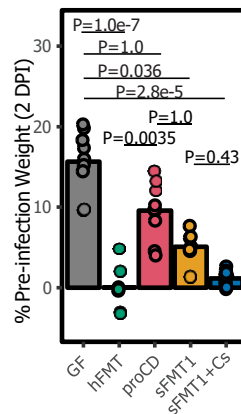
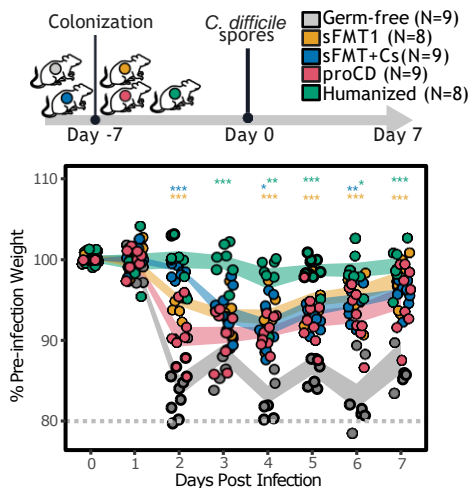
C. difficile exclusion *in vitro*



- sFMT1 and hFMT reduce *C. difficile* abundance by orders of magnitude
- ProCD (organisms positively correlated with *C. difficile*) has no significant effect

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Gnotobiotic infection model



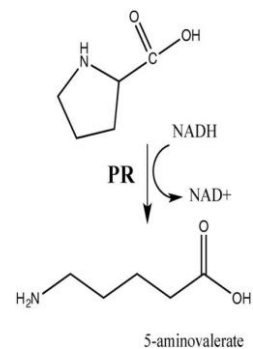
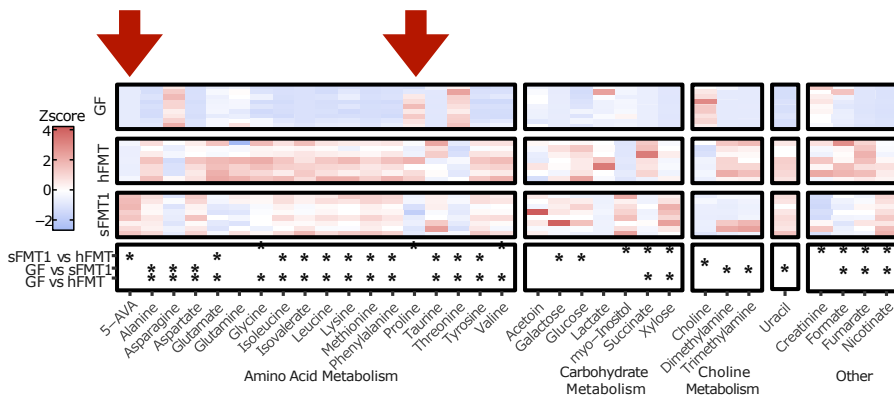
- Colonization reduces disease severity and virulence factor expression

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IV. Determining sFMT Mechanism(s) of Action

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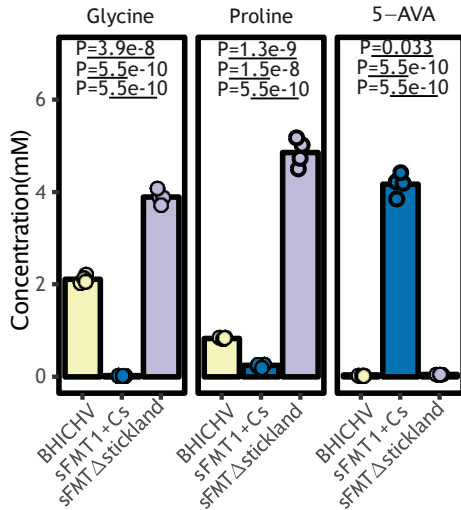
Stickland fermentation



- Proline fermentation is an important pathway for *C. difficile in vivo*, could sFMT1 members be competing for proline?

50

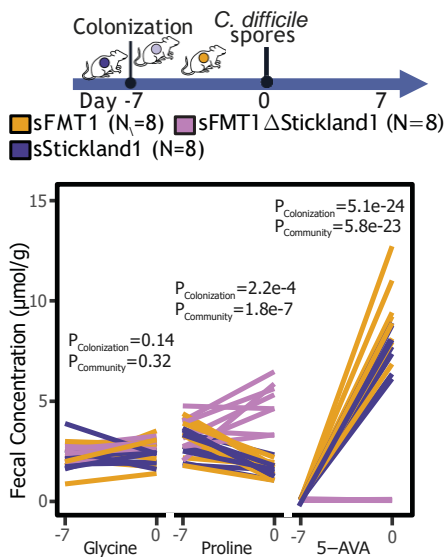
Designing Δ Stickland functional knockout



- Stickland fermenting strains predicted on basis of possessing proline reductase homologs (Nstrains=8)
- Verified *in vitro* using NMR

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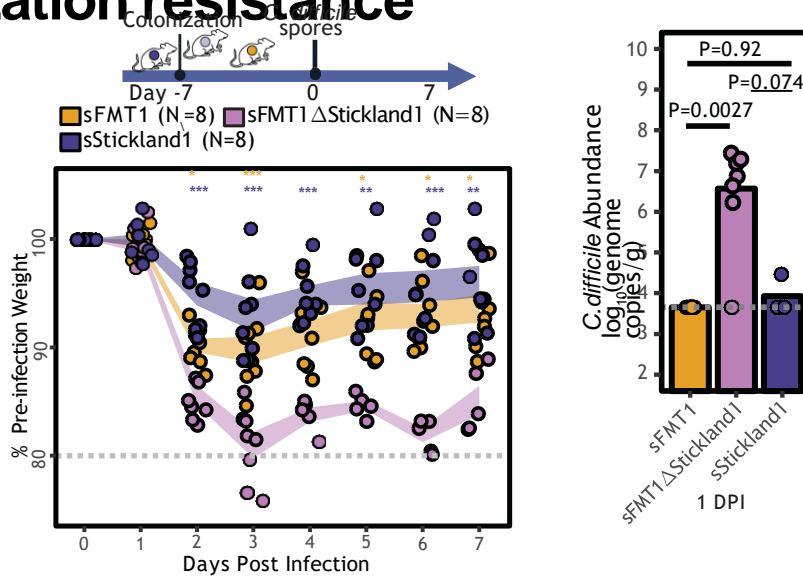
Testing Δ Stickland functional knockout



- Compared 3 groups:
 - original sFMT1 (N=37 strains)
 - sStickland1 (N=8 strains predicted to reduce proline)
 - sFMT1 Δ Stickland1 (N=29 strains [37-8])
- NMR confirms functional knockout *in vivo*

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Δ Stickland loses colonization resistance



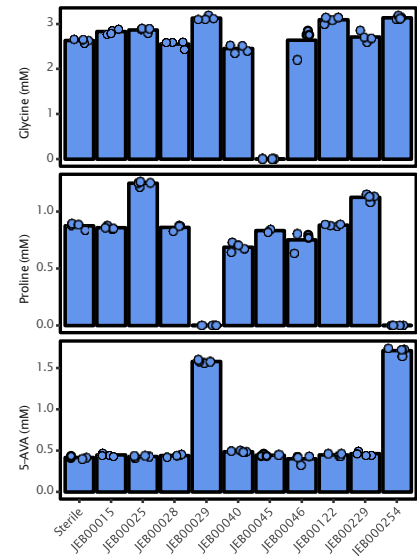
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But can we refine further?

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Reducing sStickland1 complexity

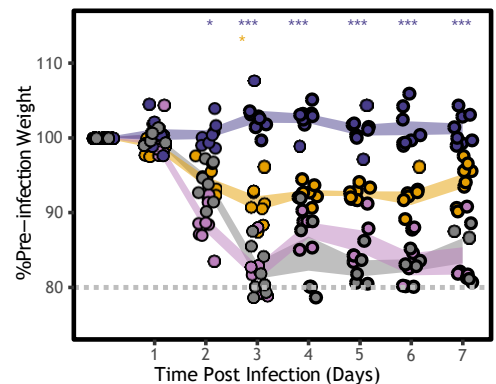
- Validated Stickland fermentation within sStickland1 members *in vitro*
- 2 strains of *Dorea longicatena* and *Peptostreptococcus anaerobius* demonstrate most convincing activity
- Contrasted:
 - Germ-free
 - sFMT1 (37 strains)
 - sStickland2 = JEB00029 + JEB000254
 - sFMT1 Δ Stickland2 = sFMT1 - sStickland 2



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Reducing sStickland1 complexity

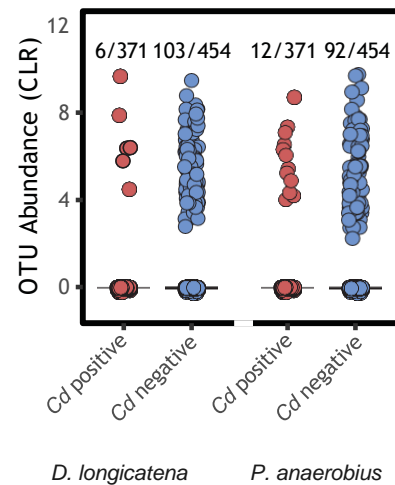
- Validated Stickland fermentation within sStickland1 members *in vitro*
- 2 strains of *Dorea longicatena* and *Peptostreptococcus anaerobius* demonstrate most convincing activity
- Contrasted:
 - Germ-free
 - sFMT1 (37 strains)
 - sStickland2 = JEB00029 + JEB000254
 - sFMT1 Δ Stickland2 = sFMT1 - sStickland 2



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Translational targets

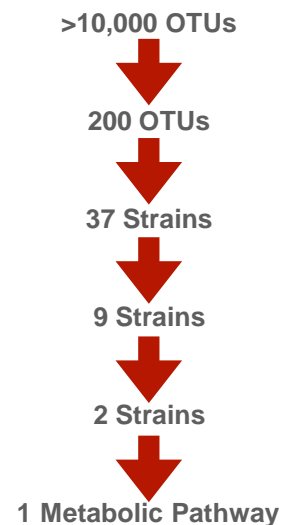
- Predictive power not driven by differential abundance, but differential presence
- These two species are found in ~20% of individuals without *C. difficile* while largely absent in carriers
- Could these be key predictors of susceptibility and/or potential therapeutic targets?



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Conclusions

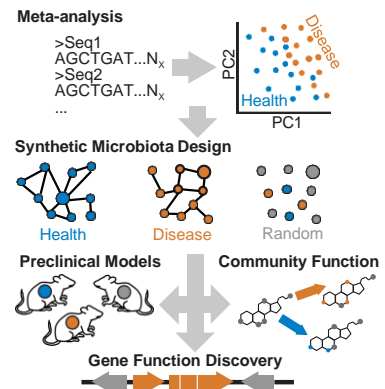
- Meta-analysis allowed the design of a functional synthetic community
- *C. scindens* may be dispensable for *C. difficile* resistance in a complex community, but strains which conduct Stickland fermentation of proline are necessary and sufficient
- Limitation of proline availability may be key to microbial suppression of *C. difficile*



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Conclusions

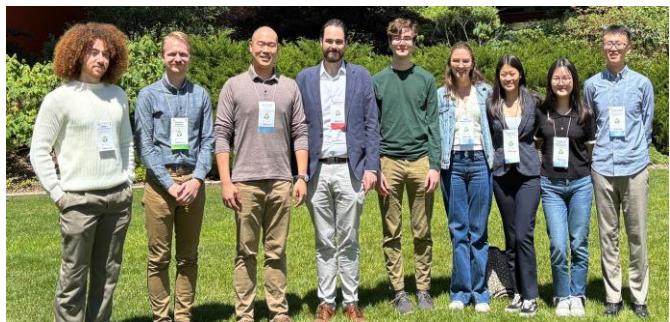
- Synthetic microbiomes are tractable tools for mechanistic study coupling big data with experimental opportunities
- Synthetic fecal transplants and derivatives thereof (sFMT) may have potential for clinical translation



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Acknowledgements

- Bisanz Lab @PSU
 - Susan Tian
 - Min Soo Kim
 - Ben Anderson
 - Daniella Betancurt Anzola
 - Shane Connolly
 - Jingcheng Zhao PhD
 - Kerim Heber
 - Patterson Lab @PSU
 - Andrew Patterson
 - Fuhua Hao
 - Stephanie Collins
 - Yuan Tian
- David Koslicki (PSU)
- Vishal Singh (PSU)



60

Microbiome Mechanics: Building a Healthier Gut

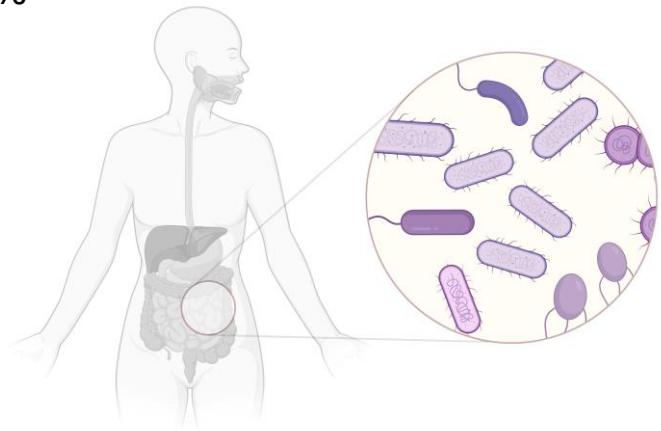
Peptidoglycan's Role in Gut Homeostasis



61

The Gut Microbiome

- The human digestive tract is populated with bacteria (~95% of the human microbiome is located here)
- Essentially a microbial organ within a host organism
- Commensal relationship

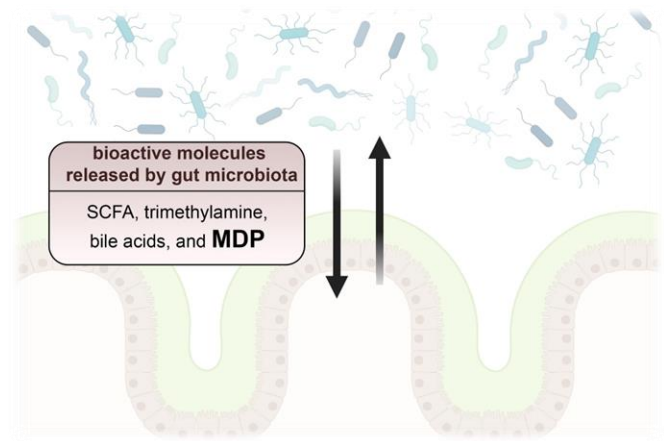


62

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The Gut Microbiome

- Gut homeostasis affects our day-to-day functioning
- Two way relationship in terms of exchange of signaling molecules
- We only know of a few biologically active molecules being produced by gut microbiota

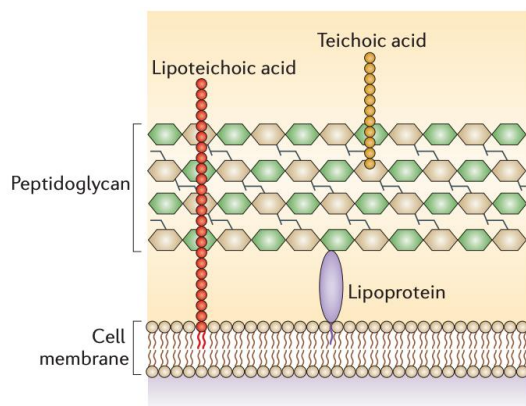


A major molecule that is now entering this small list is MDP, which happens to be a fragment of bacterial cell walls

63

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Bacterial cell wall: Peptidoglycan



- Peptidoglycan (also known as sacculi) is a single LARGE molecule that surrounds the entire bacterial cell
- All bacteria are protected by this 'jacket' like structure
- Peptidoglycan is uniquely bacteria in nature (humans do not have any molecules similar to it)

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MDP Released by Gut Microbiota

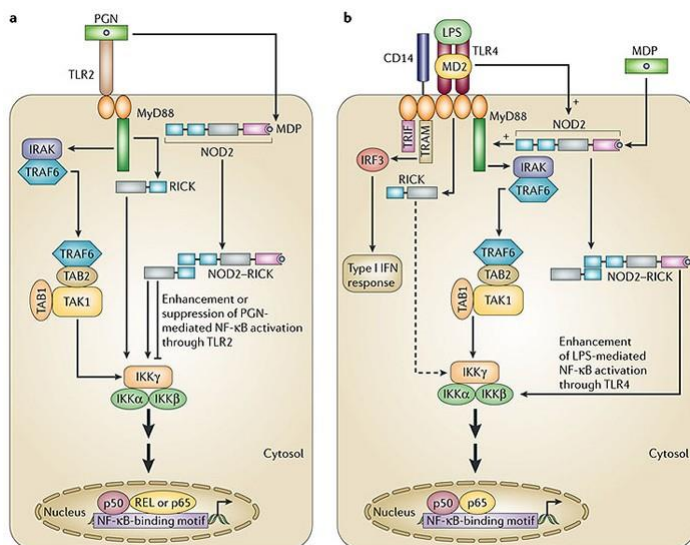


- Fragments (or 'bricks') from the cell wall are released by muramidases (e.g., lysozyme)

65

65

Sensing of NOD2



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Nature Reviews | Immunology

- MDP is a fingerprint of bacterial presence
- It gets detected by NOD2 inside mammalian cells
- This process was thought to be defensive in nature
 - signifying an infection
 - but this concept may not capture all that MDP does...

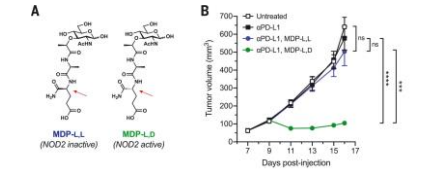
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Alternative role for NOD2?

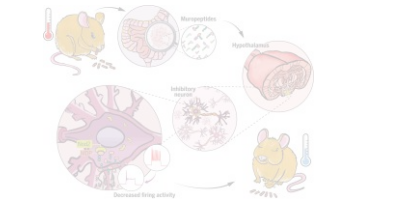
REPORT MICROBIOME
Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy

WITTENBERG L, ORENZIO J, JIANG J, LOPRINZO G, JENSEN K, BEYERS A, DONNELLY L, ... 13 authors [Authors info & Affiliations](#)



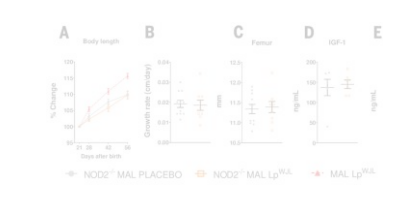
RESEARCH ARTICLE
Bacterial sensing via neuronal Nod2 regulates appetite and body temperature

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RESEARCH ARTICLE MICROBIOME
Microbe-mediated intestinal NOD2 stimulation improves linear growth of undernourished infant mice

WITTENBERG L, ORENZIO J, JIANG J, LOPRINZO G, JENSEN K, BEYERS A, DONNELLY L, ... 13 authors [Authors info & Affiliations](#)



Potentiation of Immunity

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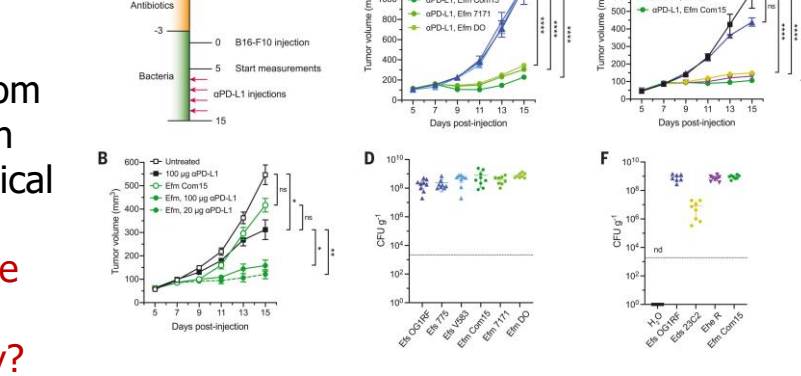
DOI: 10.1126/science.1261333

- Could NOD2 activation from microbiome peptidoglycan lead to better immunological state?
 - Can this improved state potentiate checkpoint cancer immunotherapy?

REPORT MICROBIOME
Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy

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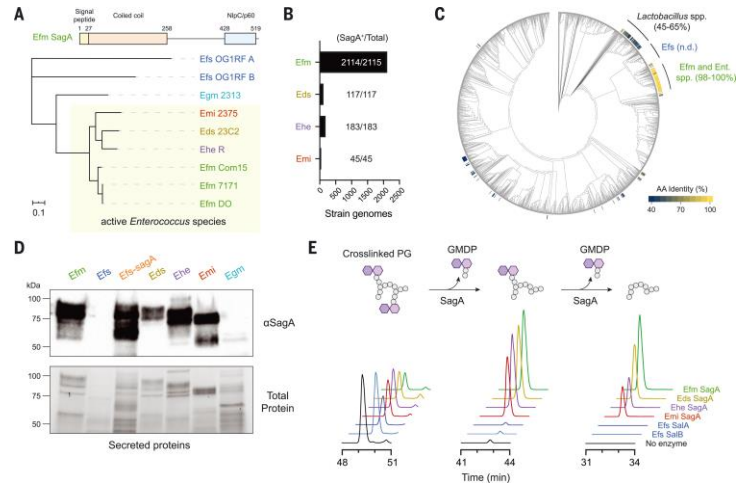


Potential of Immunity

Science

Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy

- Gut bacterial enzyme was responsible for depolymerizing peptidoglycan into NOD2 agonists



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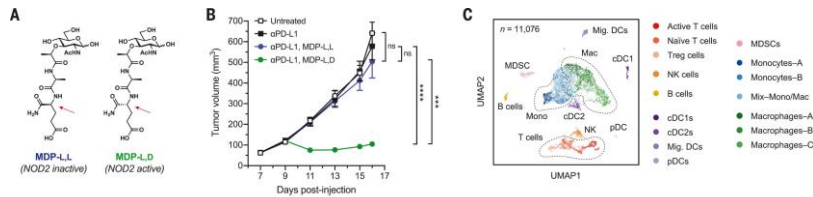
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Potential of Immunity

Science

Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy

Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy



- In mice devoid of gut bacteria, the supplementation of MDP was sufficient to replicate the anti-cancer phenotype
 - Has implications for drug design and better cancer immunotherapies

70

70

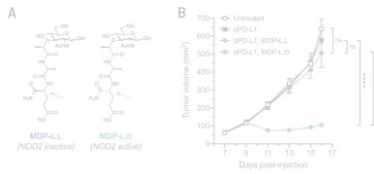
Alternative role for NOD2?

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MEDICAL RESEARCH | JUAN L. GONZALEZ | ANGELO L. BERNI | ANTONIO L. L. DE SOUZA | L. P. DE SOUZA | L. P. DE SOUZA | +12 authors | [Author info & affiliations](#)

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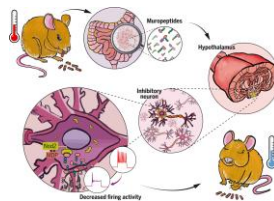
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Bacterial sensing via neuronal Nod2 regulates appetite and body temperature

LEAH GARDNER | DANIEL LEONARDI | ROBERTO AREVALO | ALAN VICTORIANO | L. I. H. FERRER-BASILE | L. L. | +12 authors | [Author info & affiliations](#)

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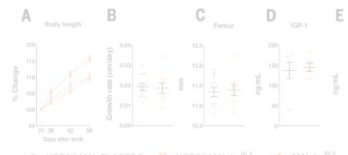


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MEDICAL RESEARCH | DANIEL LEONARDI | ANTONIO L. L. DE SOUZA | L. P. DE SOUZA | L. P. DE SOUZA | +12 authors | [Author info & affiliations](#)

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Regulation of appetite

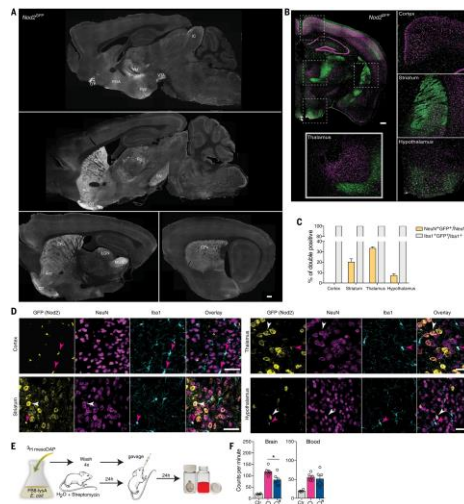
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- Could NOD2 operate in the brain?
 - If so, what physiology could it control?

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Regulation of appetite

Science

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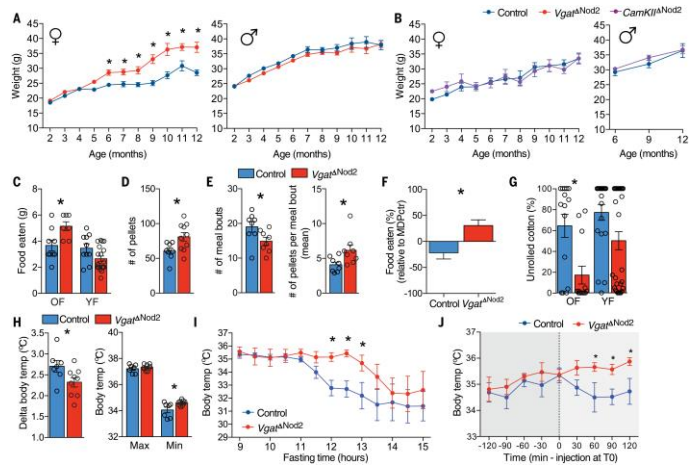
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- NOD2 expression in neurons could impact feeding and temperature in female mice

73

73

Regulation of appetite

Science

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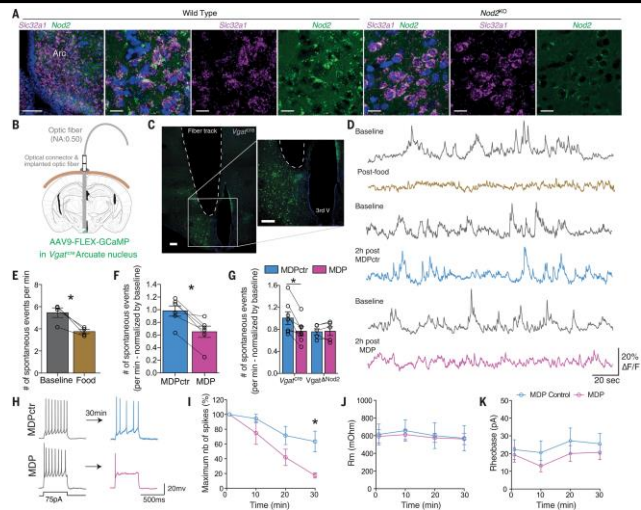
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- Supplementation of MDP (peptidoglycan fragment) can modulate neuronal activity

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NOD2 Activation Can Promote Growth

Science

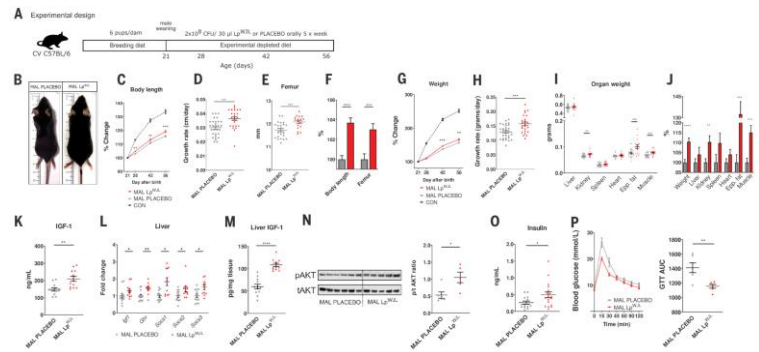
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- Probiotic with *Lactobacillus plantarum* improves intestinal NOD2 stimulation and linear growth

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NOD2 Activation Can Promote Growth

Science

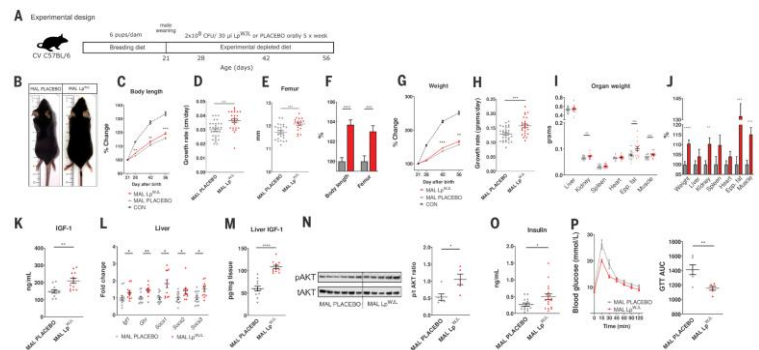
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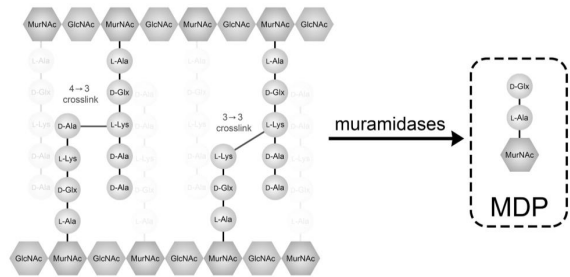


- Probiotic with *Lactobacillus plantarum* improves intestinal NOD2 stimulation and linear growth

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Open Questions - NOD2 in Host Health



- Can we visualize peptidoglycan of gut bacteria in live animals?
- Can we isolate peptidoglycan from stool samples to analyze its composition and NOD2 activation level?

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Volume 29, Issue 12, 15 December 2022, Pages 1721-1728.e5

Goal # 1 – Live Animal Imaging

We metabolically tagged the peptidoglycan of gut bacteria in live mice with near IR fluorophores

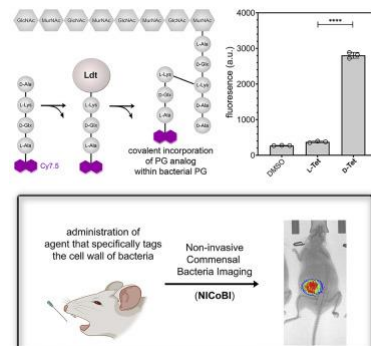
Cell Chemical Biology



Volume 29, Issue 12, 15 December 2022, Pages 1720-1728.e5

Resource
Real-time non-invasive fluorescence imaging of gut commensal bacteria to detect dynamic changes in the microbiome of live mice

Alexis I. Anastopoulos,¹ Mohendra D. Chordia,¹ Sree H. Kollu,² Brianne E. Dolanowski,¹ Melanie B. Burkhardt,¹ Marcos M. Pires,^{1,3} J. 29



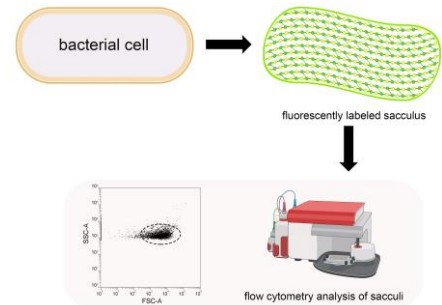
80

80

Goal # 2 – Non-invasive Sacculi Isolation

We set out to isolate peptidoglycan from fecal samples to readily interrogate NOD2 signaling

- But how?
 - Fecal samples are very complex and it is not trivial to isolate bacteria/sacculi
 - We took advantage of a special property of sacculi: its resistance to SDS/heat/DNAase/RNAase/protease



Noninvasive Analysis of Peptidoglycan from Living Animals

Karl L. Ocius, Sree H. Kollu, Saadman S. Ahmad, Jules M. Dressler, Mahendra D. Chordia, Brandon L. Jutras, Melanie R. Rutkowski, and Marcos M. Pires*

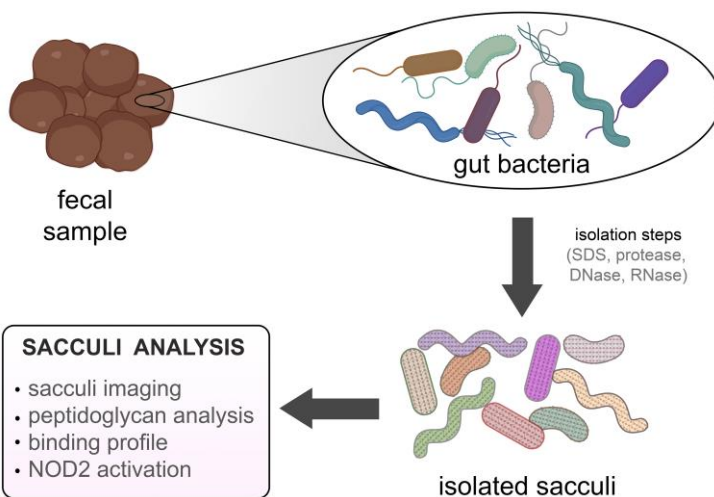
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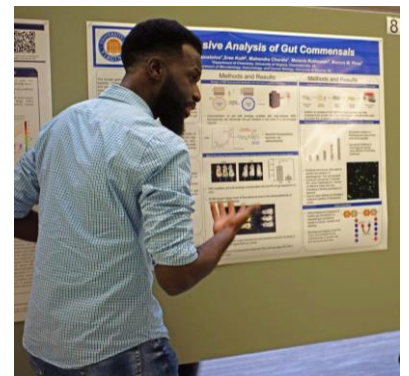
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Isolation of Sacculi



SACCULI ANALYSIS

- sacculi imaging
- peptidoglycan analysis
- binding profile
- NOD2 activation

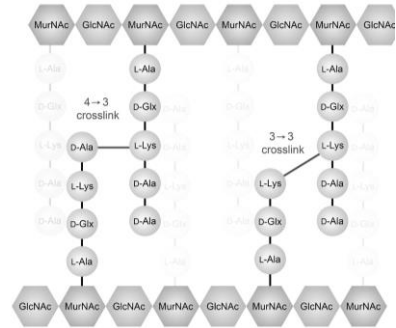


82

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The Gut Microbiome

- Peptidoglycan from gut bacteria operates as a biologically active mediator of host health via NOD2 sensing



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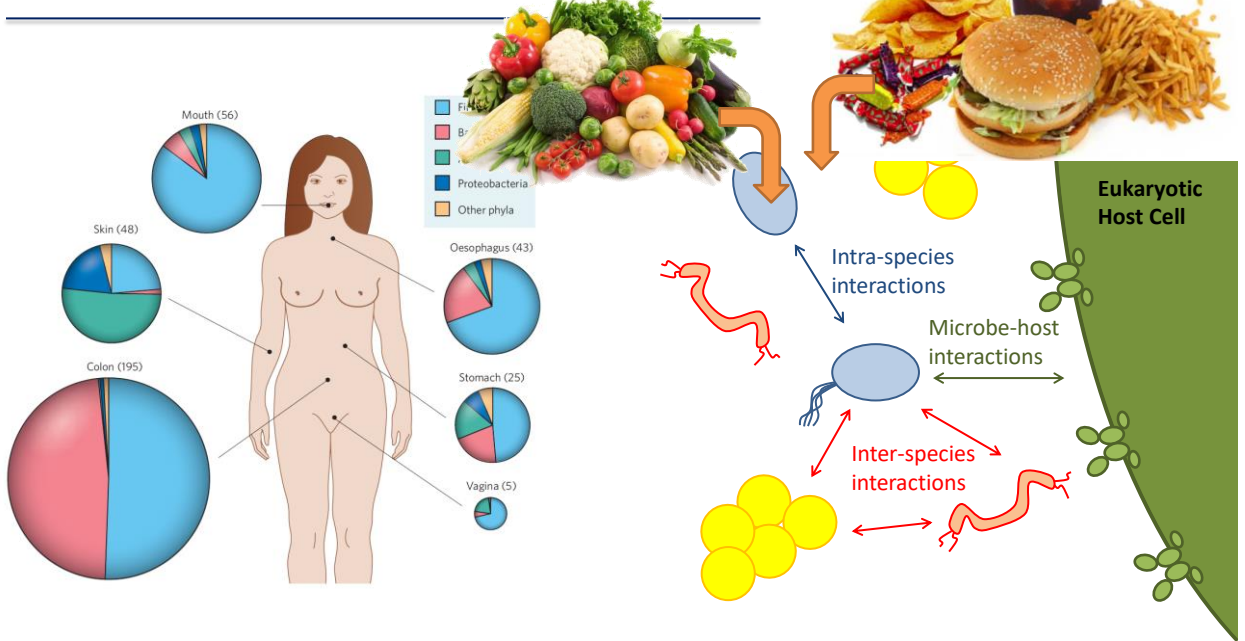
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Gut Microbial Metabolism of Dietary Input Matters for Host Health

Jan Claesen

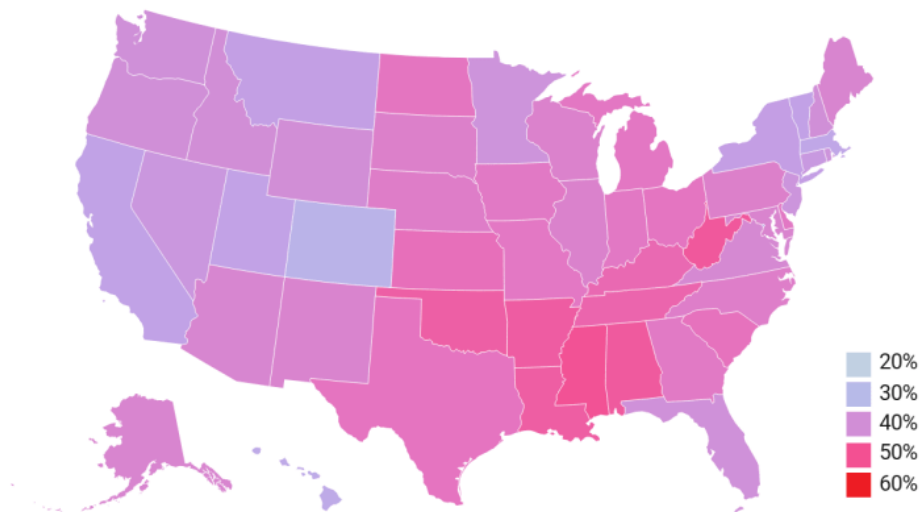
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Molecular interactions in the human microbiome



85

The American Obesity Epidemic

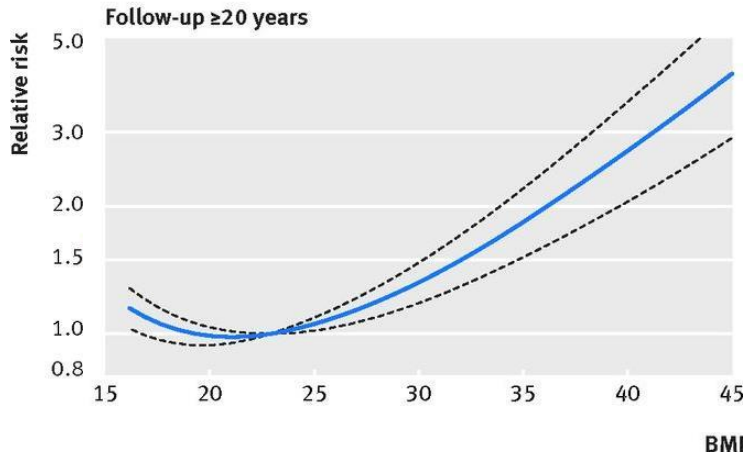


Obesity is defined as a BMI over 30

Map: Elijah Wolfson for TIME • Source: N Engl J Med 2019;381:2440-50. • Created with Datawrapper

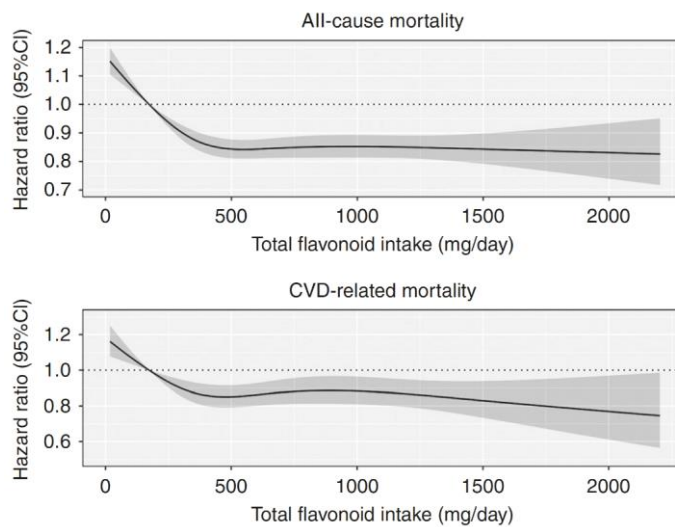
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Obesity Increases Propensity of All-Cause Mortality

Dagfinn et al. 2016 *BMJ*

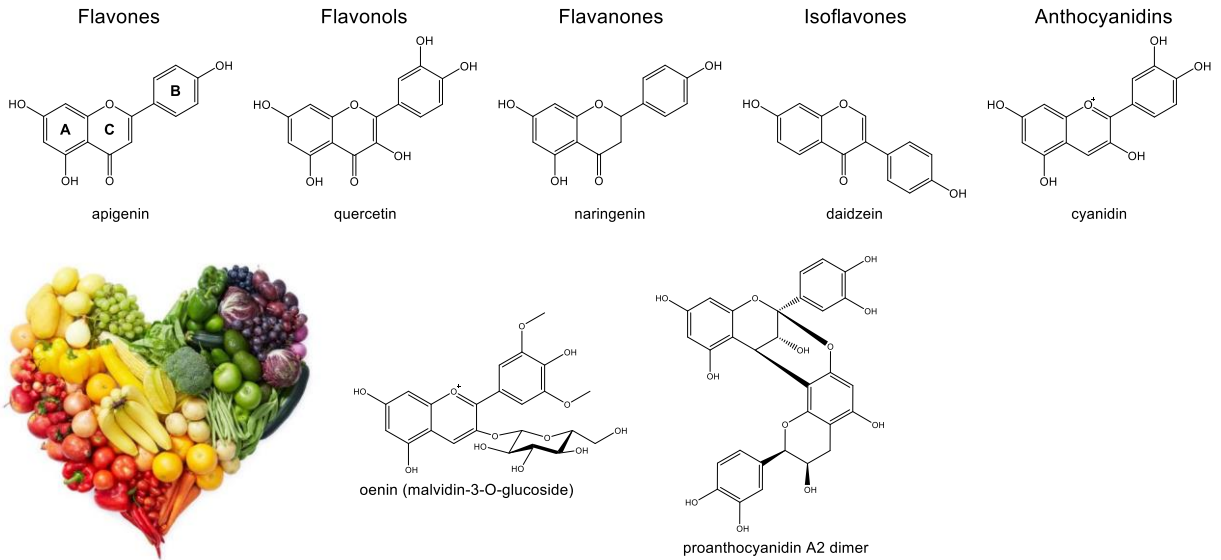
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Moderate Flavonoid Consumption is Negatively Associated With Mortality

Bondonno et al. (2019) *Nat Commun*

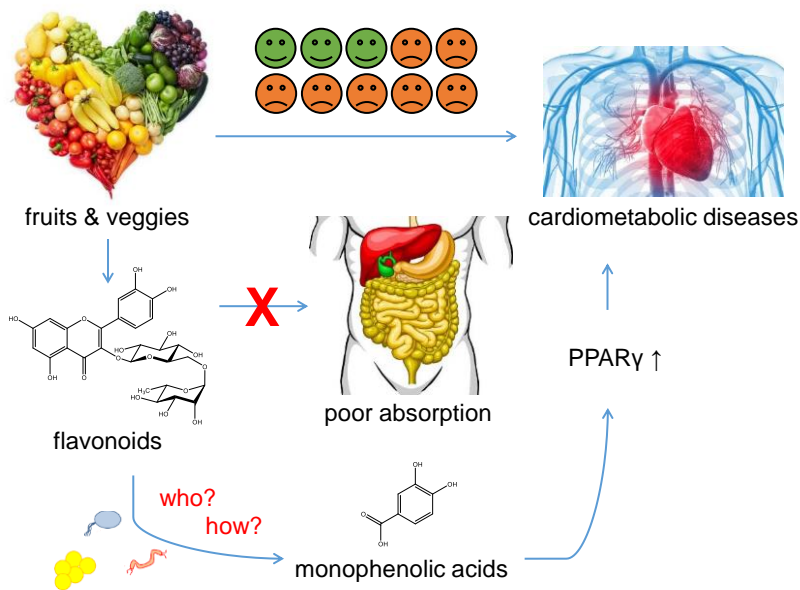
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Flavonoids are a large family of plant secondary metabolites



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Gut bacterial flavonoid catabolism & cardiometabolic disease



Luke Osborn



Karlee Schultz



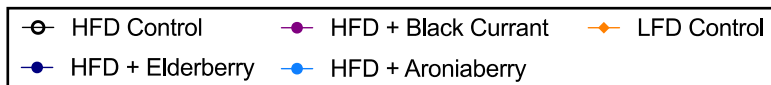
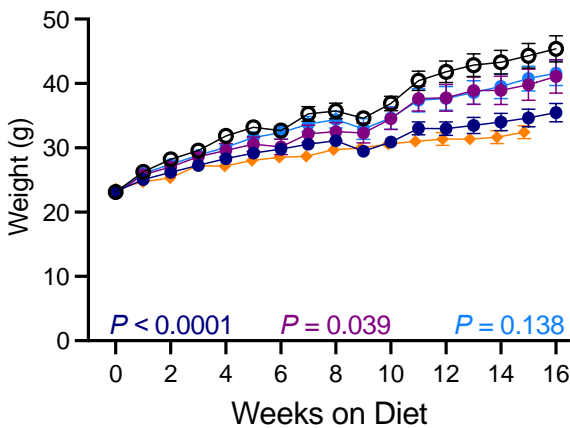
Sara Alqudah

90

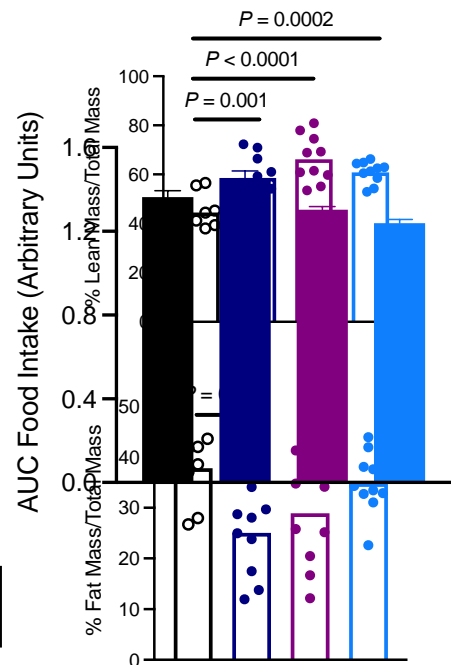
Hypothesis: Monophenolic acids stemming from microbial flavonoid catabolism are responsible for the anti-obesogenic effect of flavonoid consumption.

91

Berry extracts attenuate HFD-induced obesity

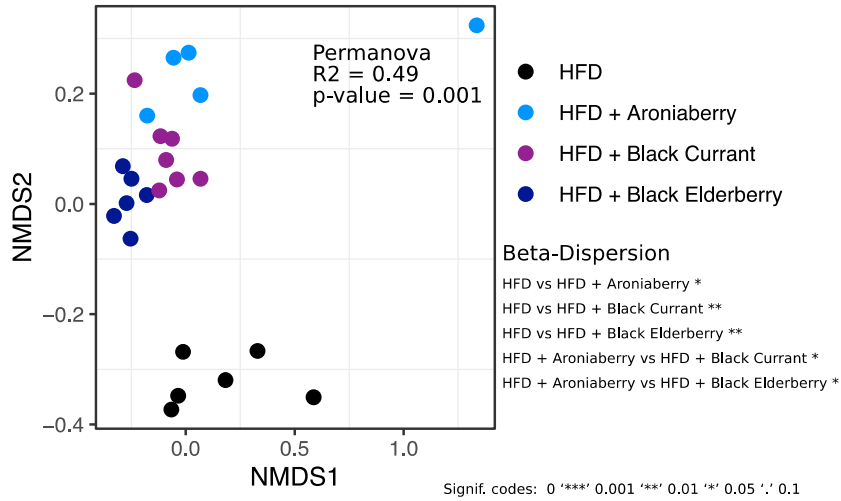


Osborn et al. (2022) PNAS



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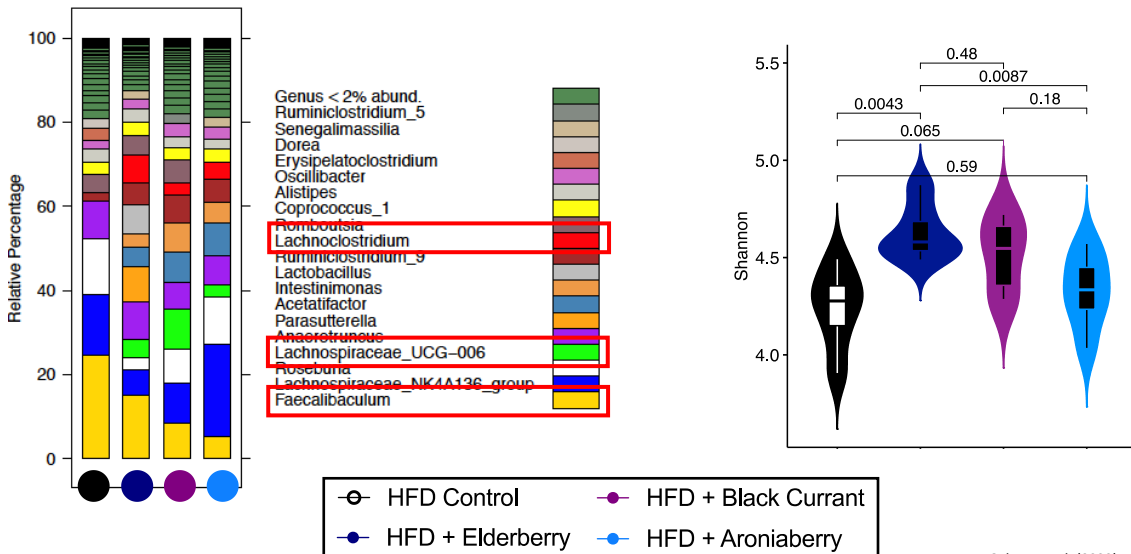
Diet Informs Gut Microbial Composition



Osborn et al. (2022) PNAS

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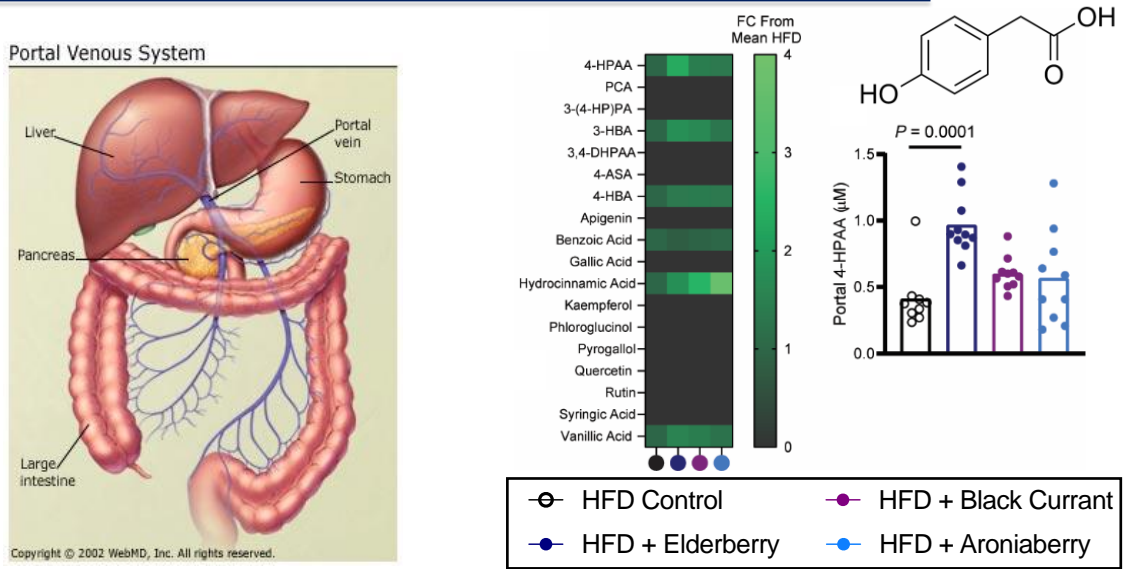
Berry Diets Promote Microbial Diversity



Osborn et al. (2022) PNAS

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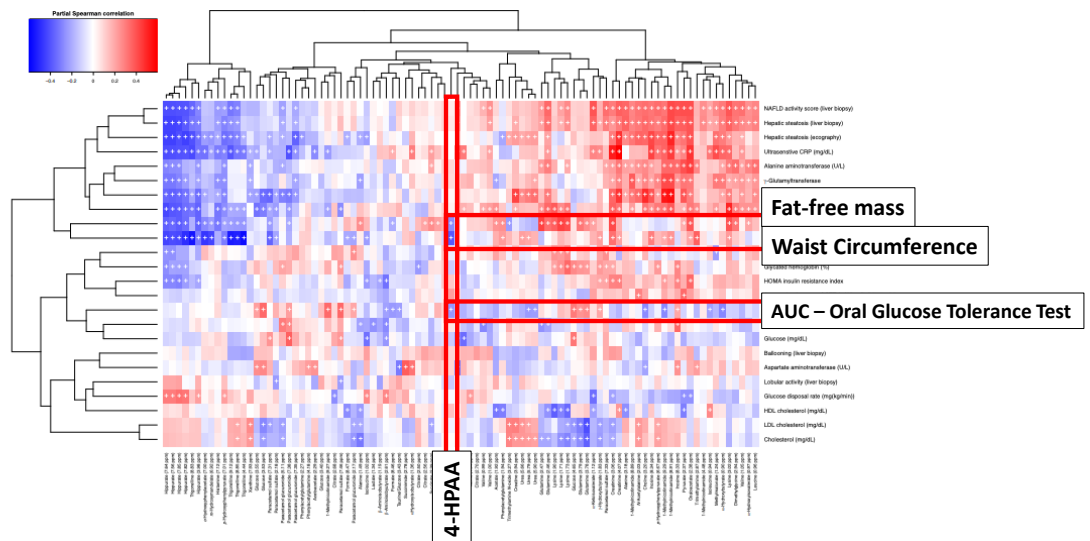
Targeted Mass Spec on Microbial Portal Blood Flavonoid Catabolites



Osborn et al. (2022) PNAS

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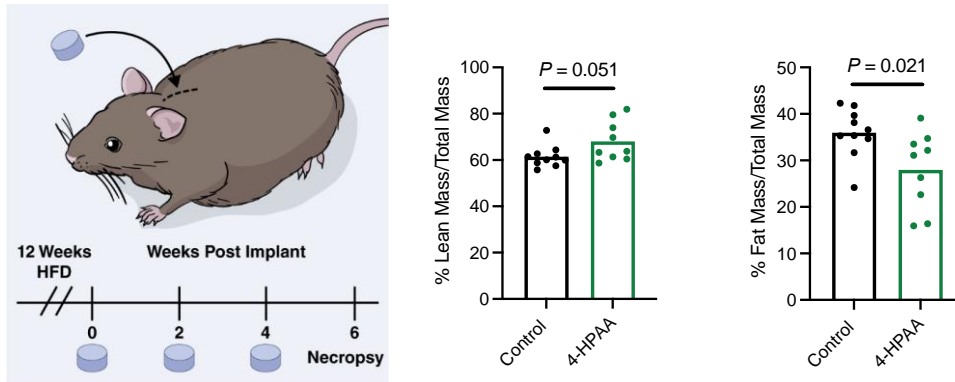
4-Hydroxyphenylacetic acid is correlated with improved metabolic parameters



Hoyles et al. (2018) Nat Med

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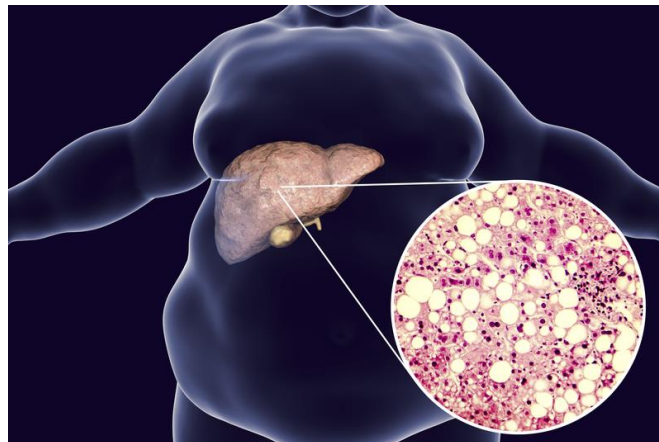
A Single Monophenolic Acid (4-HPAA) Reprograms Global Fat Storage



Osborn et al. (2022) PNAS

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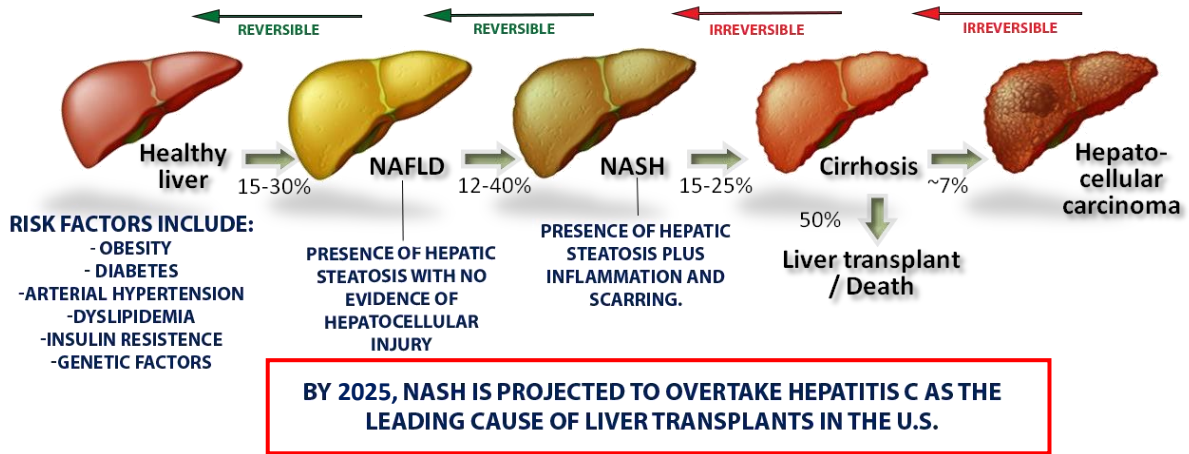
Non-Alcoholic Fatty Liver Disease (NAFLD)



NAFLD is often a consequence of obesity and is a risk factor for cardiometabolic disease

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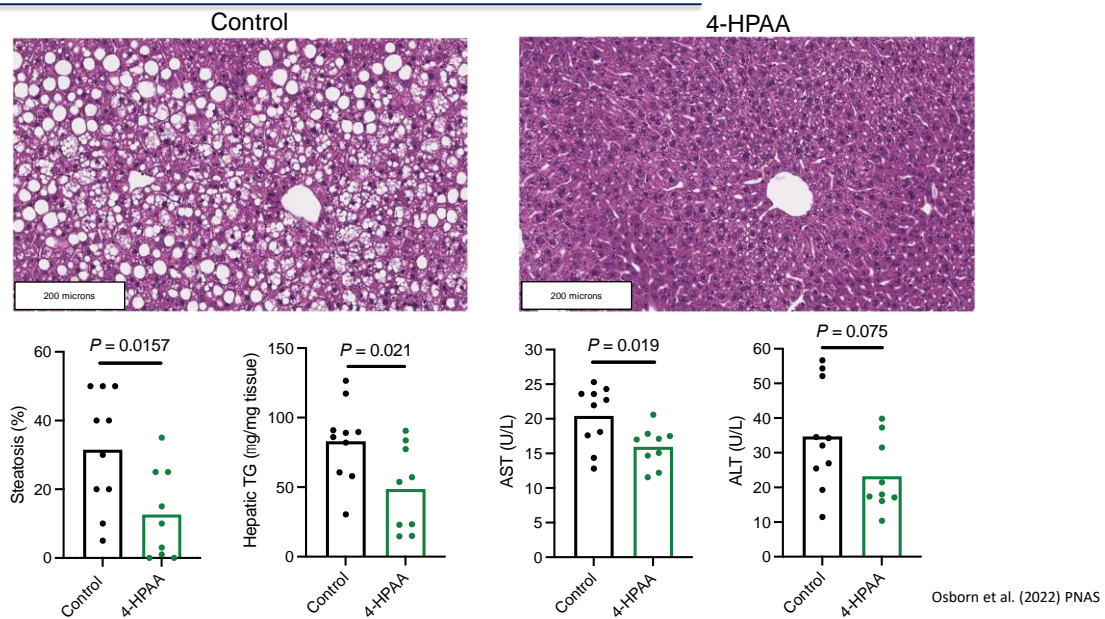
The Non-Alcoholic Fatty Liver Disease (NAFLD) Spectrum



Texas Liver Institute

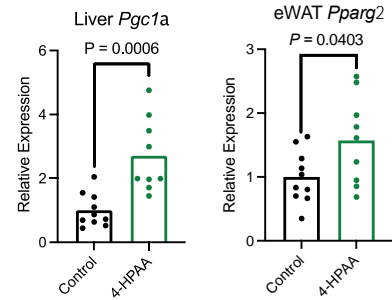
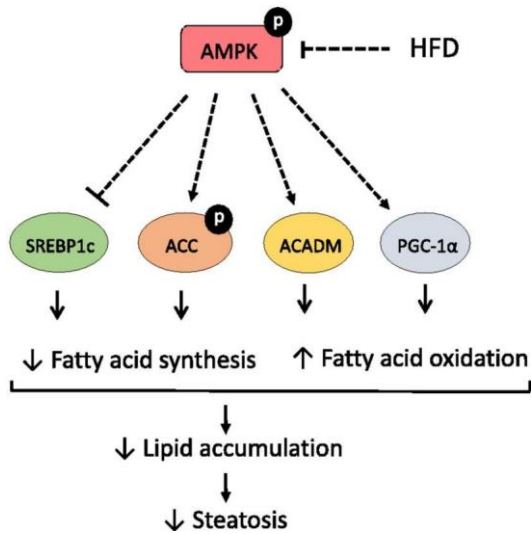
99

4-HPAA Reverses High Fat Diet-Induced Steatosis



100

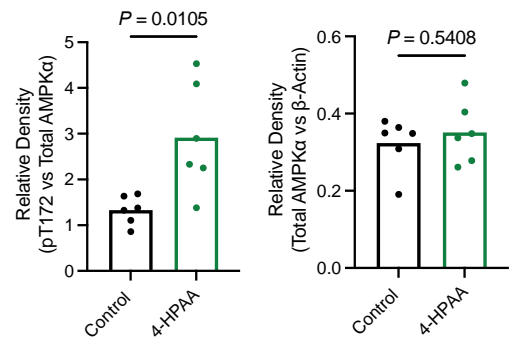
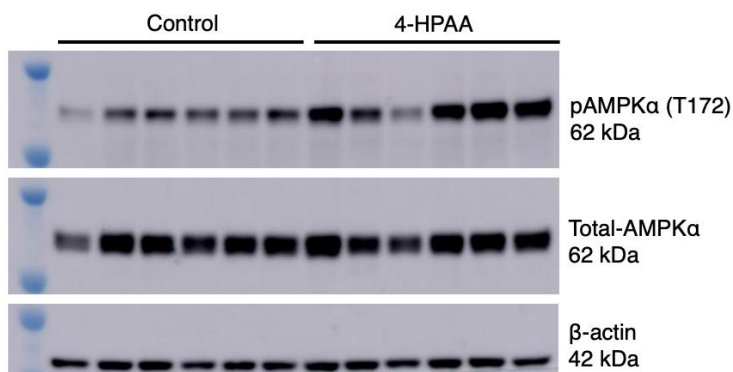
AMPK Regulates Liver Lipid Metabolism



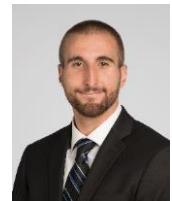
Osborn et al. (2022) PNAS

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4-HPAA Induced Hepatic Activation the AMPK Pathway



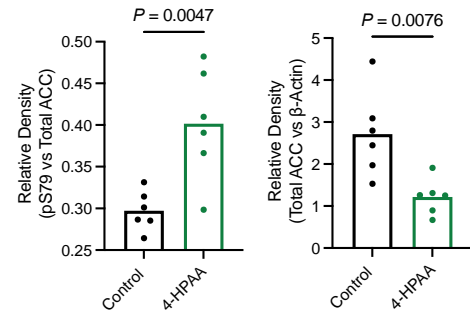
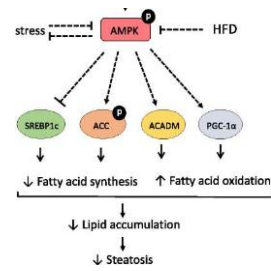
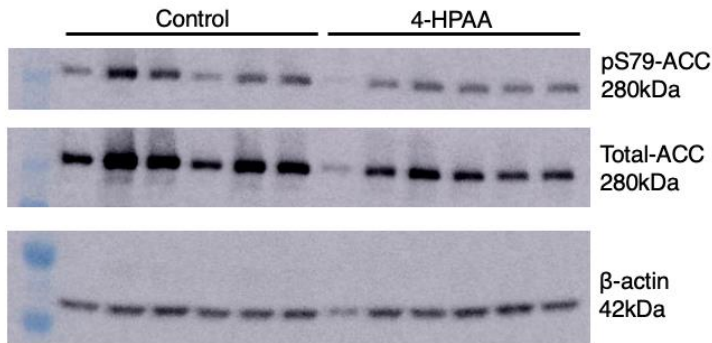
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4-HPAA Downregulates Hepatic Fatty Acid Synthesis

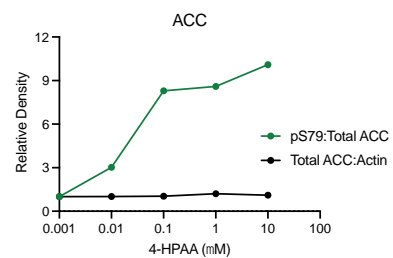
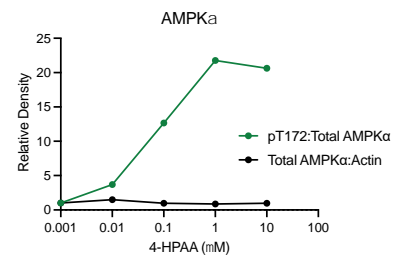
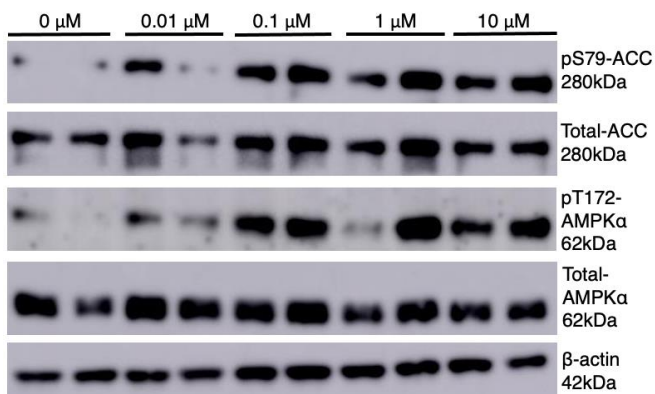


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4-HPAA Directly Activates AMPK in Primary Hepatocytes in a Dose Dependent Manner

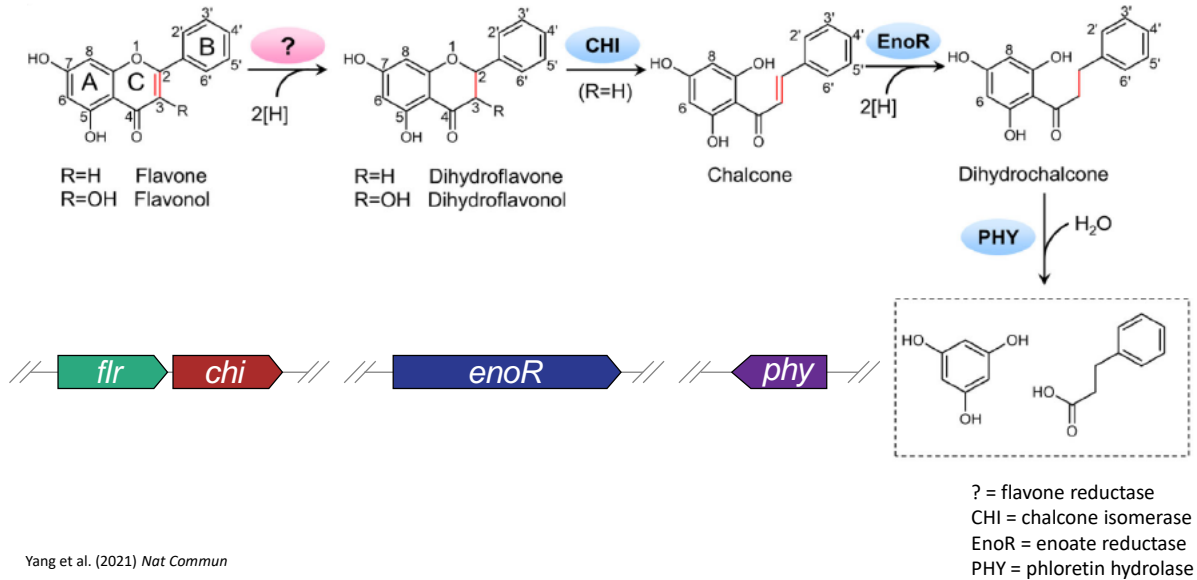


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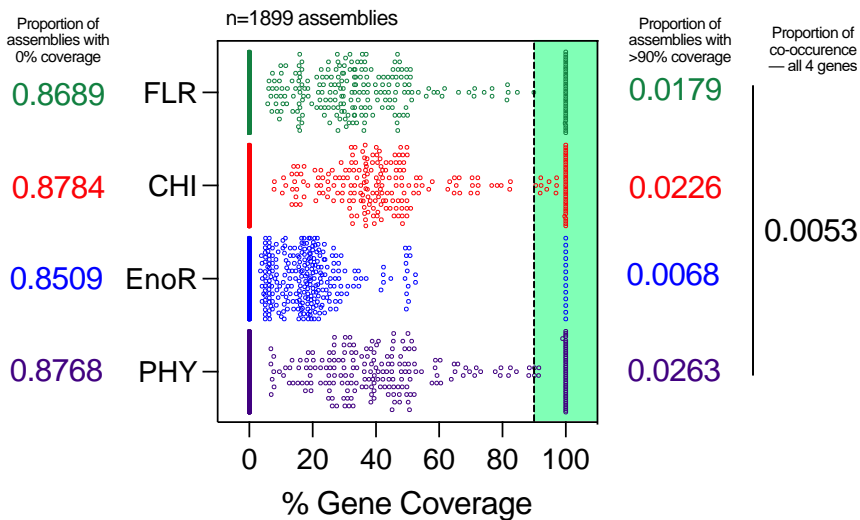
Identification of the initiating step in flavonol catabolism



Yang et al. (2021) *Nat Commun*

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Homologs of *F. plautii* Catabolic Genes are Rare in Human Fecal Microbiomes



Naseer Sangwan

Osborn et al. (2022) *PNAS*

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Conclusions

- Supplementing a HFD with flavonoid-rich **elderberry extract** significantly **attenuated HFD-induced obesity** 4-HPAA was enriched in the portal plasma of these mice
- Continuous subcutaneous delivery of **4-HPAA** was sufficient to **reverse HFD-induced hepatic steatosis**
- This anti-steatotic effect is associated with the **activation of AMP-activated protein kinase α (AMPK α)**
- In a large survey of **healthy human gut metagenomes**, **about two percent** contained homologues of all four characterized bacterial genes required to catabolize flavonols into 4-HPAA.

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Acknowledgements



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Becky DeLucia
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Yaheya Idris
Isabel Johnston
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Shreyaa Nagajothi
Luke Osborn
Karlee Schultz

<https://claesengroup.org/>



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