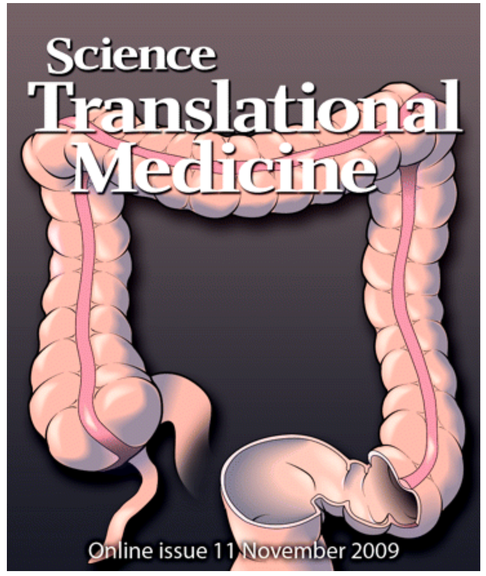
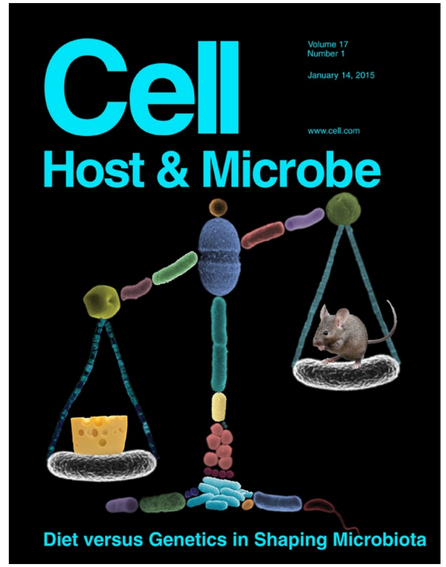
They are what you eat: how food and drugs interact with the gut microbiome





Peter J. Turnbaugh, Ph.D., Professor
University of California, San Francisco Department of Microbiology & Immunology
G.W. Hooper Foundation, Benioff Center for Microbiome Medicine, CZ Biohub

Learn more at:
turnbaughlab.ucsf.edu | microbiome.ucsf.edu | gnotobiotics.ucsf.edu | @PTurnbaugh

Diet: a century-old hypothesis

Arthur Kendall
JBC 1909

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"As this food passes through the alimentary canal…at different levels of the tract it is decomposed in part by various types of bacteria. The predominating types of bacteria which take part in the decomposition are ***determined largely by the nature of the diet***."

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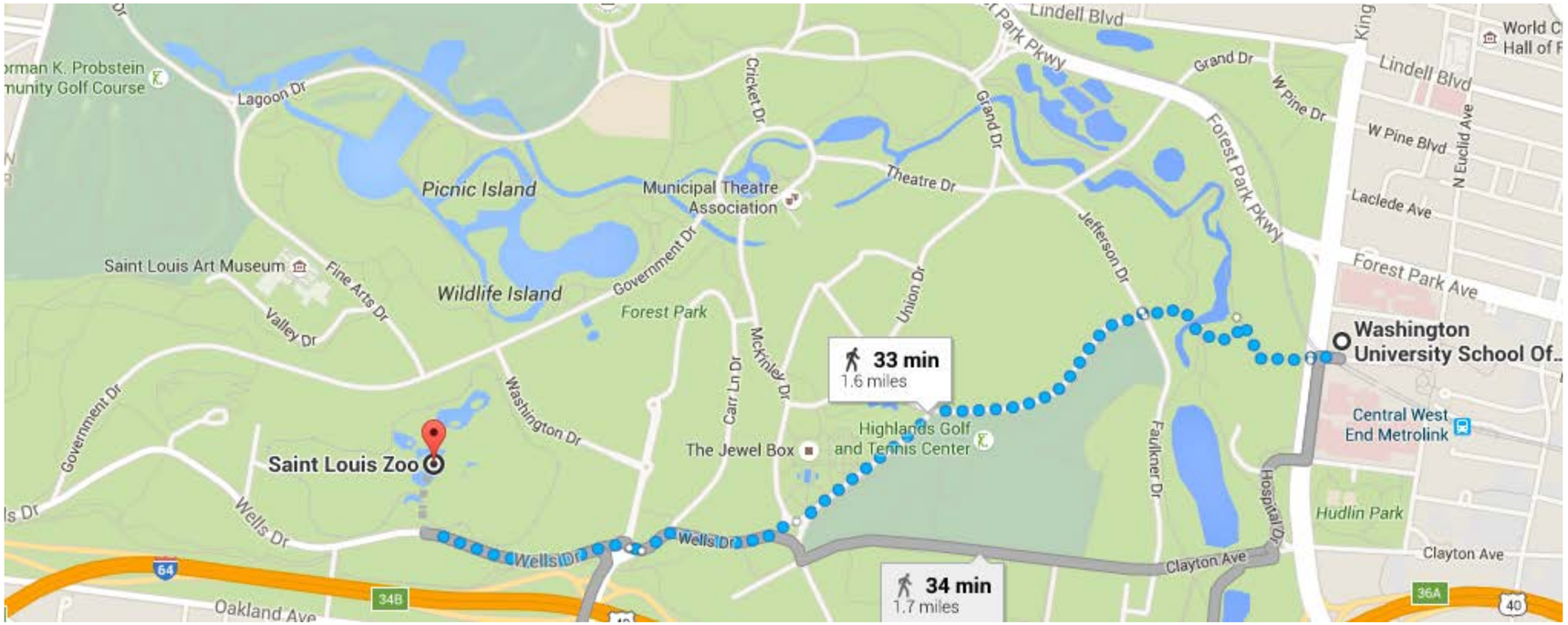
"this correlation between diet, intestinal [microbiota] and end products has been **largely overlooked**"

A field trip to the zoo



Ley *et al.*, Science 2008

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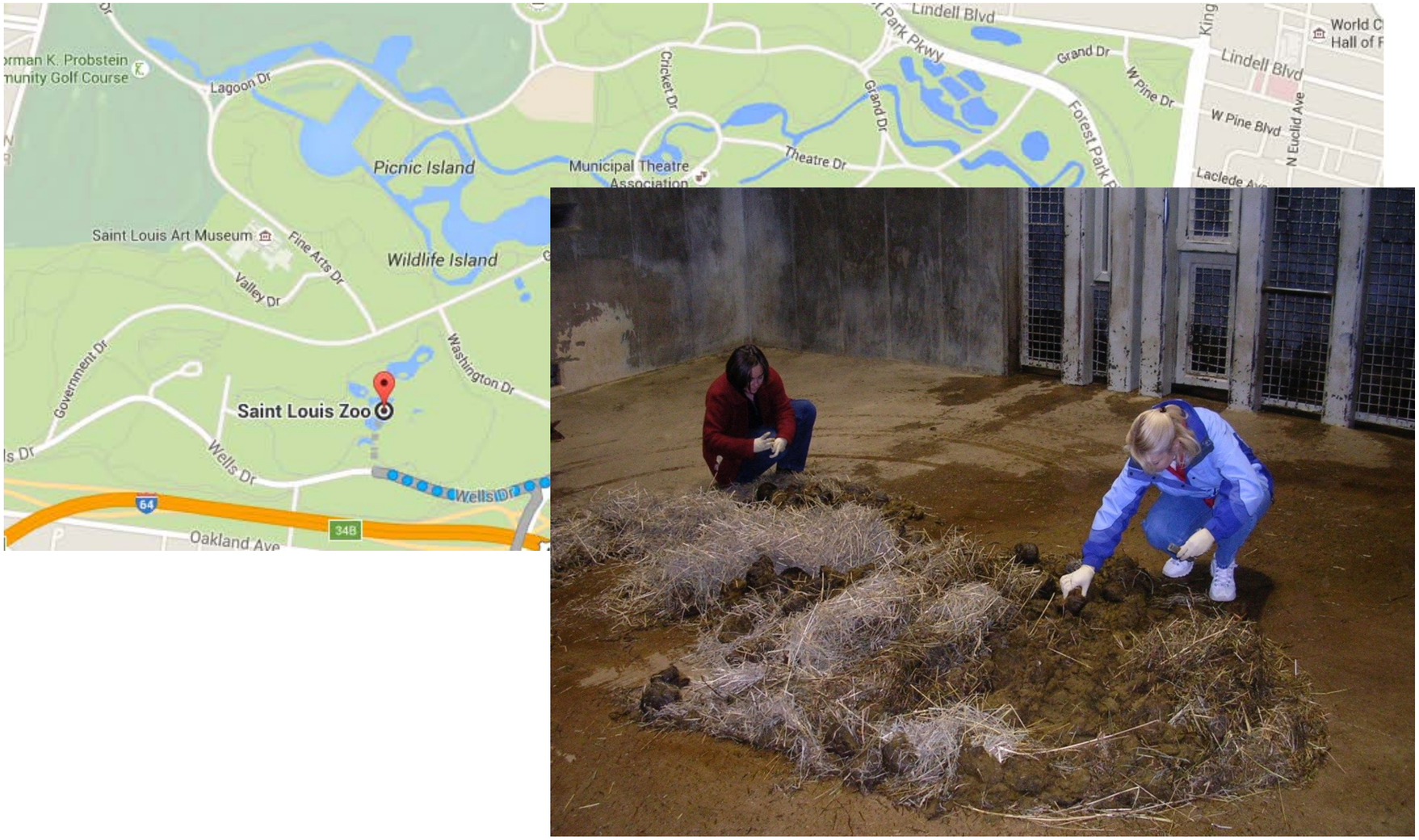

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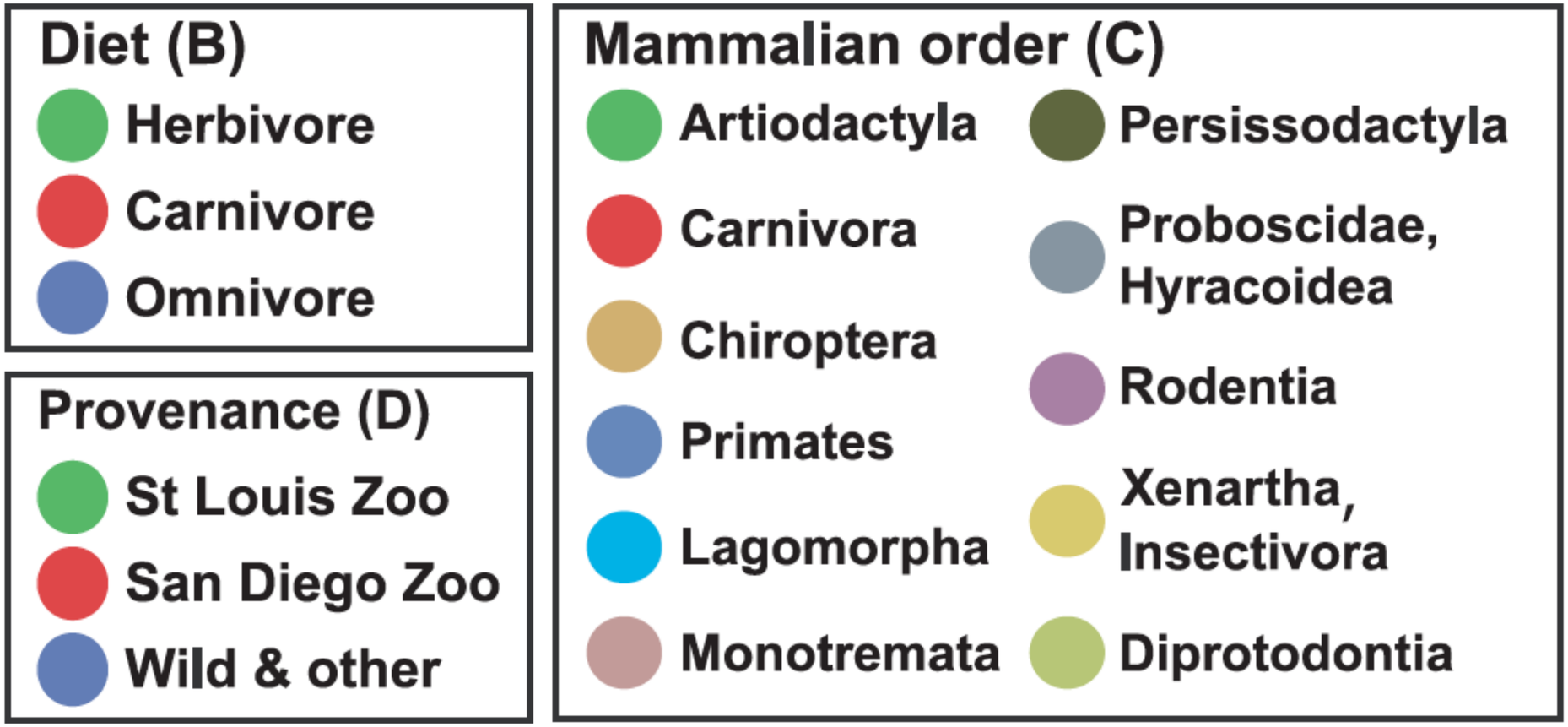
A representative set of mammals



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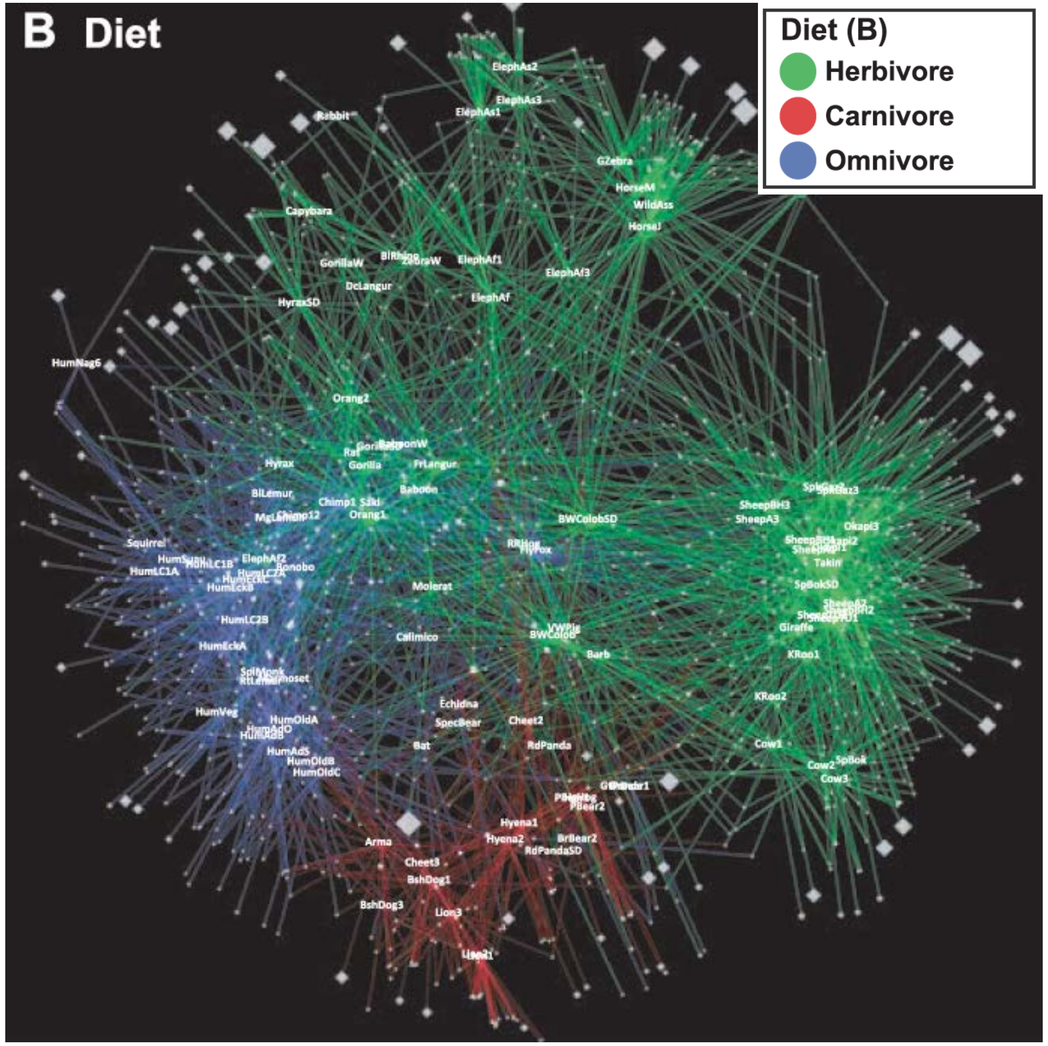
Mammalian gut microbiomes group by diet



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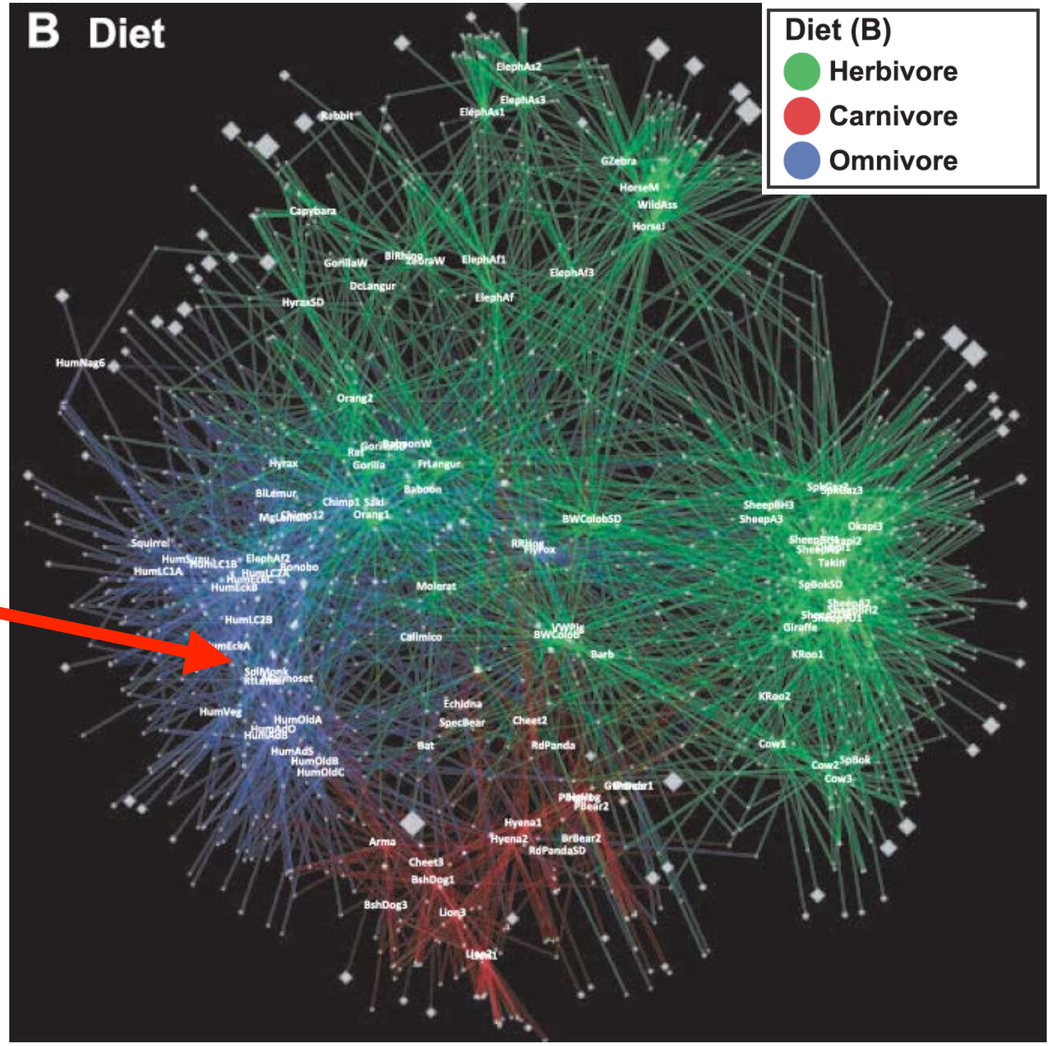

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Our gut microbes are what we eat

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Ley *et al.,* Nature 2006;
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Nutrition Facts

8 servings per container

Serving size 2/3 cup (55g)

Amount per 2/3 cup

Calories 230

% DV*	
12%	**Total Fat** 8g
5%	**Saturated Fat** 1g
	Trans **Fat** 0g
0%	**Cholesterol** 0mg
7%	**Sodium** 160mg
12%	**Total Carbs** 37g
14%	**Dietary Fiber** 4g
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	Protein 3g
10%	**Vitamin D** 2mcg
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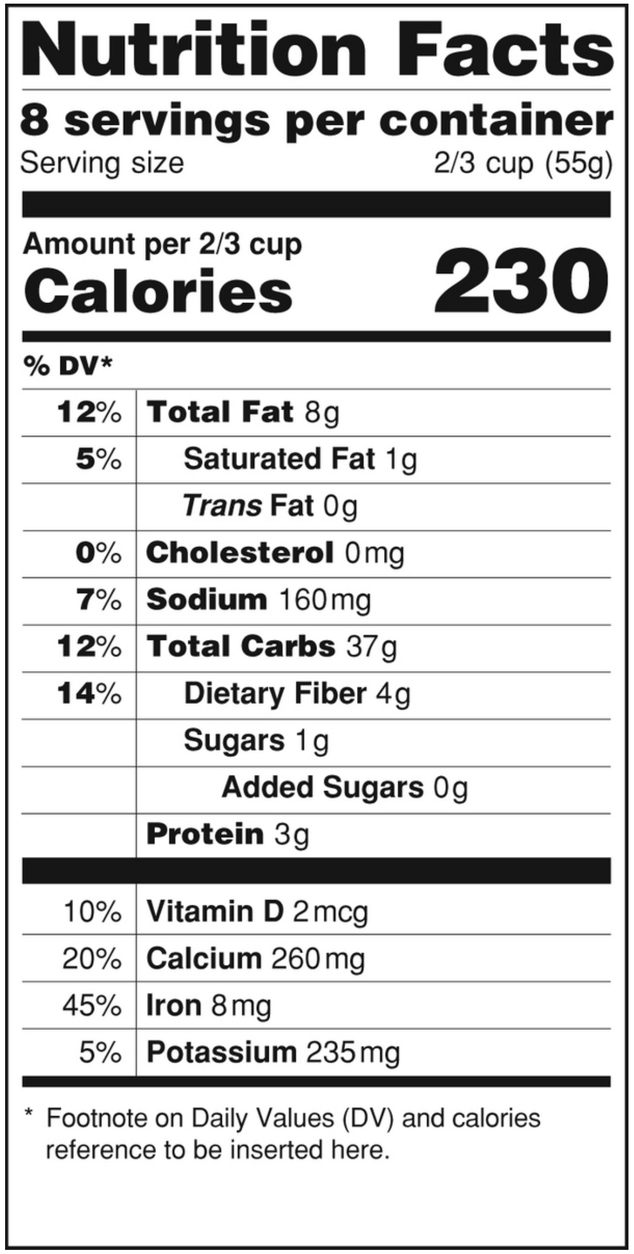

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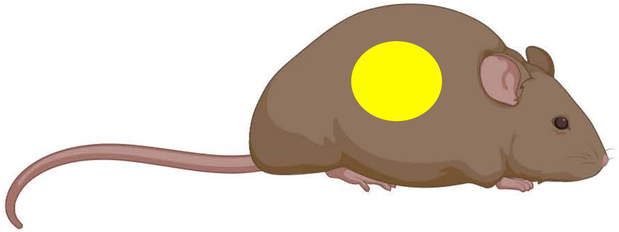
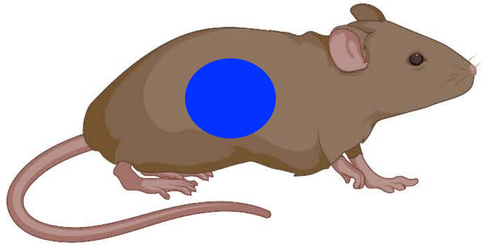
Hypothesis: differences in the microbes in our gut impact the energy we gain from our diet

Differences in gut microbes impact body fat (in mice)

Obese donor





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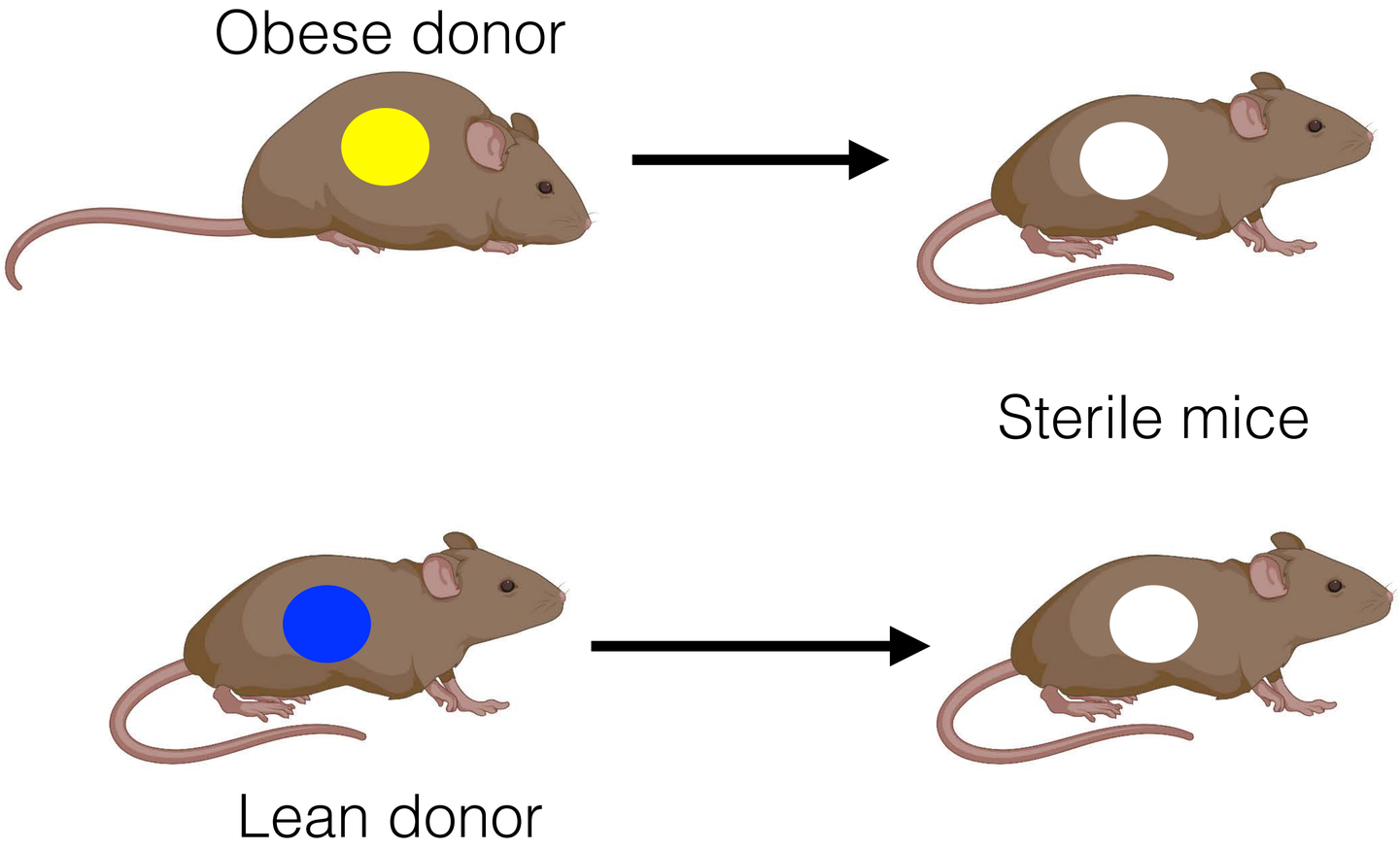

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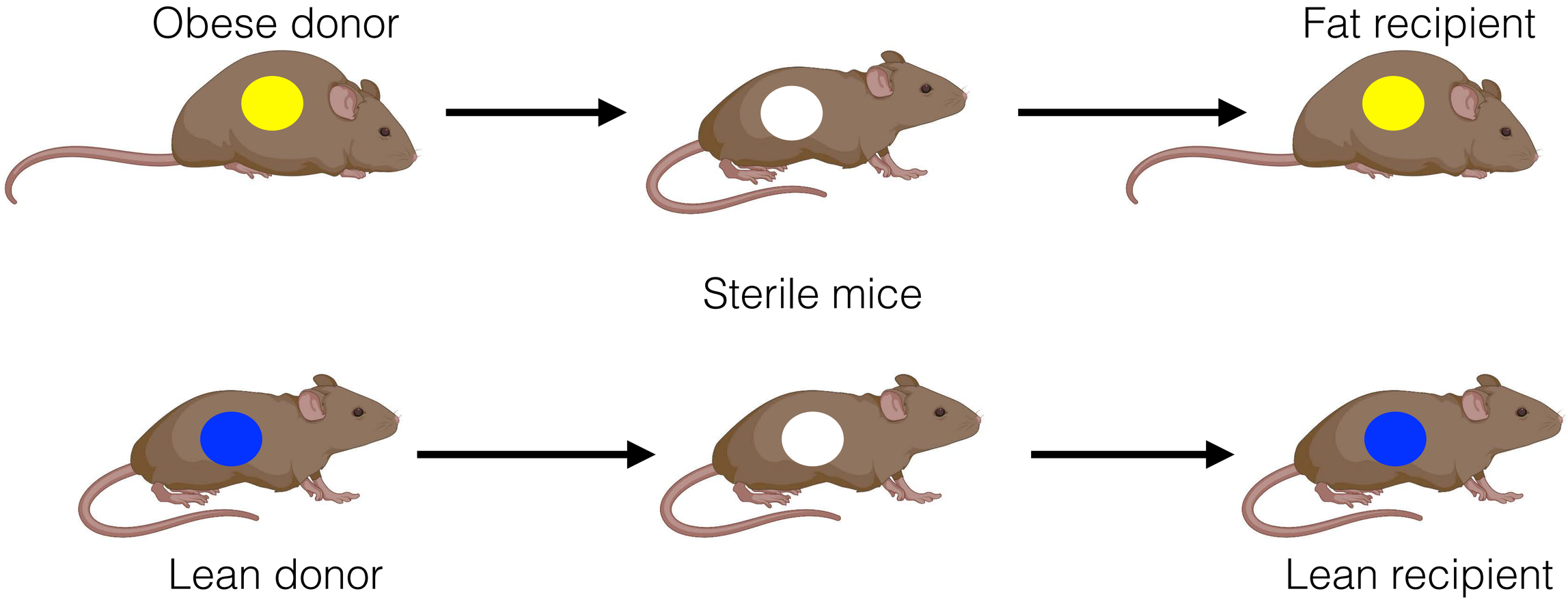

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THE "FAT GENE" MAKES ME OVERWEIGHT!
NAH. TRIED THAT ONE. ONLY WORKED FOR A WHILE.
THE "STRESS HORMONE" MAKES ME OVERINDULGE!
HO-HUM. BEEN THERE, BELIEVED THAT.
THE "OVERLY EFFICIENT INTESTINAL MICROBES" IN MY SYSTEM MAKE ME GAIN WHILE OTHERS LOSE!
GOODBYE, MIRACLE DIETS. HELLO, MIRACLE EXCUSES.
WE FOUND ONE THAT WE CAN REALLY STICK WITH THIS TIME!


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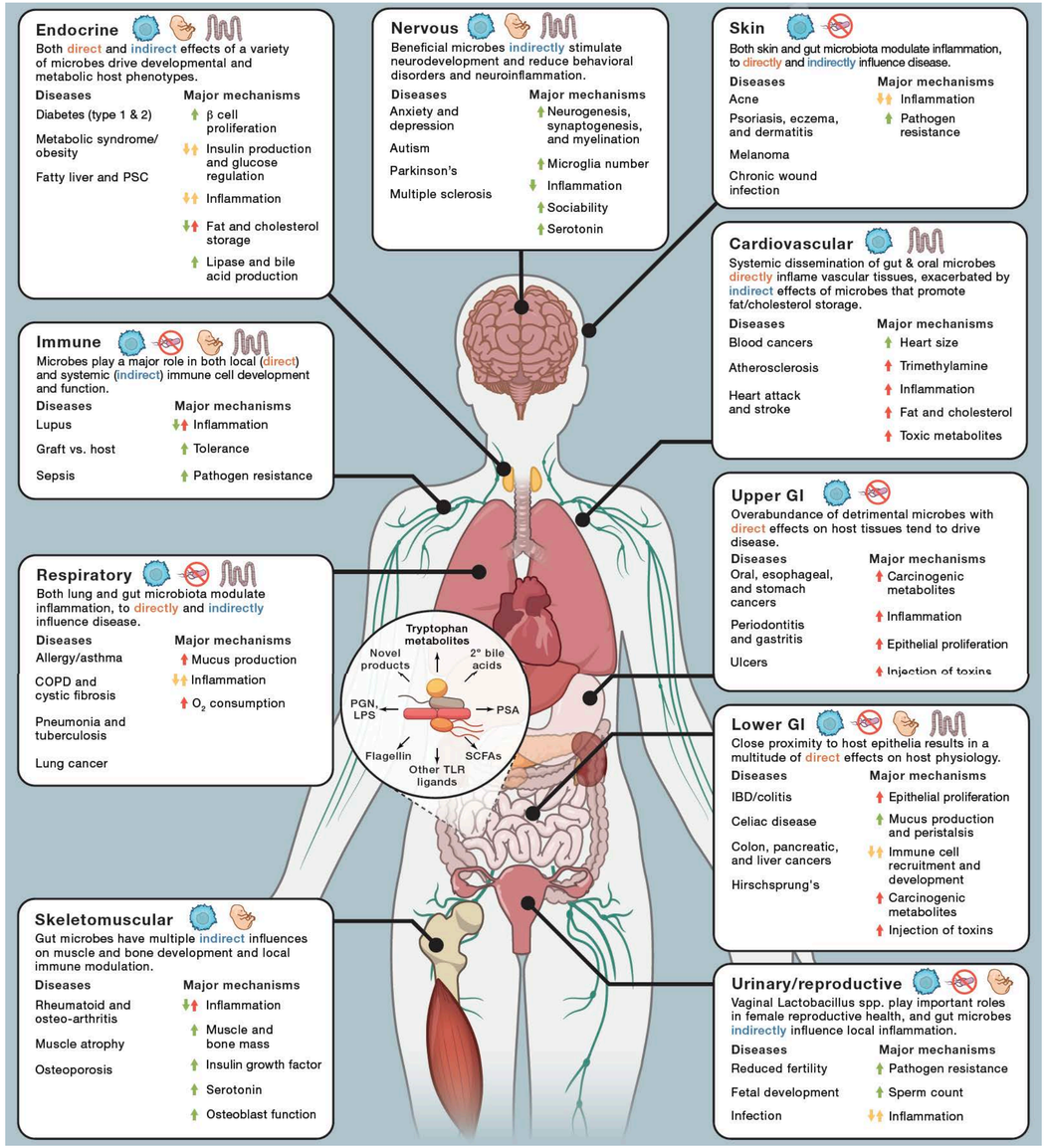
First evidence in humans!

(Basolo *et al.,* Nature Medicine 2020)

The microbiome has broad impacts on host physiology



Hill & Round, Cell 2021

The microbiome has broad impacts on host physiology

Despite all this information we cannot yet predict disease risk from microbiome sequencing data

Hill & Round, Cell 2021

Most of what we know comes from gnotobiotic mice

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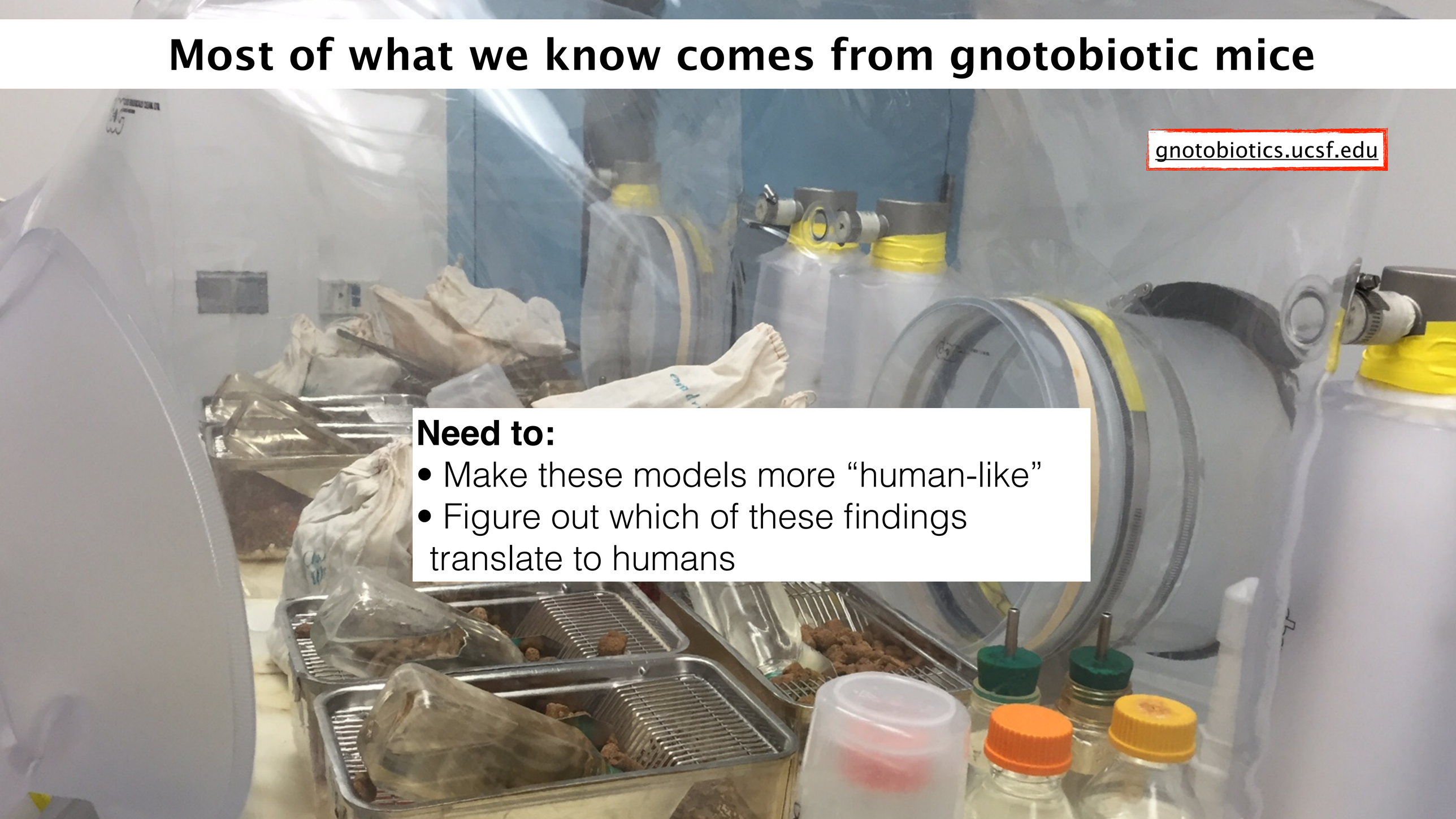
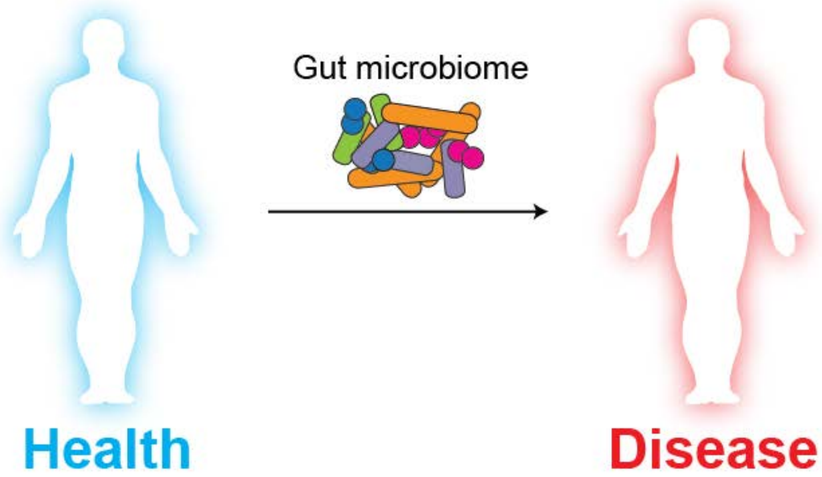


gnotobiotics.ucsf.edu

Need to:

- Make these models more “human-like”
- Figure out which of these findings translate to humans

Shifting our focus to the treatment of disease



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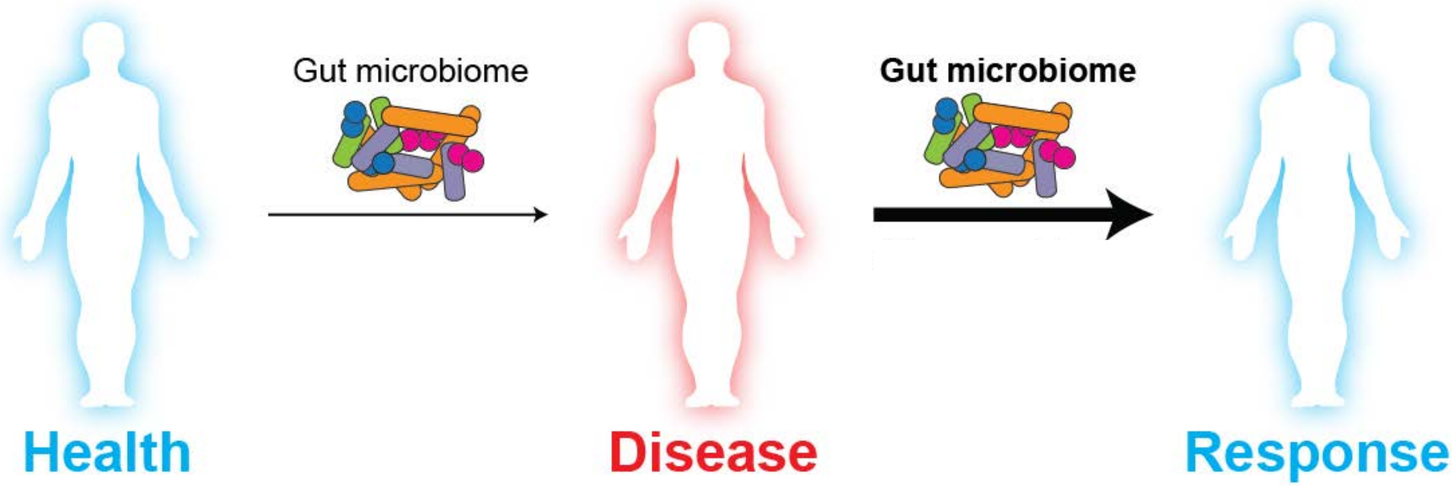

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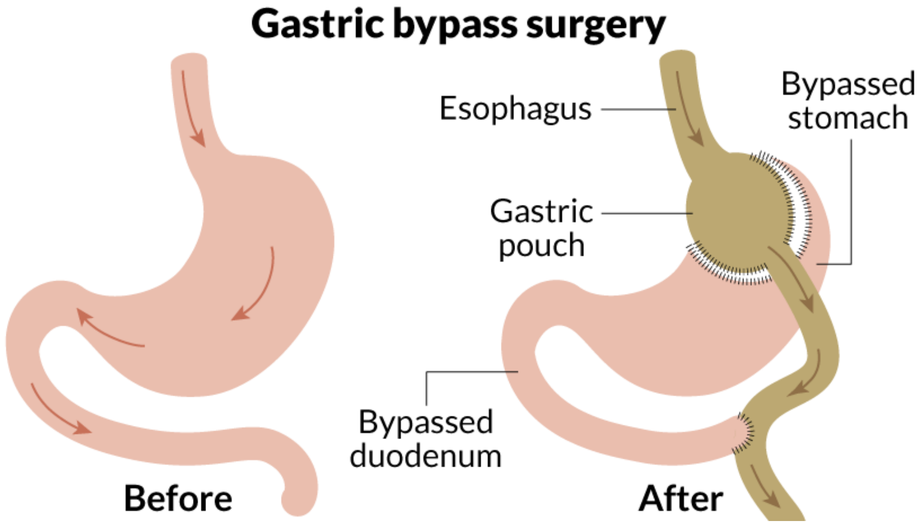

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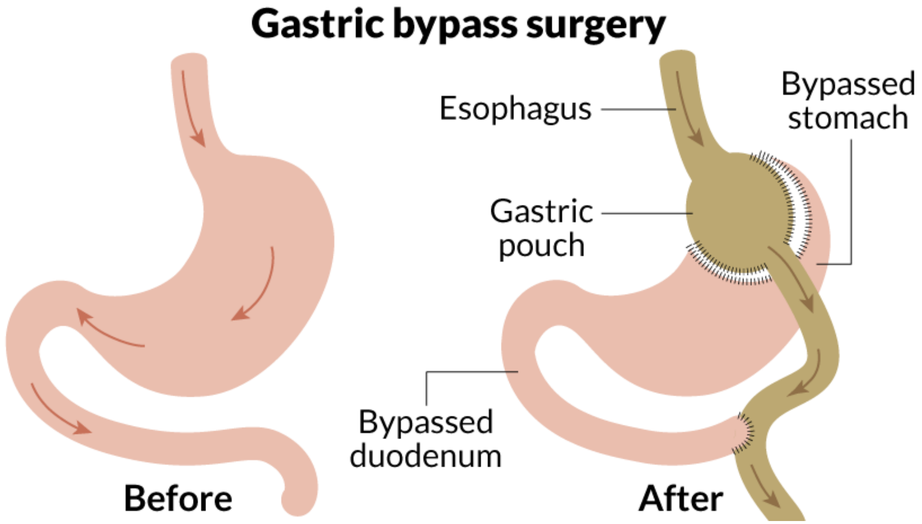

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It’s not just what you eat, it’s how the food is prepared

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Carmody *et al.*, **Nature Micro** 2019

Food coloring

Zou *et al.*, **PNAS** 2021

The promise of probiotics

"**Live** microorganisms that, when administered in **adequate amounts**, confer a **health benefit** on the host" (ISAPP, Nat Rev Gastro Hep 2014)

Mackowiak, Frontiers in Public Health 2013

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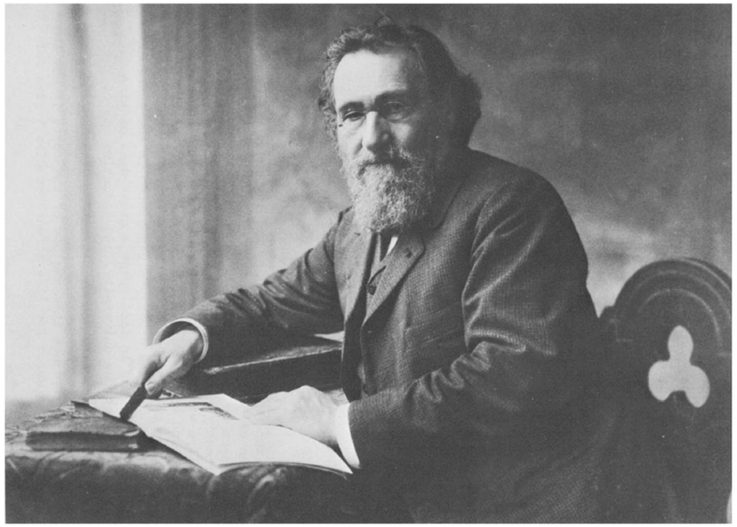

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(1845-1916)

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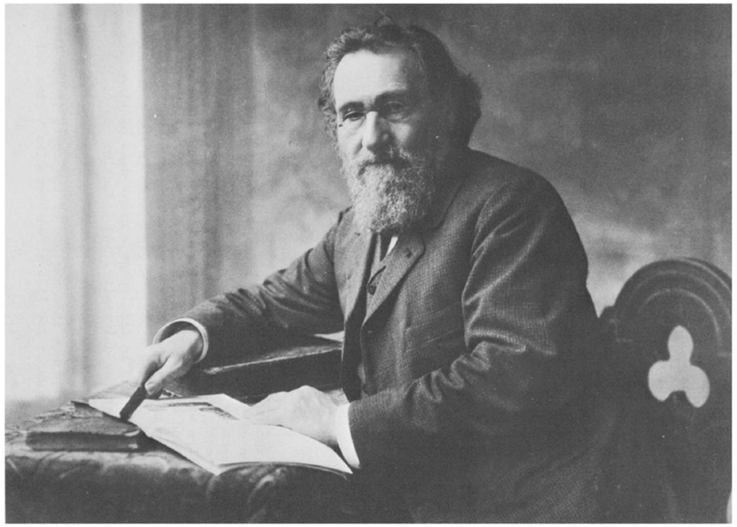

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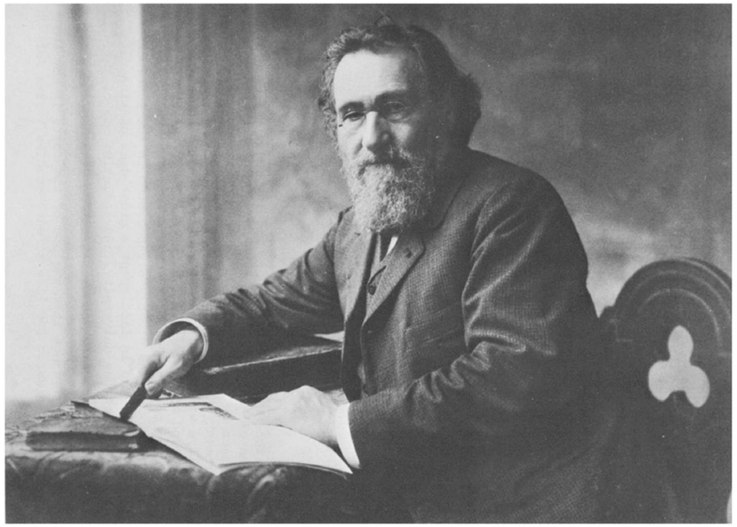

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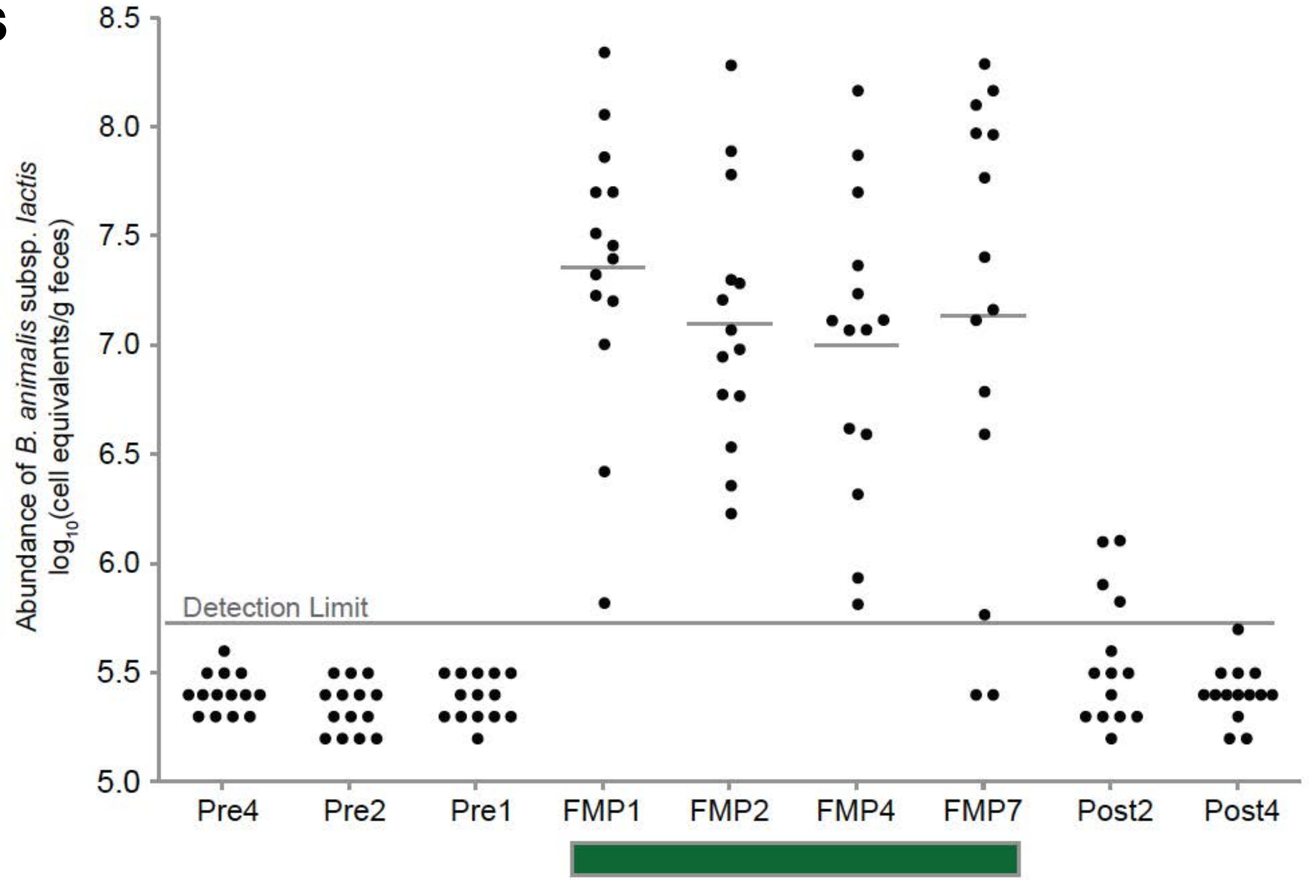
Recommended "soured milk" (yogurt) prepared using *Lactobacillus bulgaricus*

Mackowiak, Frontiers in Public Health 2013

Probiotics and other ingested bacteria don't typically colonize the gut

Humans



McNulty *et al.,* Science Tranl Med 2011

But they can still have permanent effects

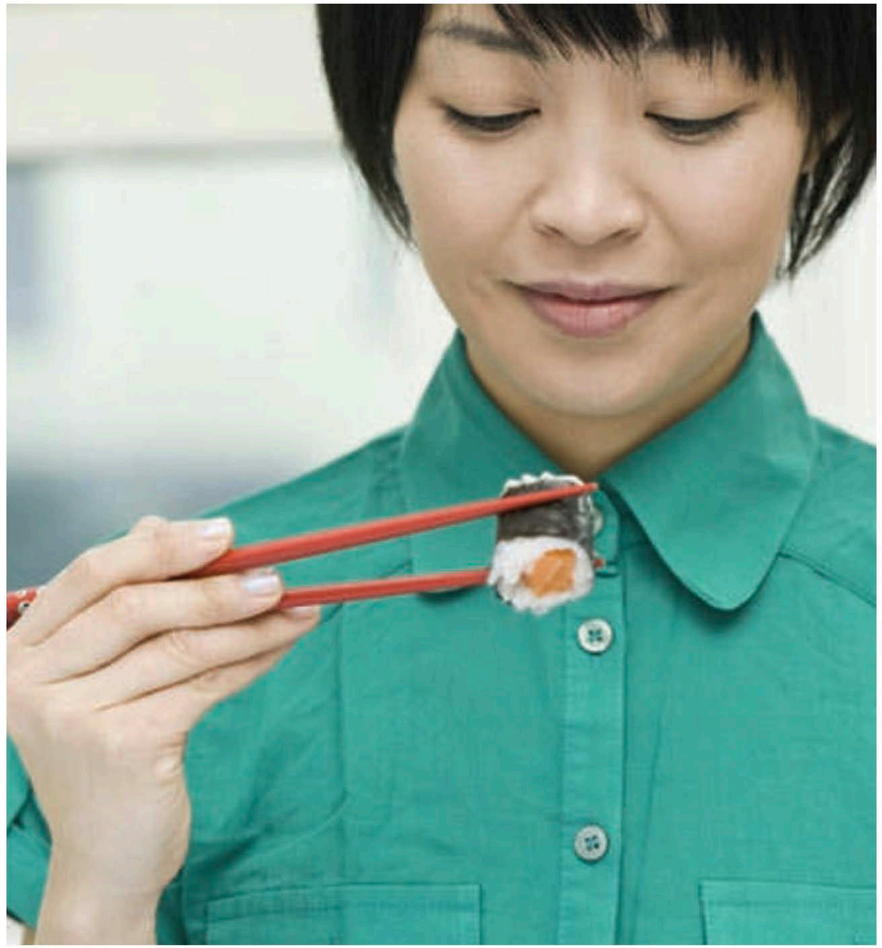


Figure 1 | Hidden helpers. Marine microorganisms that live on seaweed — such as the nori used to wrap sushi — have contributed genes to the intestinal microbiome of Japanese individuals[1].

Hehemann *et al.,* Nature 2010;
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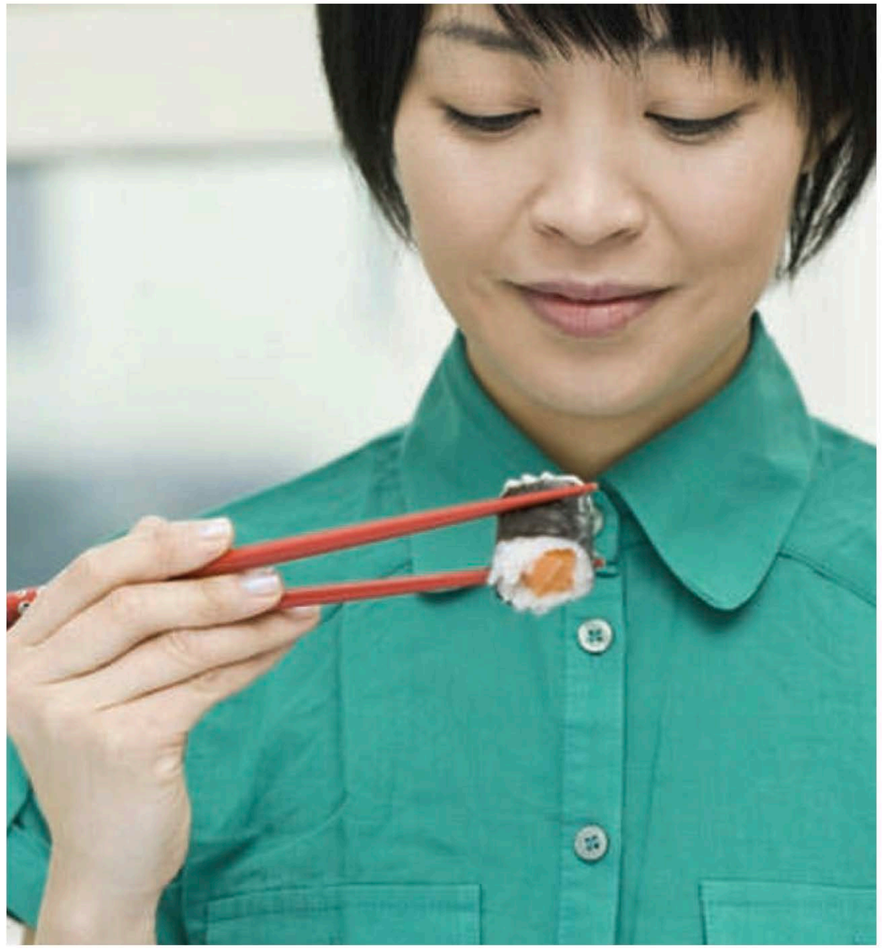

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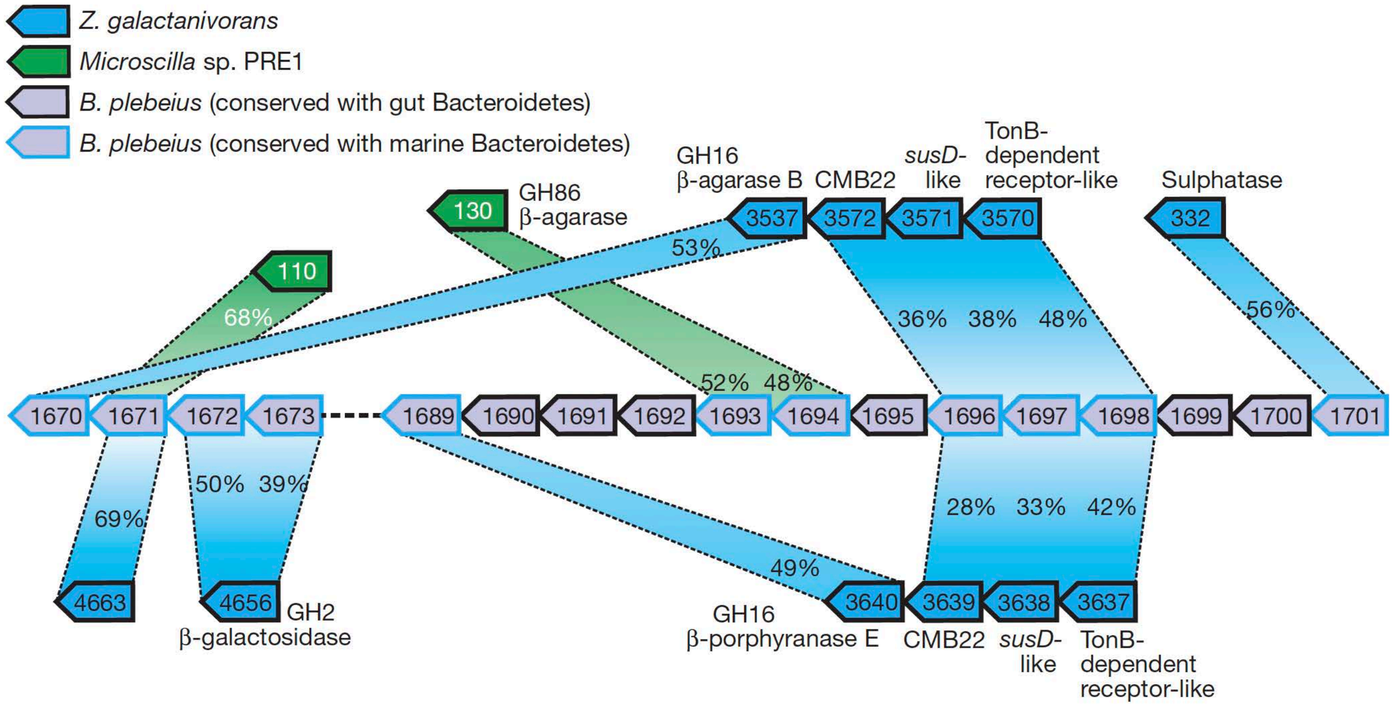

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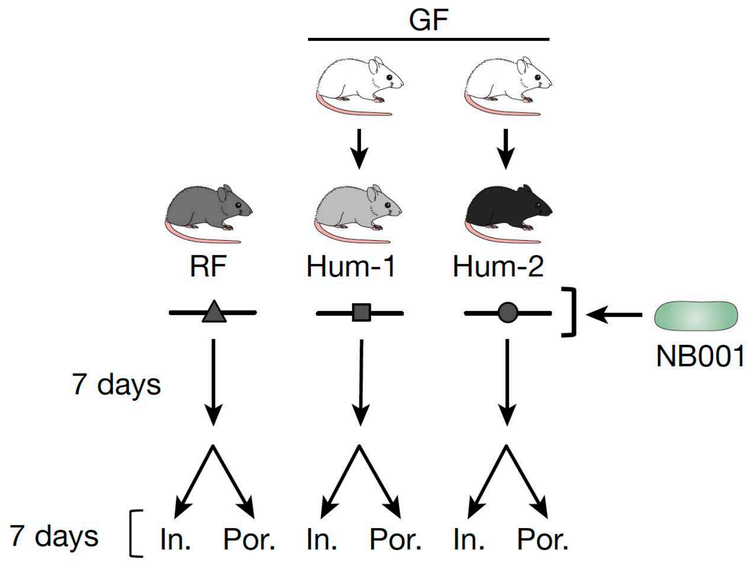
Aiding bacterial colonization with dietary polysaccharides



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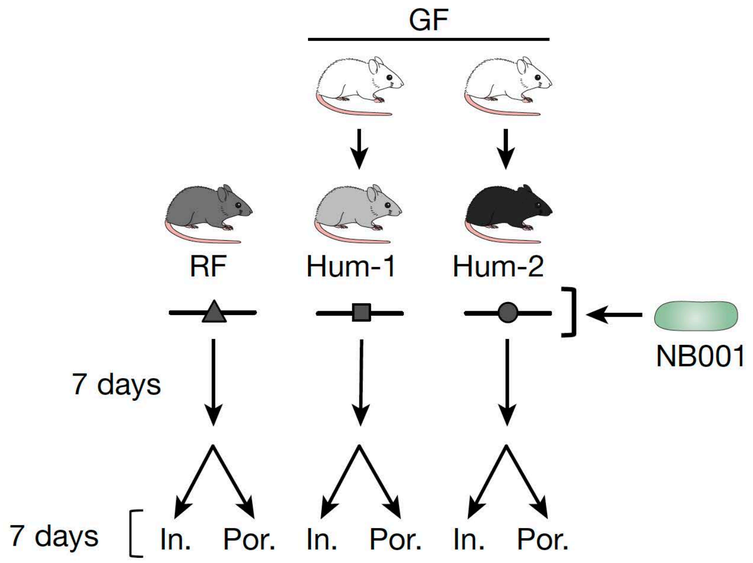

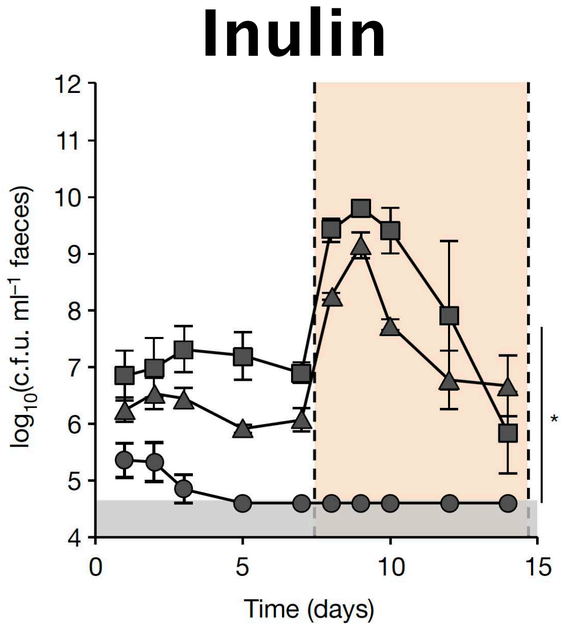

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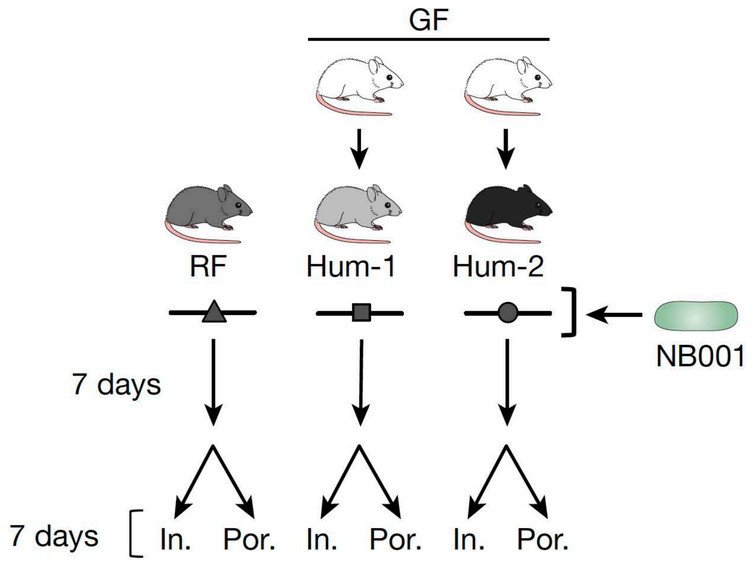

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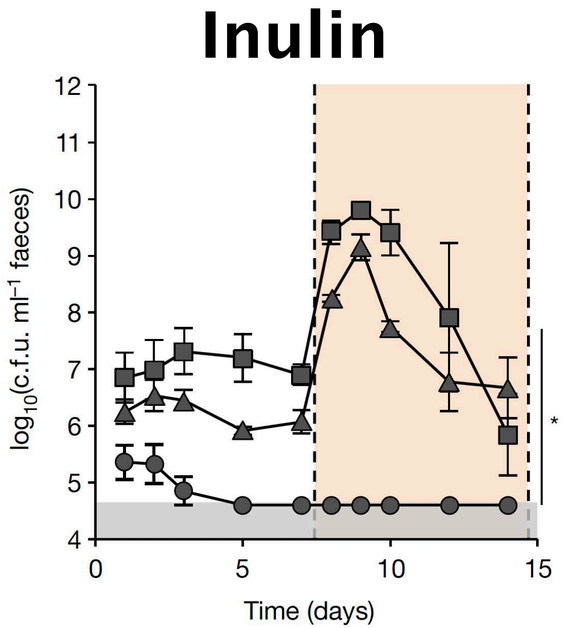

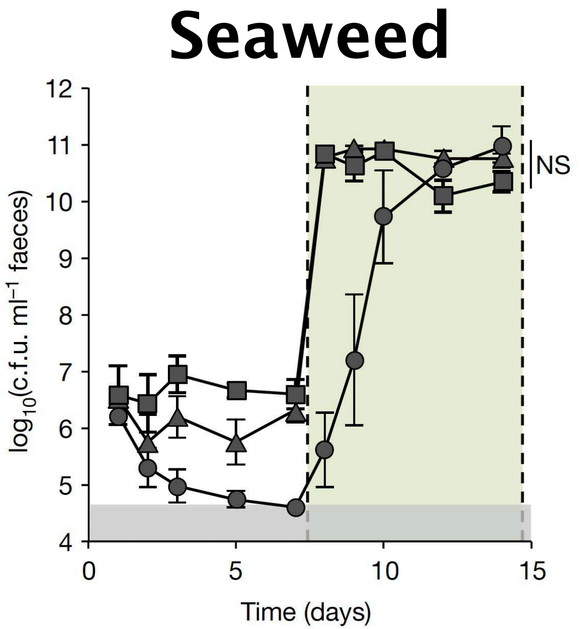

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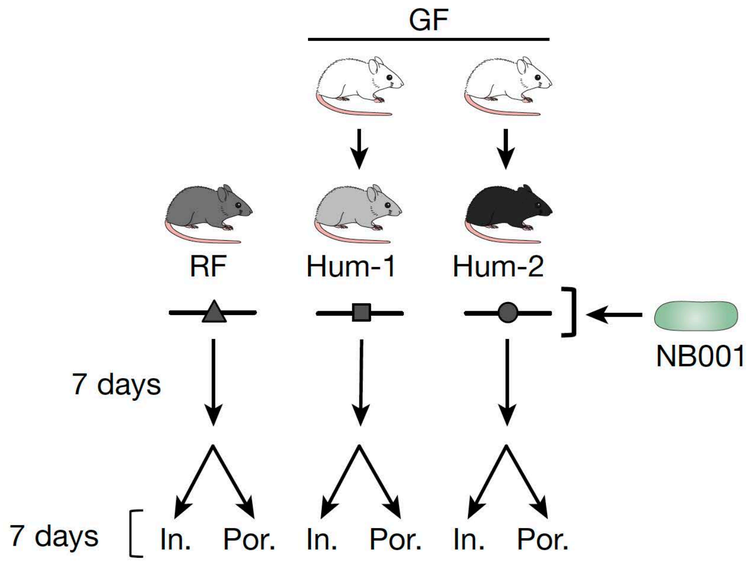

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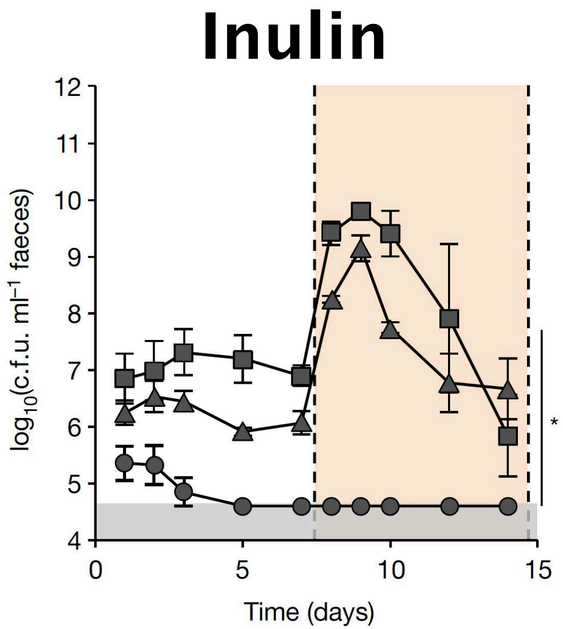
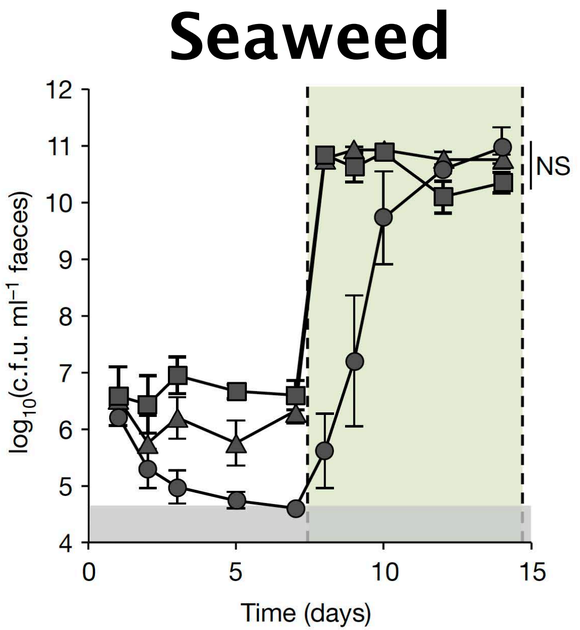




NOVOME BIOTECHNOLOGIES

Shephard *et al.*, Nature 2018

a d M e 2.0

absorption	distribution	metabolism	excretion

Bisanz *et al.*, Drug Metabolism & Disposition 2018

ADME 2.0

absorption	distribution	metabolism	excretion

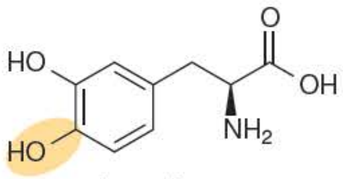
Bisanz *et al.*, Drug Metabolism & Disposition 2018

100s of drugs can be metabolized by gut bacteria

Cancer

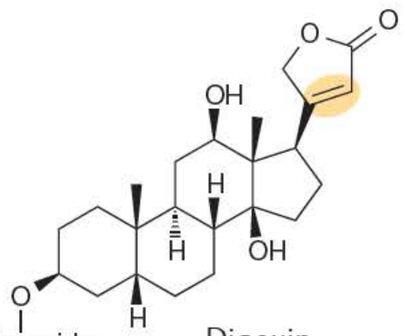
5-Fluorouracil

Parkinson's



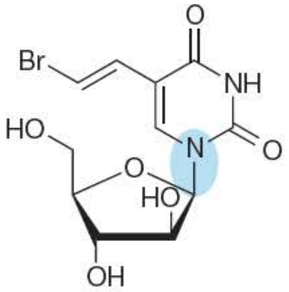
Levodopa

Heart disease



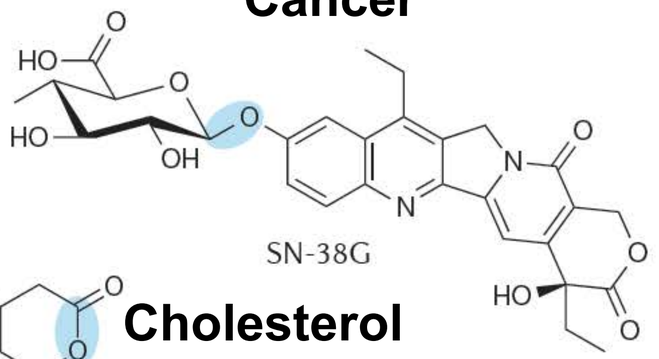
Triglycoside Digoxin

Viral infection



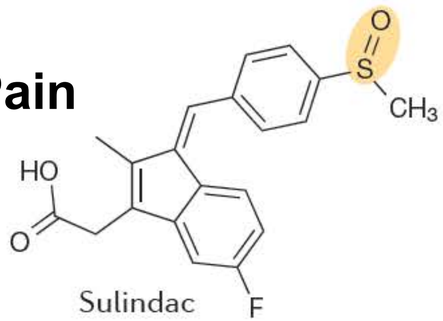
Sorivudine

Cancer



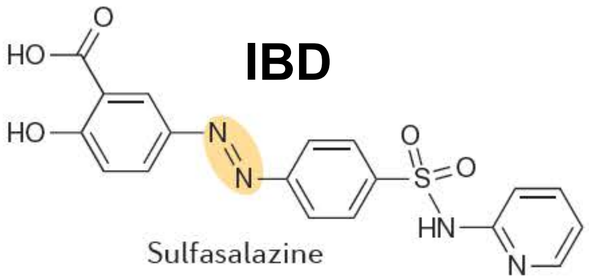
SN-38G

Pain



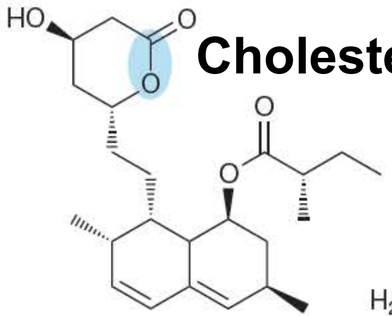
Sulindac

IBD



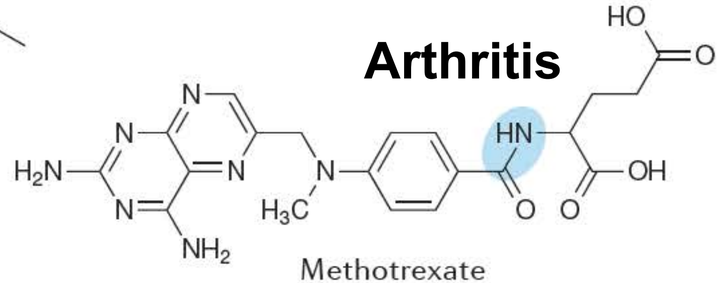
Sulfasalazine

Cholesterol



Lovastatin

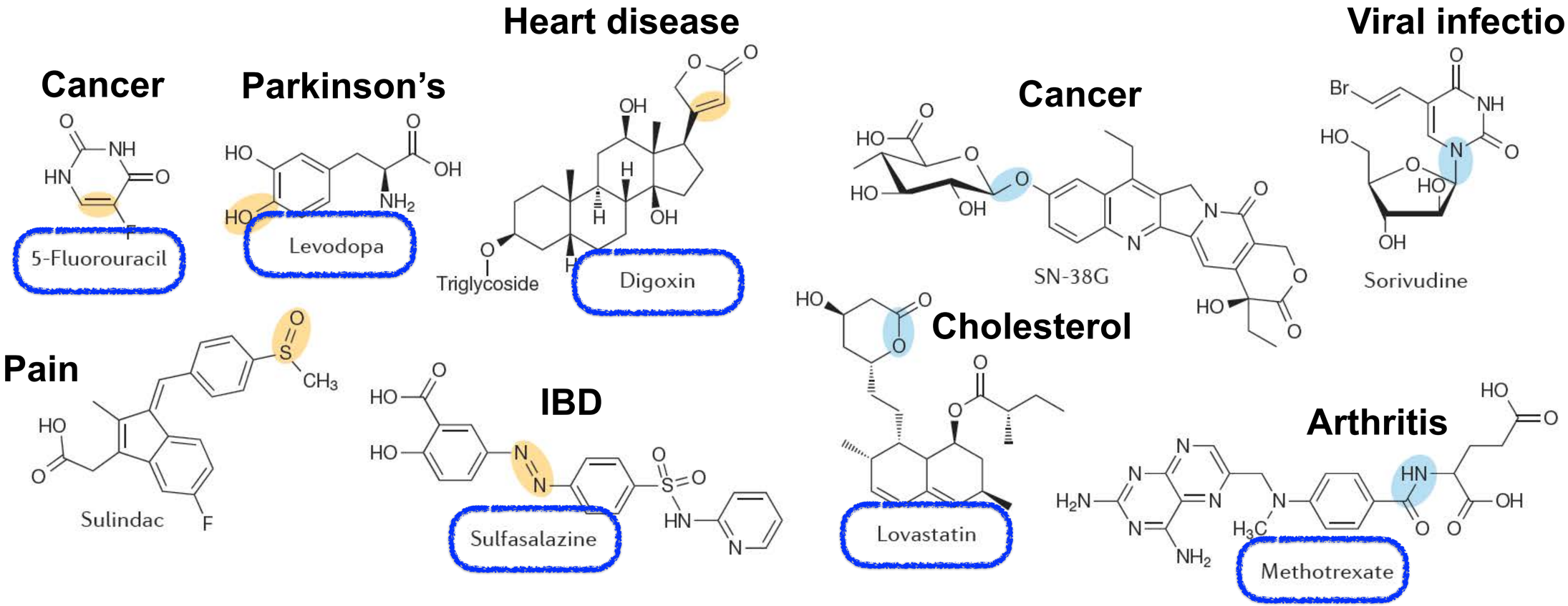
Arthritis



Methotrexate

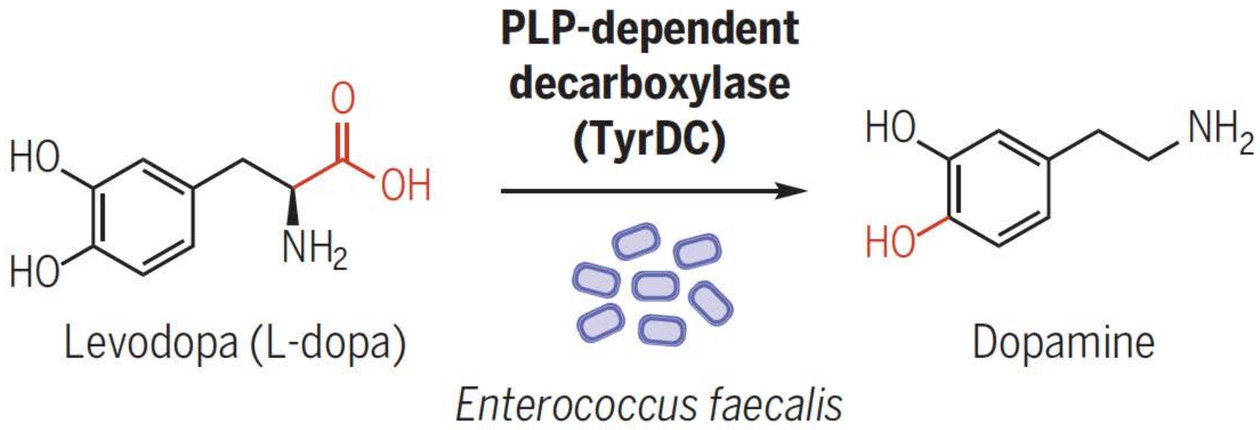
Spanogiannopoulos *et al*., Nature Reviews Microbiology 2016; Lam *et al.,* Cell Host & Microbe 2019; Zimmermann *et al.,* Nature 2019; Javdan *et al.,* Cell 2020

100s of drugs can be metabolized by gut bacteria



Spanogiannopoulos *et al*., Nature Reviews Microbiology 2016; Lam *et al.,* Cell Host & Microbe 2019; Zimmermann *et al.,* Nature 2019; Javdan *et al.,* Cell 2020

Improving the treatment of Parkinson's disease



Rekdal *et al.,* Science 2019

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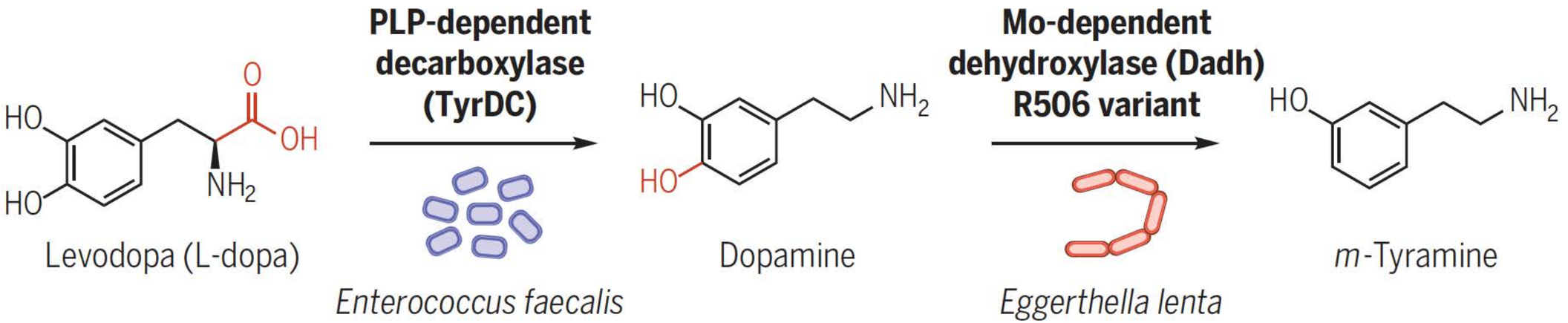

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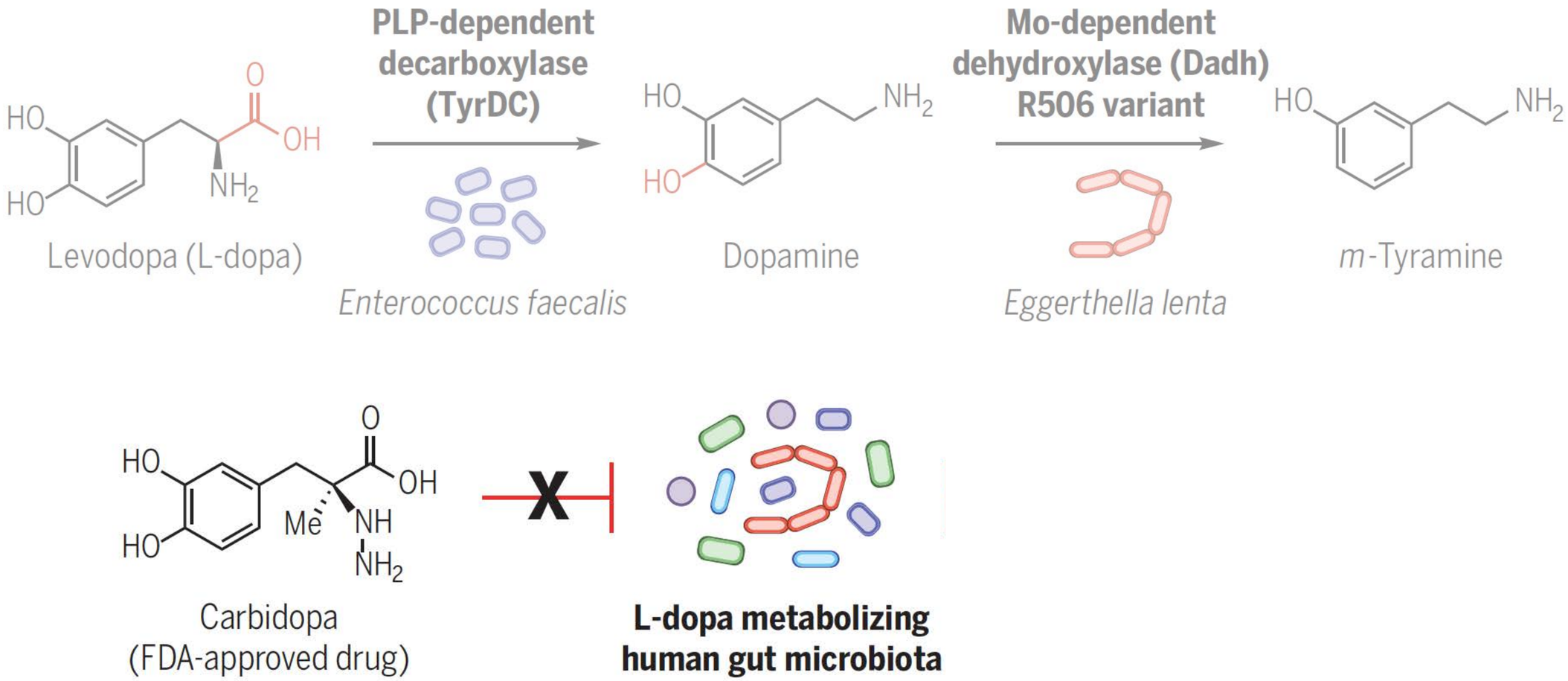

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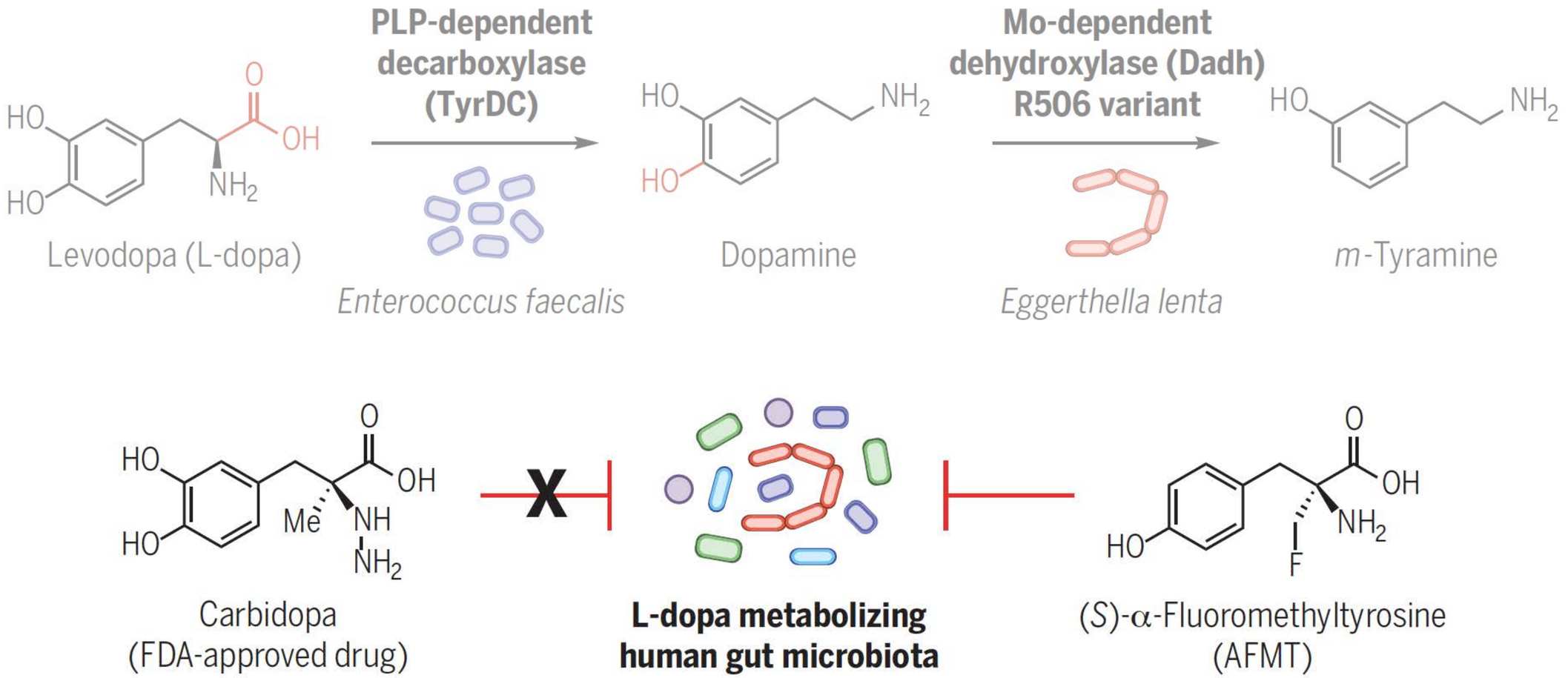


Rekdal *et al.*, Science 2019

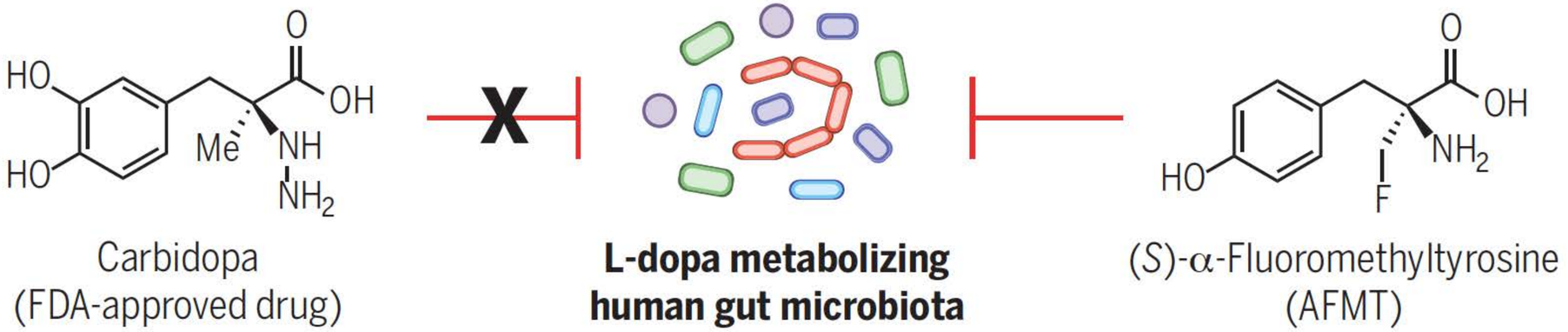
Improving the treatment of Parkinson's disease

Parkinson's Foundation

ClinicalTrials.gov Identifier: NCT03575195

Recruitment Status : Recruiting
First Posted : July 2, 2018
Last Update Posted : August 14, 2020

See **Contacts and Locations**



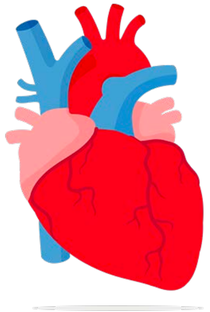
Carbidopa
(FDA-approved drug)

L-dopa metabolizing human gut microbiota

(*S*)-α-Fluoromethyltyrosine
(AFMT)

Rekdal *et al.*, Science 2019

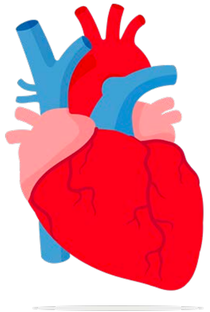
Broad impacts across multiple diseases



Dietary supplements **prevent** bacterial drug inactivation

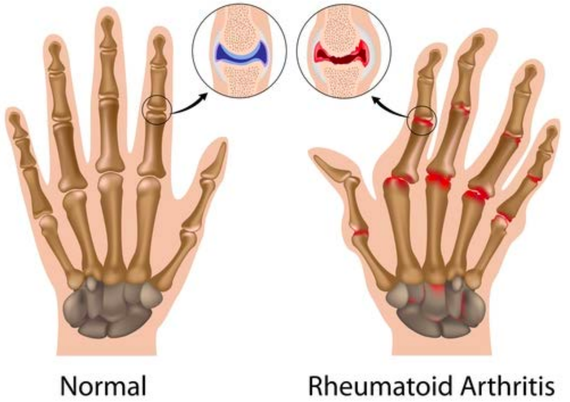
Haiser *et al.,* Science 2013; Isaac *et al.,* Arthritis & Rheumatology 2021; Nayak *et al.,* Cell Host & Microbe 2020; Kyaw *et al.,* BioRxiv 2022

Broad impacts across multiple diseases



Dietary supplements **prevent** bacterial drug inactivation

Predict and **improve** treatment response



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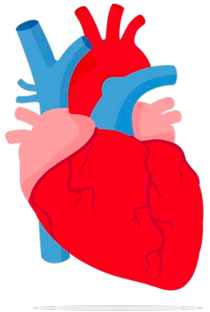

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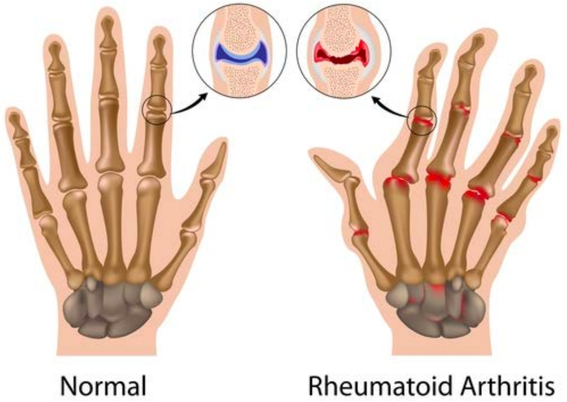
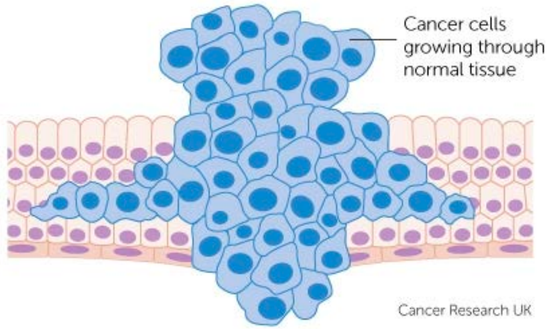
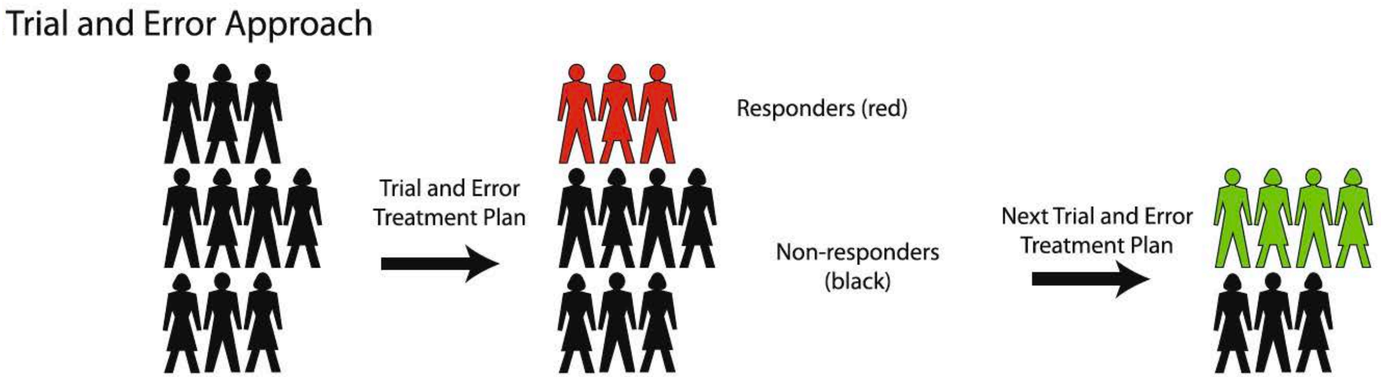




Lessen **side effects** and improve **drug sensitivity**

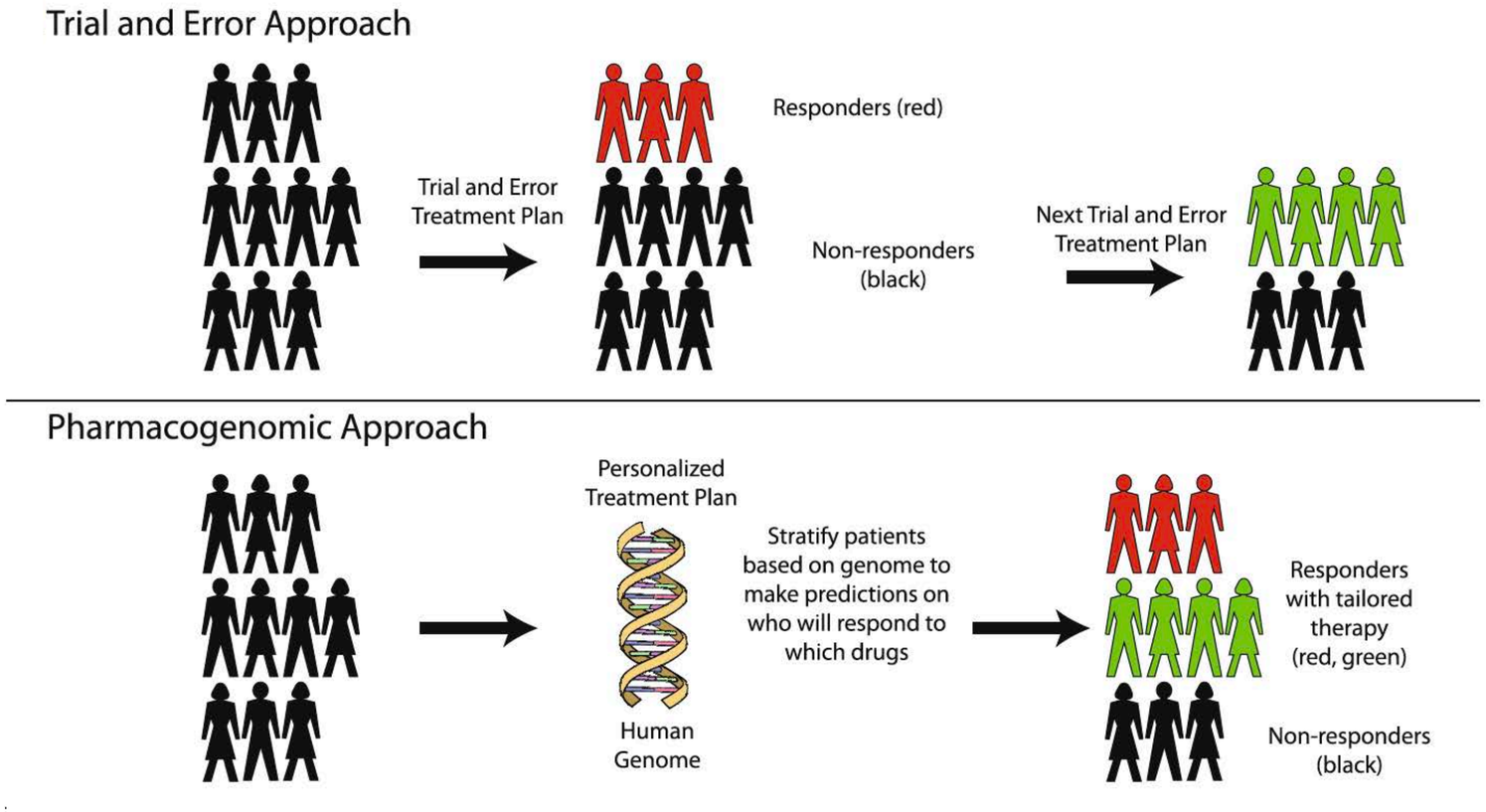
Haiser *et al.,* Science 2013; Isaac *et al.,* Arthritis & Rheumatology 2021; Nayak *et al.,* Cell Host & Microbe 2020; Kyaw *et al.,* BioRxiv 2022

Towards microbiome-based precision medicine



Nayak *et al.*, BMC Med 2016

Towards microbiome-based precision medicine



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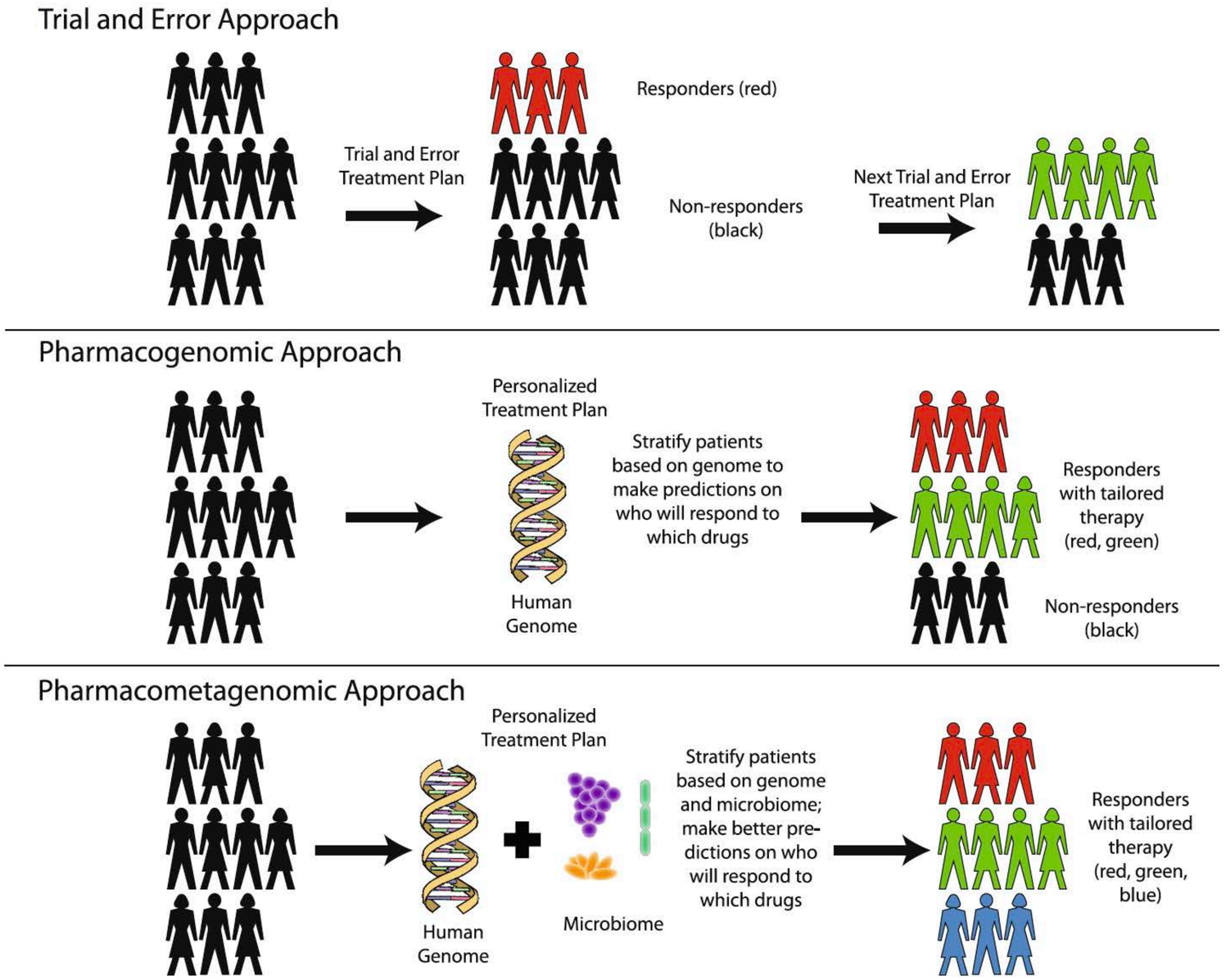

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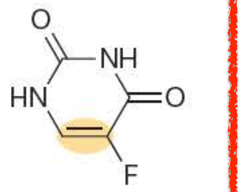
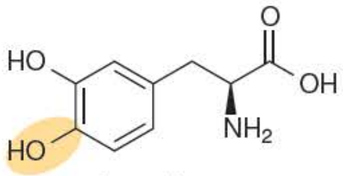


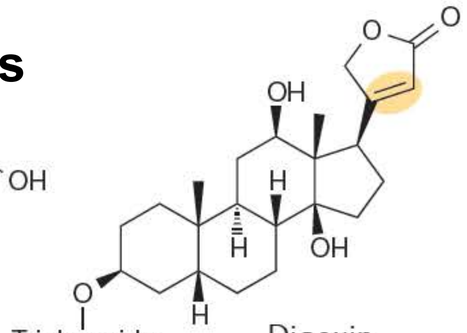
5-Fluorouracil

Parkinson's



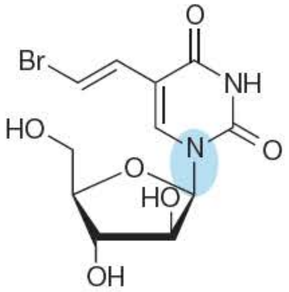
Levodopa

Heart disease



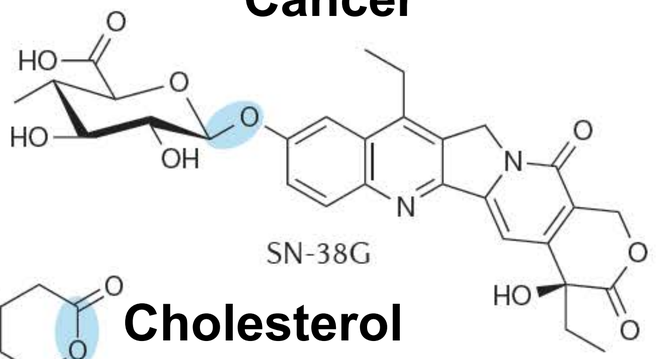
Triglycoside Digoxin

Viral infection



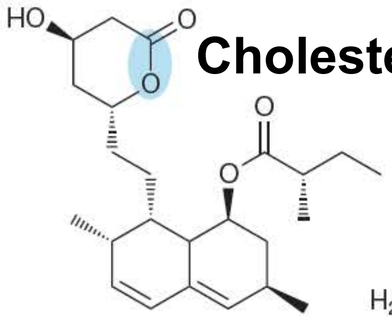
Sorivudine

Cancer



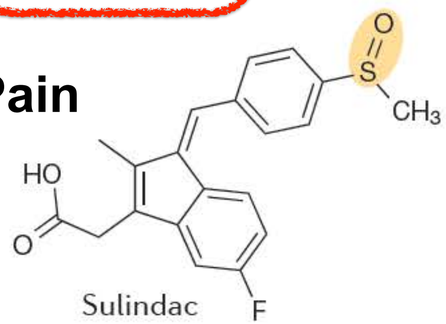
SN-38G

Cholesterol



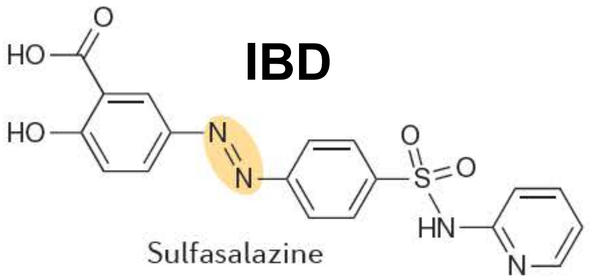
Lovastatin

Pain



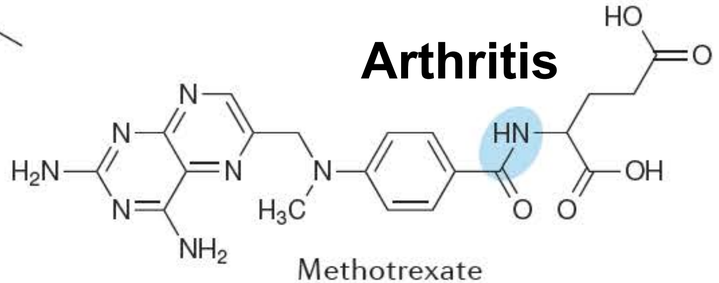
Sulindac

IBD



Sulfasalazine

Arthritis



Methotrexate

Spanogiannopoulos *et al*., Nature Reviews Microbiology 2016; Lam *et al.,* Cell Host & Microbe 2019; Zimmermann *et al.,* Nature 2019; Javdan *et al.,* Cell 2020

Clinical motivations for this work

Oral cancer chemotherapy

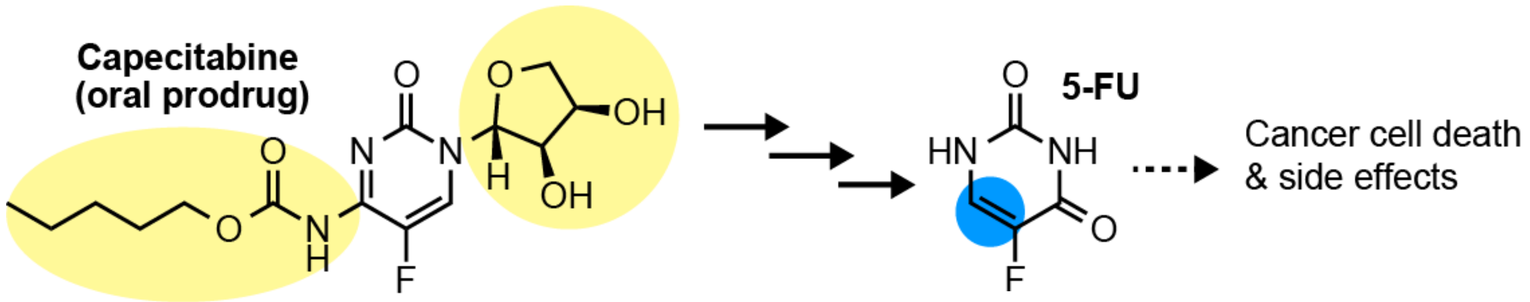
Capecitabine (CAP):

- Meets FDA criteria for a “highly variable” drug
- Diet and host genetics do not explain variations in PK
- Adverse reactions require dose adjustments in 35% of patients, end of therapy in 10%
- GI side effects are common
- Unexplained regional differences in tolerability

Peter Spanogiannopoulos
CIHR fellow
Now at Novome Biotech

Saif *et al.,* 2007, Haller *et al.,* 2008, Leonard *et al.,* 2011, Gadiko *et al.,* 2012, Jennings *et al.,* 2013

Microbiological motivations for this work



Horowitz *et al.,* 1960, Bloch & Hutchison 1964, Stringer *et al.,* 2009, von Bultzingslowen *et al.,* 2003, Stringer *et al.,* 2007, van Vliet *et al.,* 2009, Garcia-Gonzalez *et al.,* Cell 2017, Rosener *et al.,* 2020

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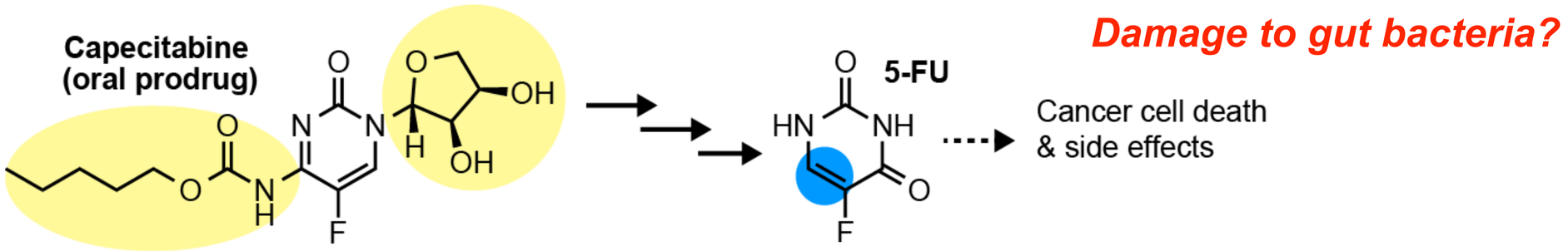

Damage to gut bacteria?

Horowitz *et al.,* 1960, Bloch & Hutchison 1964, Stringer *et al.,* 2009, von Bultzingslowen *et al.,* 2003, Stringer *et al.,* 2007, van Vliet *et al.,* 2009, Garcia-Gonzalez *et al.,* Cell 2017, Rosener *et al.,* 2020

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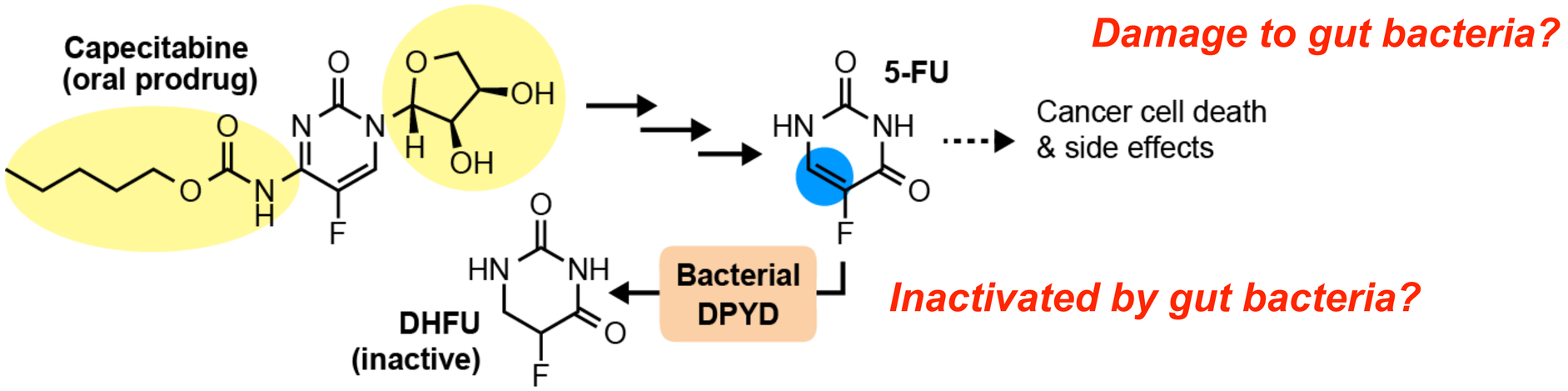

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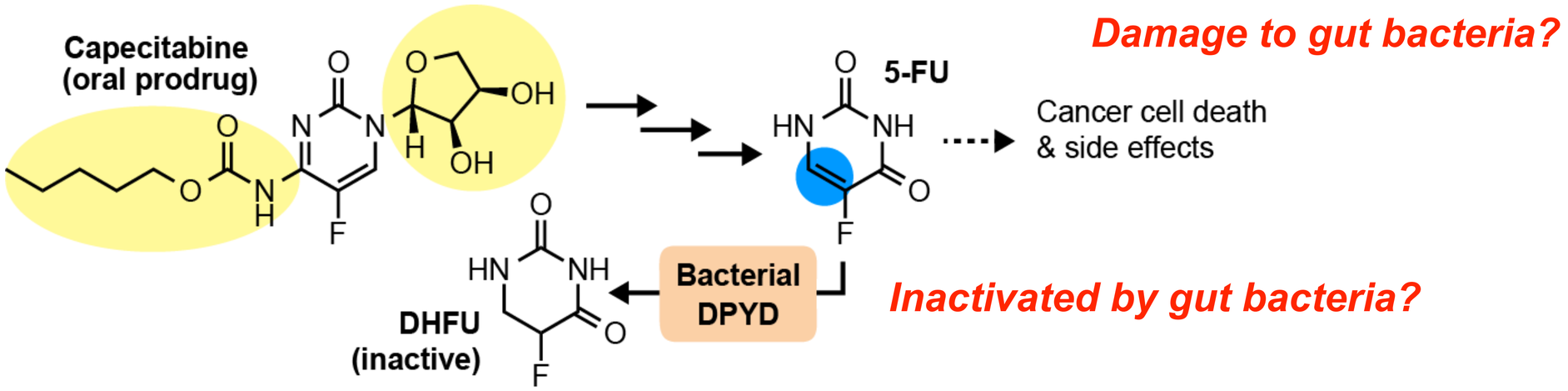
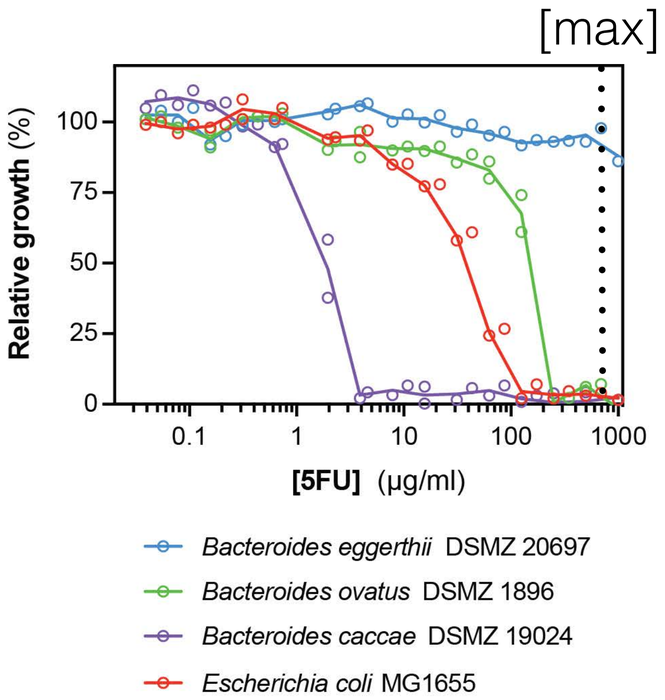


- Data in bacterial cultures, rats, and humans suggest that fluoropyrimidines alter the gut microbiota
- Data in worms demonstrate that genetic differences in dietary *E. coli* lead to altered drug toxicity

Horowitz *et al.,* 1960, Bloch & Hutchison 1964, Stringer *et al.,* 2009, von Bultzingslowen *et al.,* 2003, Stringer *et al.,* 2007, van Vliet *et al.,* 2009, Garcia-Gonzalez *et al.,* Cell 2017, Rosener *et al.,* 2020

5-FU inhibits the growth of diverse human gut bacteria



Spanogiannopoulos*, Kyaw*, *et al., Nature* in review; BioRxiv 2022

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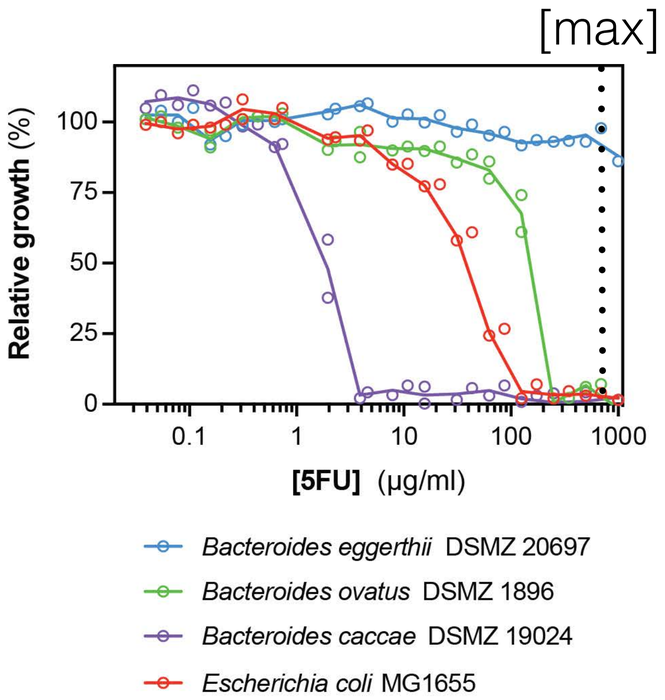

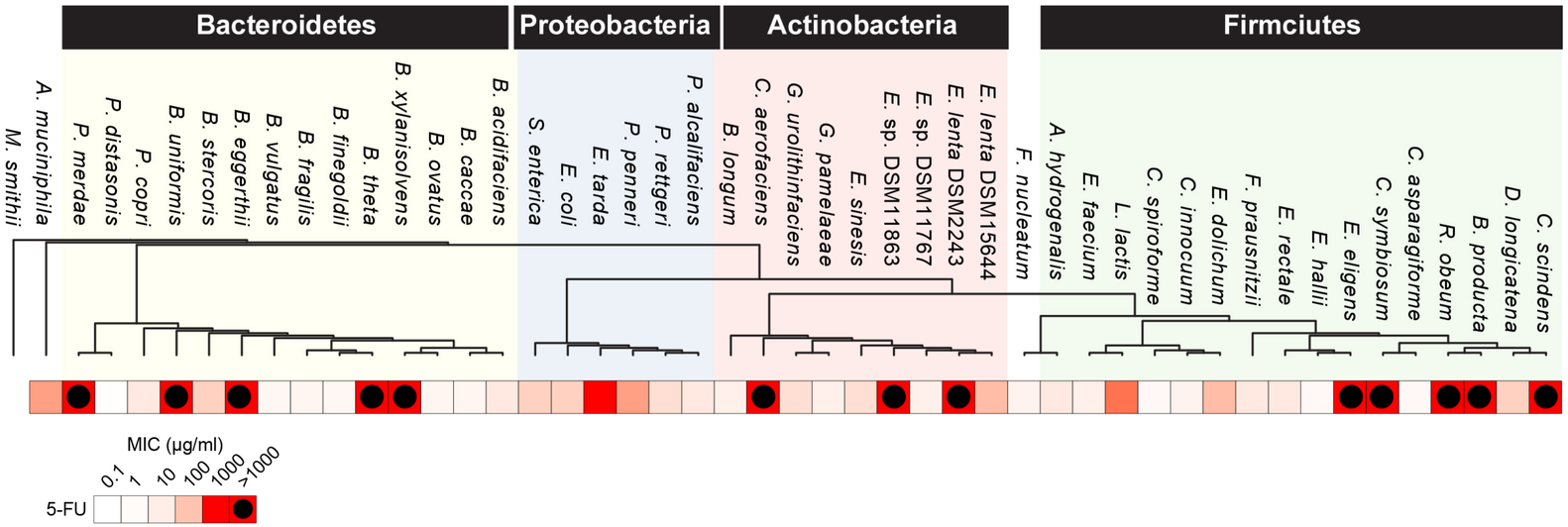

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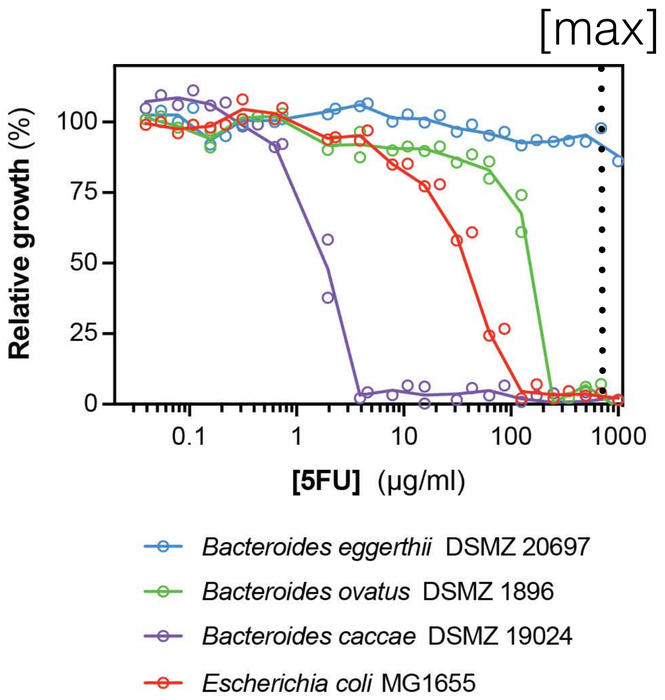
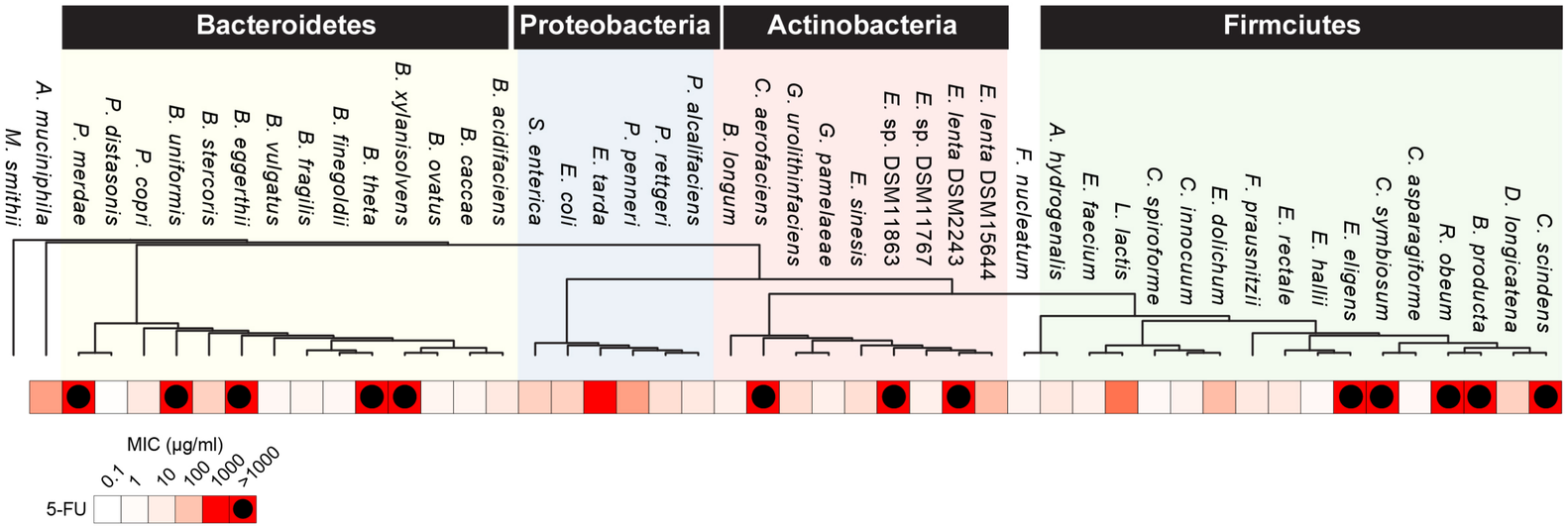
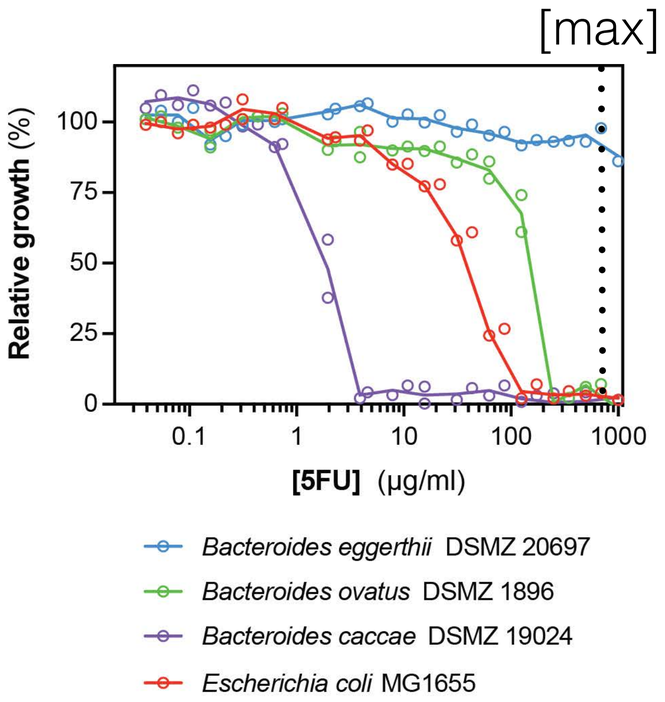


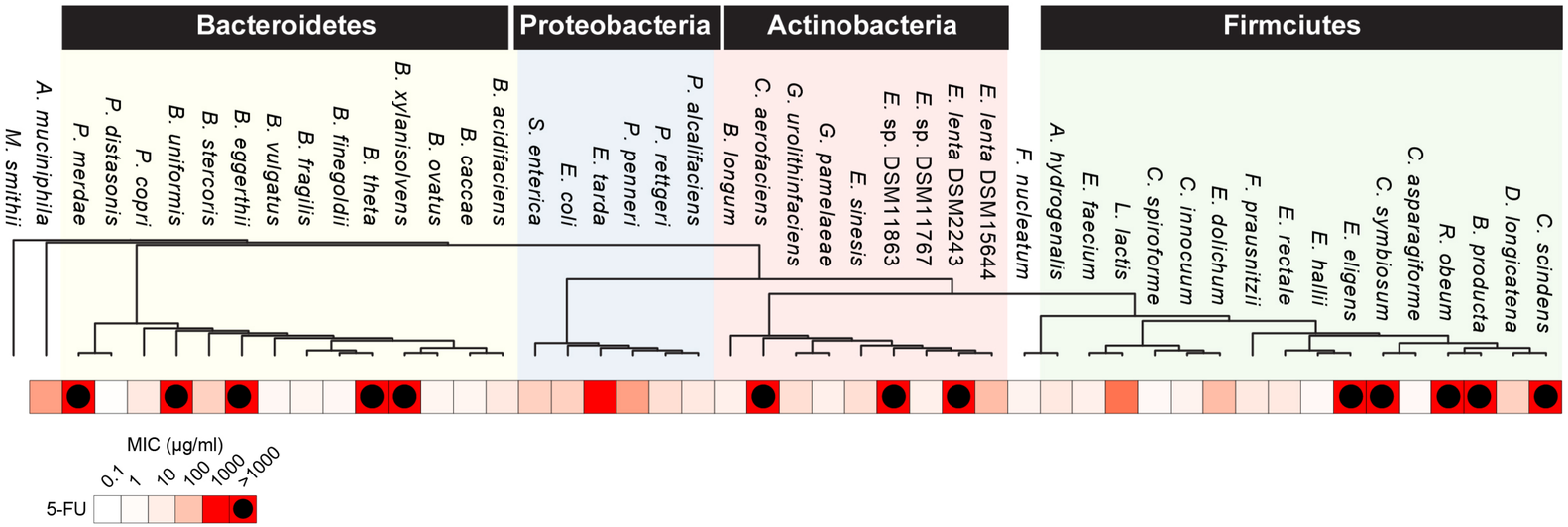


- Media supplementation / genetics support the expected target thymidylate synthase

Spanogiannopoulos*, Kyaw*, *et al., Nature* in review; BioRxiv 2022

5-FU inhibits the growth of diverse human gut bacteria

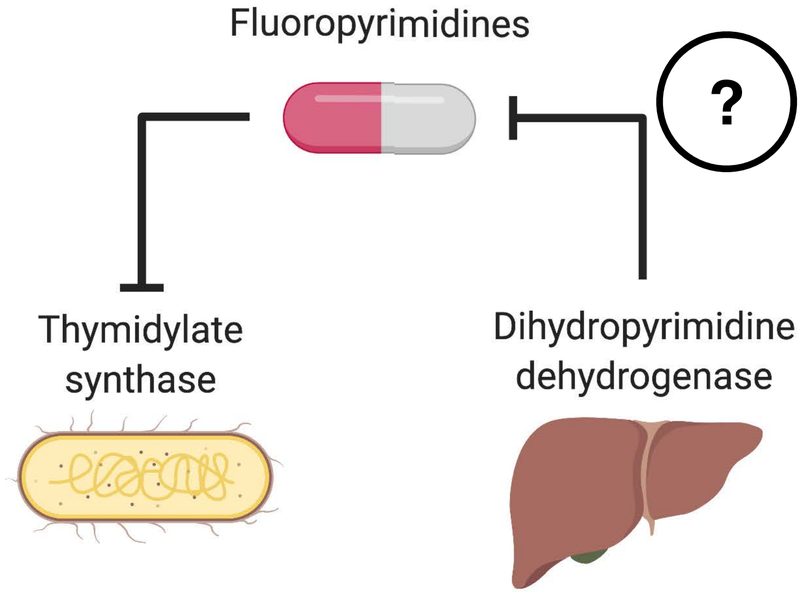




- Media supplementation / genetics support the expected target thymidylate synthase
- Identified downstream pathways impacted by RNA sequencing

Spanogiannopoulos*, Kyaw*, *et al., Nature* in review; BioRxiv 2022

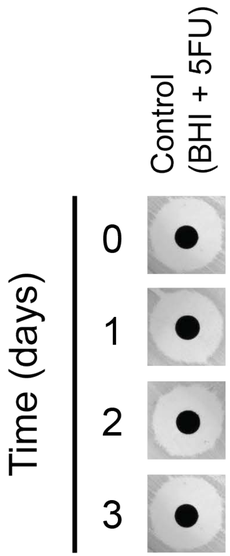
The targets are conserved, but what about the mechanisms for drug inactivation?



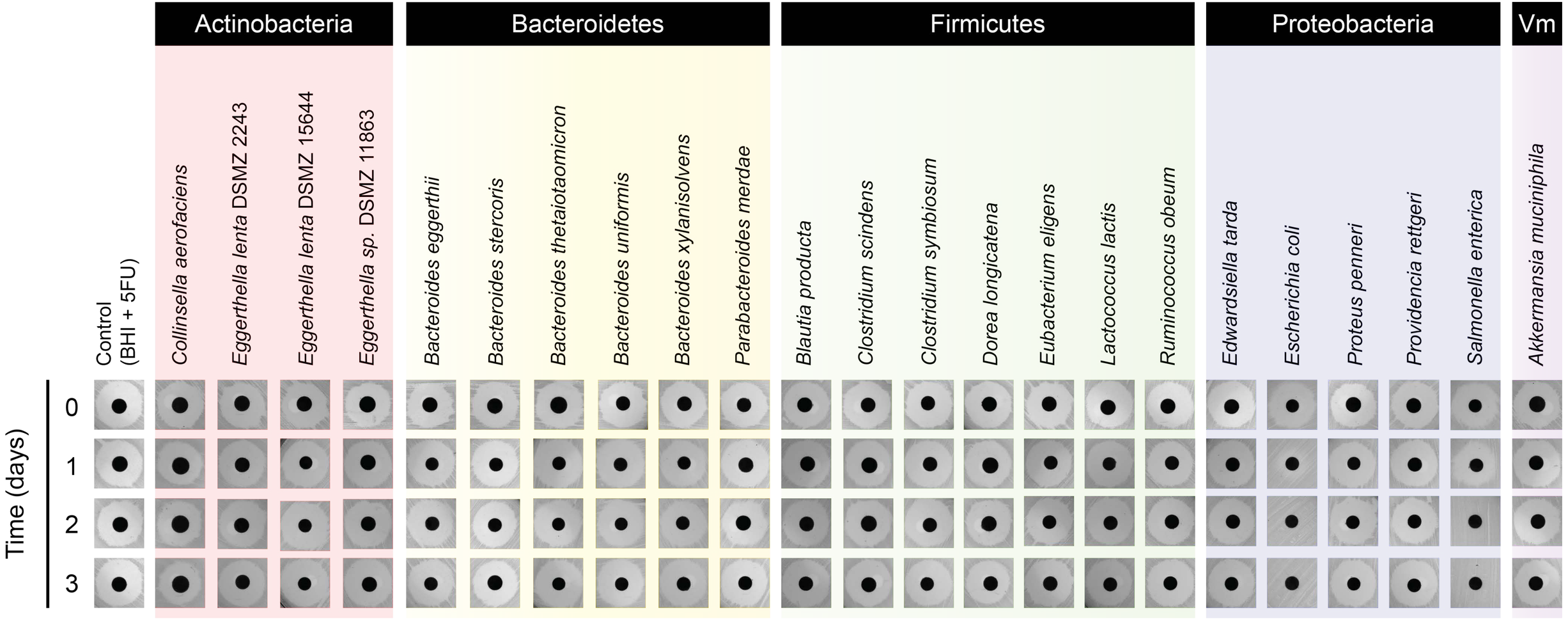
Peter Spanogiannopoulos
CIHR fellow
Now at Novome Biotech

Spanogiannopoulos*, Kyaw*, *et al., Nature* in review; BioRxiv 2022

Select human gut bacterial strains inactivate 5-FU



Select human gut bacterial strains inactivate 5-FU



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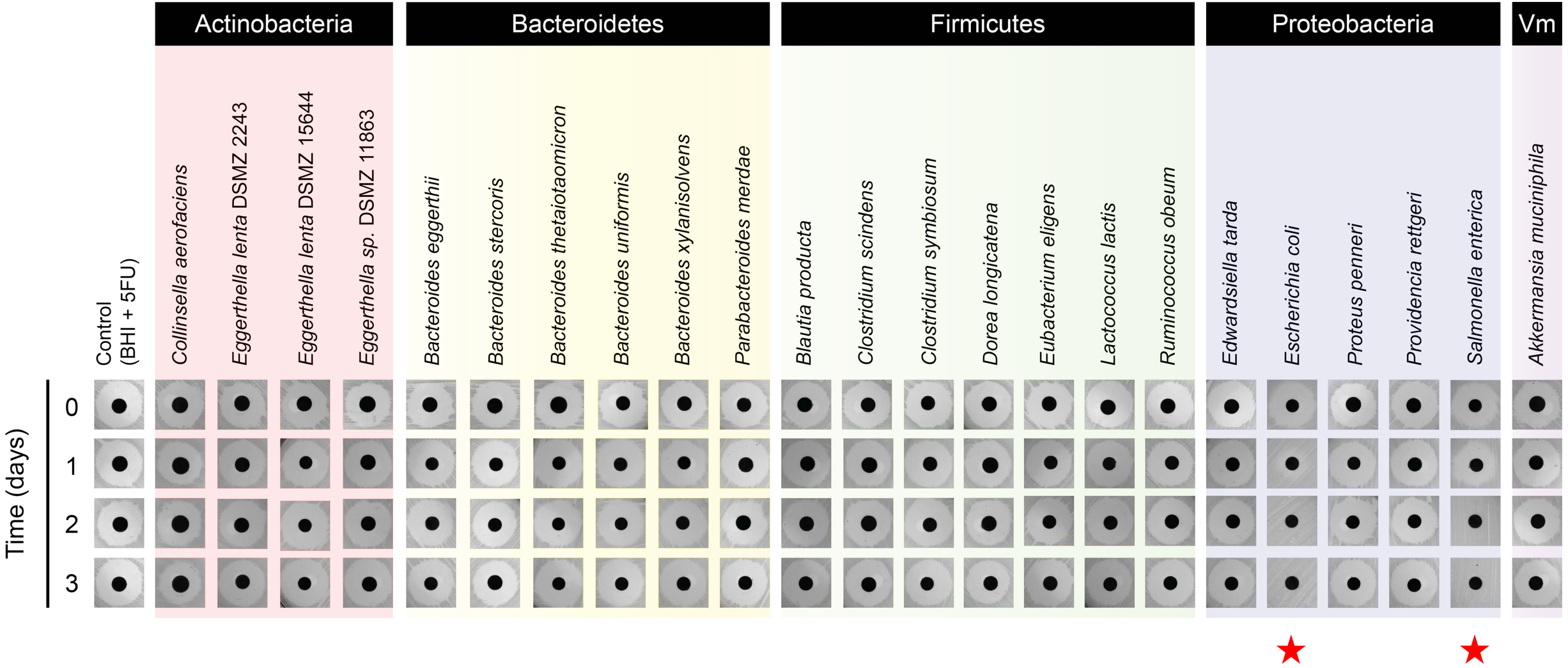

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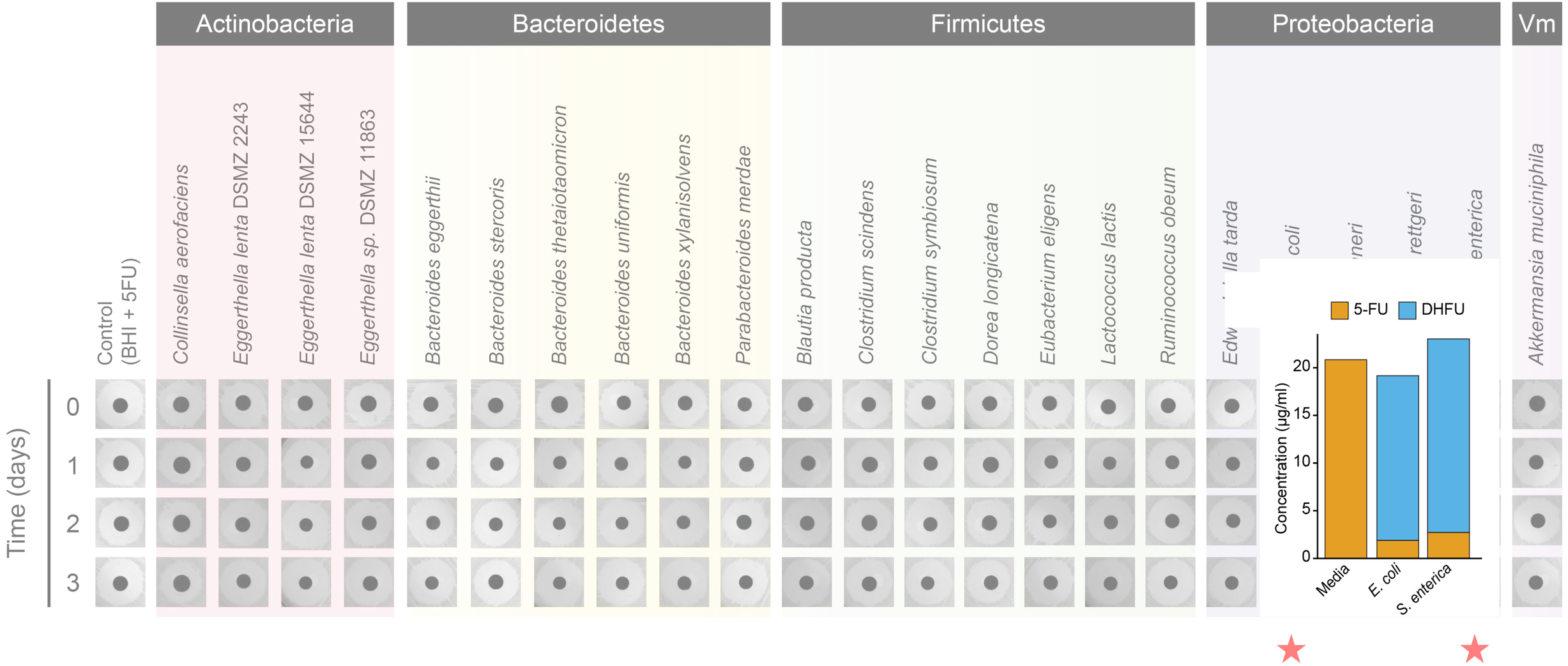
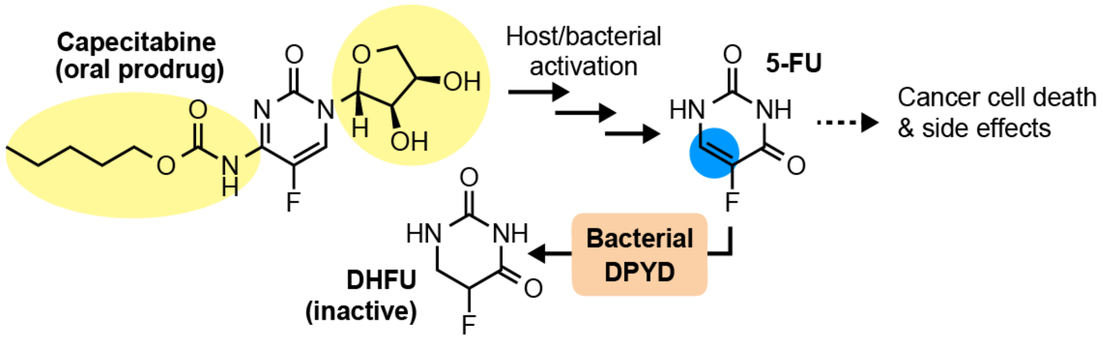


Candidate gene: bacterial dihydropyrimidine dehydrogenase (DPYD)



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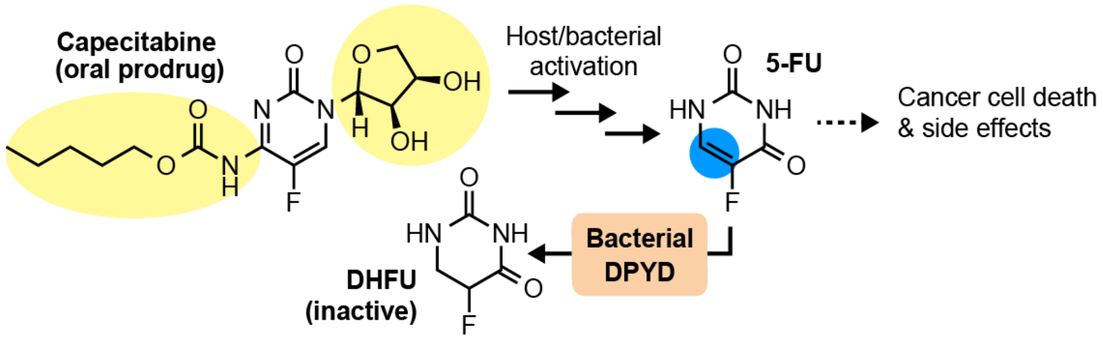

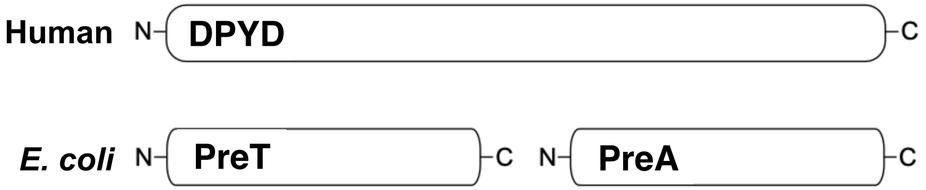

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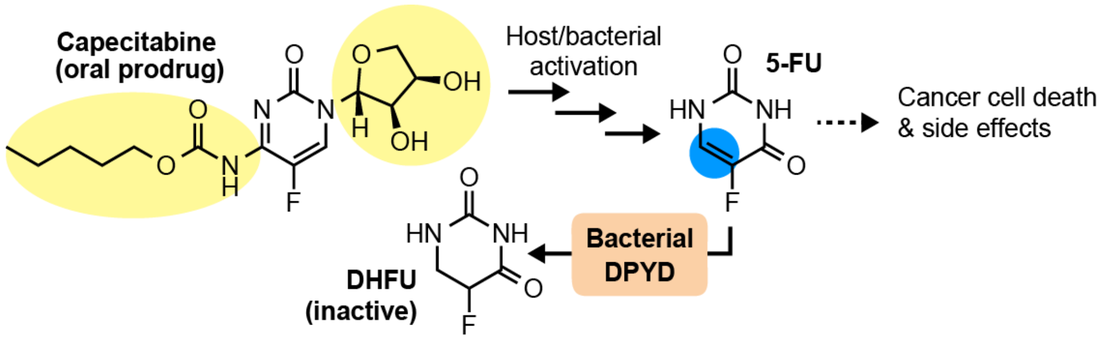

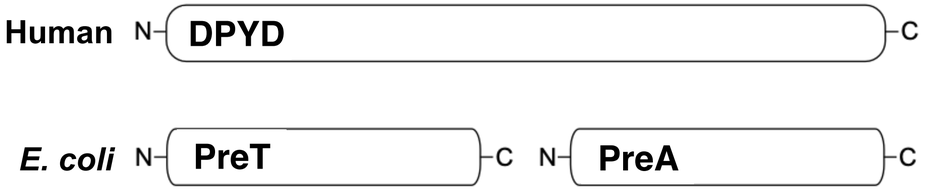

- 30% amino acid similarity to human DPYD
- Iron-sulphur flavoenzyme, requires NADH
- DHU is a backup pyrimidine pool

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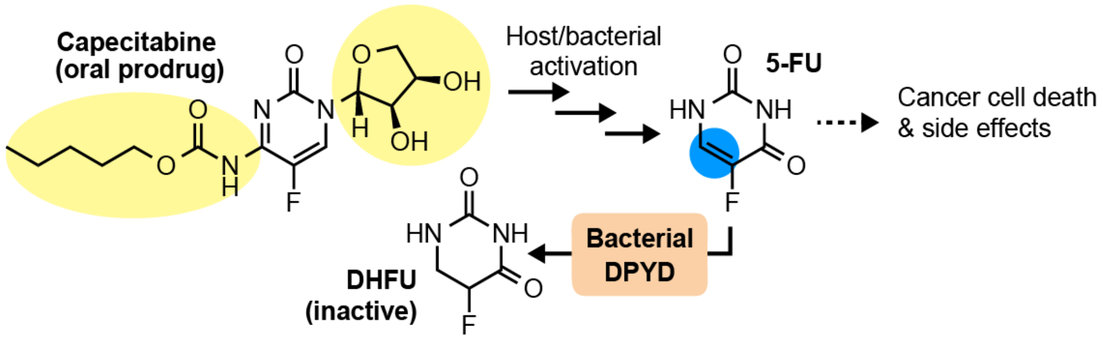

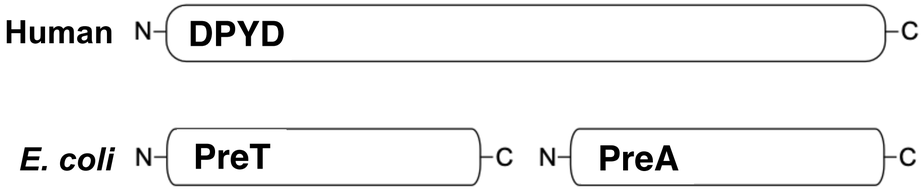

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Is preTA **necessary** for 5-FU inactivation?

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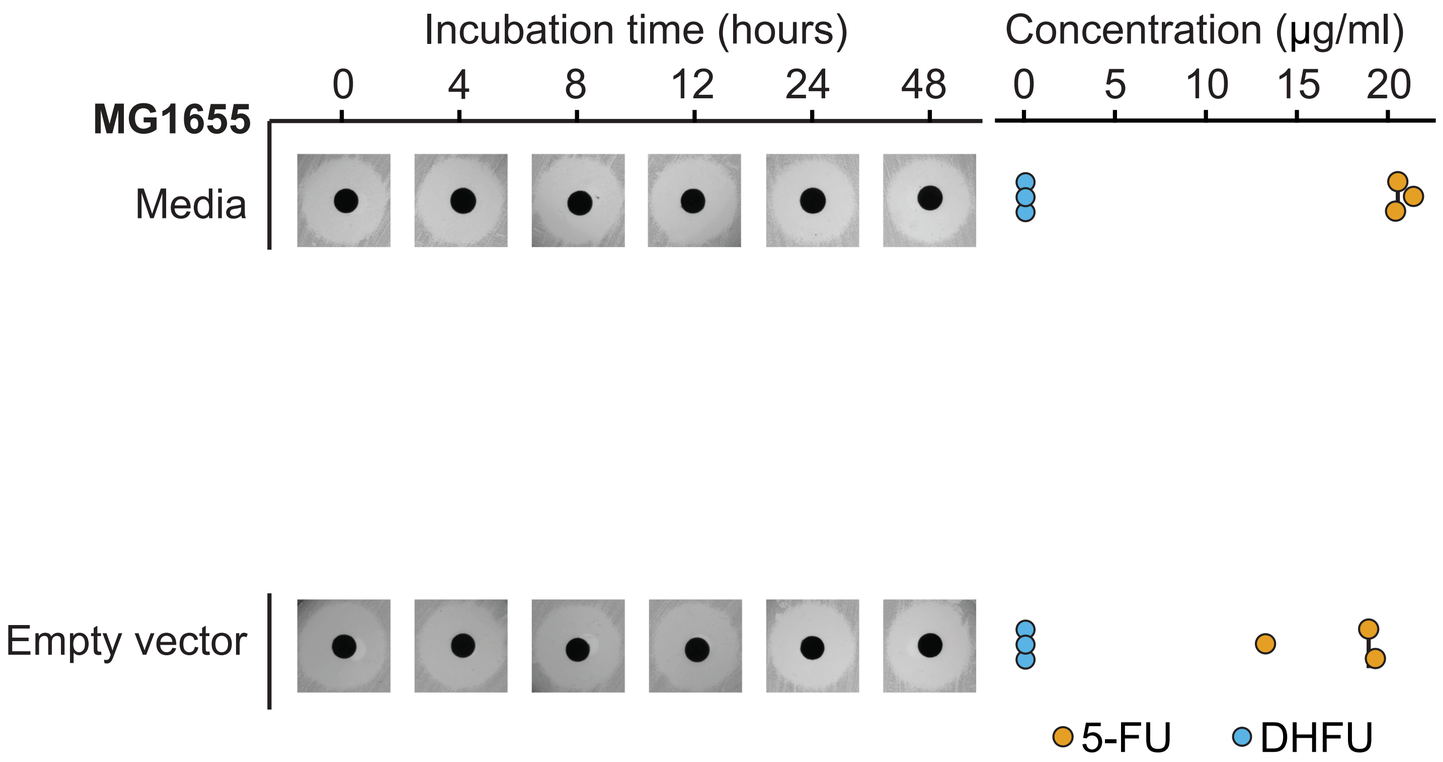
preTA is necessary for 5-FU inactivation by E. coli



Thanks to Jonathan Melamed, Gerona lab (UCSF)

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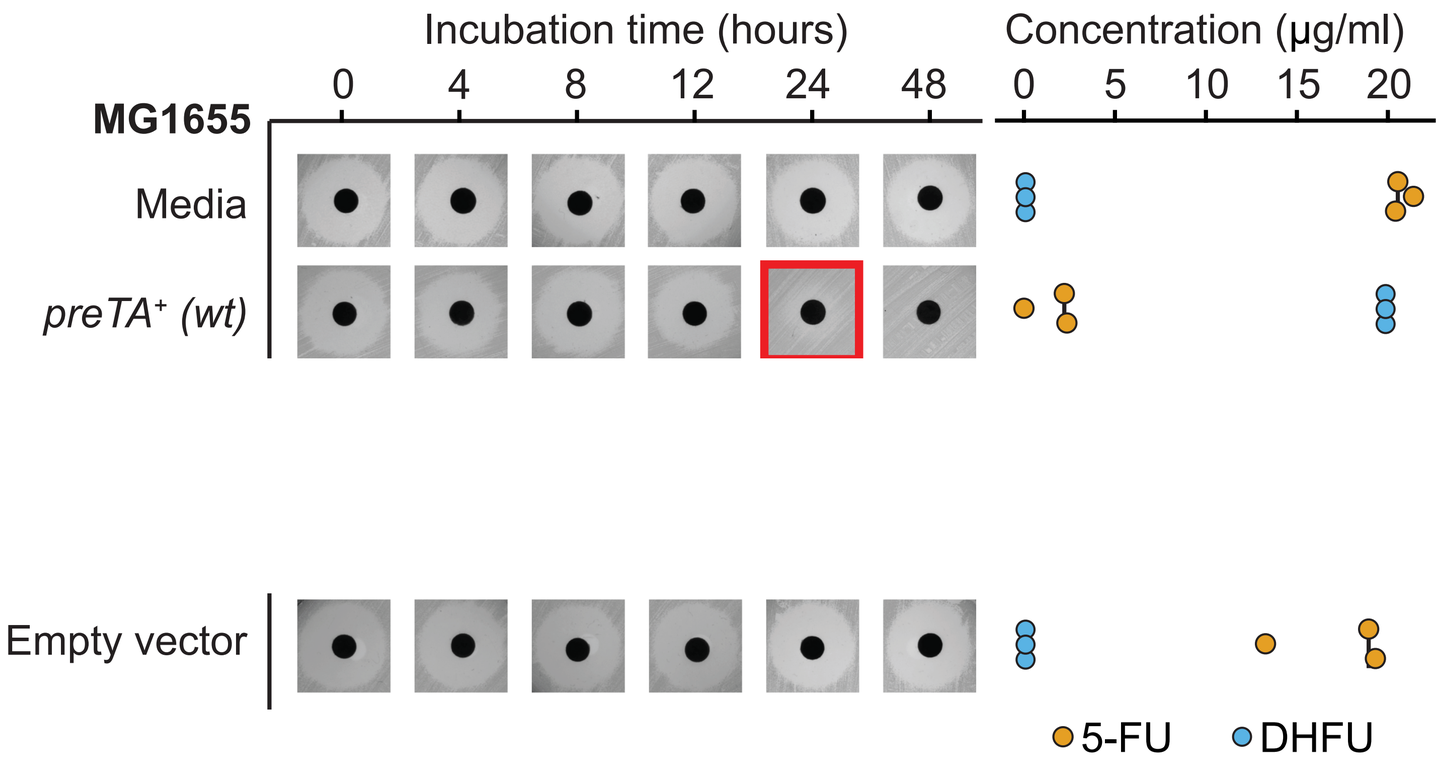

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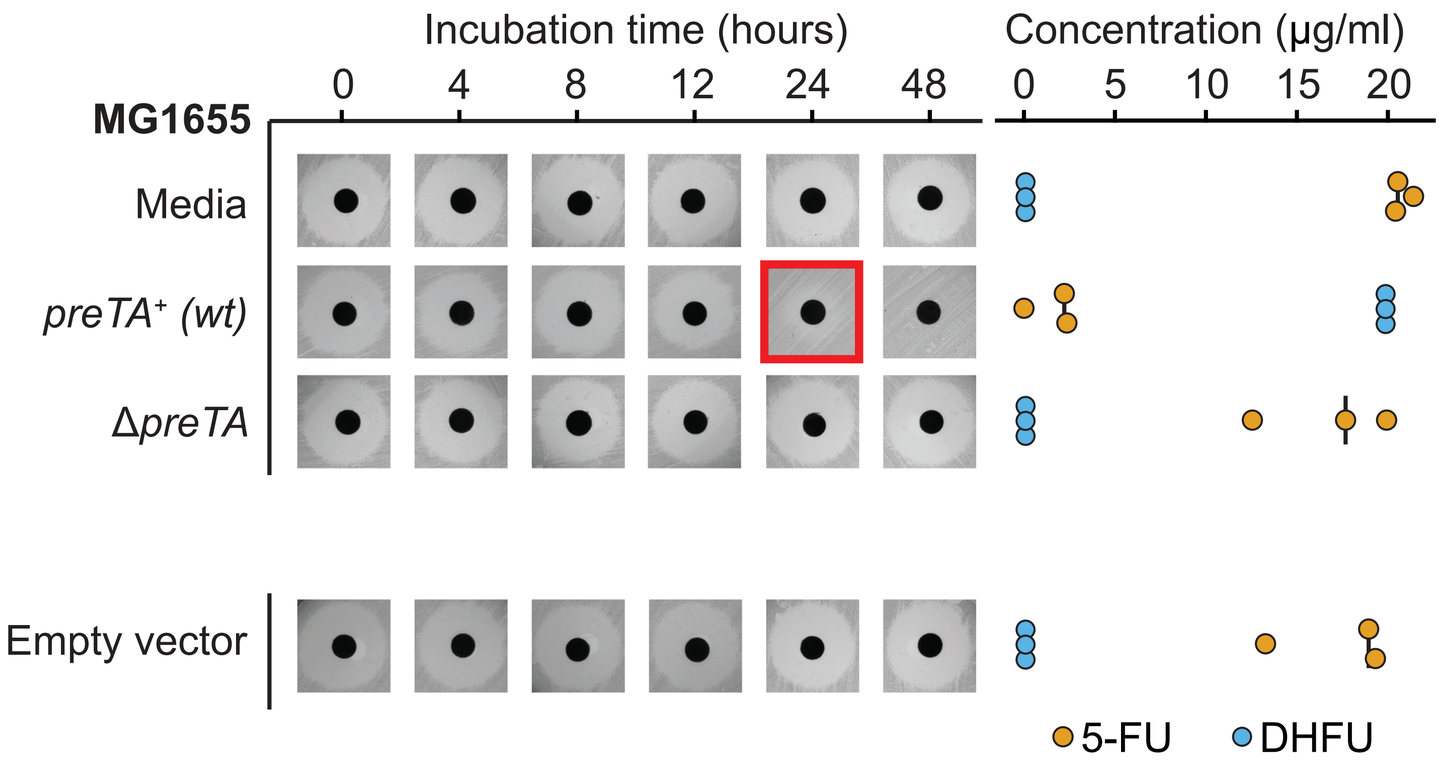

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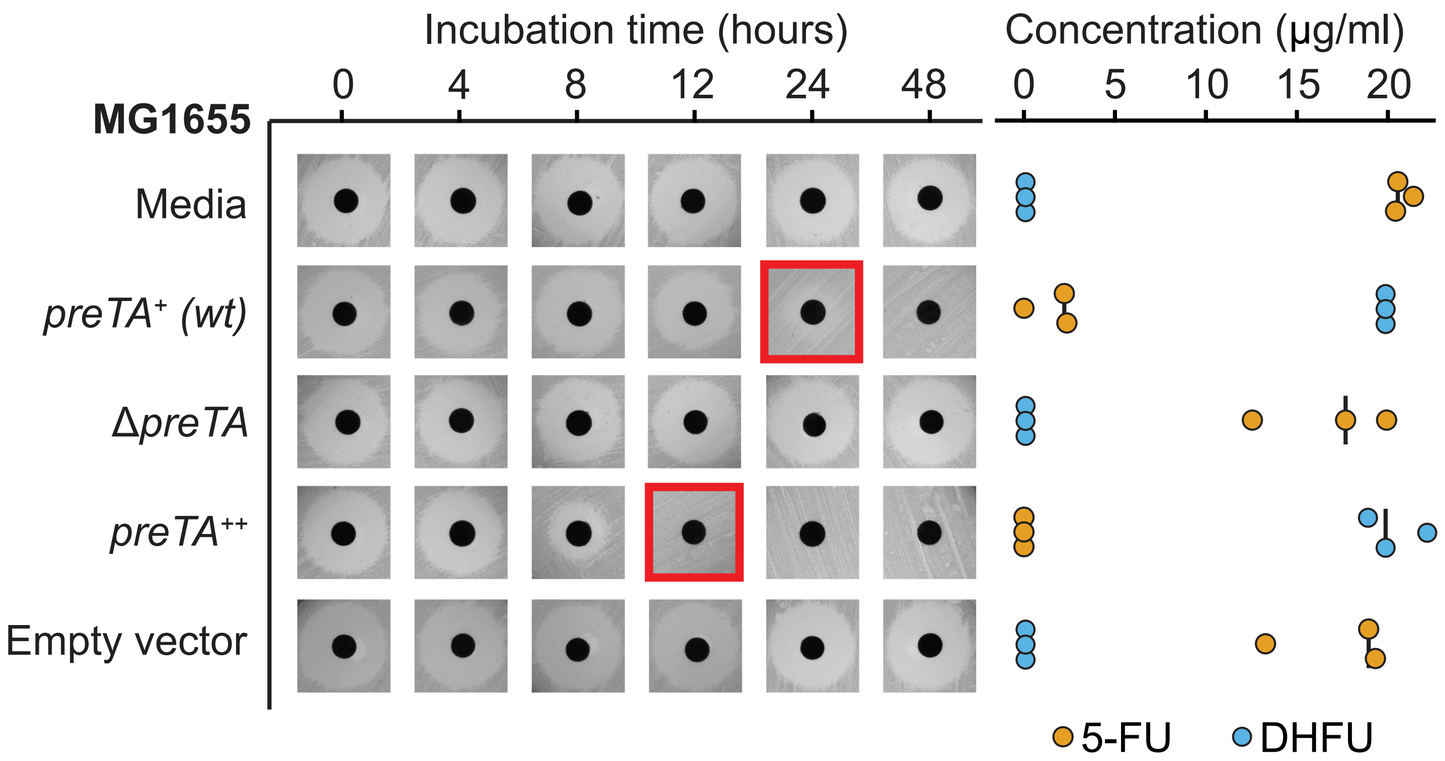

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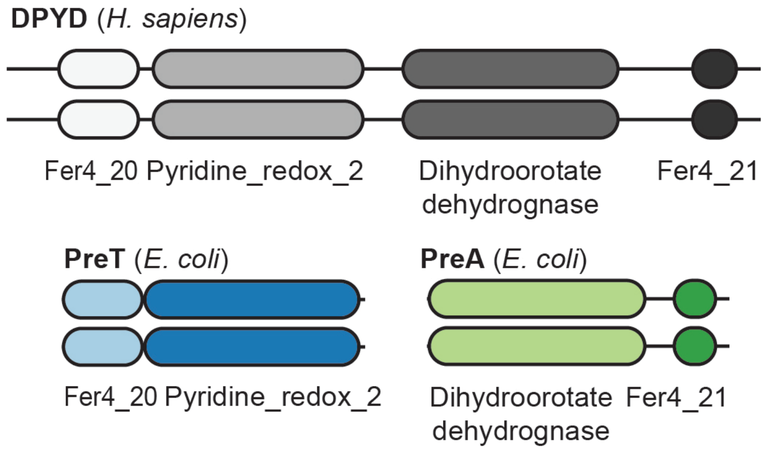
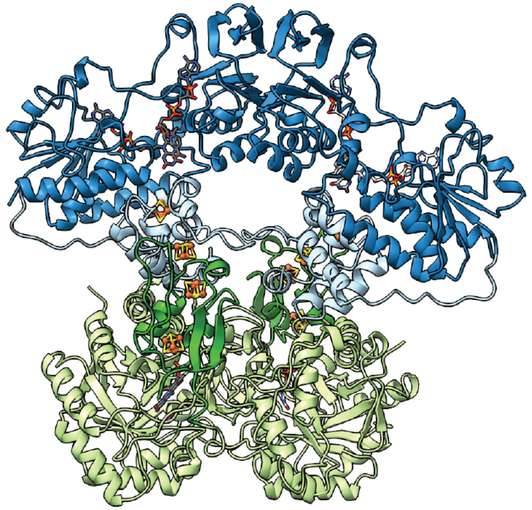
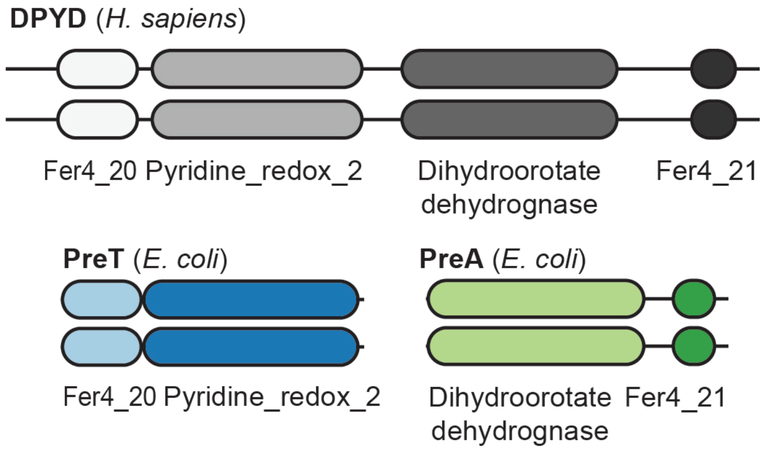
Biochemical characterization of PreTA

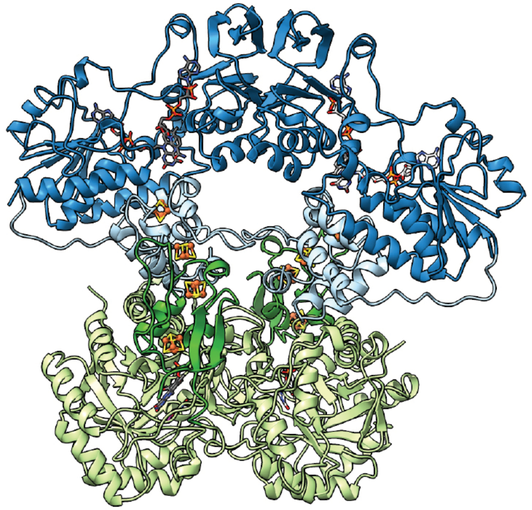


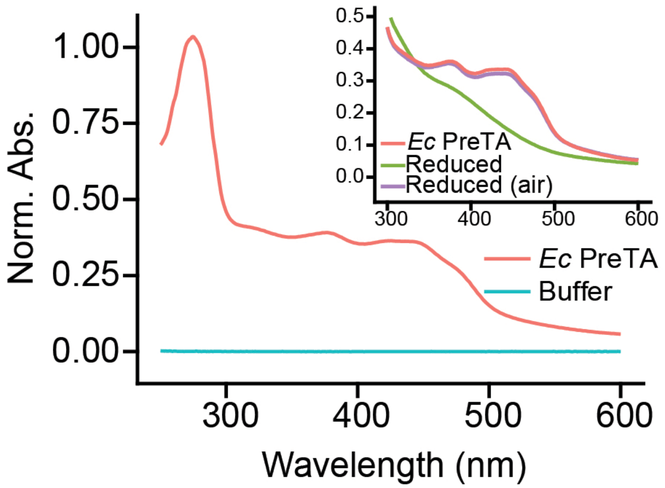


Ben Guthrie
Damon Runyon Fellow

Biochemical characterization of PreTA







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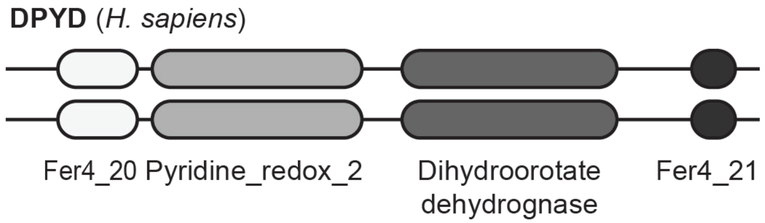

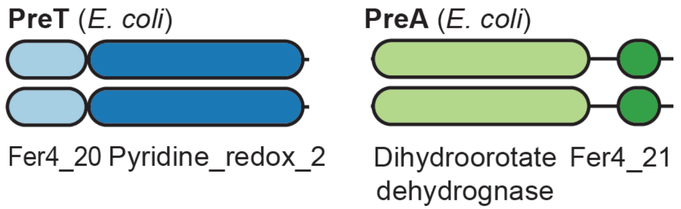

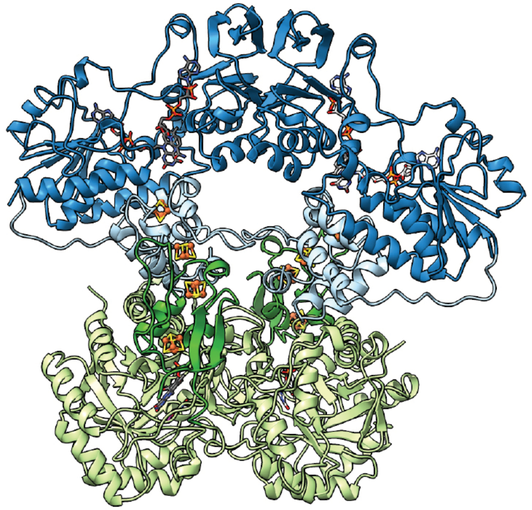

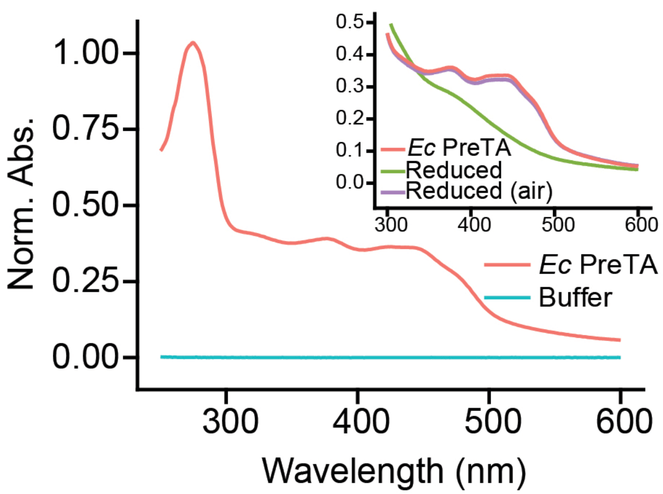

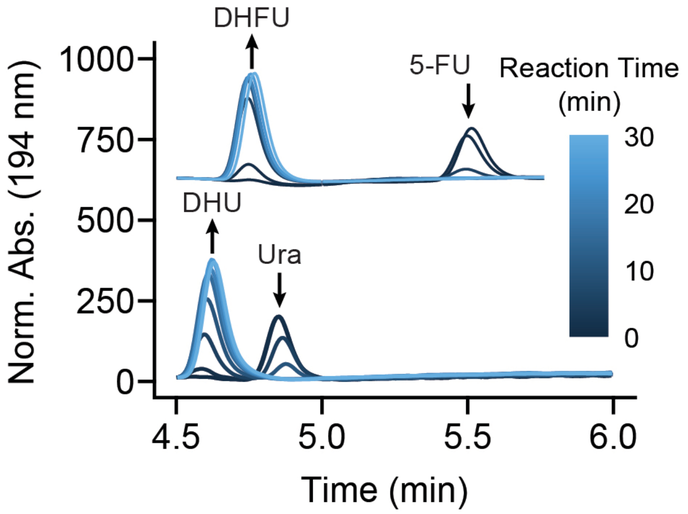

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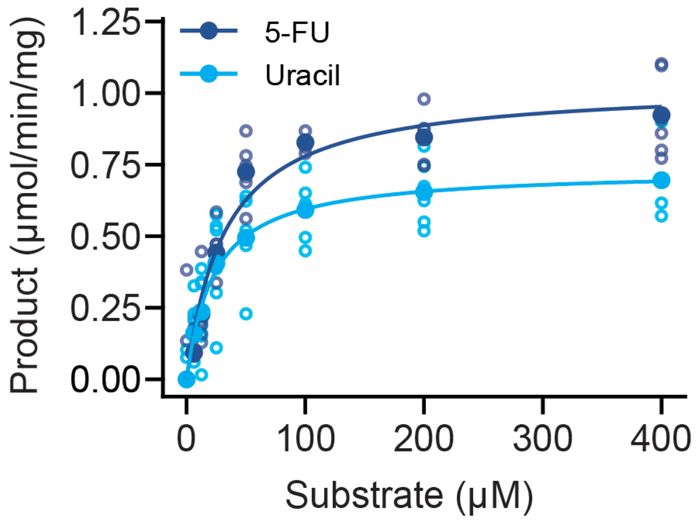
PreTA is essentially irreversible at physiological concentrations



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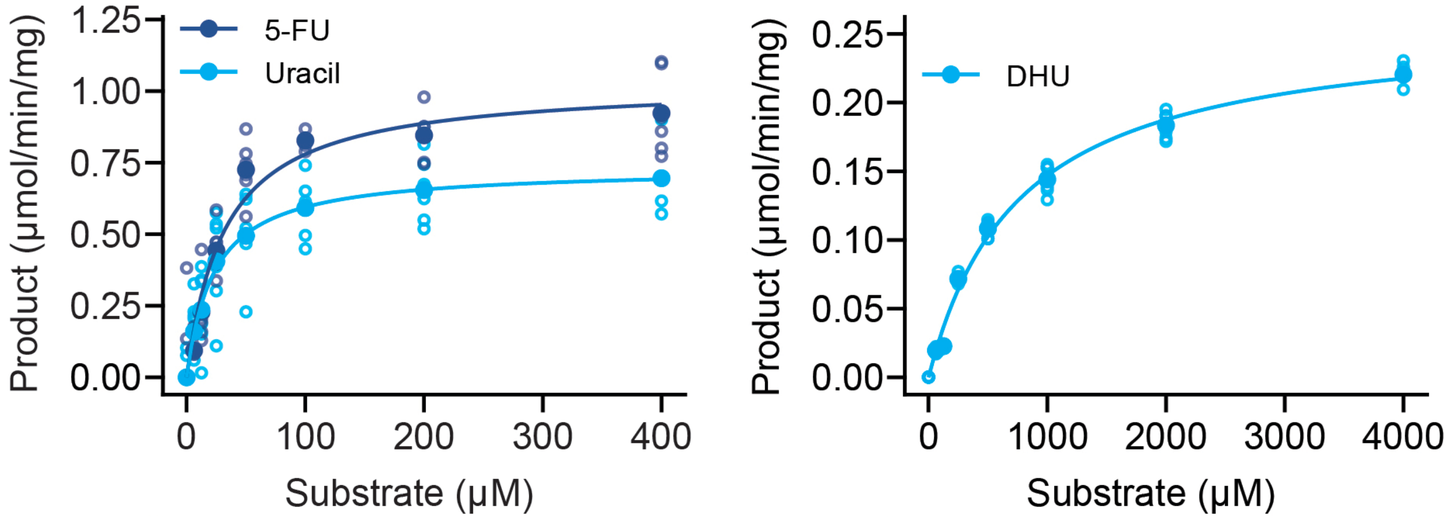

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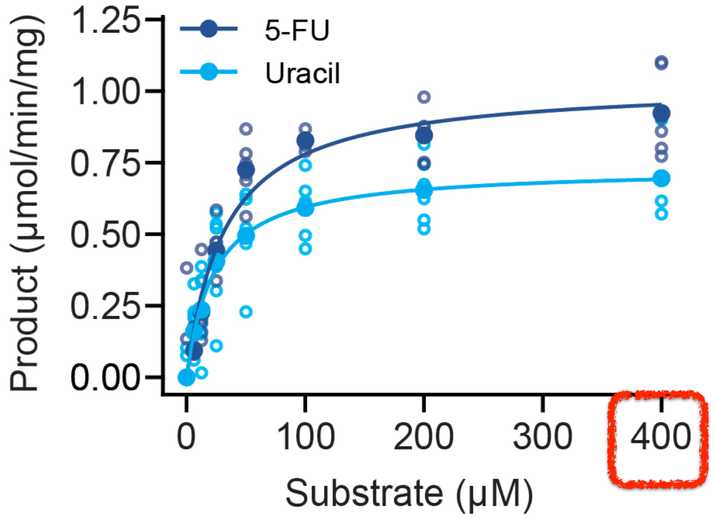

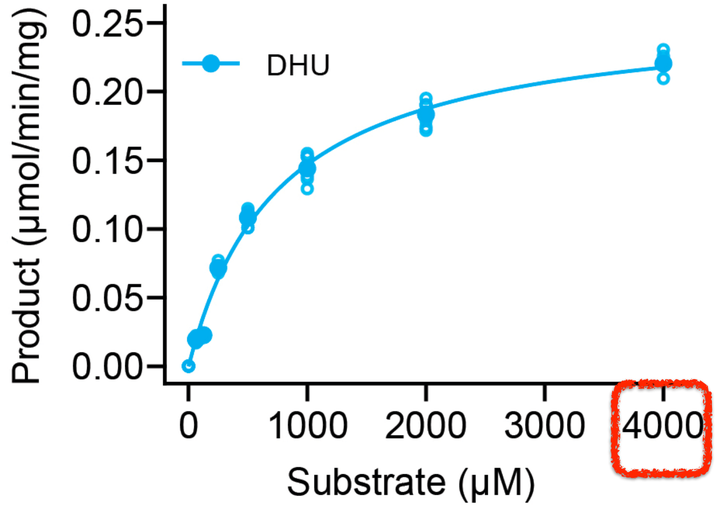

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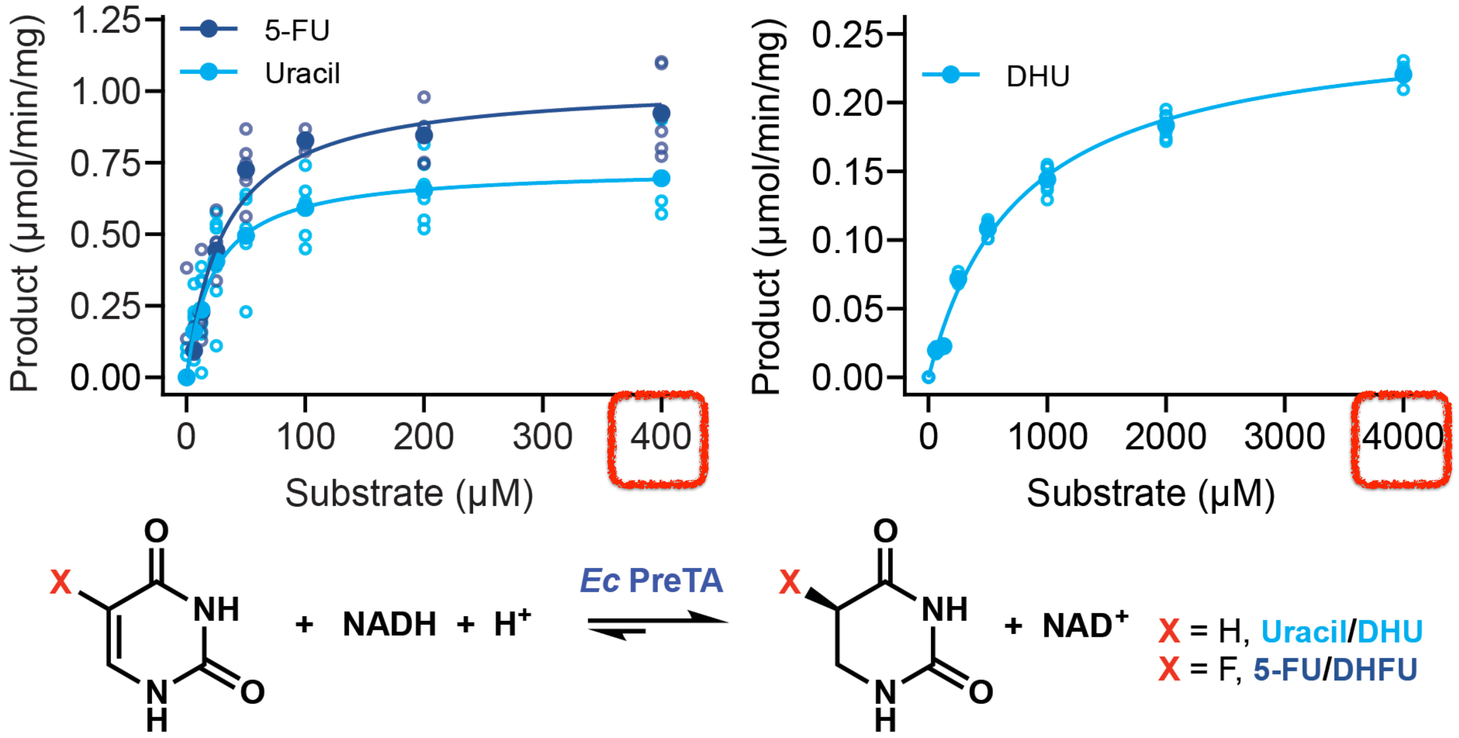
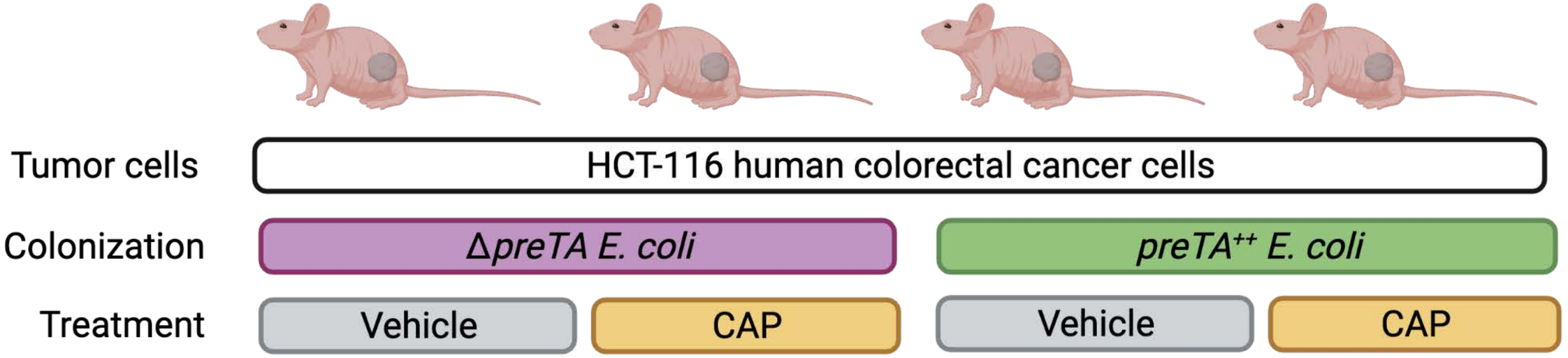


Testing drug efficacy in a xenograft model

Tumor cells | HCT-116 human colorectal cancer cells

Than Kyaw (MSTP)
w/Joyce Lee (Goga lab)

Testing drug efficacy in a xenograft model



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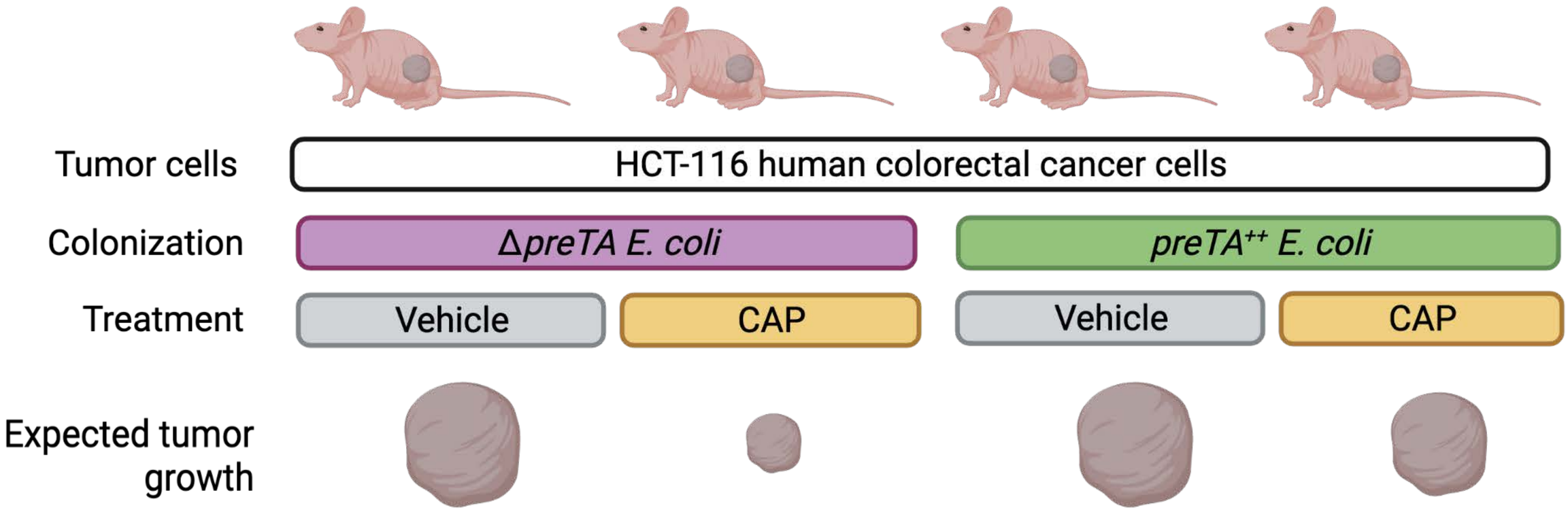

Than Kyaw (MSTP)
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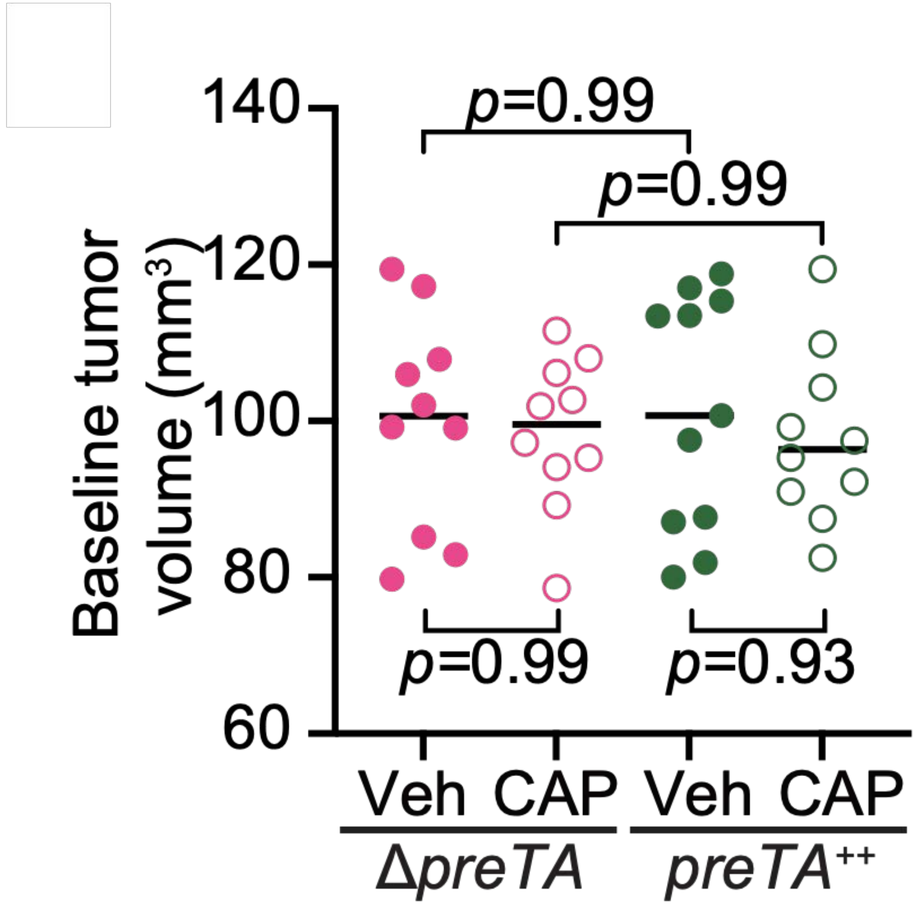
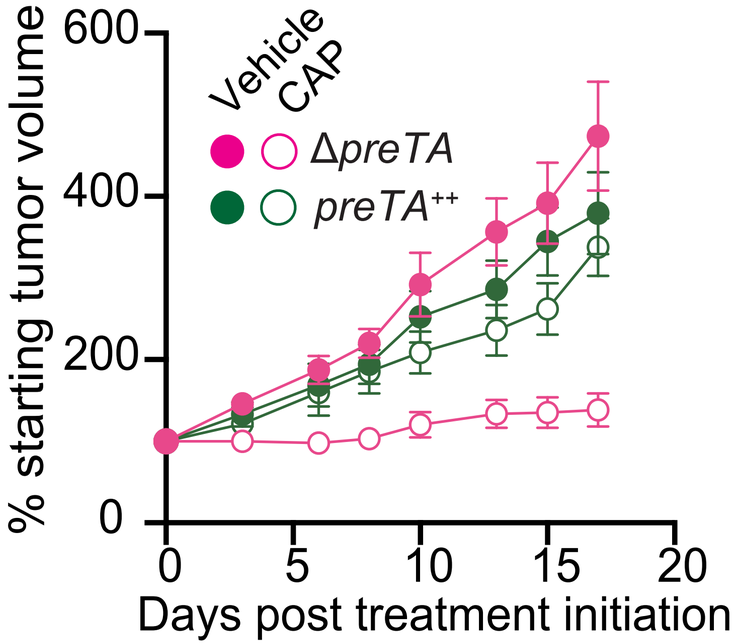
No differences in baseline tumor volumes



3 independent experiments
Experiment #3 shown: 10-11 mice/group

PreTA impairs the efficacy of oral CAP treatment



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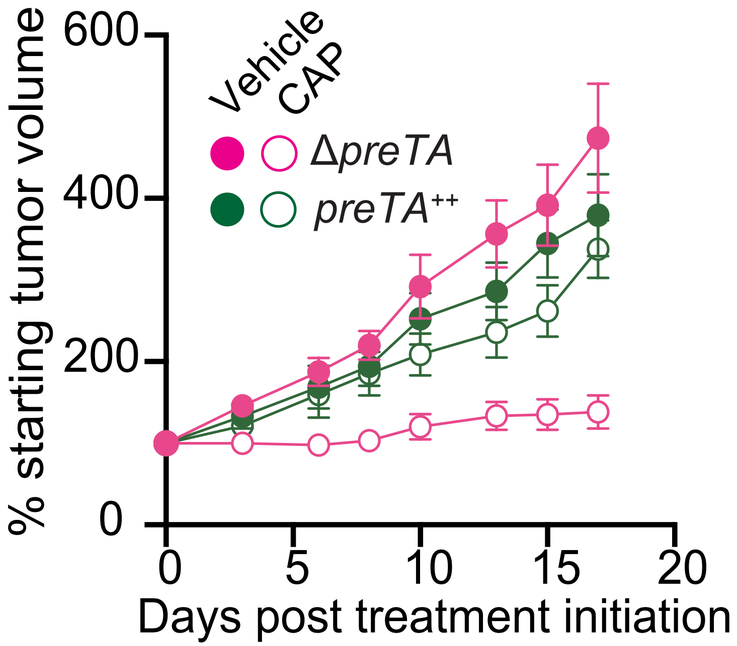

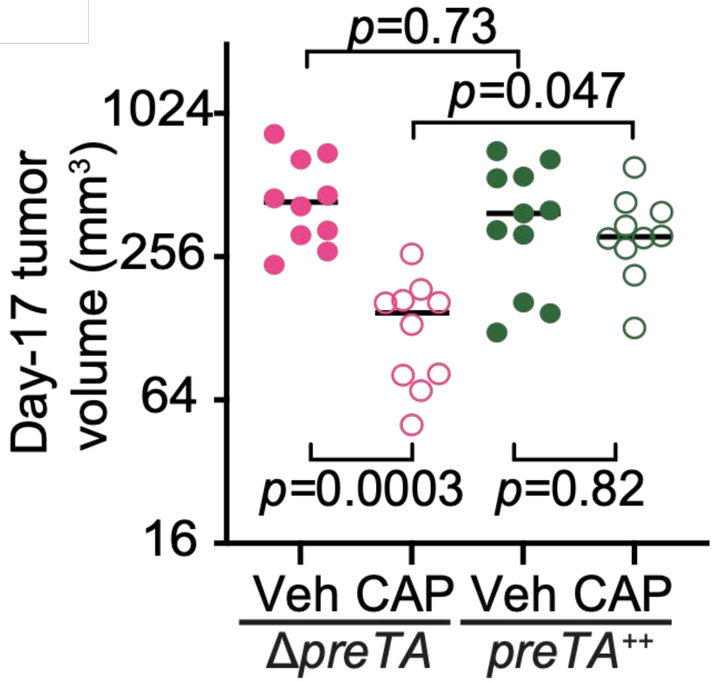

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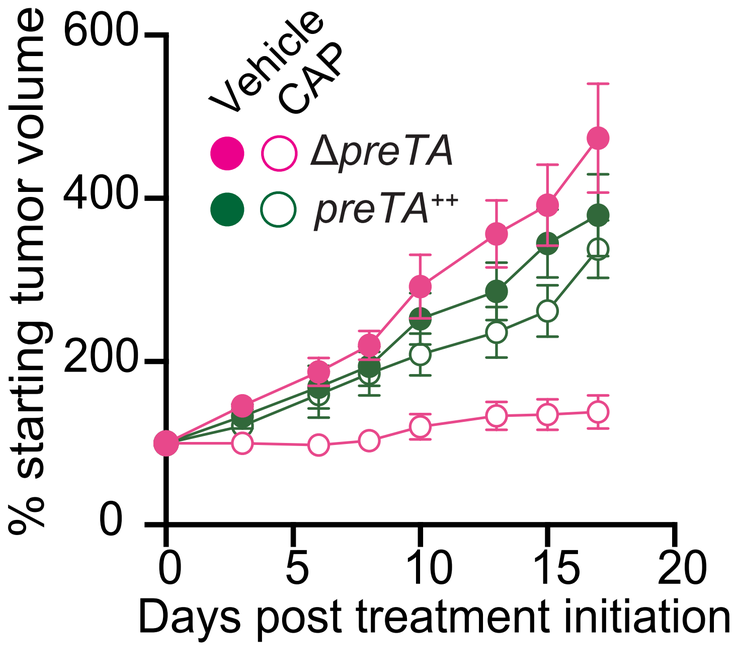

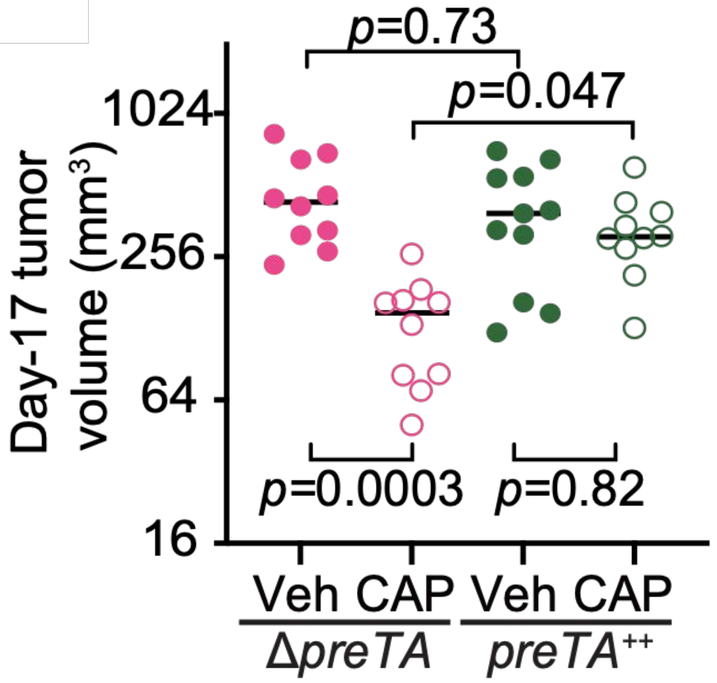

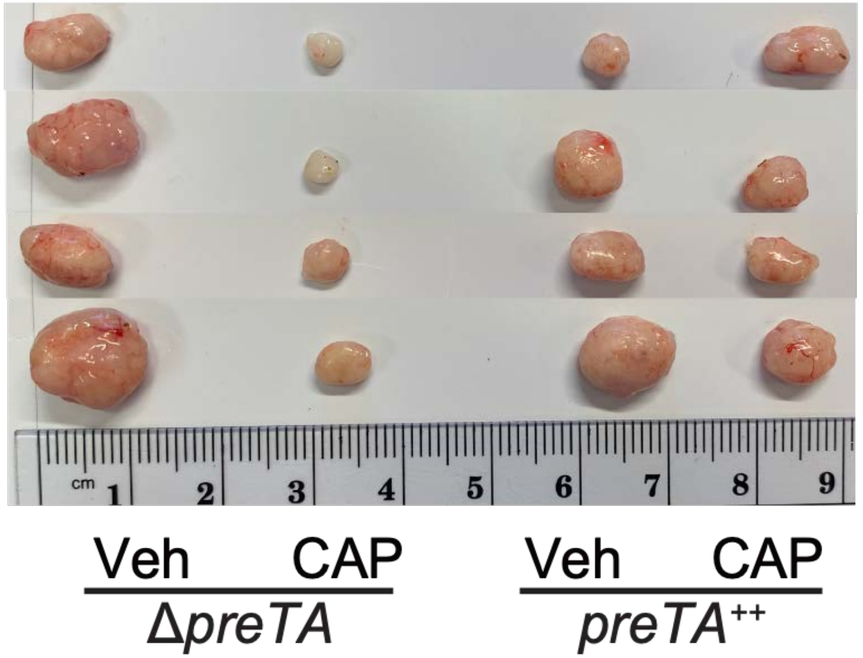

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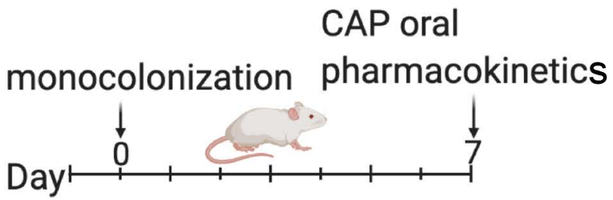

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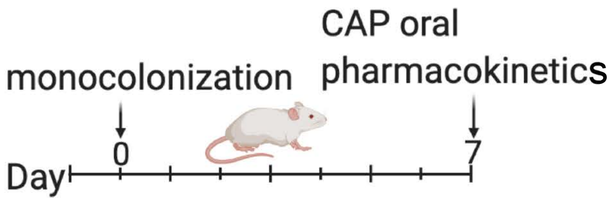

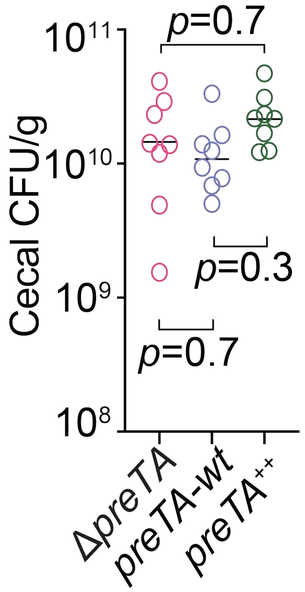

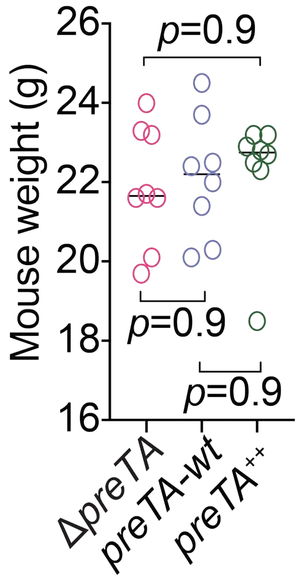

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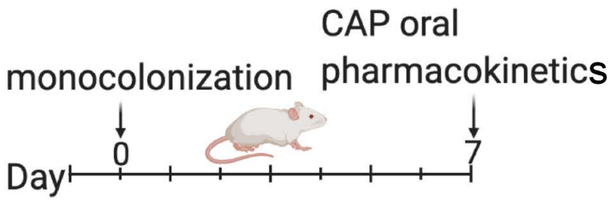

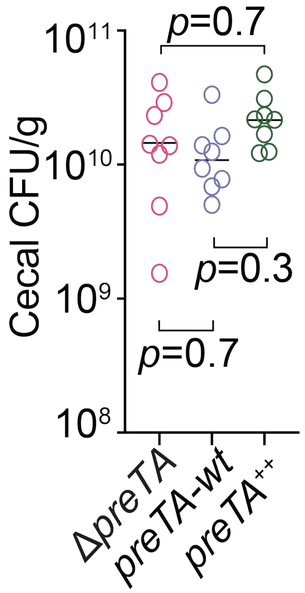

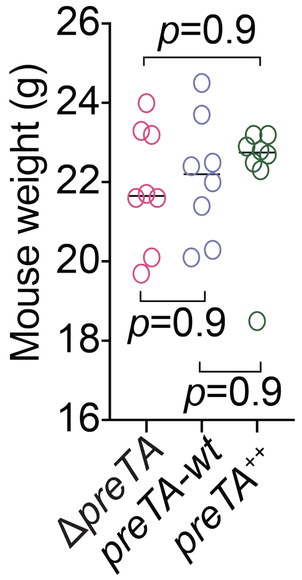

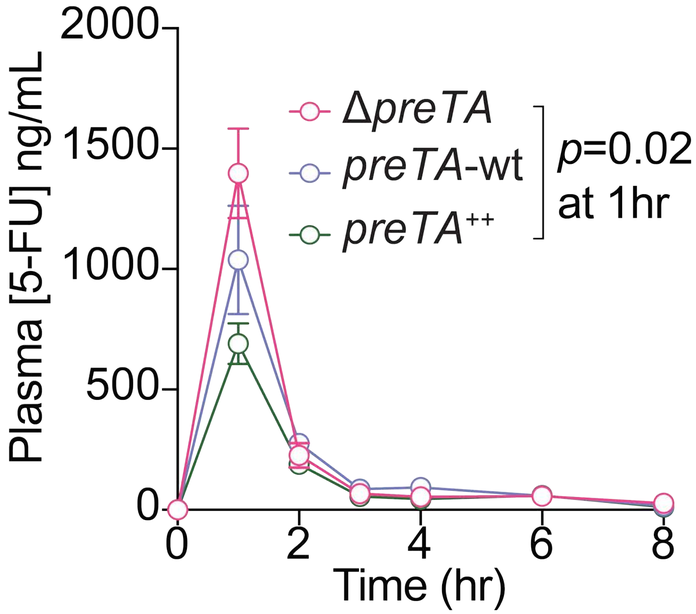

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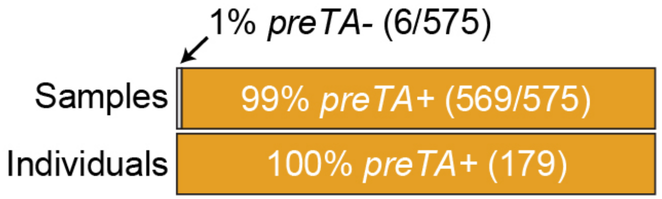
PreTA is prevalent in colorectal cancer patients



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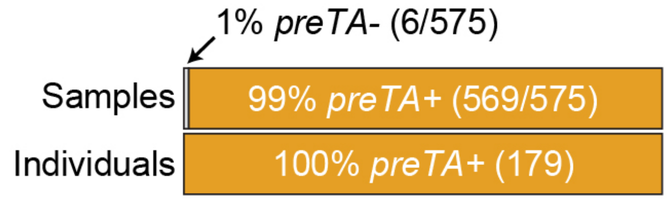

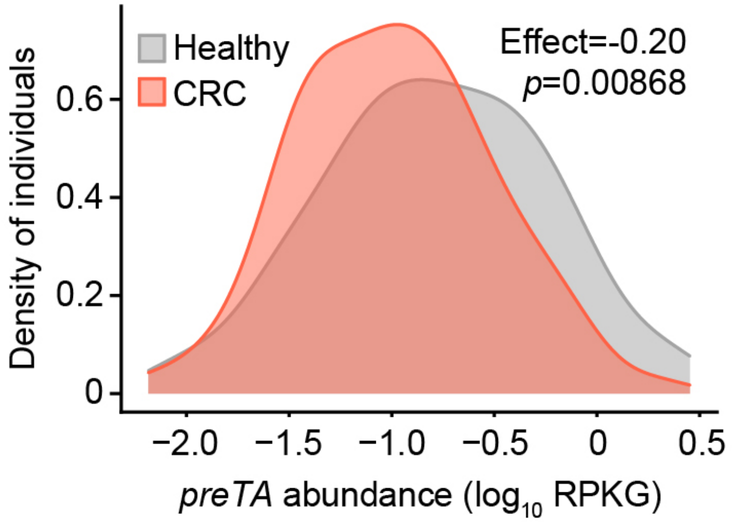

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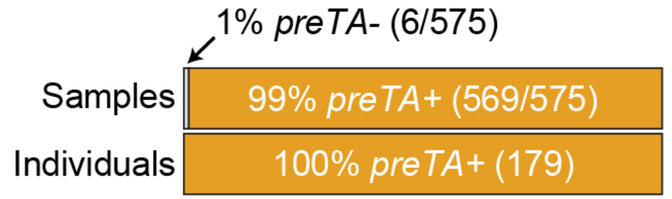

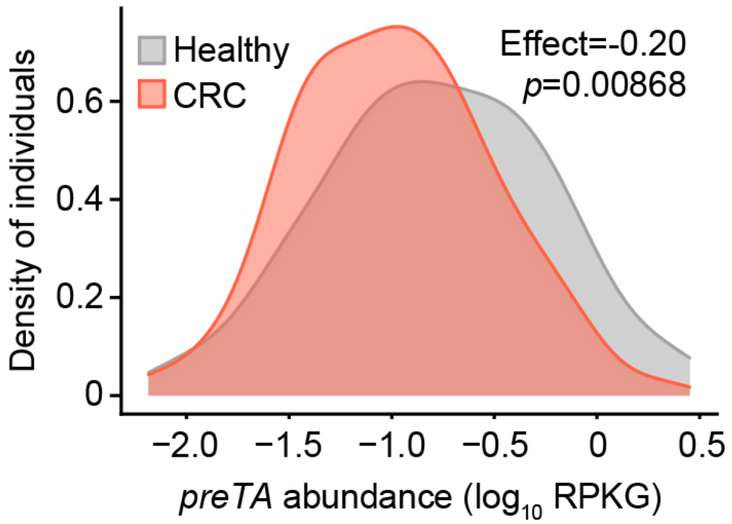

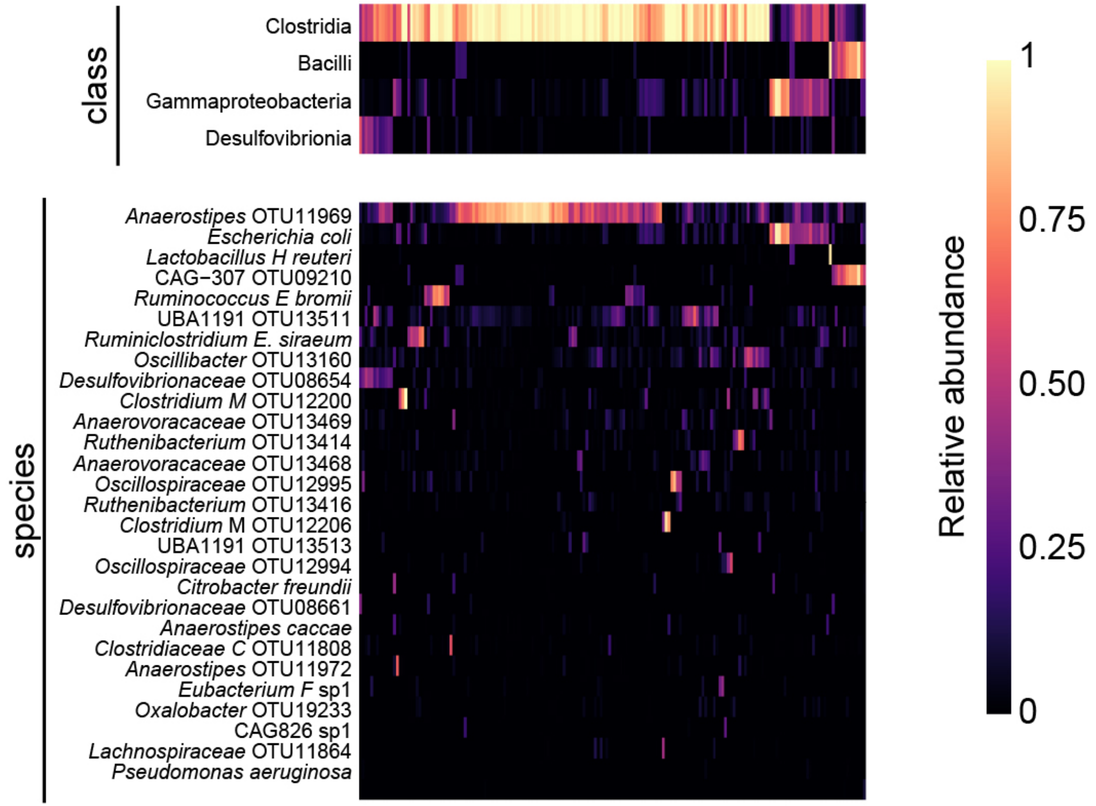

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PreTA is dynamic during treatment

GO: **G**ut Microbiome and **O**ral Fluoropyrimidine Study in Patients with Colorectal Cancer

Recruiting 60 colorectal adenocarcinoma patients initiating oral fluoropyrimidines

Wes Kidder
UCSF GI Oncology

NIH NATIONAL CANCER INSTITUTE

Chloe Atreya, R21 from NCI

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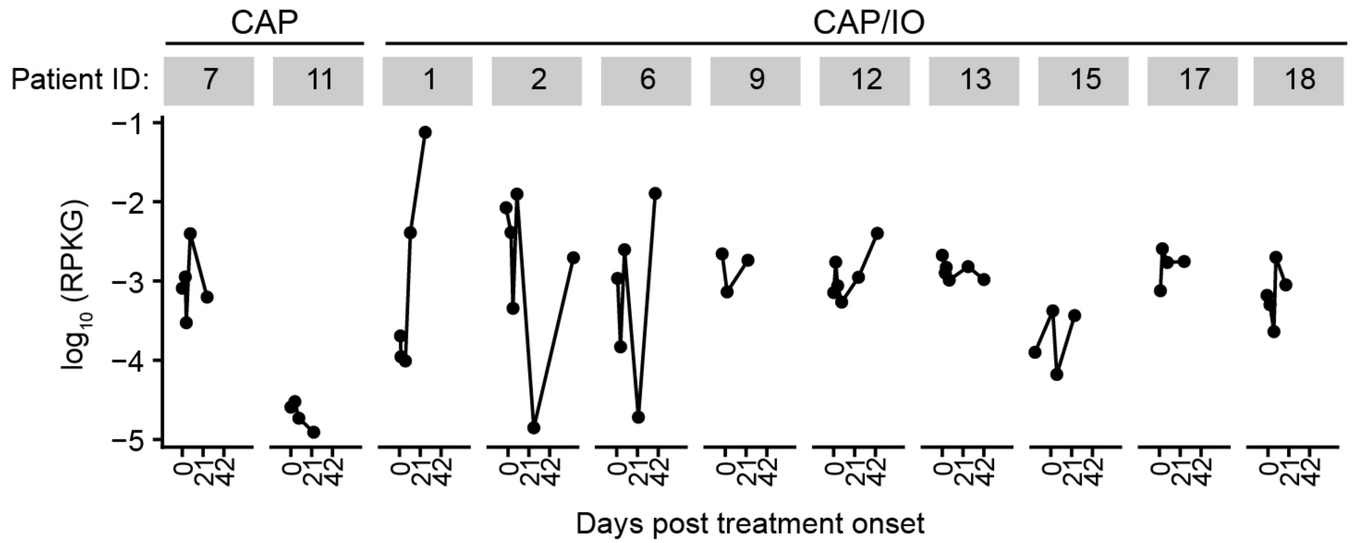

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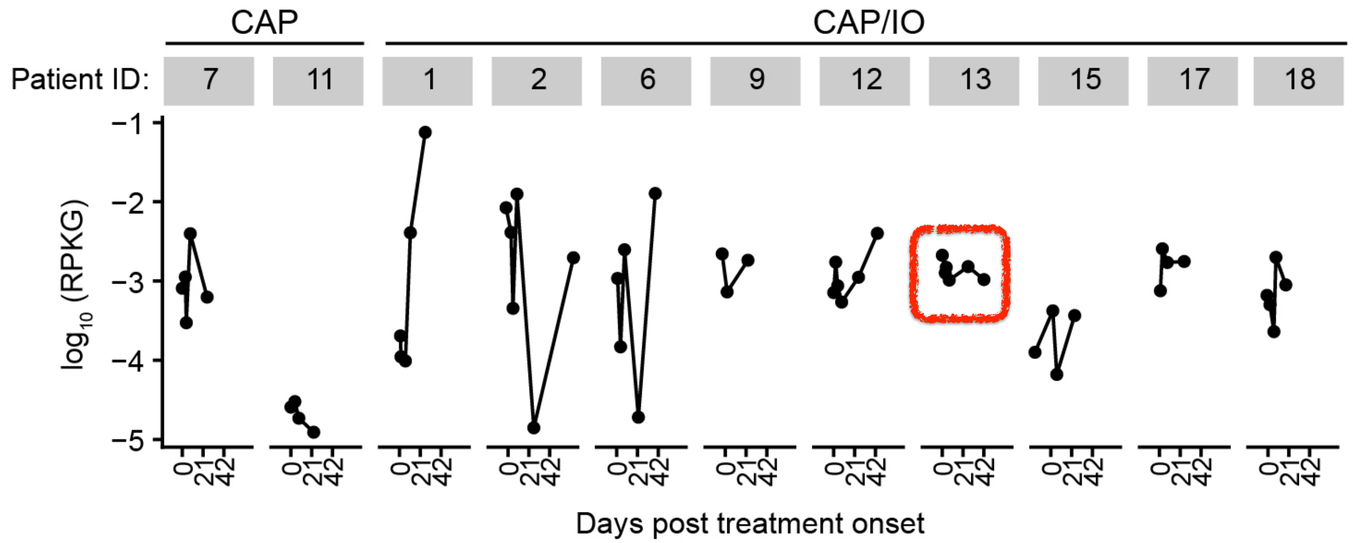

Wes Kidder
UCSF GI Oncology

NIH NATIONAL CANCER INSTITUTE

Chloe Atreya, R21 from NCI

PreTA is dynamic during treatment

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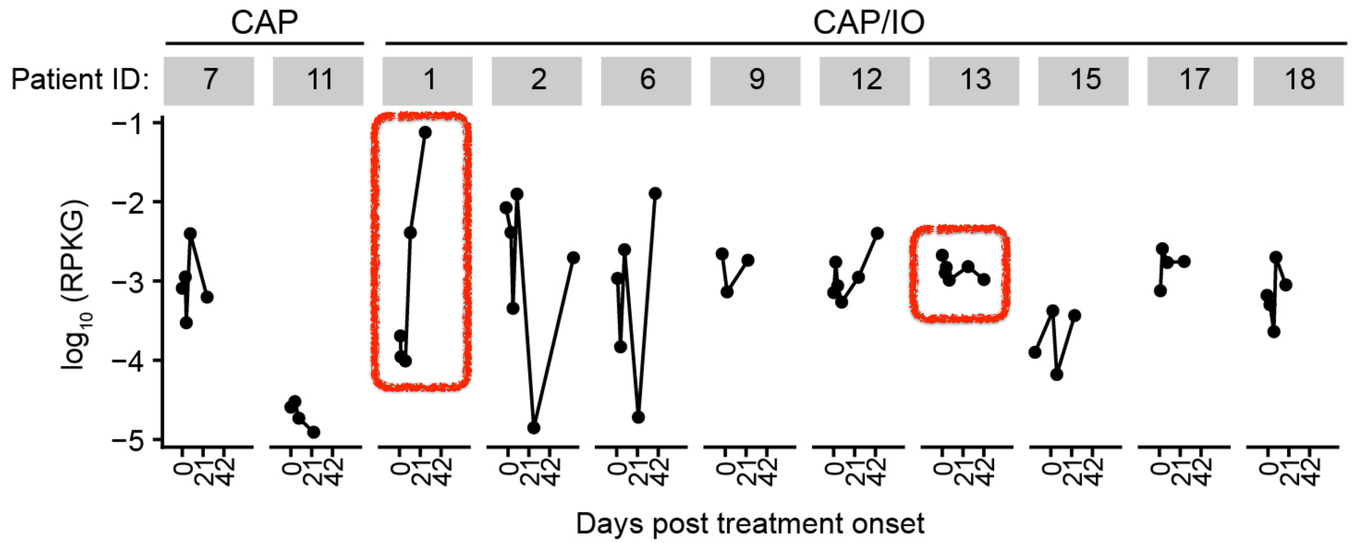

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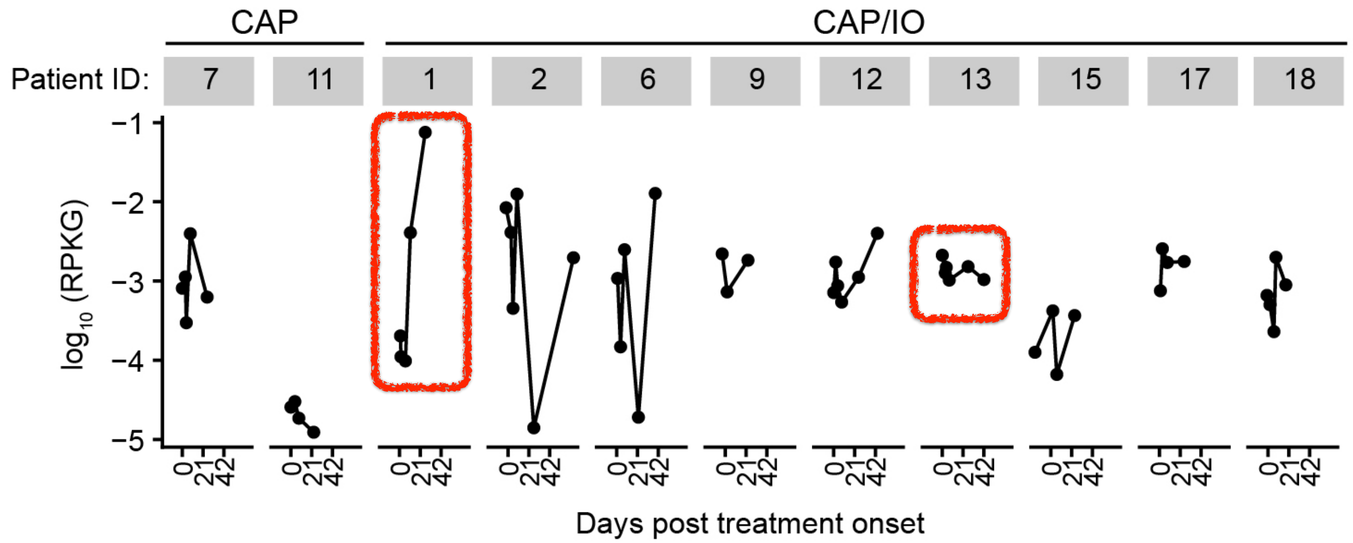

Taxonomic source is consistent with the first cohort:
Escherichia/Anaerostipes

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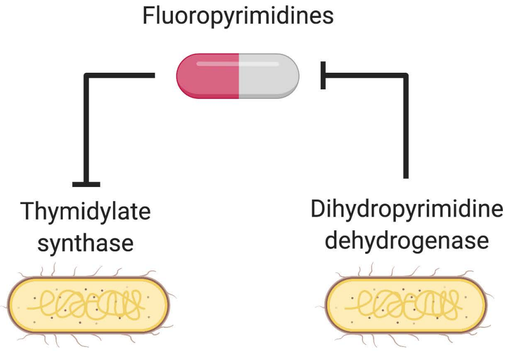
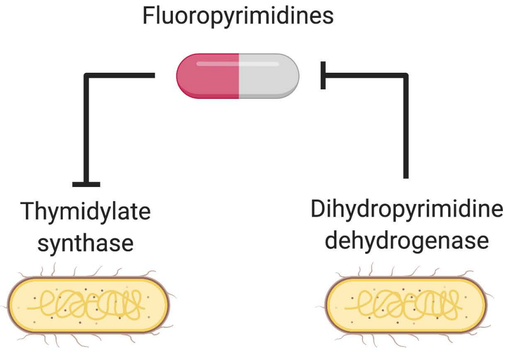


Take home points

Spanogiannopoulos*, Kyaw*, *et al., Nature* in review; BioRxiv 2022



Take home points

Gut bacteria **inactivate** 5-FU in an **essentially irreversible** manner

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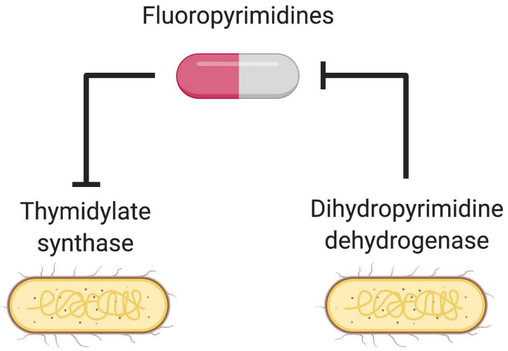

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Bacterial inactivation **decreases** drug efficacy and bioavailability

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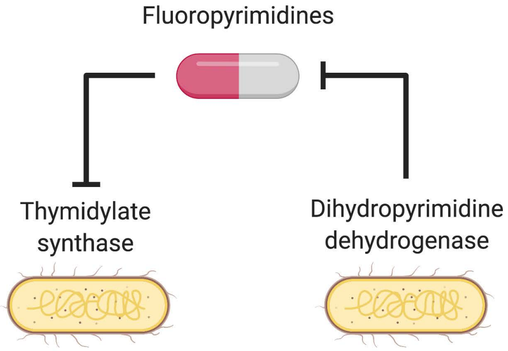

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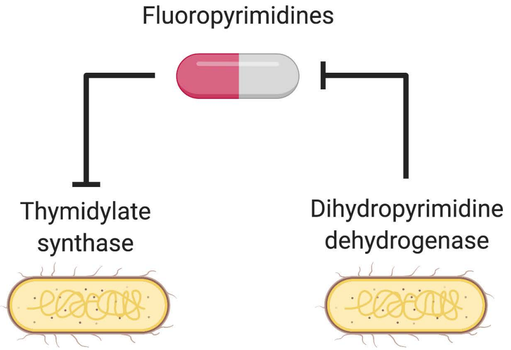

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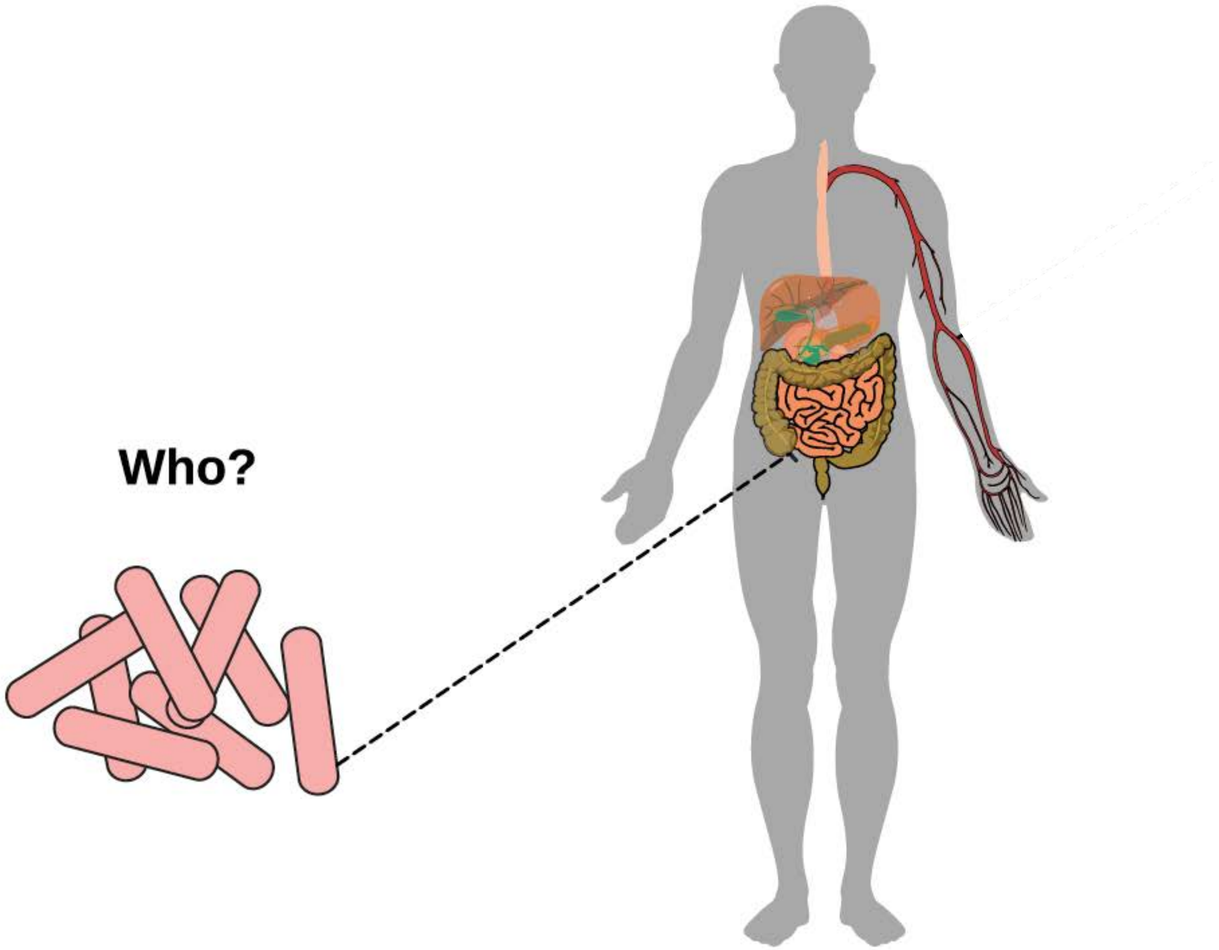
Highlights **challenge** of attributing metabolic reactions to host vs. microbial enzymes

Spanogiannopoulos*, Kyaw*, *et al., Nature* in review; BioRxiv 2022

We’ve got a lot of work to do!



Lam *et al.,* Cell Host & Microbe 2019 (PMID:31295421)

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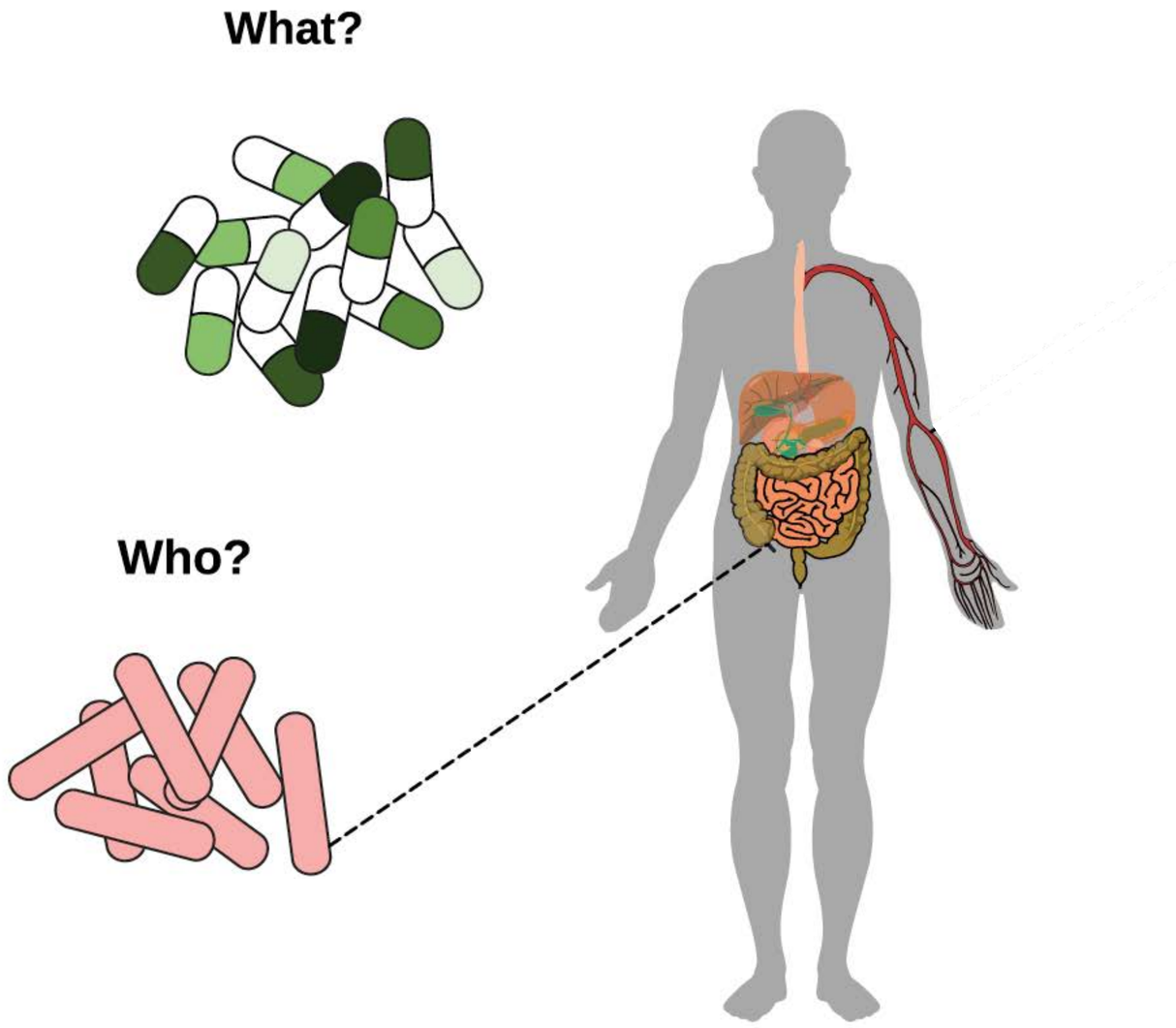

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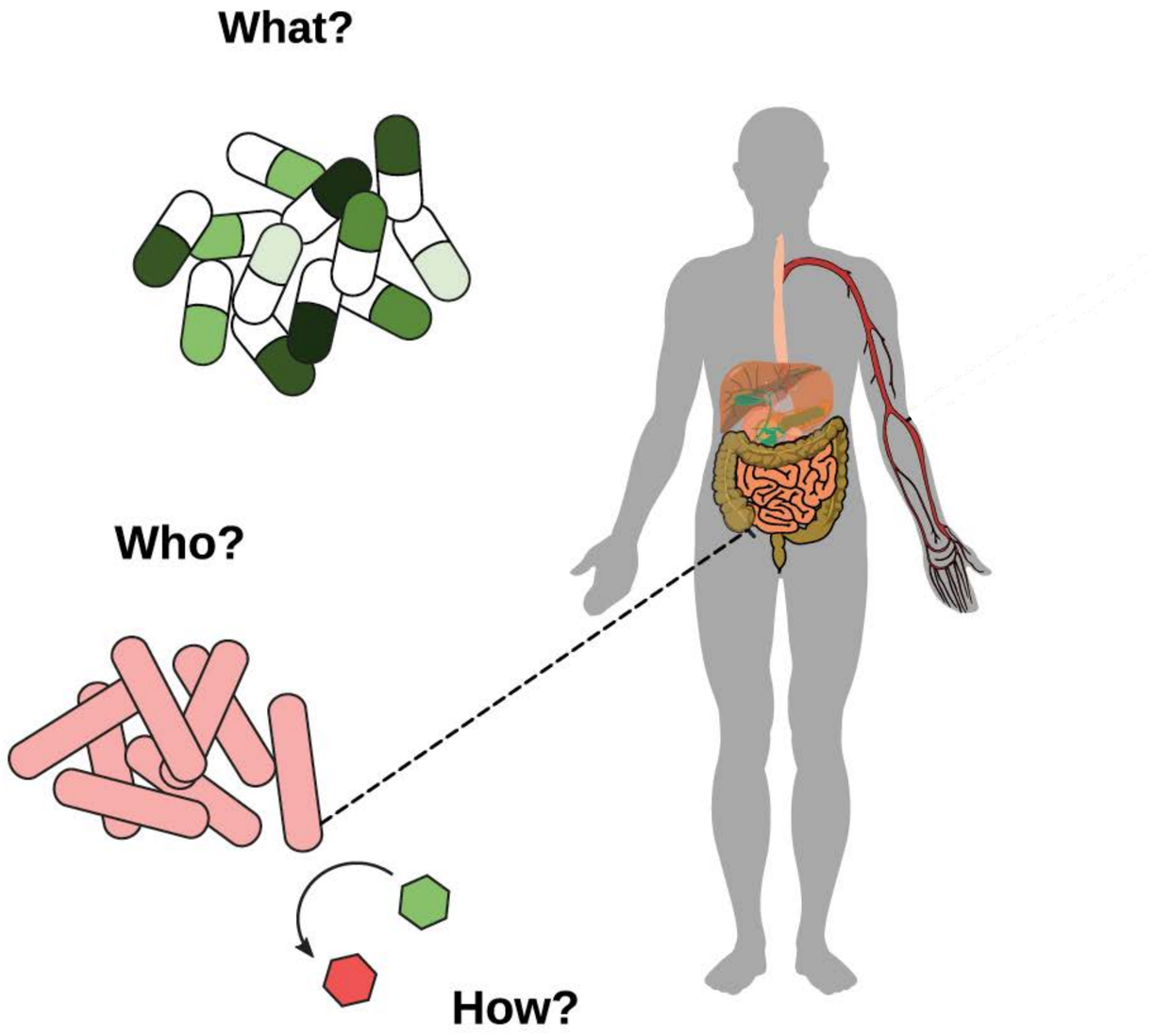

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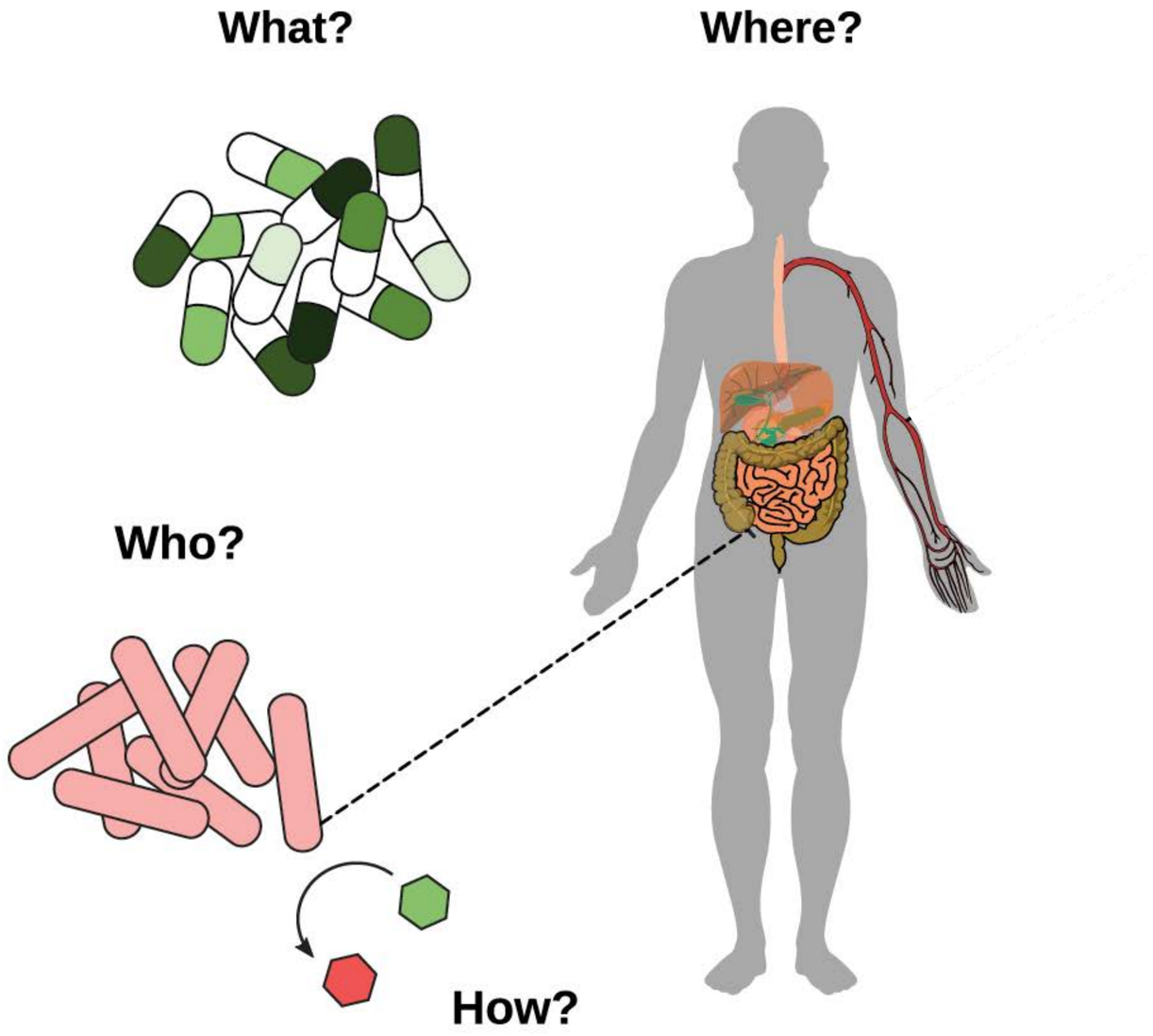

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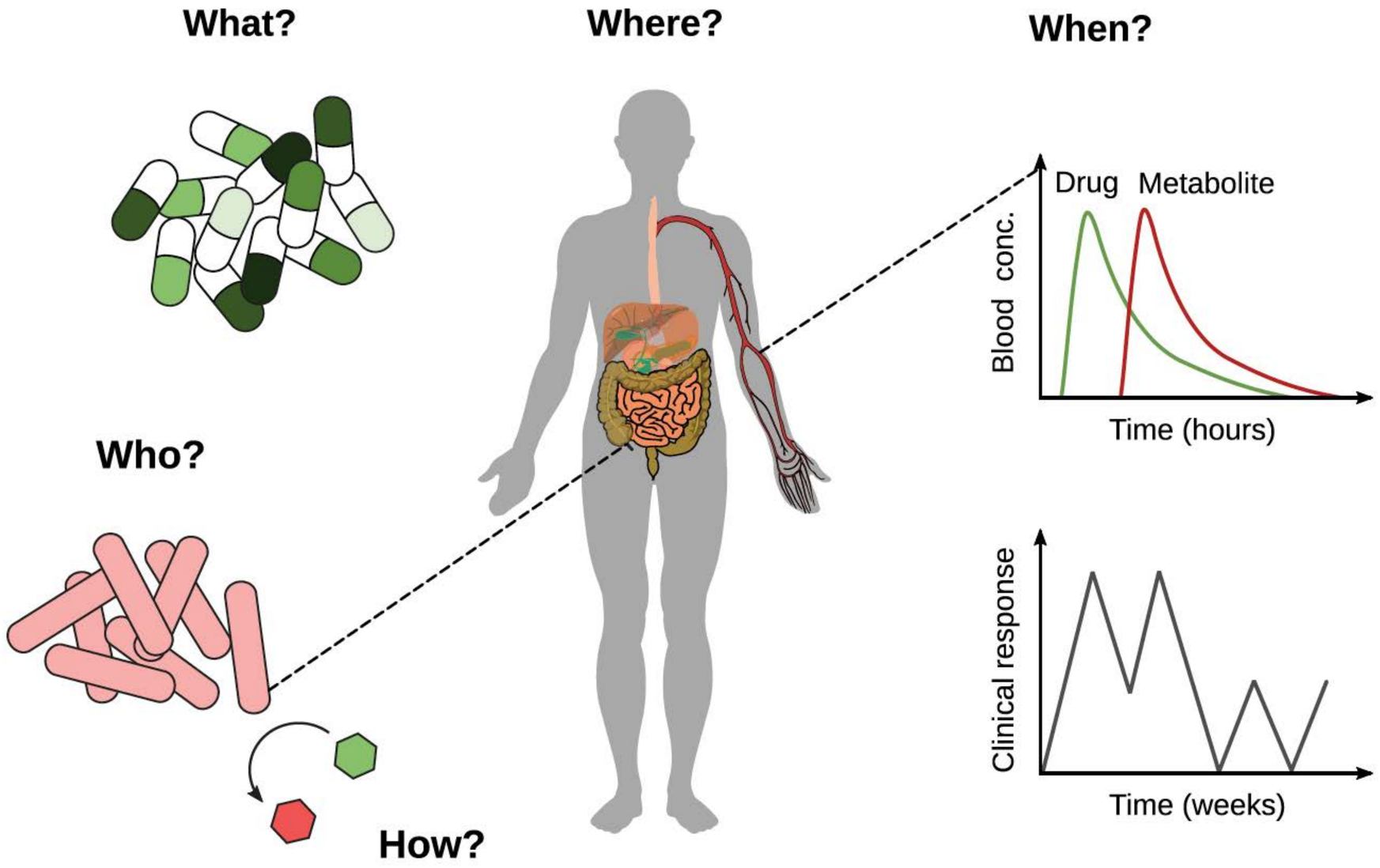

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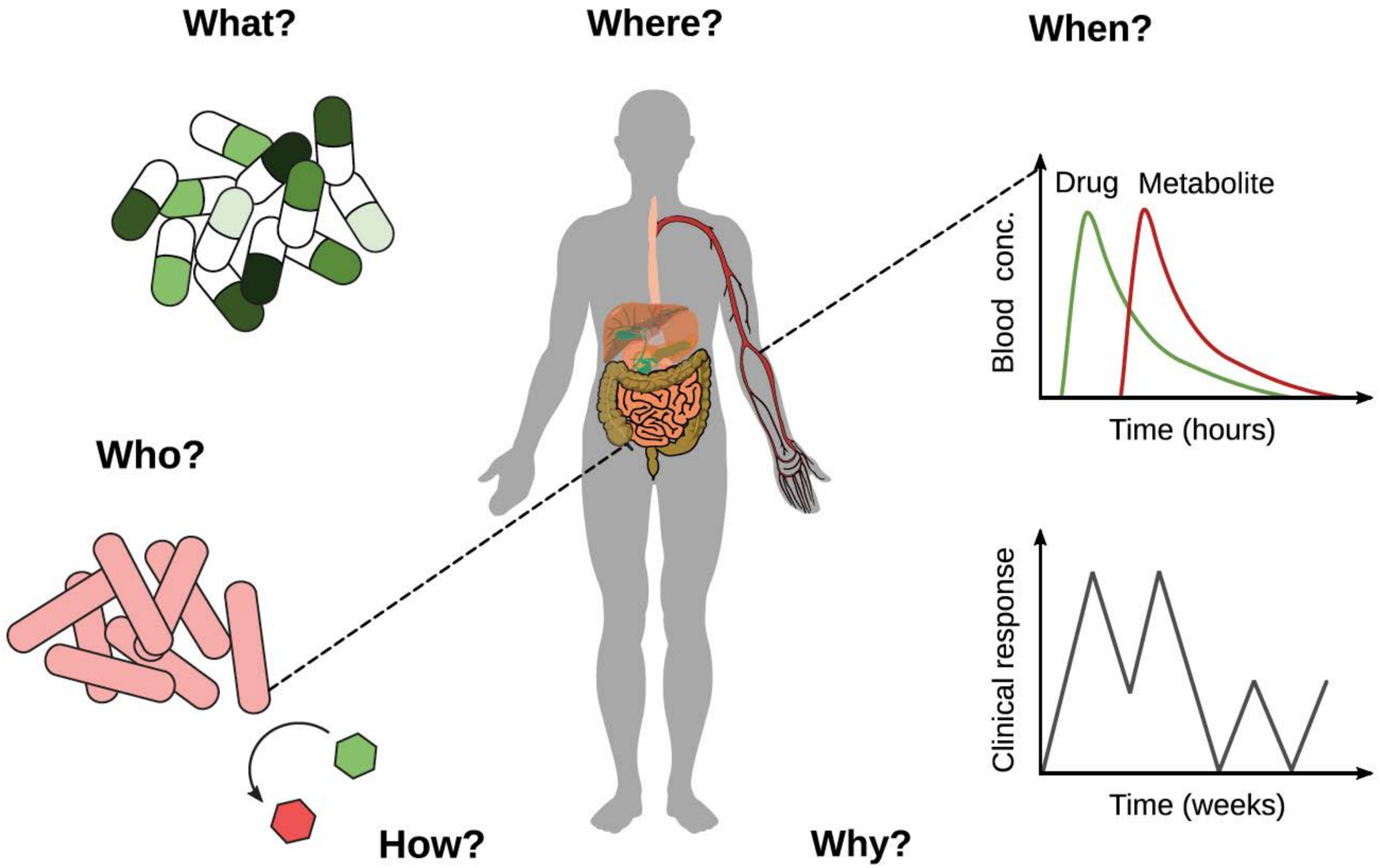
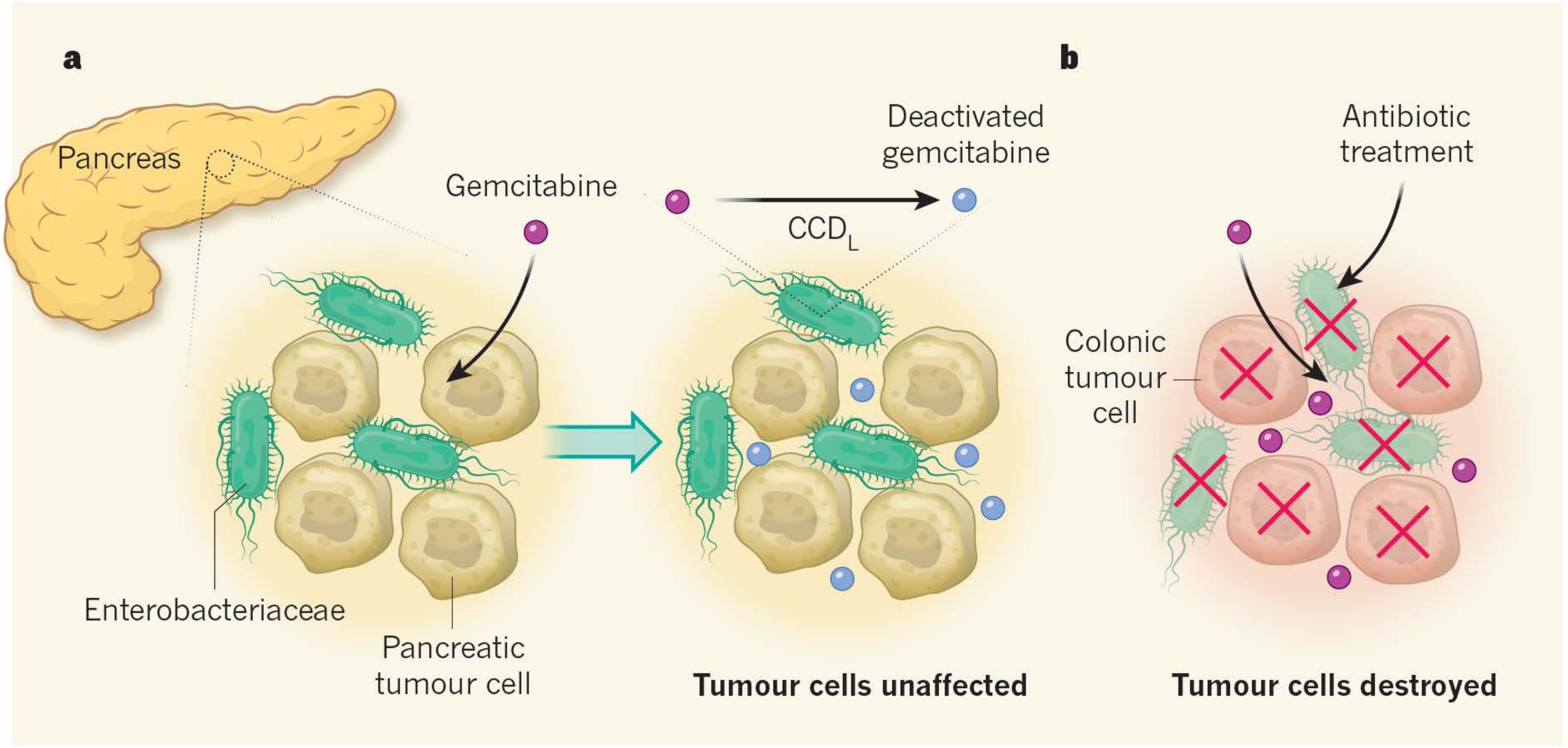


Lam *et al.,* Cell Host & Microbe 2019 (PMID:31295421)

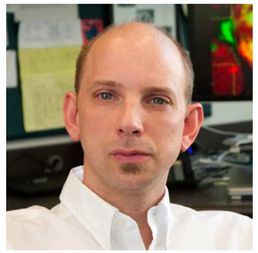
Inactivation of anti-cancer drugs within the tumor tissue



Geller *et al.,* Science 2017 (PMID:28912244); image from Nature commentary (PMID:29052621)

Immunotherapy 101

BAKAR IMMUNO



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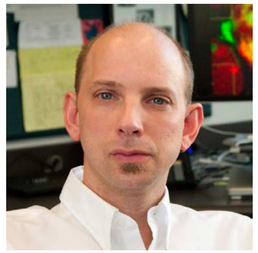

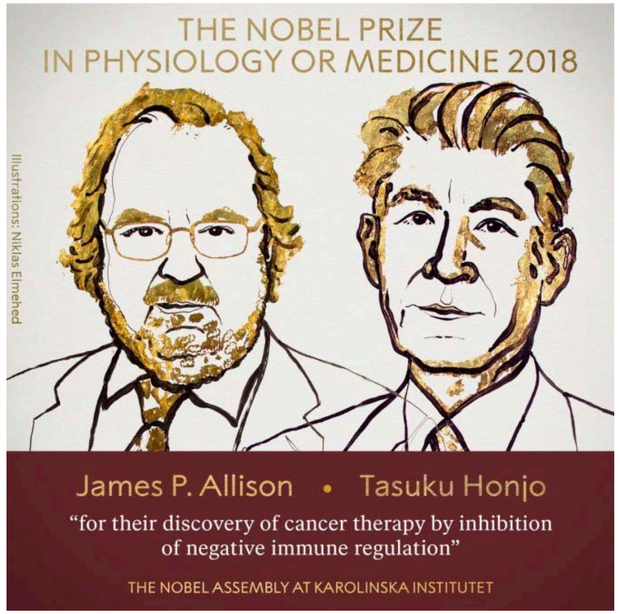

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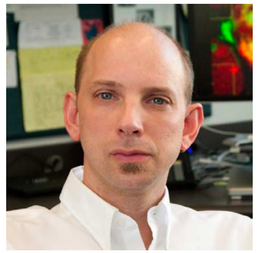

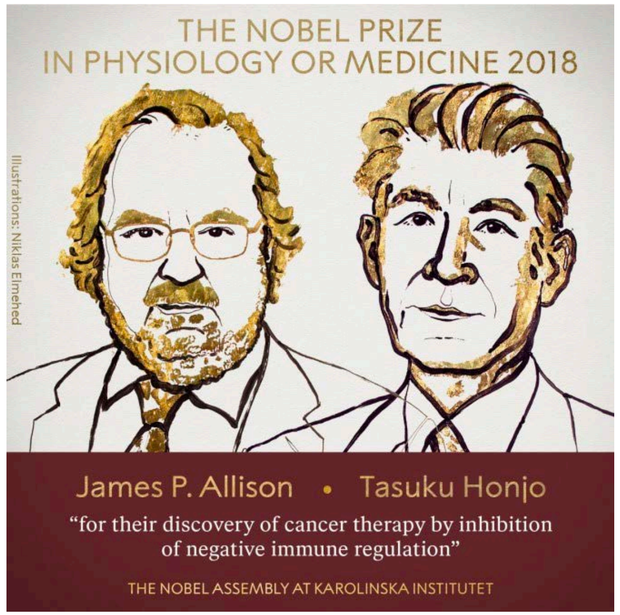

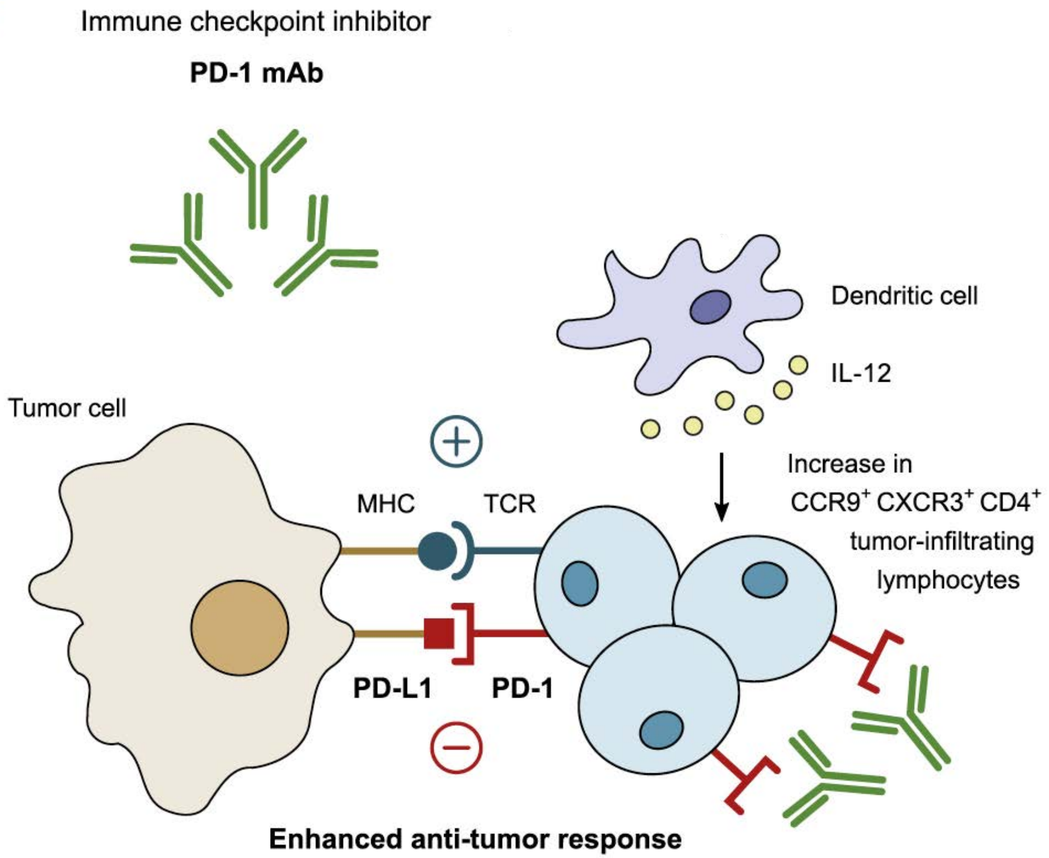

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Why would gut bacteria impact immunotherapy?

Cancer therapies
Anticancer treatment modalities and co-medications (such as antibiotics) affect the integrity of the epithelial barrier.

Zitvogel *et al.,* Science 2018 (PMID:29567708)

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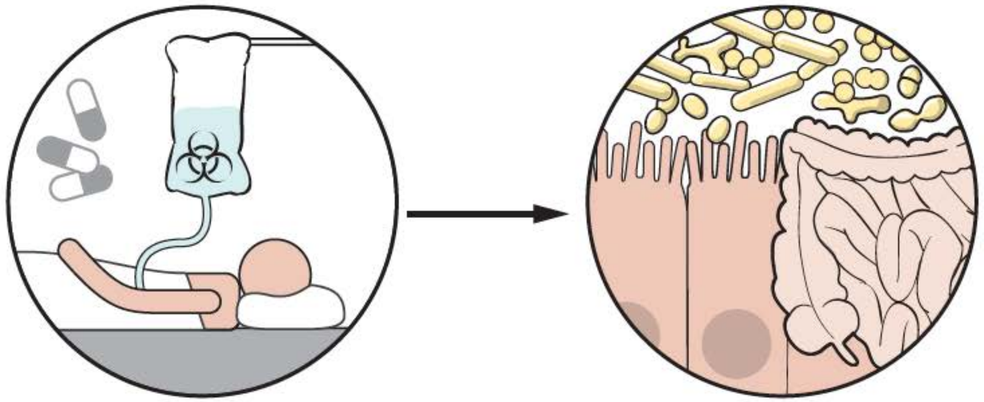

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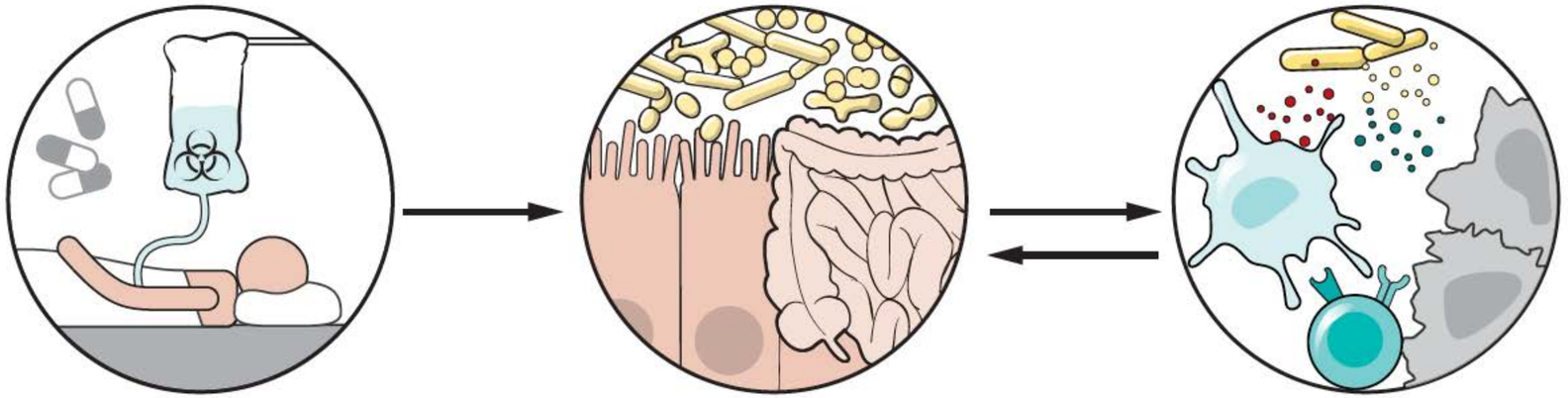
Immune responses
The gut microbiota has systemic effects throughout the meta-organism via secretion of anti-inflammatory cytokine/chemokines, metabolites, antimicrobial and neuropeptides.



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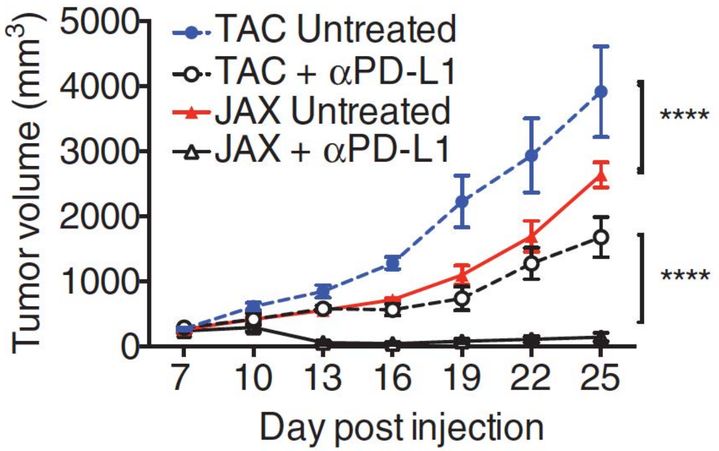
Mice from different vendors differ in tumor growth rates



Sivan *et al.*, Science 2015 (PMID:26541606)

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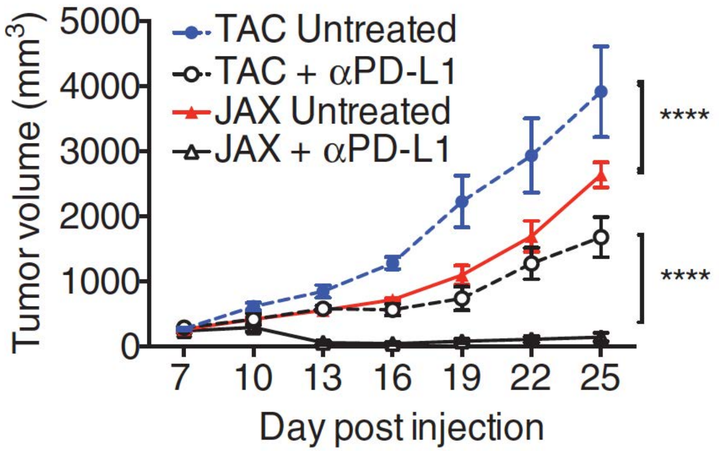

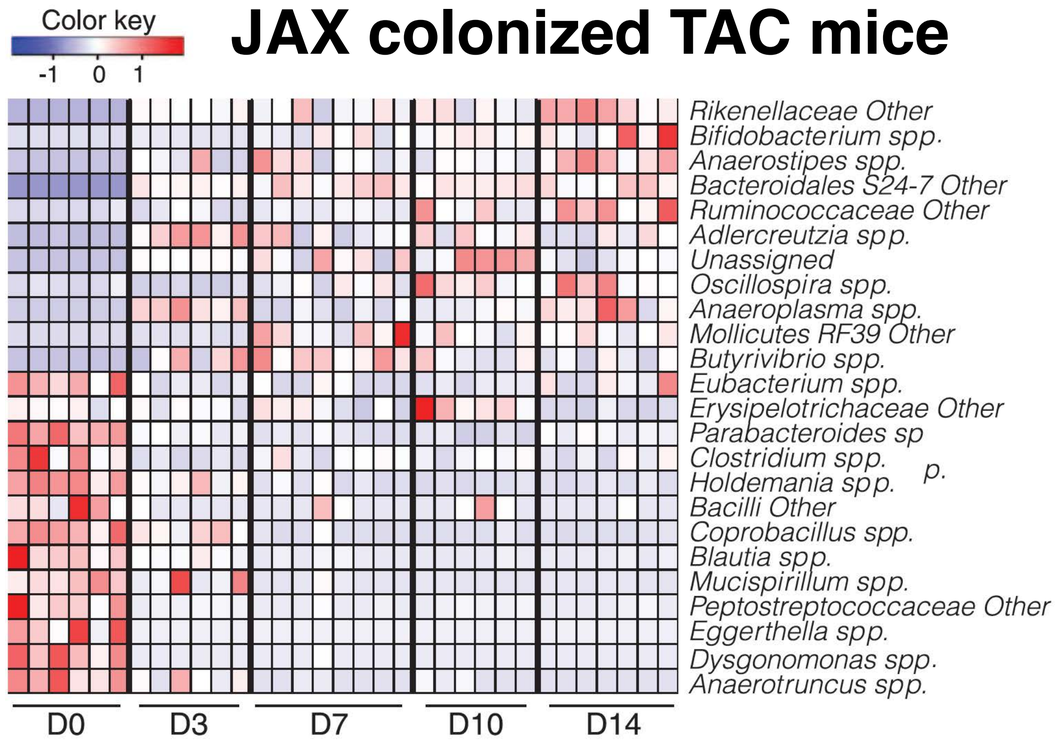

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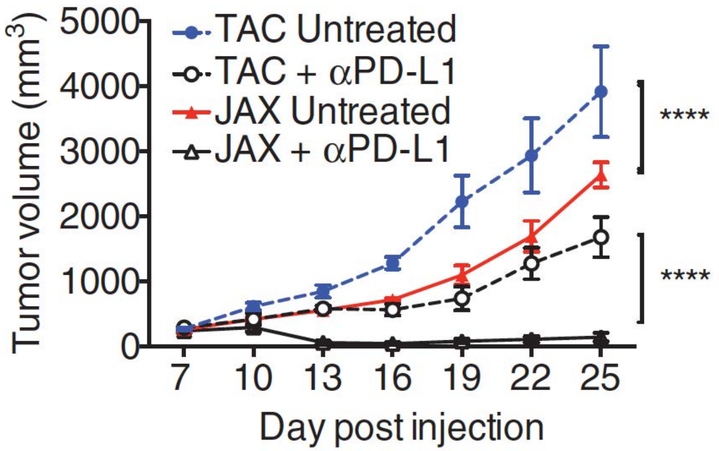

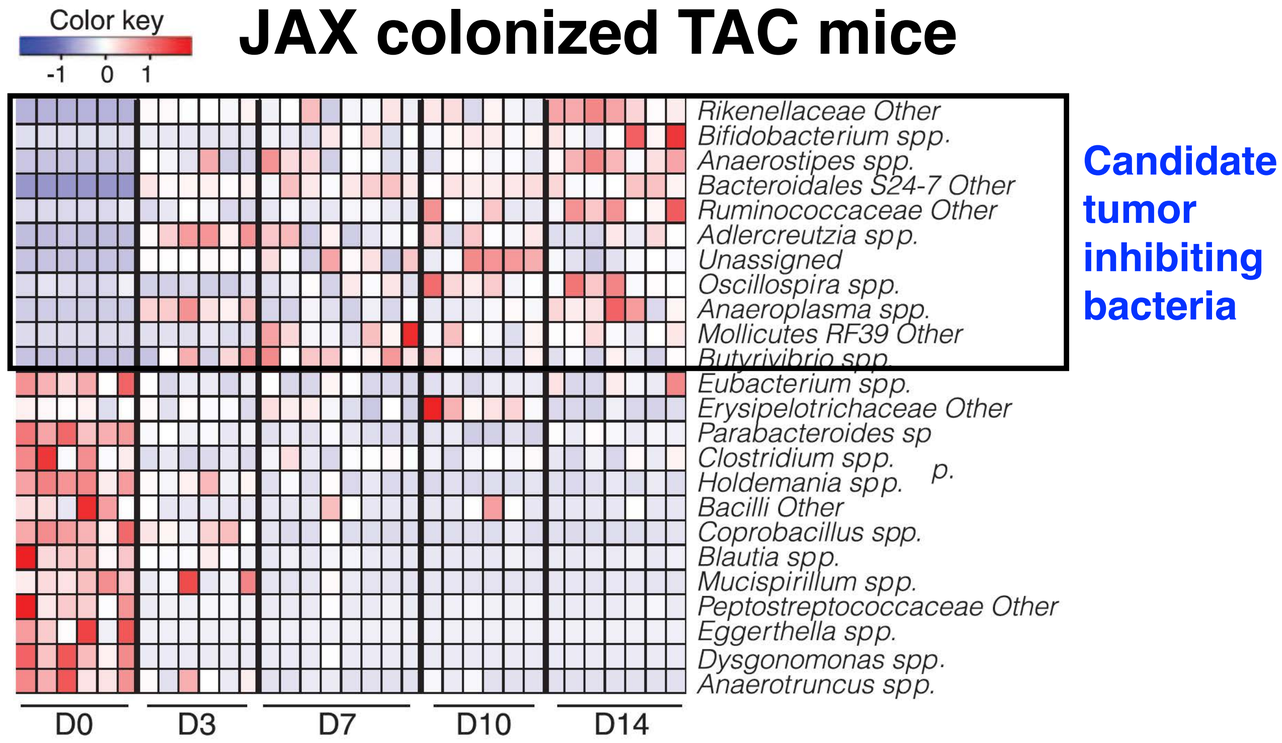

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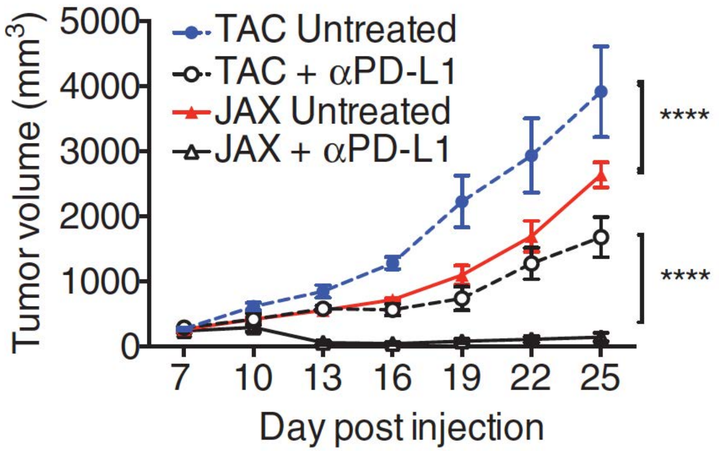

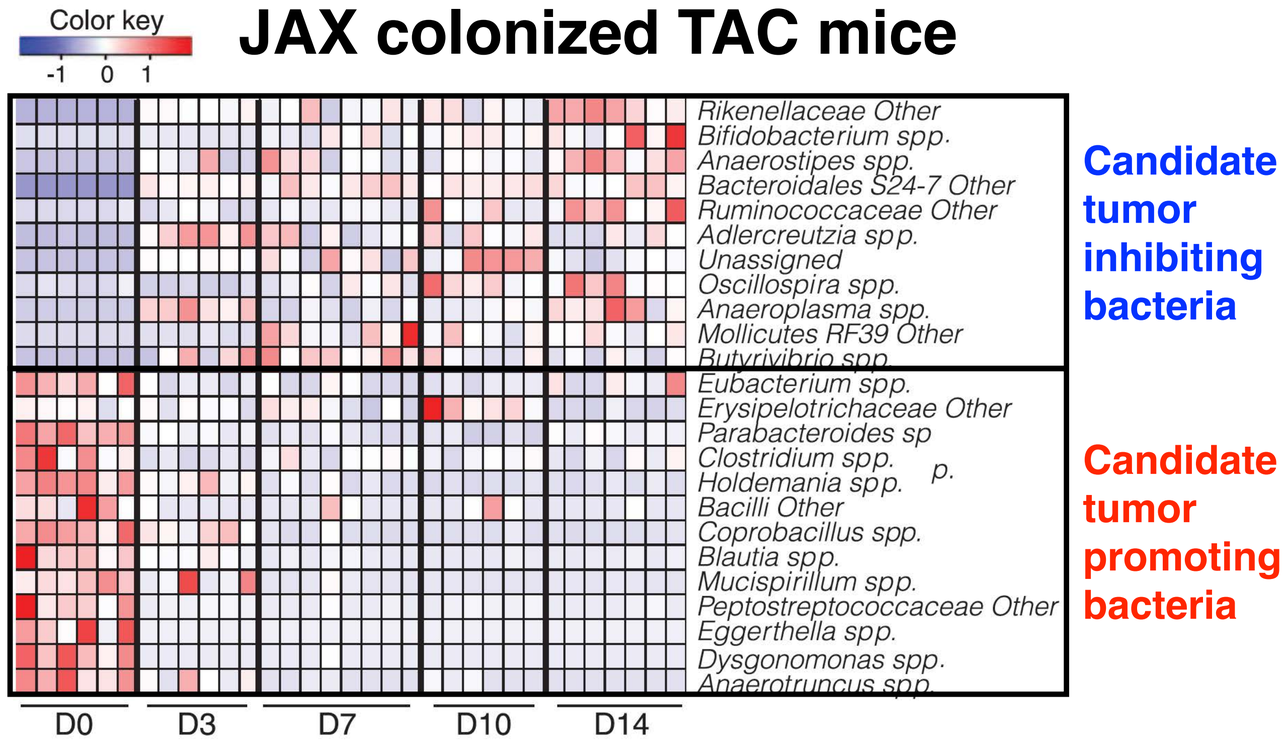

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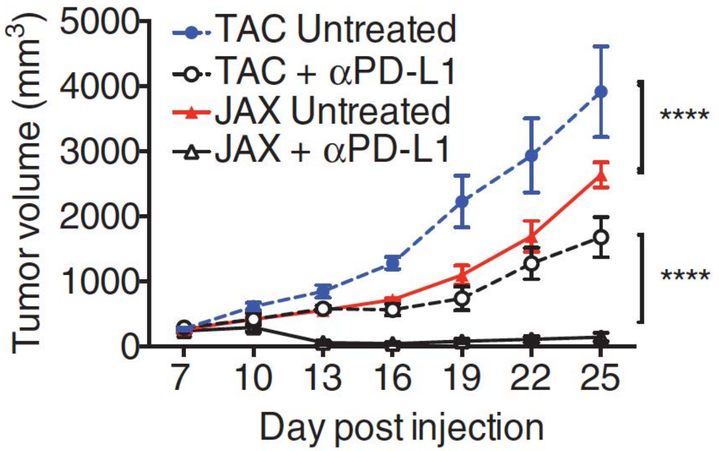

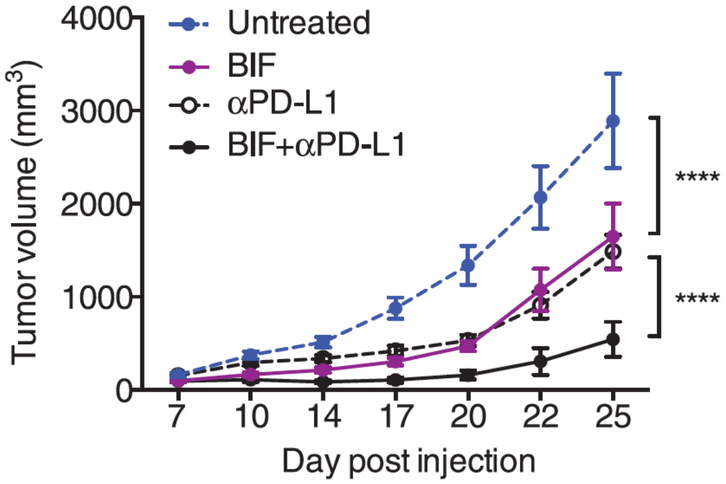

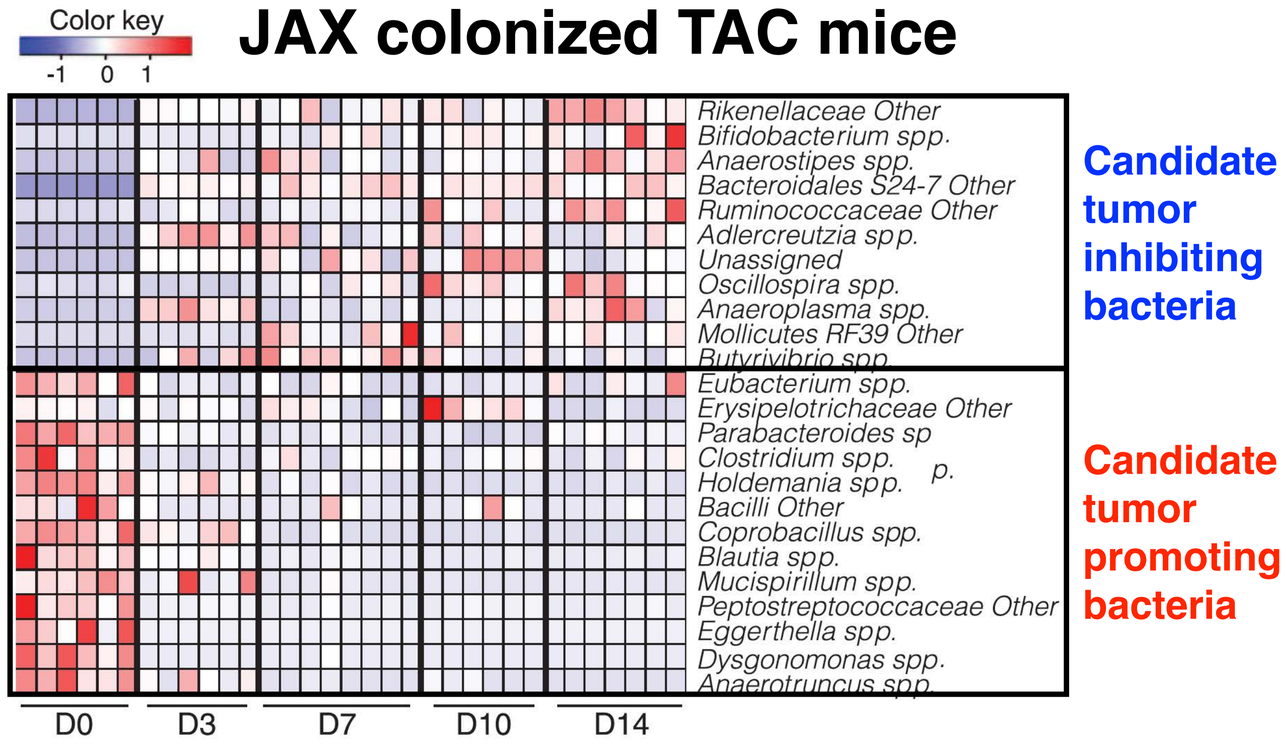

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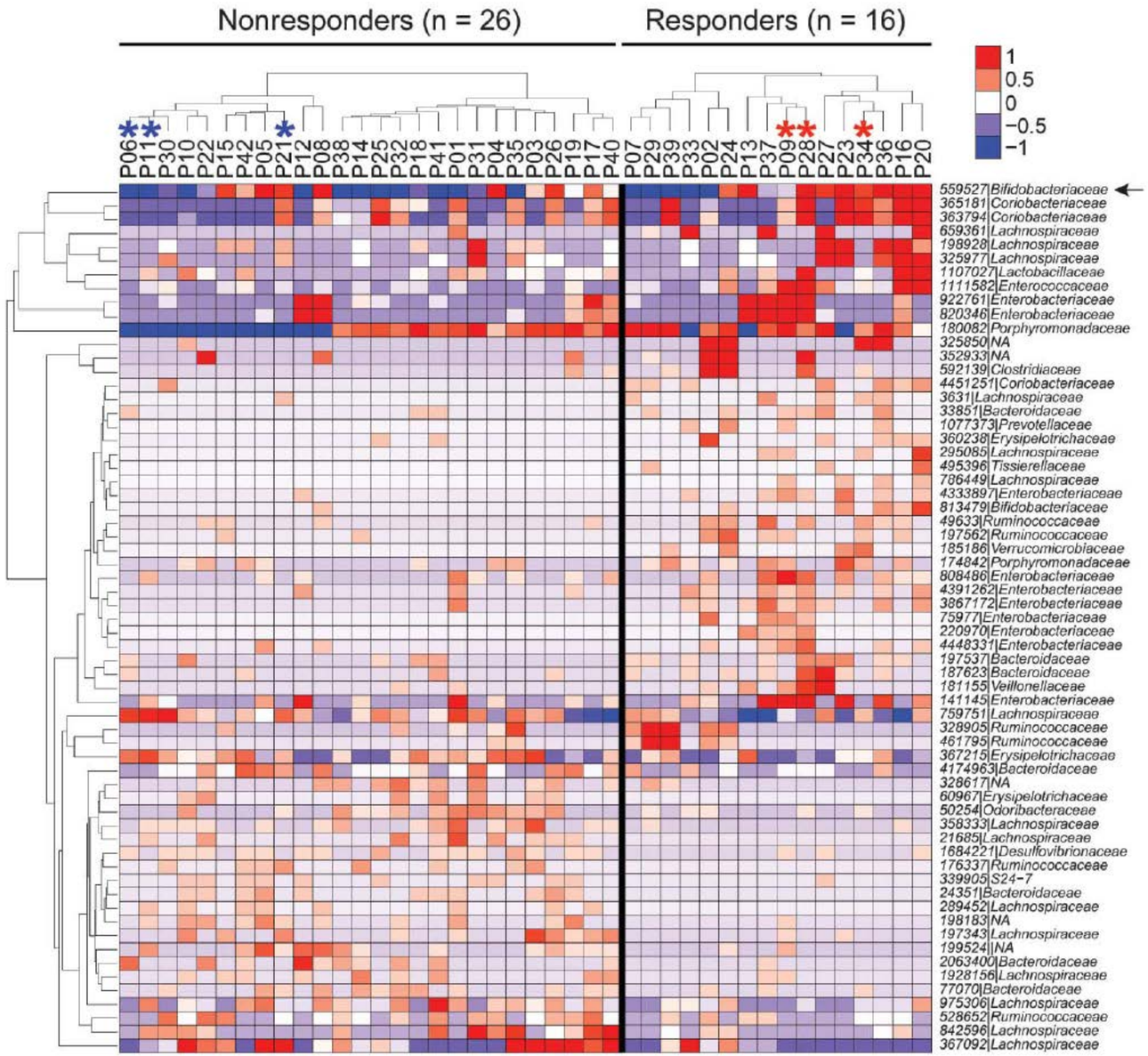
Bifidobacteria are associated with treatment response in metastatic melanoma patients



Matson *et al.,* Science 2018 (PMID:29302014)

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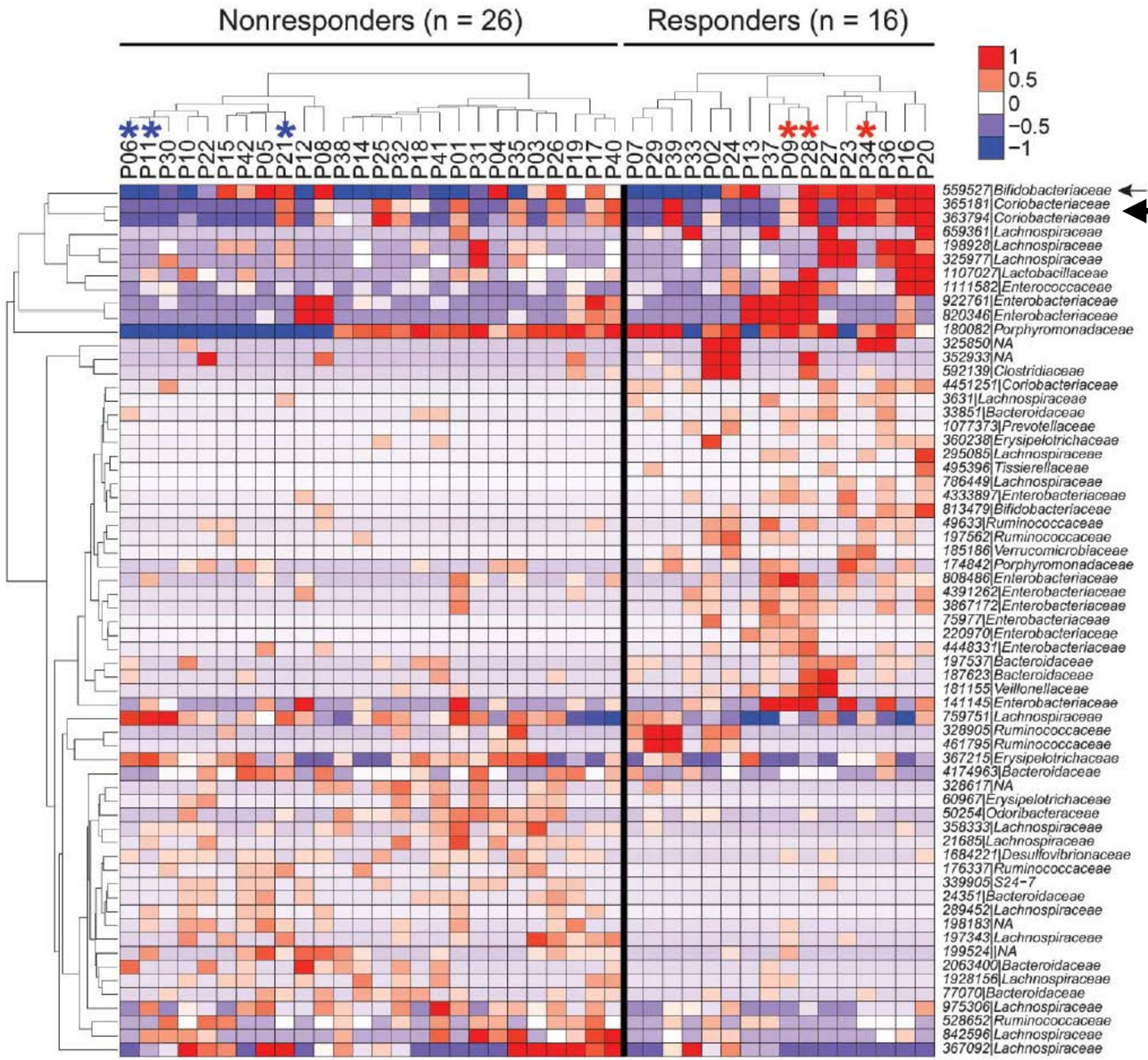

← Our favorite bacteria!

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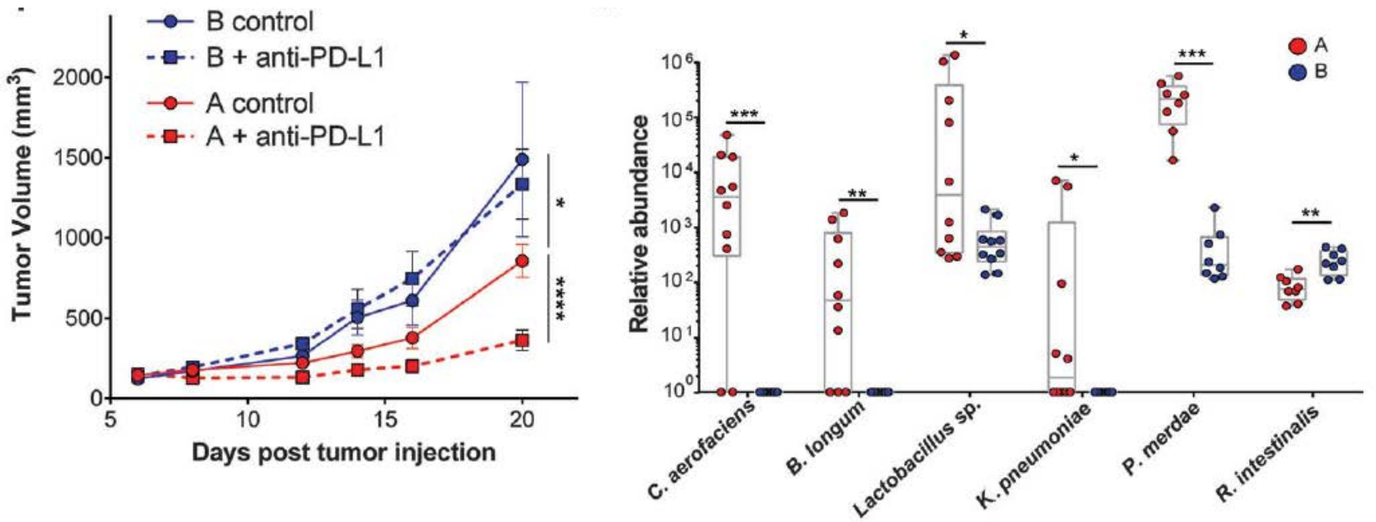

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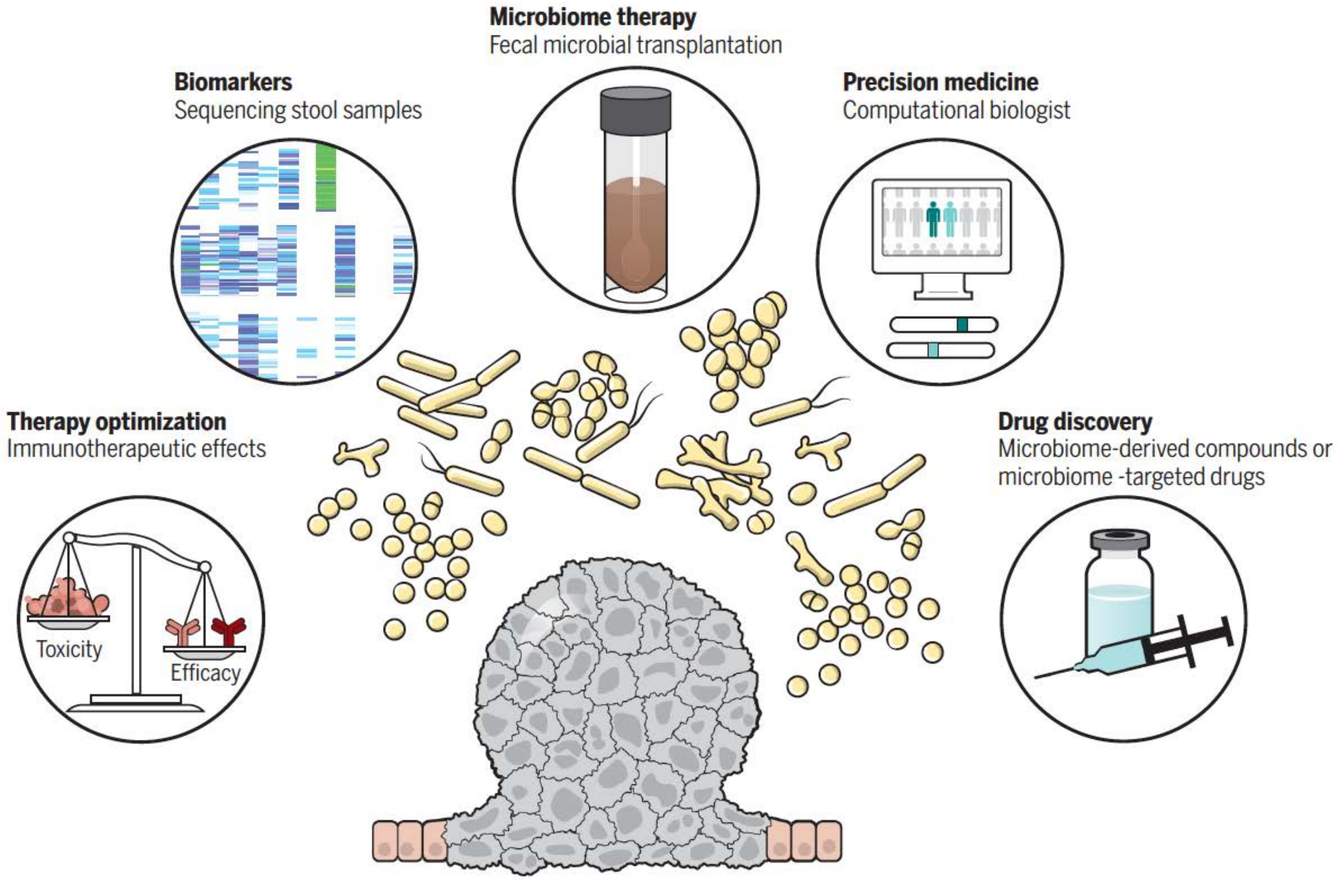
Towards microbiome-based adjuvant medicines



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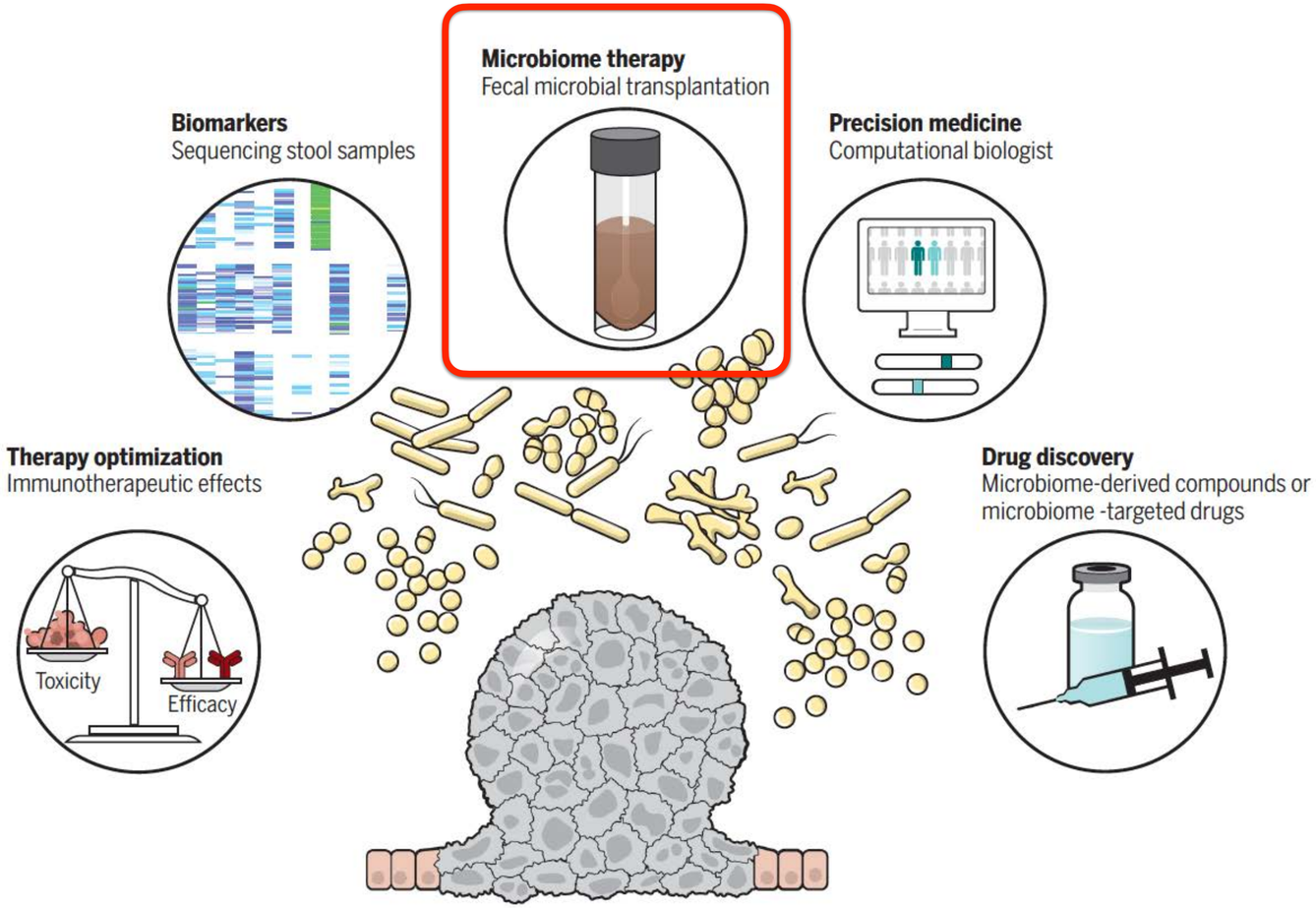

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MIRACLE
POOP

How old is fecal microbiota transplantation?

Zhang *et al.*, **Gastroenterology** 2012

How old is fecal microbiota transplantation?

“During the Dong-jin dynasty in the **4th century** in China, Ge Hong, a well-known traditional Chinese medicine doctor, described the **use of human fecal suspension by mouth for patients who had food poisoning or severe diarrhea.** This yielded positive results and was considered a medical miracle that brought patients back from brink of death.”

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"Later, in the Ming dynasty of the **16th century**, Li Shizhen described a series of prescriptions using fermented fecal solution, fresh fecal suspension, dry feces, or infant feces for effective treatment of abdominal diseases with severe diarrhea, fever, pain, vomiting, and constipation…the herb doctors…called it **yellow soup**"

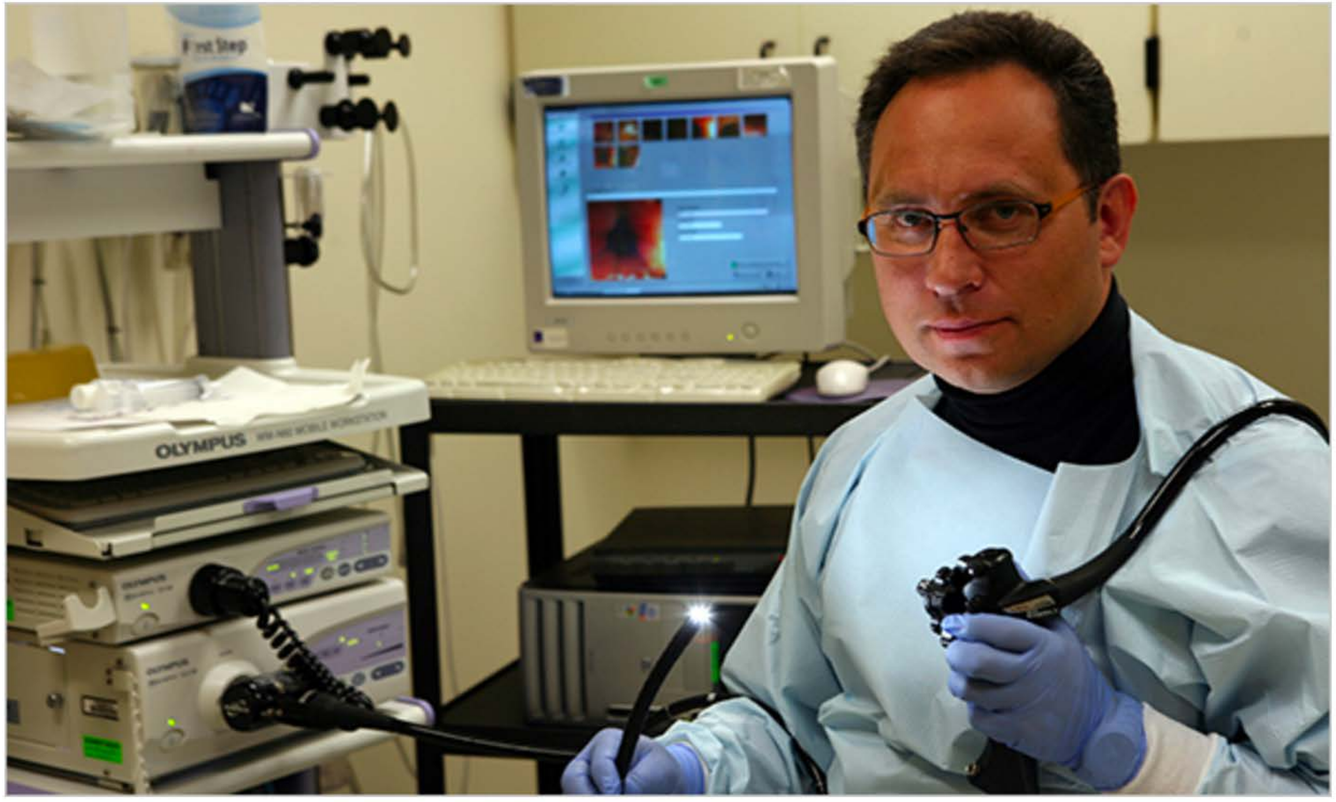
李时珍画像（1-147　3-16　蒋兆和绘）

Zhang *et al.,* **Gastroenterology** 2012

SCIENCE

How Microbes Defend and Define Us

By CARL ZIMMER JULY 12, 2010



Dr. Alexander Khoruts, a gastroenterologist at the University Minnesota, used bacteriotherapy to help cure a patient suffering from a gut infection. Allen Brisson-Smith for The New York Times

SCIENCE

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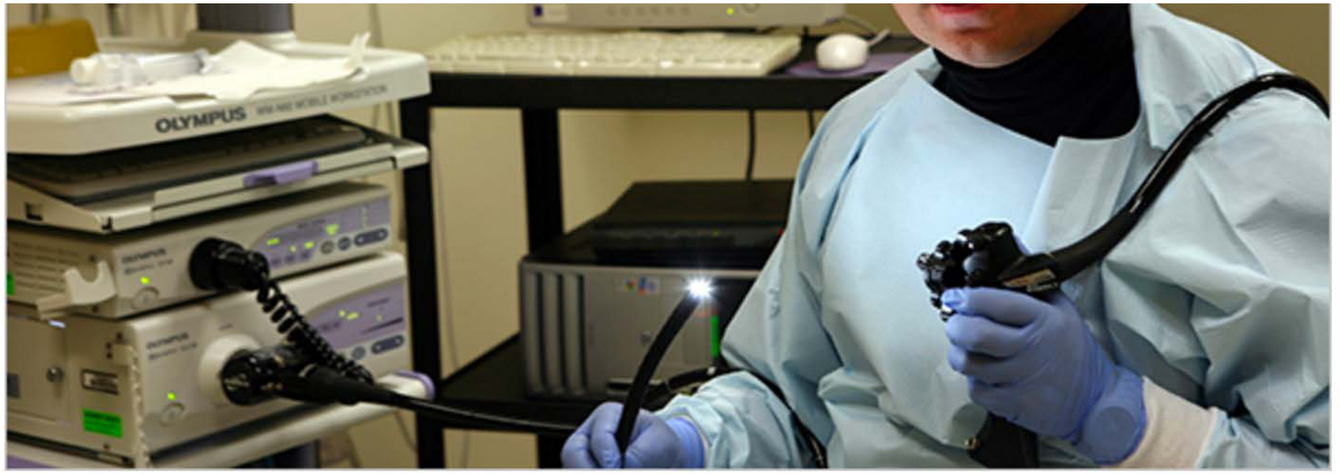
Not so different from ancient China!



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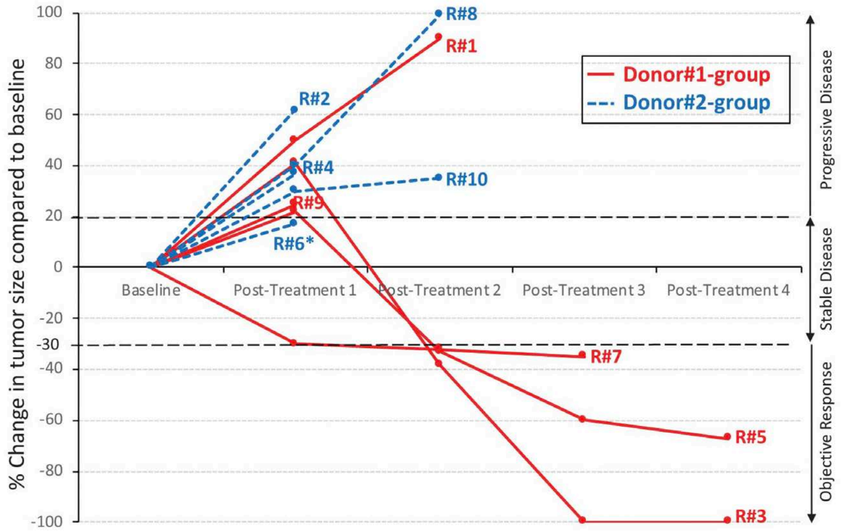
FMT might improve immunotherapy responsiveness in melanoma patients

Tel Aviv (3/10)



Baruch *et al.,* and Davar *et al.,* Science 2021
(PMIDs:33542131/33303685)

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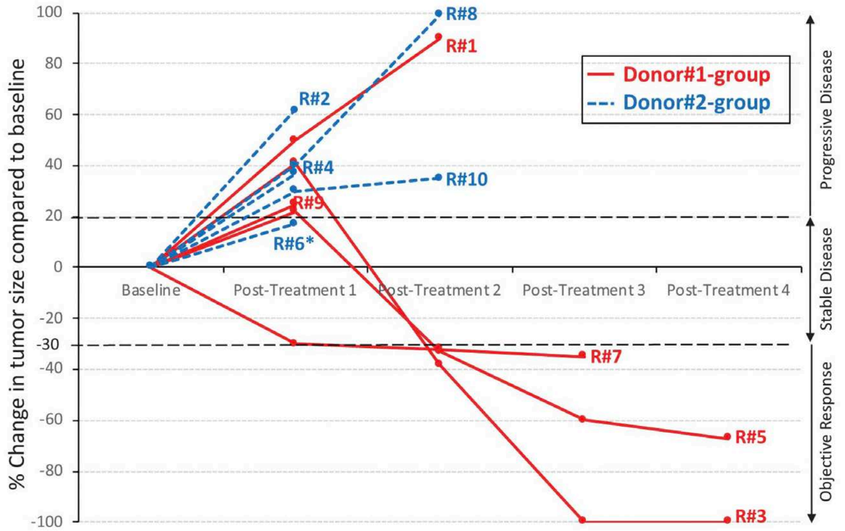
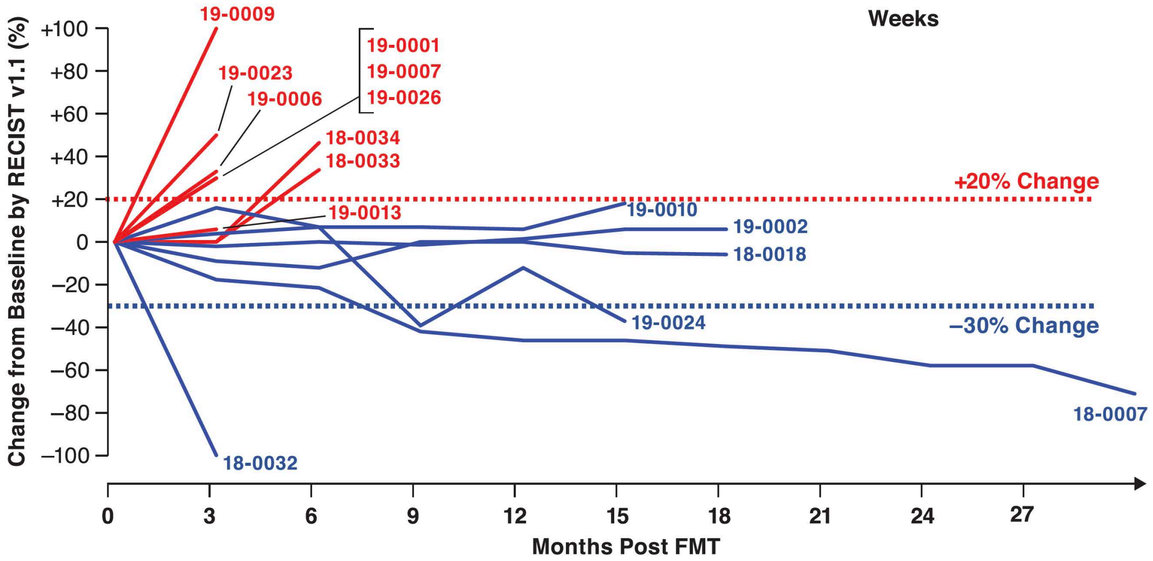


Pittsburgh (3-6/15)



Baruch *et al.,* and Davar *et al.,* Science 2021
(PMIDs:33542131/33303685)

FMT has potential side effects

BRIEF REPORT

Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant

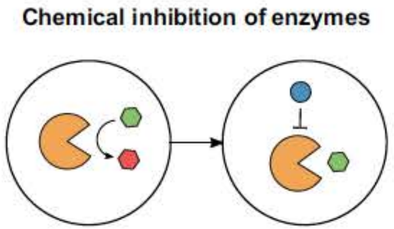
Zachariah DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamad R.A. Sater, Ph.D., Miriam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

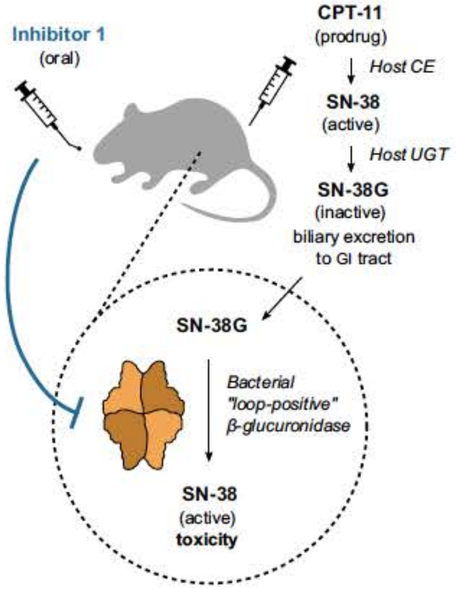
SUMMARY

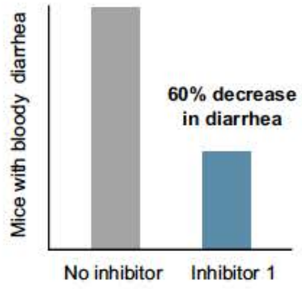
Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory *Clostridioides difficile* infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infectious events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

DeFilipp *et al.*, **NEJM** 2019

Alternatives to FMT







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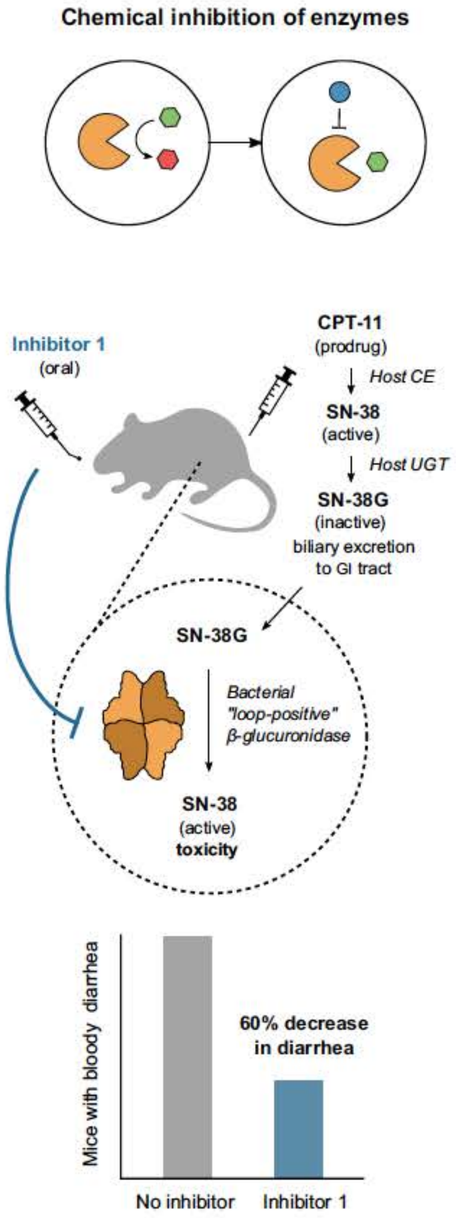
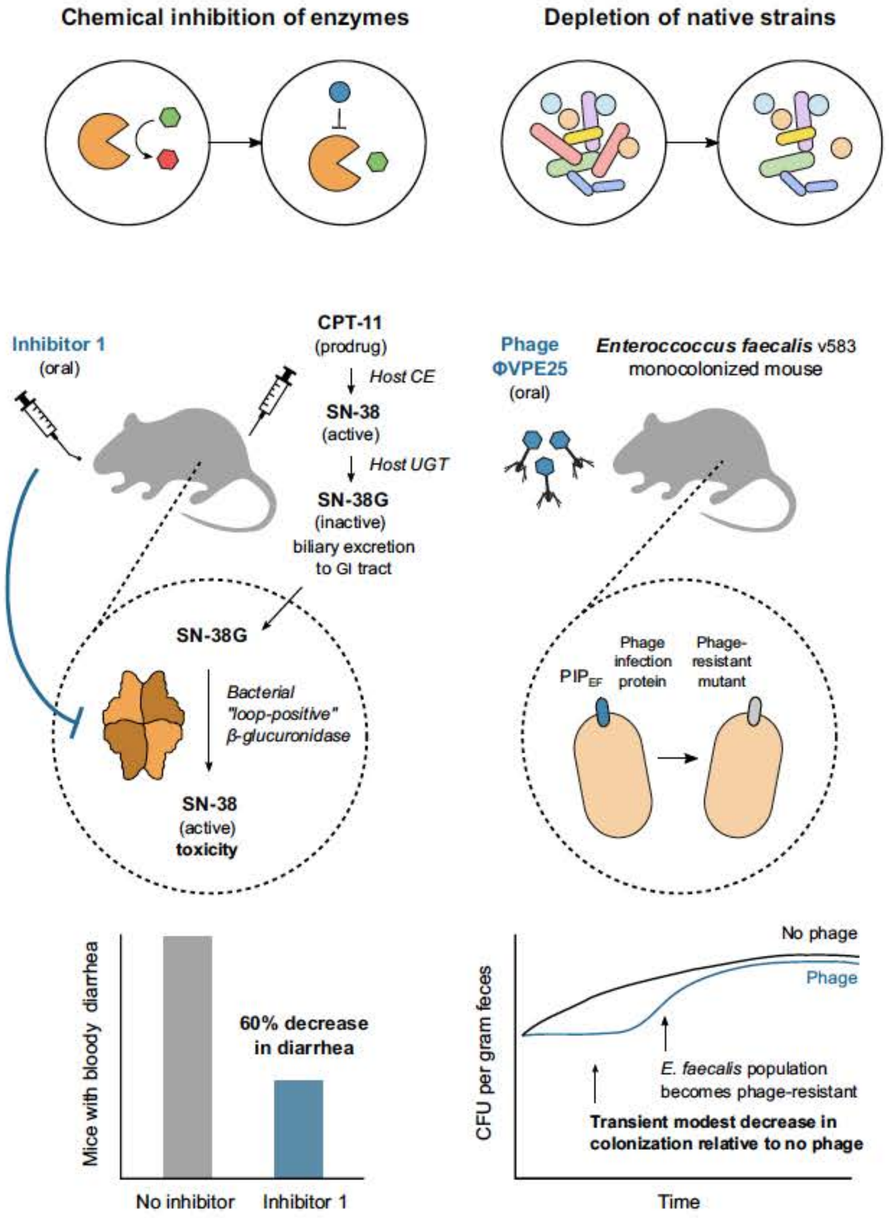


Lam *et al.,* Cell Host & Microbe 2019 (PMID:31295421)

Alternatives to FMT



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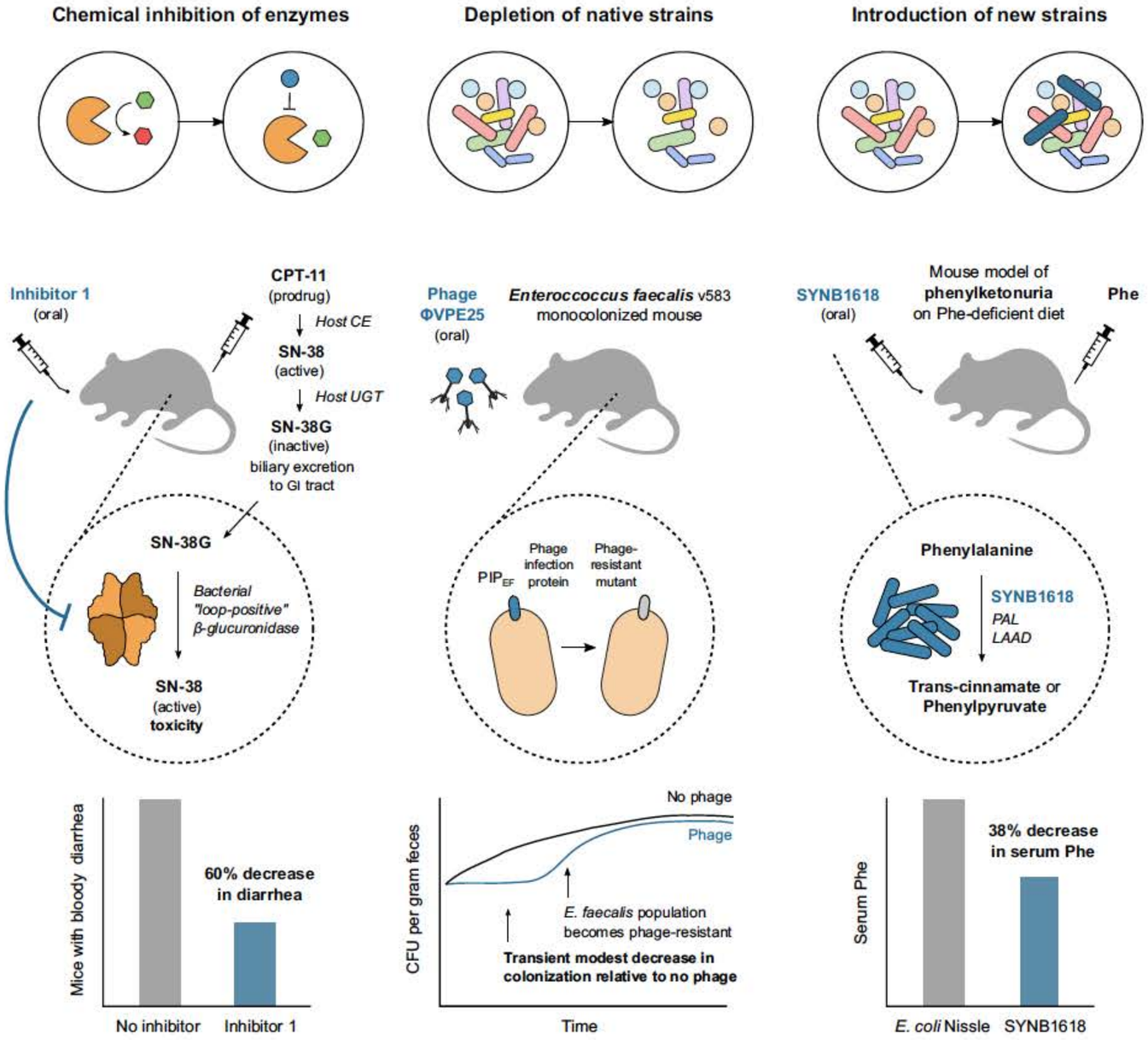
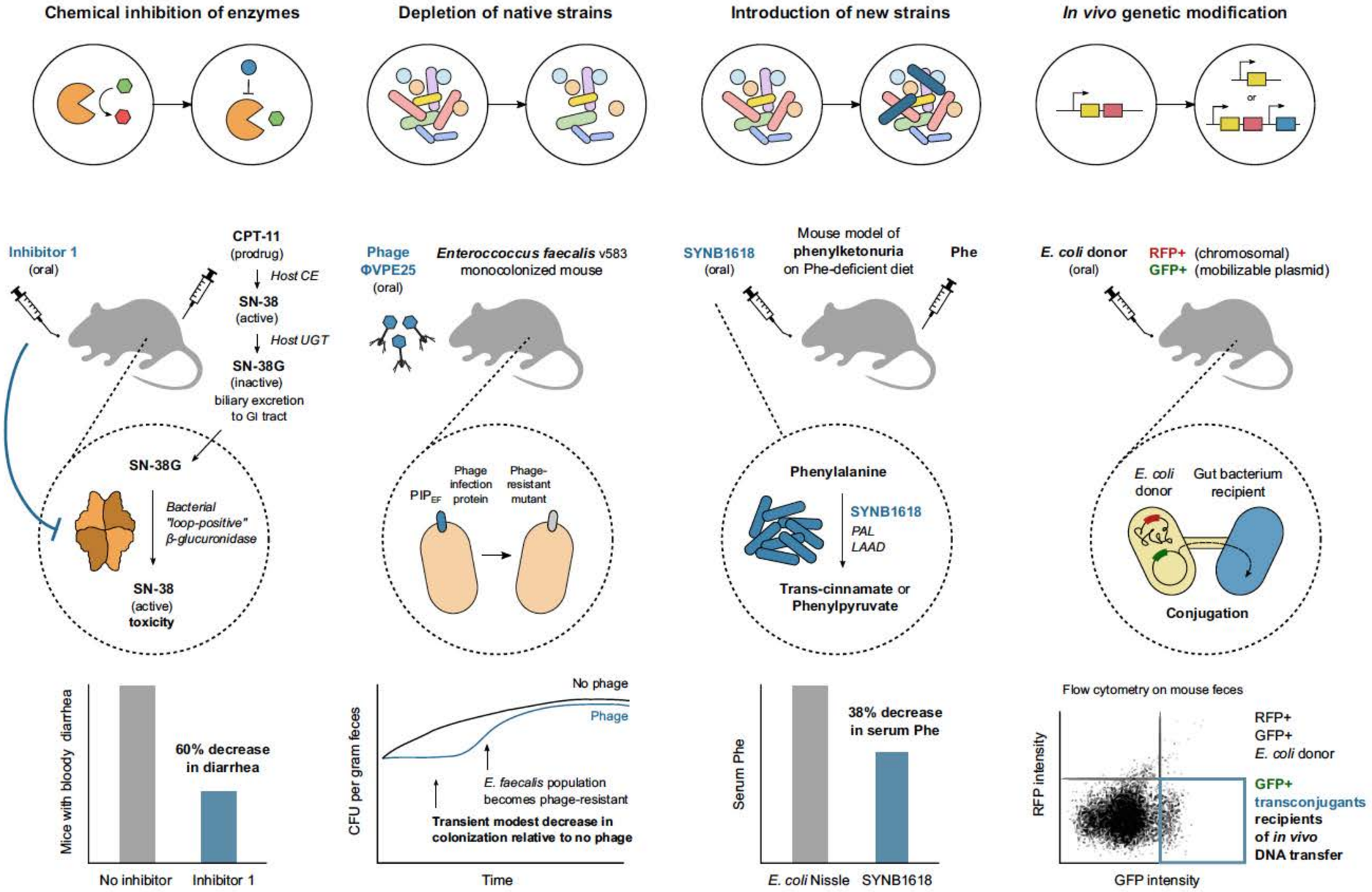


Lam *et al.,* Cell Host & Microbe 2019 (PMID:31295421)

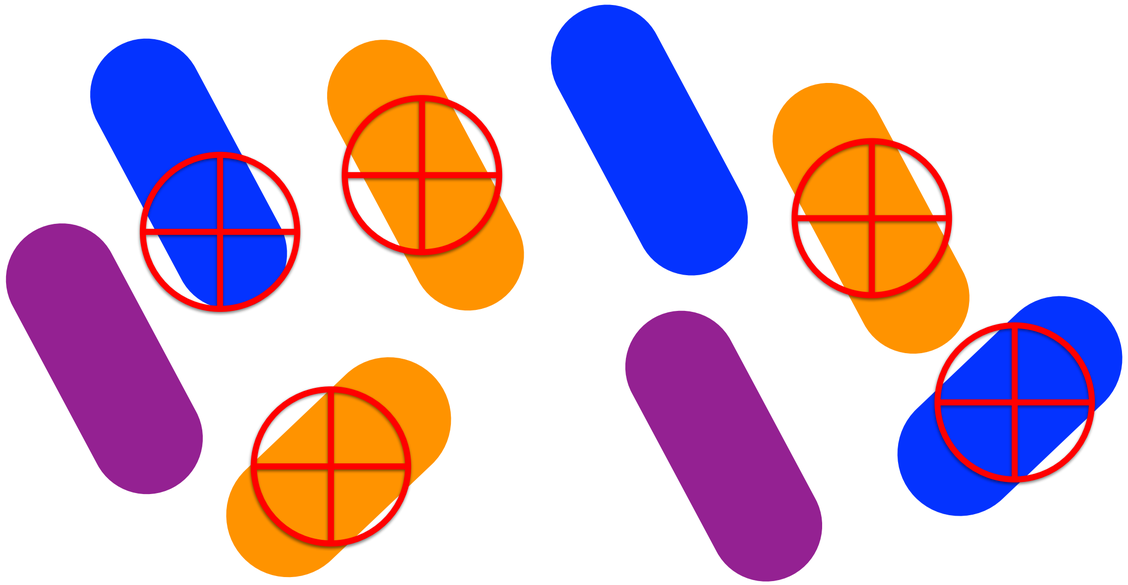
Alternatives to FMT



Lam *et al.,* Cell Host & Microbe 2019 (PMID:31295421)

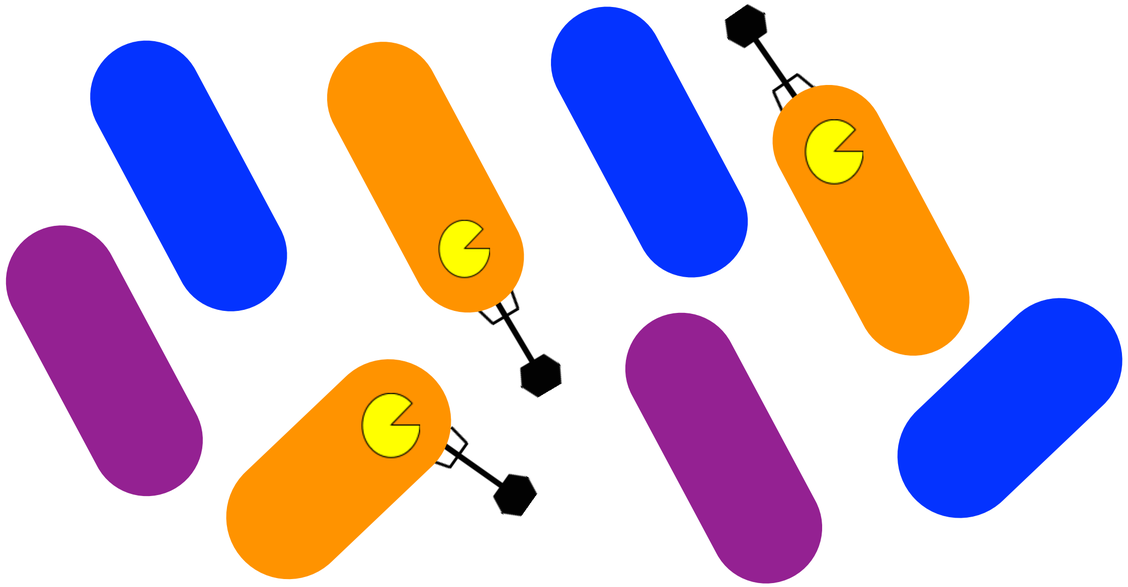
Precise removal of bacteria using CRISPR and phage

Precise removal of bacteria using CRISPR and phage



Problem: current approaches to target bacteria lack precision

Precise removal of bacteria using CRISPR and phage



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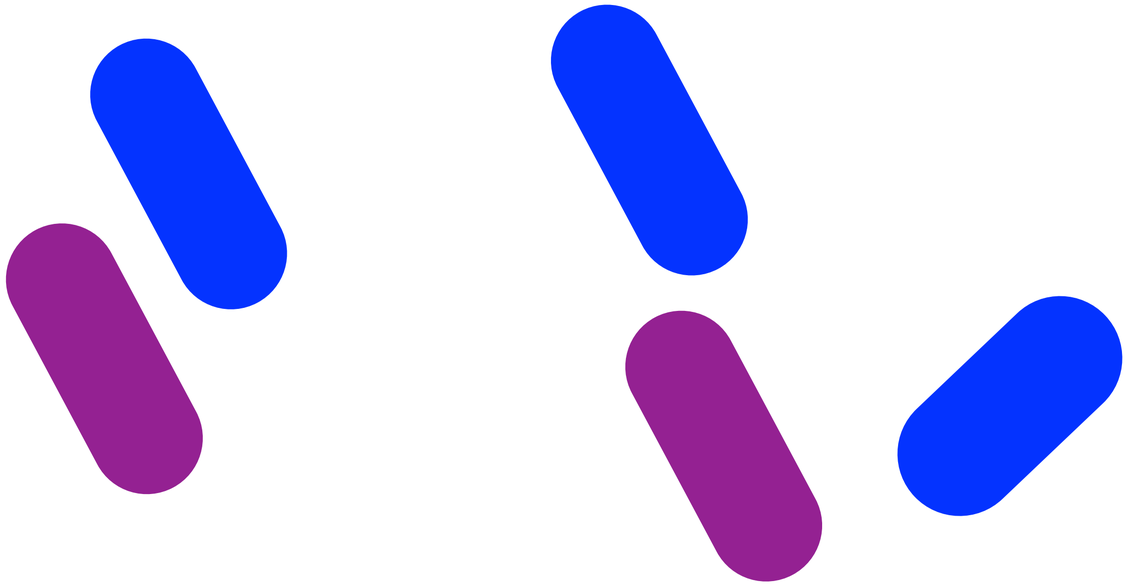
Solution: use bacterial viruses to deliver a programmed CRISPR-Cas system

Precise removal of bacteria using CRISPR and phage



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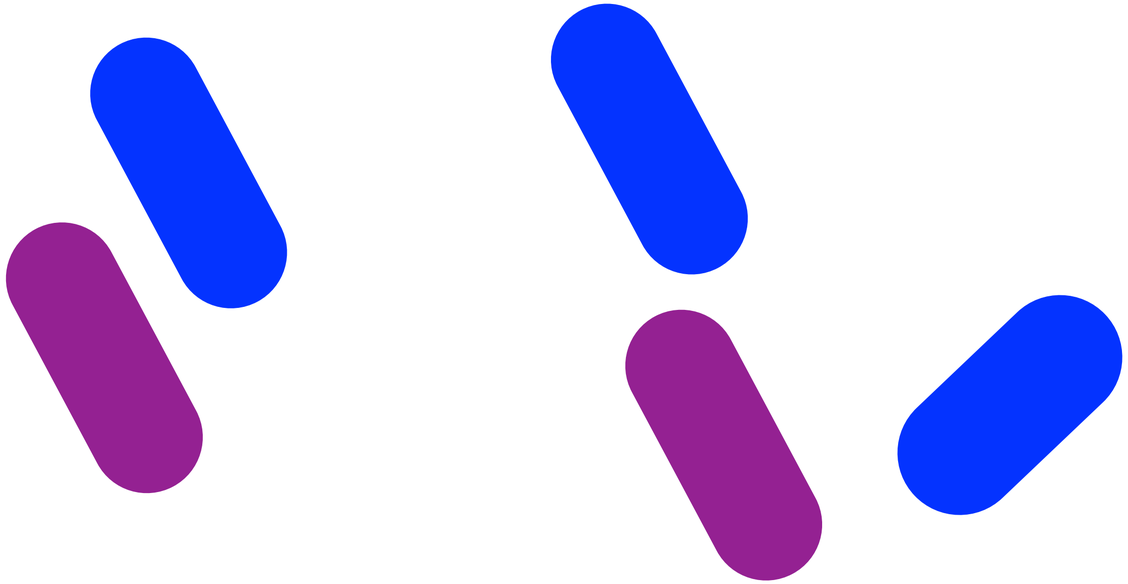

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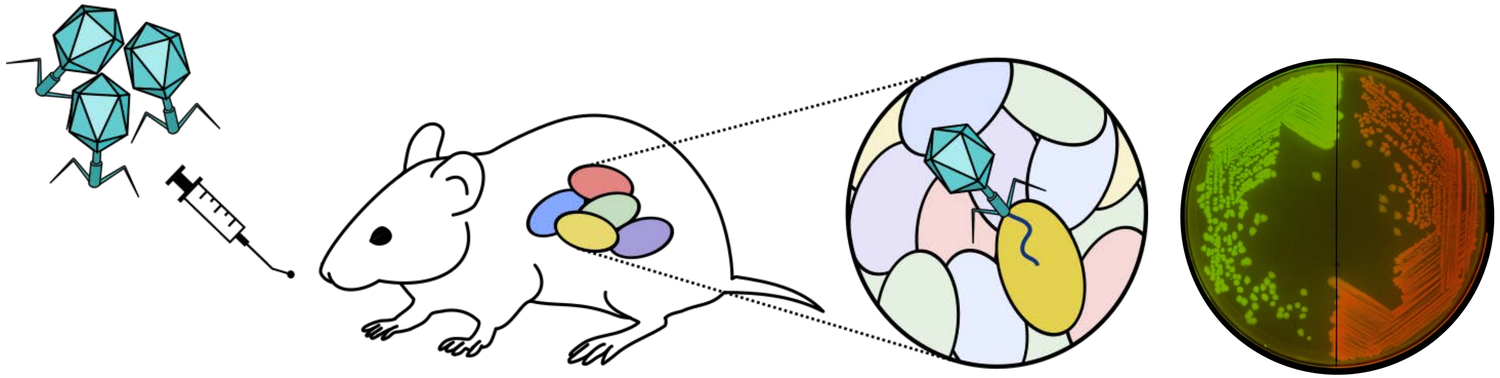

Lam *et al.*, Cell Reports 2021

Research • November 22, 2021

Infecting Gut Microbes with CRISPR-loaded Virus Demonstrates Potential for Microbiome Gene Editing

By Lindzi Wessel

Thank you!

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