The "Force" of the Gut Microbiome in Hematologic Malignancies

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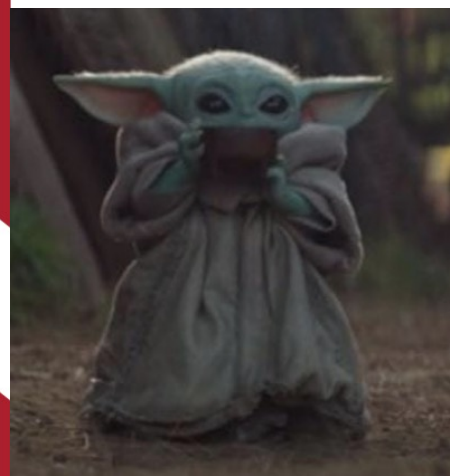
UNMC
1/19/2023



Microbi
cardiom

Science. 2018 May 25;360(6391):eaan5931. doi: 10.1126/science.aan5931.

Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells

Sebastian Fram

Gut. 2021 Apr;70(4):698-706. doi: 10.1136/gutjnl-2020-323020. Epub 2021 Jan 11.

Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19

Yun Kit Yeoh [#1,2], Tao Zuo [#2,3,4], Sandhu [1], Ritz [4],

Proc Natl Acad Sci U S A. 2017 Oct 3;114(40):10713-10718. doi: 10.1073/pnas.1711235114. Epub 2017 Sep 11.

Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models

Egle Cekanaviciute [1], Bryan B Yoo [2], Tessel F Runia [1], Justine W Debelius [3], Sneha Singh [1],

HOME > SCIENCE > VOL. 374, NO. 6575 > DIETARY FIBER AND PROBIOTICS INFLUENCE TH

REPORT | IMMUNOTHERAPY

Dietary fiber and probiotics influen melanoma immunotherapy respon

CHRISTINE N. SPENCER, JENNIFER L. MCQUADE, VANCHESWARAN GOPALAKRISHNAN, JOHN A. MCCULLOCH, [...], AND JENNIFER A. WARGO +84 authors Authors Info & Affiliations

bum [1], Elaine M Richards [1], Richard C Holbert [2],

SCIENCE · 23 Dec 2021 · Vol 374, Issue 6575 · pp. 1632-1640 · DOI: 10.1126/science.aaz7015

How Can The Microbiome Do All This?

- Hope or Hype?

Outline

- Introduction to the Microbiome
- Connections to Host Immunity as a Mechanism
- Associations with Oncologic Diseases
- Novel Approaches for Therapeutic Manipulation

The gut microbiome

- A community of bacteria, viruses, fungi, and parasites
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Is this a “New Immune Organ” or “The Force of Oncology…. A New Hope?”

Microbiome Endpoints/Targets

- Unclear which are the key features of the gut microbiome to target, not mutually exclusive
  - At what time points?

- Microbiome diversity?
  - Better characterized, associated with survival in variety of oncologic settings/therapies
  - Hard to change
  - Diversity ≠ healthy (at least not necessarily)

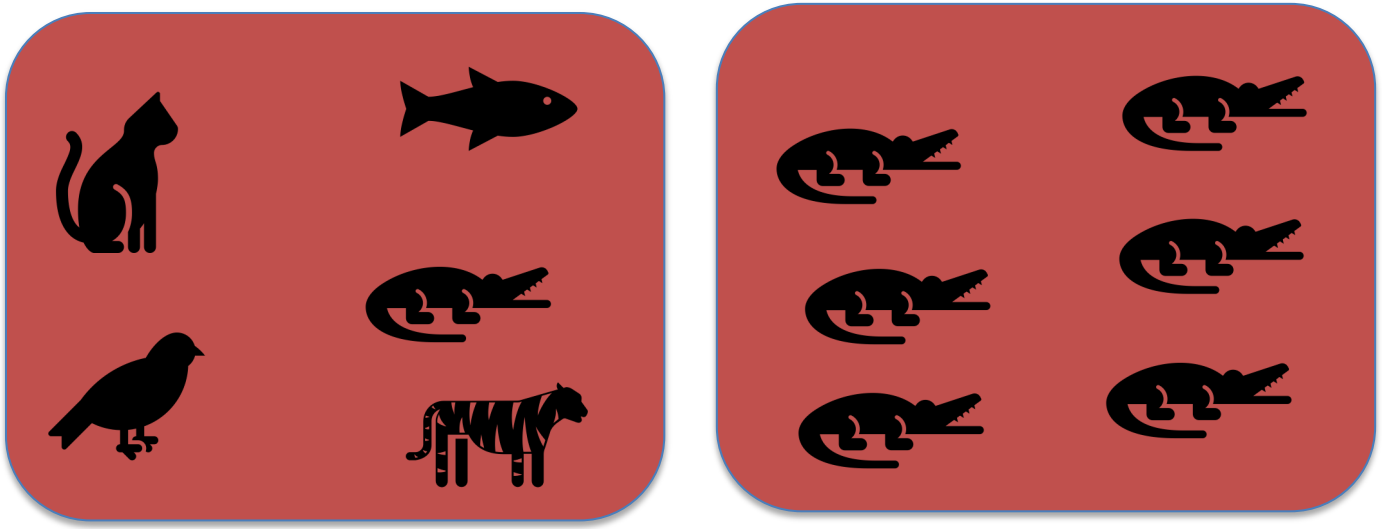
- Specific populations?
  - Eubacterium sp. -> reduced relapse in myeloma allo-SCT (Peled et al, JCO 2017)
  - Blautia sp. -> reduced mortality from GvHD (Jenq et al, BBMT 2015)
  - Prevotella heparinolytica -> presence associated with IL-17 driven myeloma progression in mice (Calcinotto et al, Nat Commun 2018)

- Metabolomics?
  - Provide a readout of the system extending beyond bacterial populations (fungi, viral, epithelial)
  - Short chain fatty acids i.e. butyrate associated with anti-lymphoma activity, regulatory T-cell stimulation

- Endpoint or Process?
  - Does how we reach these endpoints (ie diversity) matter?
  - Ie. antibiotic exposure

Gut Microbiota Diversity

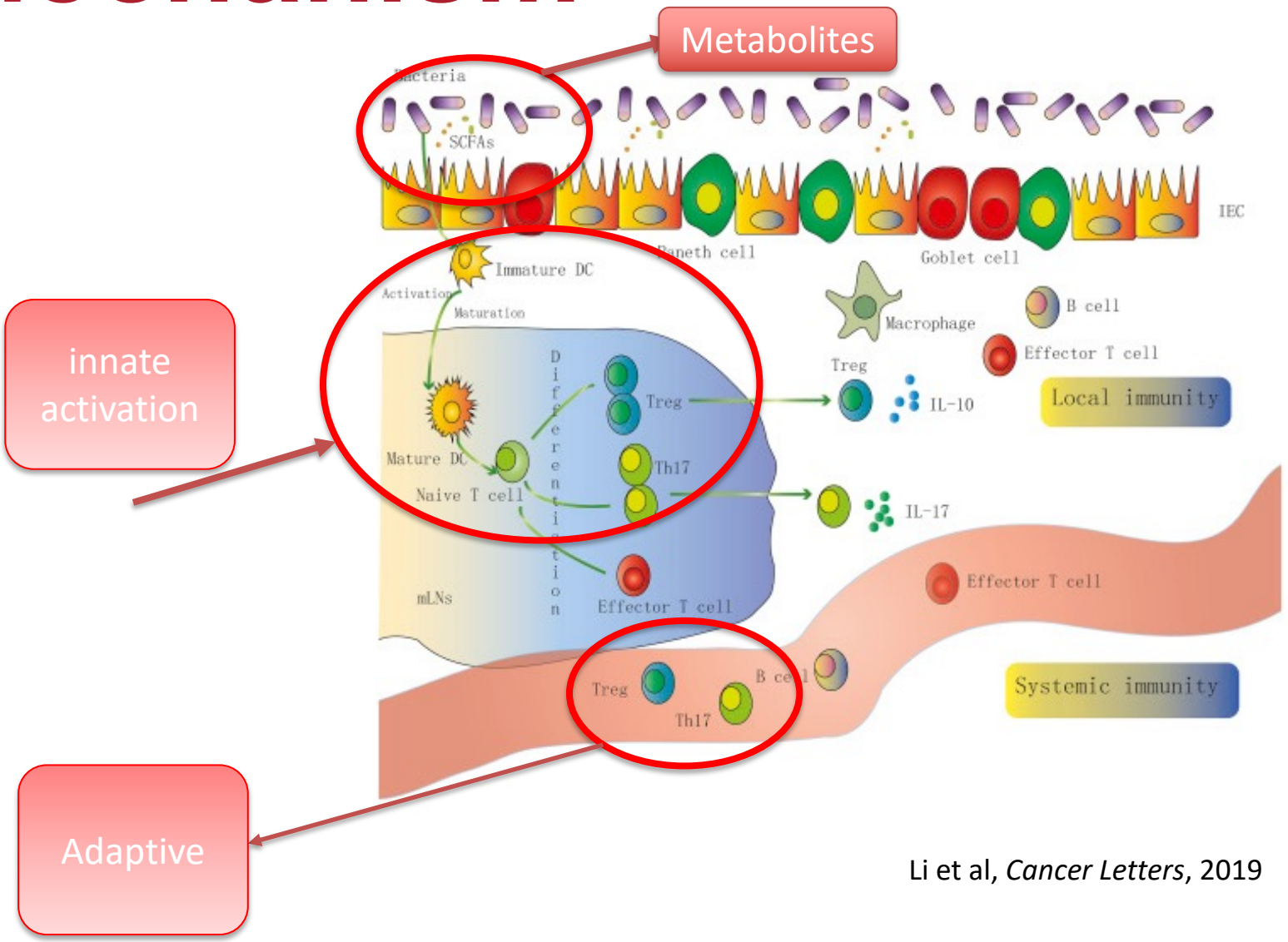
- Alpha diversity: measures the observed diversity for a given community
  - Comprised of:
    - Species richness (number)
    - Uniqueness (how many diff)
    - Evenness
- Beta diversity
  - How *communities* differ
  - i.e. –populations in a swamp compared to each other
    - Or pre- post- gut microbiota transplant profiles



Mechanism

Metabolites

innate activation



Adaptive

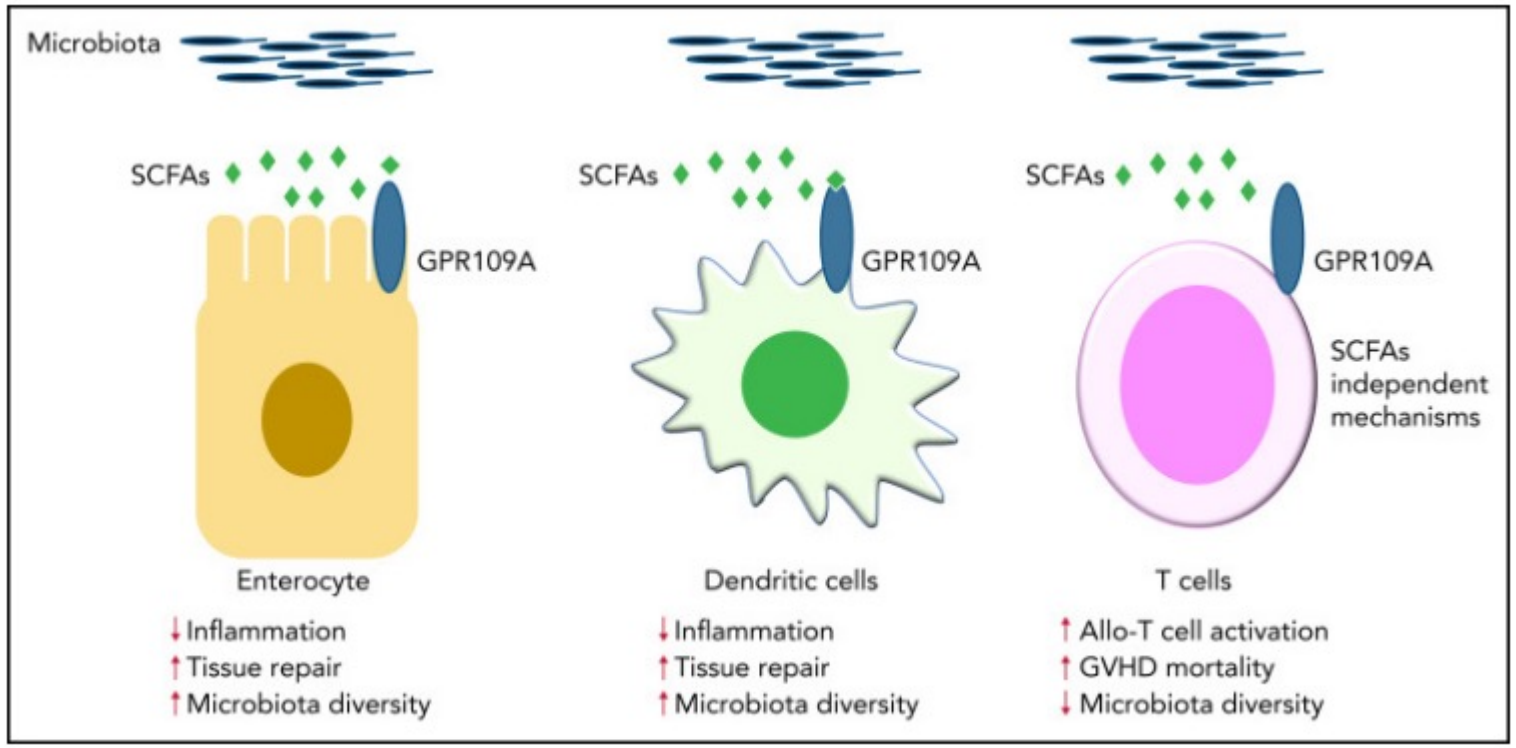
Li et al, *Cancer Letters*, 2019

Microbiome Mediated Immune Activation

- Metabolites: not an exclusive list
  - Short chain fatty acids

Butyrate: SCFA du jour

- Regulate T-cell populations in the gut
- Potential epigenetic mechanism as a histone deacetylase inhibitor
- Effect differs across cell types and receptors
- G-protein receptor-mediated effects
- HDAC-inhibition effects



Toubai et al, Blood 2022

Short-chain fatty acids can activate effector T-cell populations including CAR-T

Mechanis
HD
mT
GP
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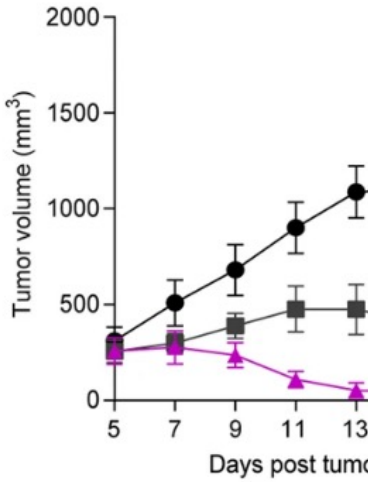
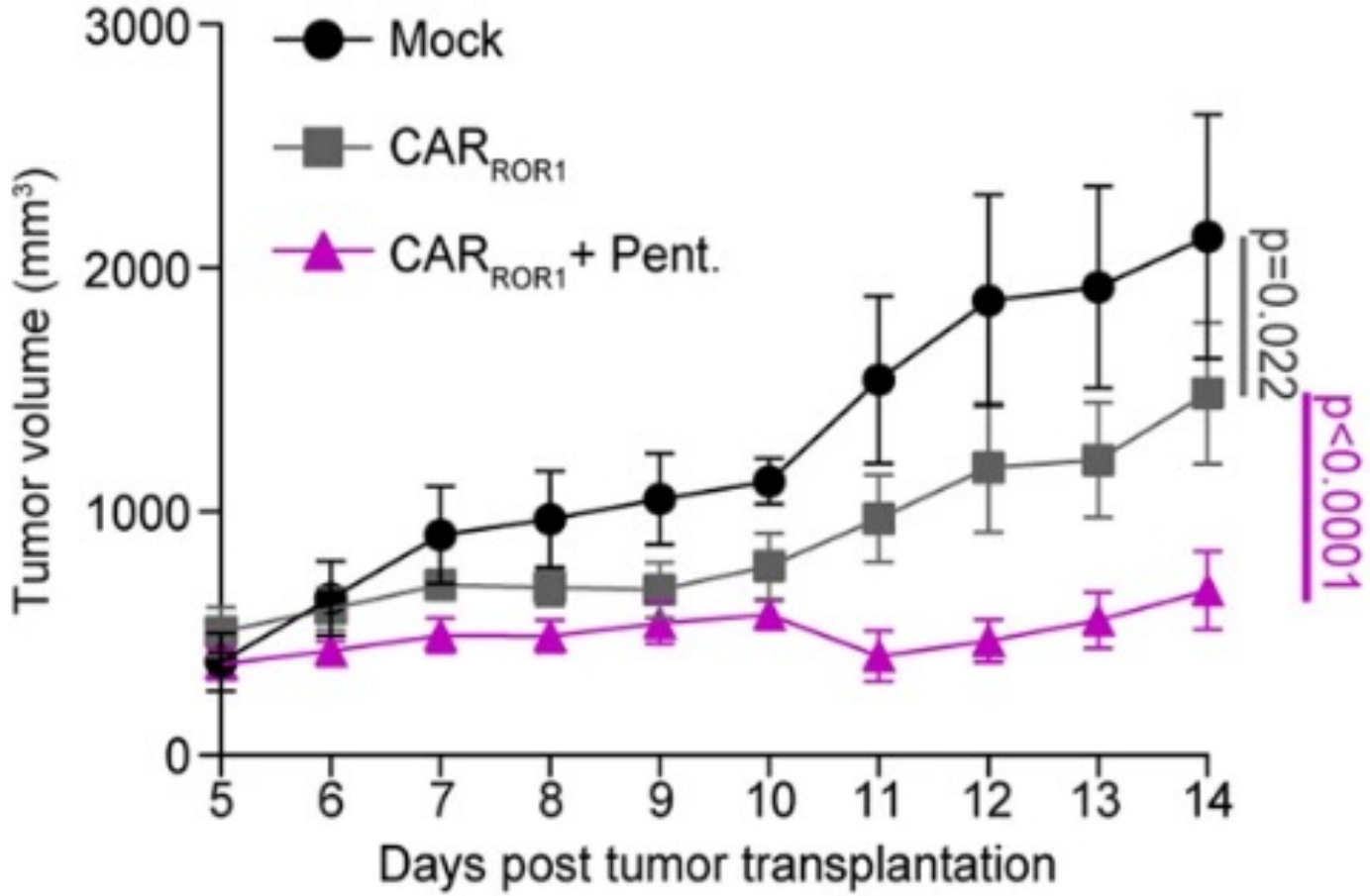
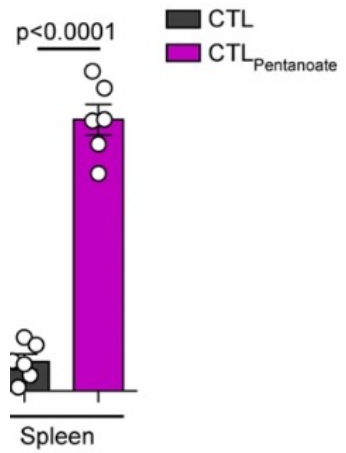


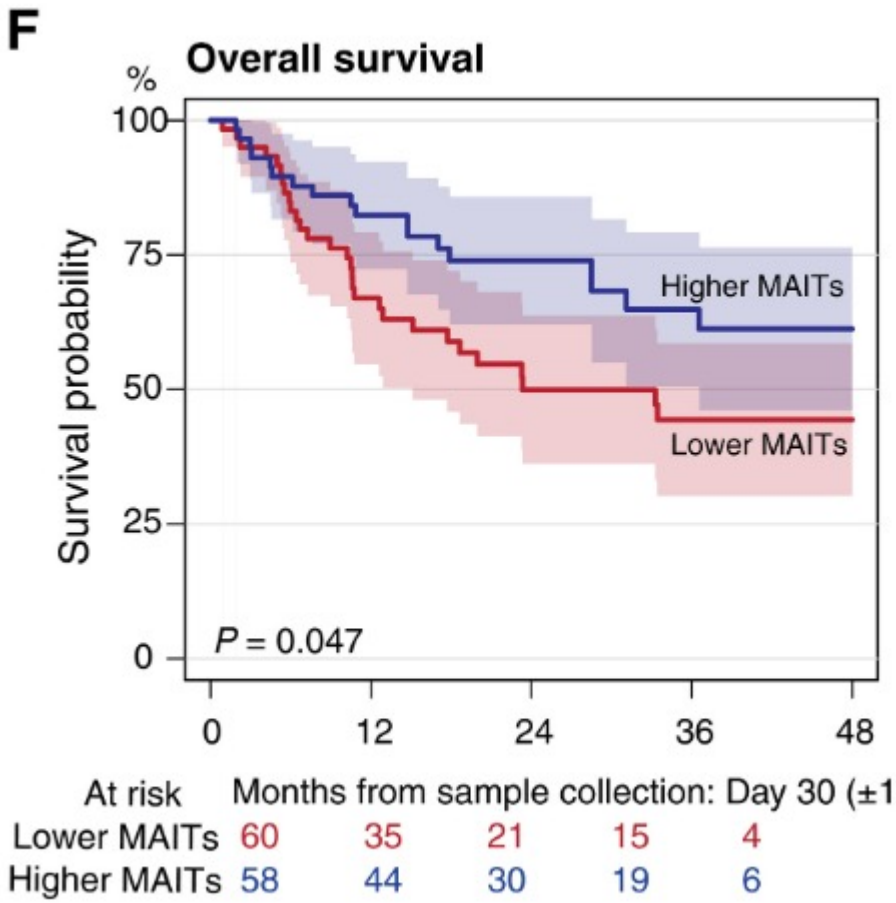


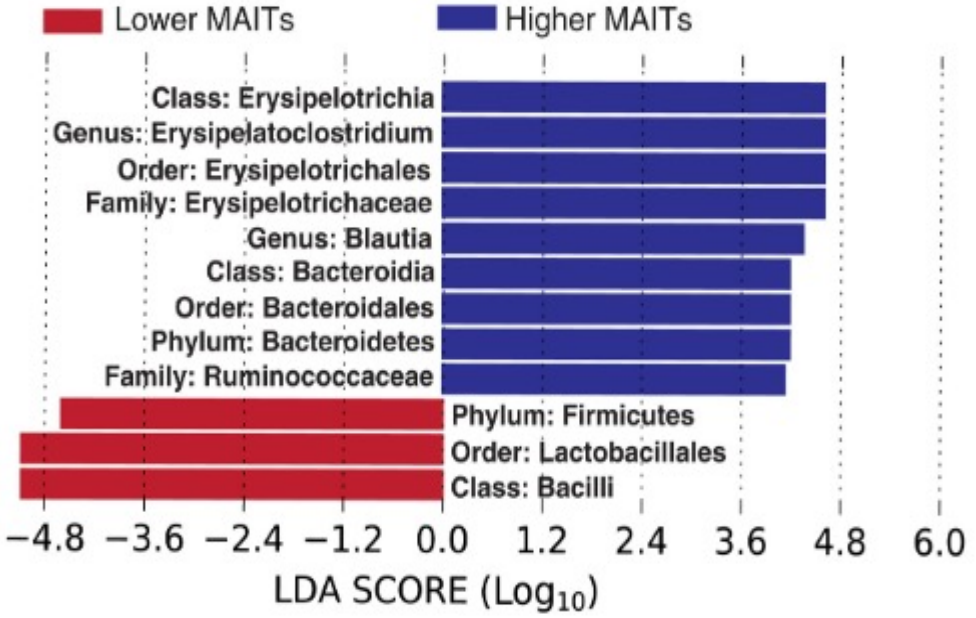


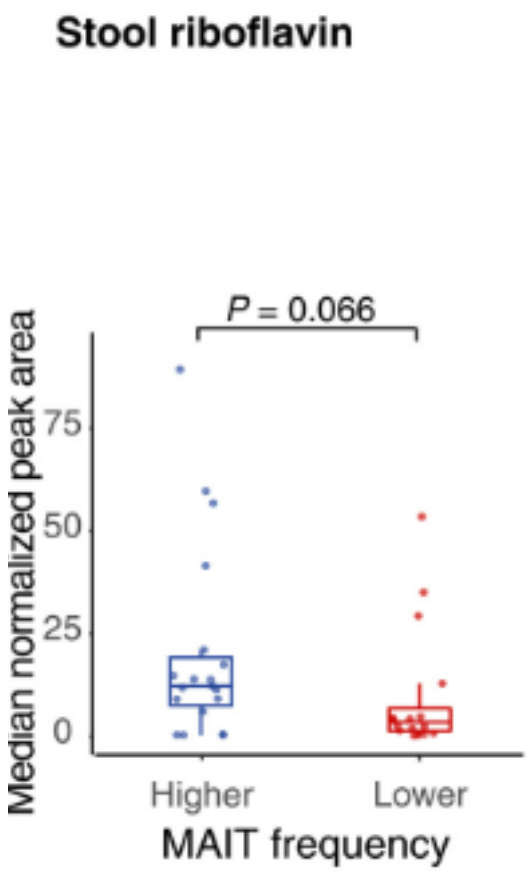
Lu et al, *Nature Communications* 2021

Mucosal associated invariant T-cells (MAIT) and Riboflavin

- In human subjects post allogeneic stem cell transplant
- Potential *in vivo* anti-cancer responses, recognize riboflavin metabolites







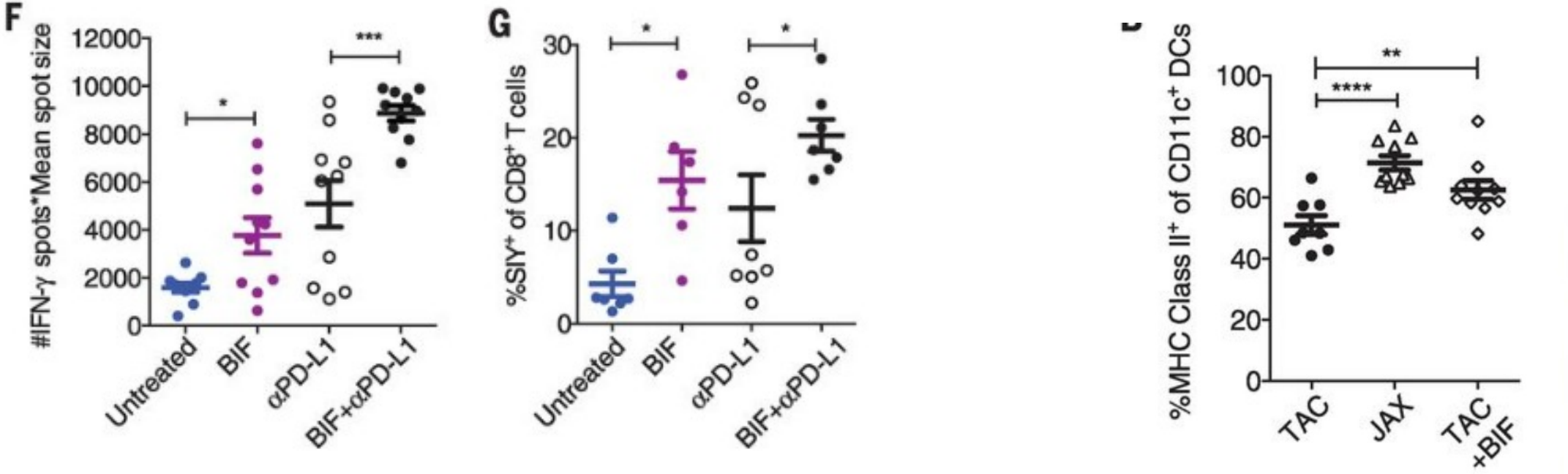
Andrlova et al, *Science Transl Med*, 2022

Microbiome and Immune Cell Activation

- Dendritic cell activation in a murine melanoma model
- Th17 activation in multiple myeloma

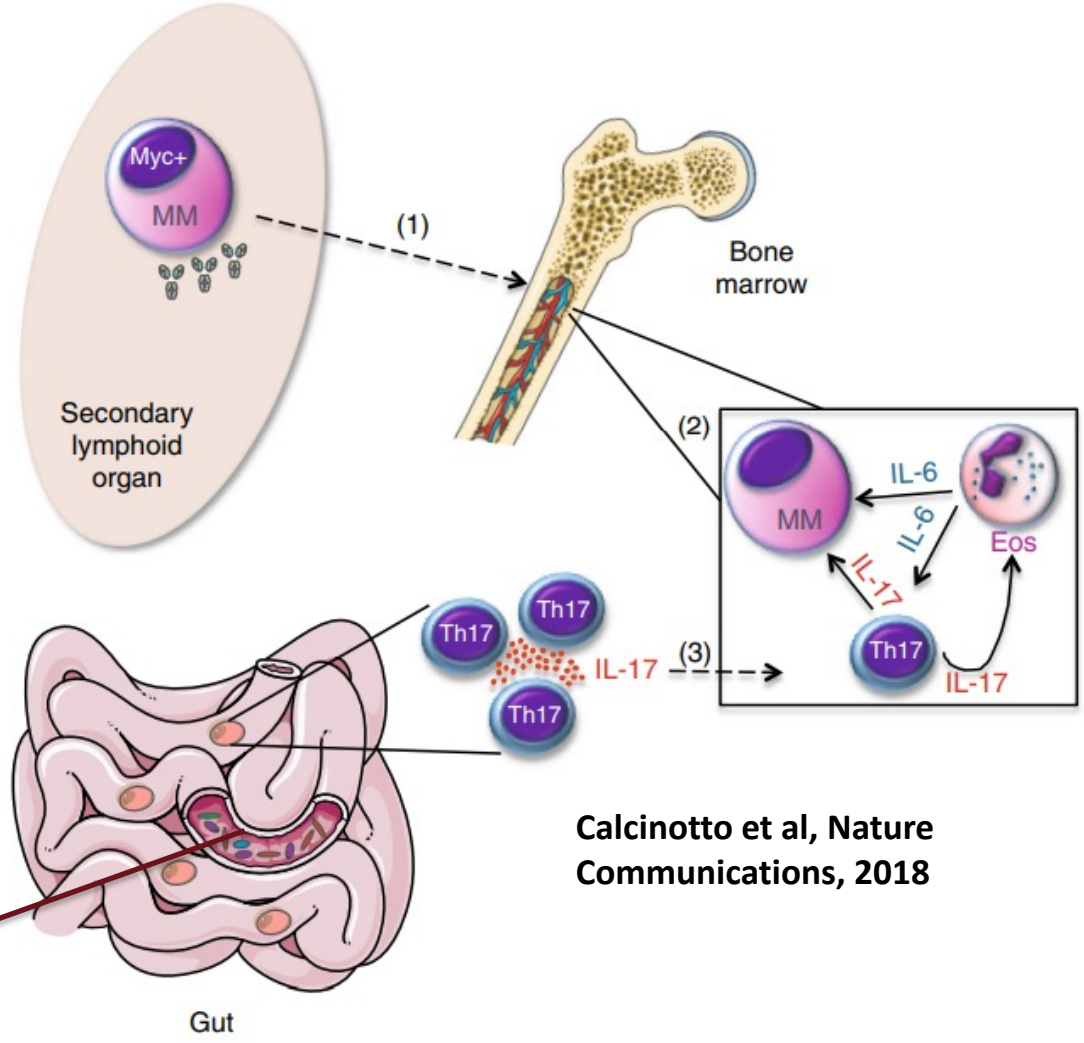
Dendritic Cell -> CTL activation

Cytotoxic T-cell Activation is Driven by Upstream Dendritic Cell activation from addition of commensal Bifidobacterium sp. in Mouse Melanoma Model



Sivan et al, Science, 2015

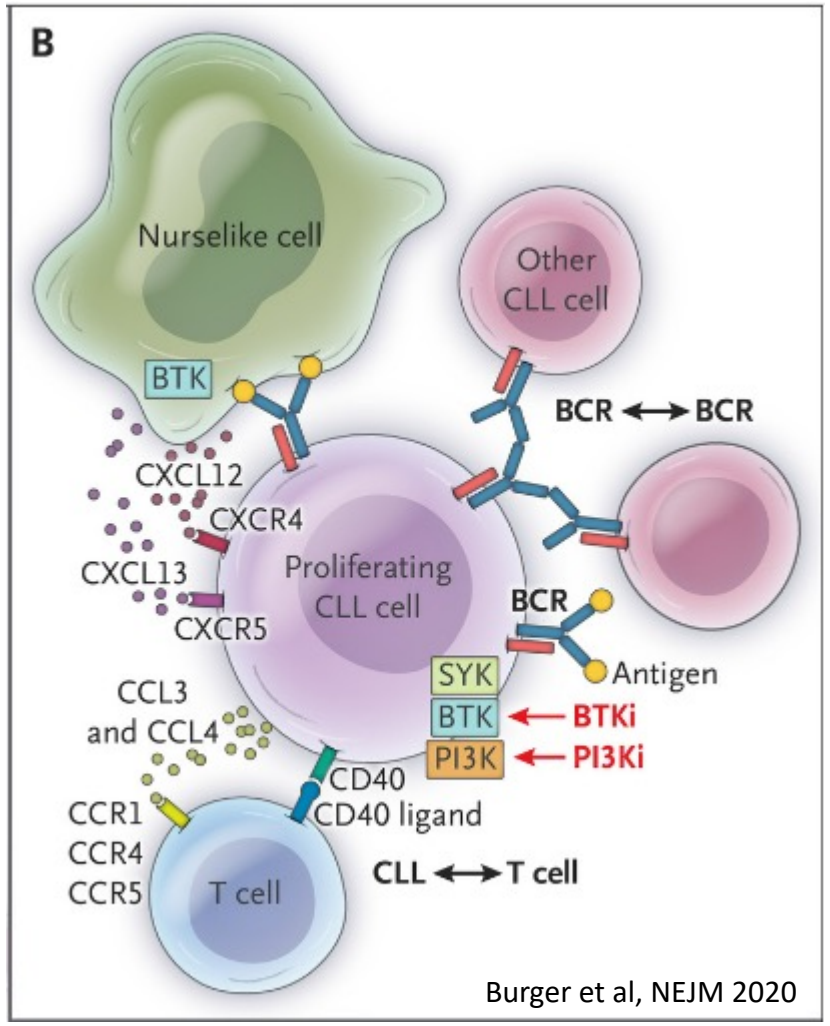
Microbiome communities drive Th17 skewing and migration to BM to foster myeloma progression



Calcinotto et al, Nature Communications, 2018

Prevotella heparinolytica

Microbiome and CLL



Burger et al, NEJM 2020

CLL and the Gut Microbiome

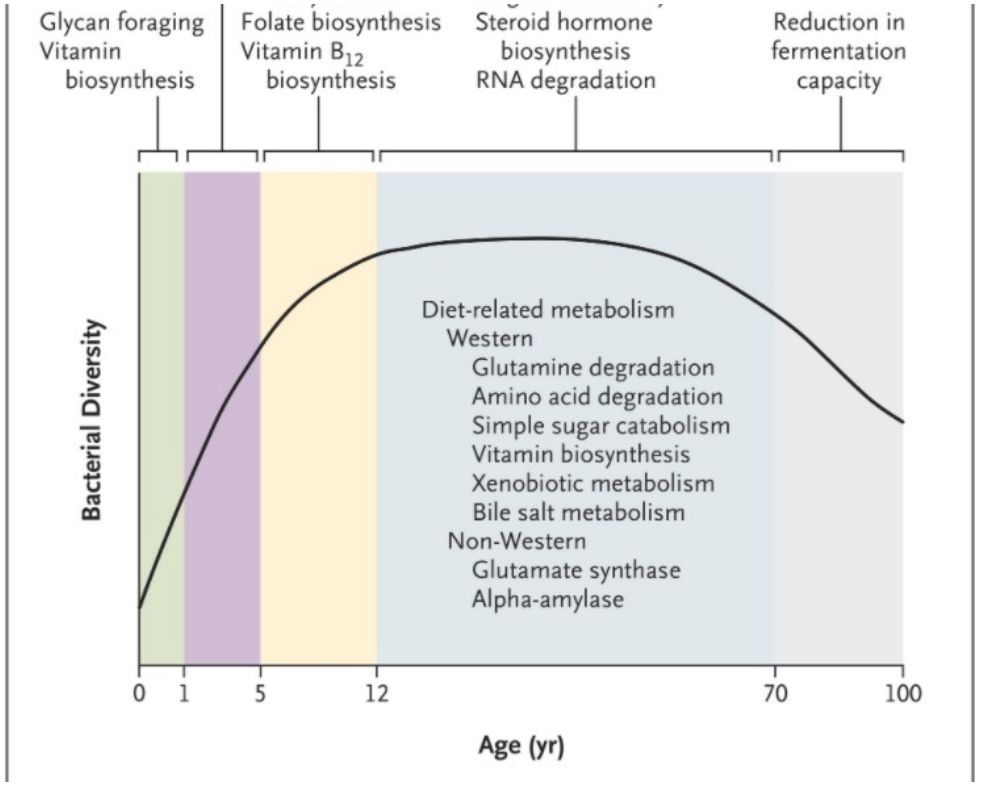
Observations

Clinical

- Median age onset ~72
- Variable clinical presentation
- Geographic disparity

Biological

- Pathogenesis occurs in lymphoid organs
- linked to chronic B-cell receptor signaling
- Microbial antigens can activate BCR
- inflammatory cytokines linked to outcome

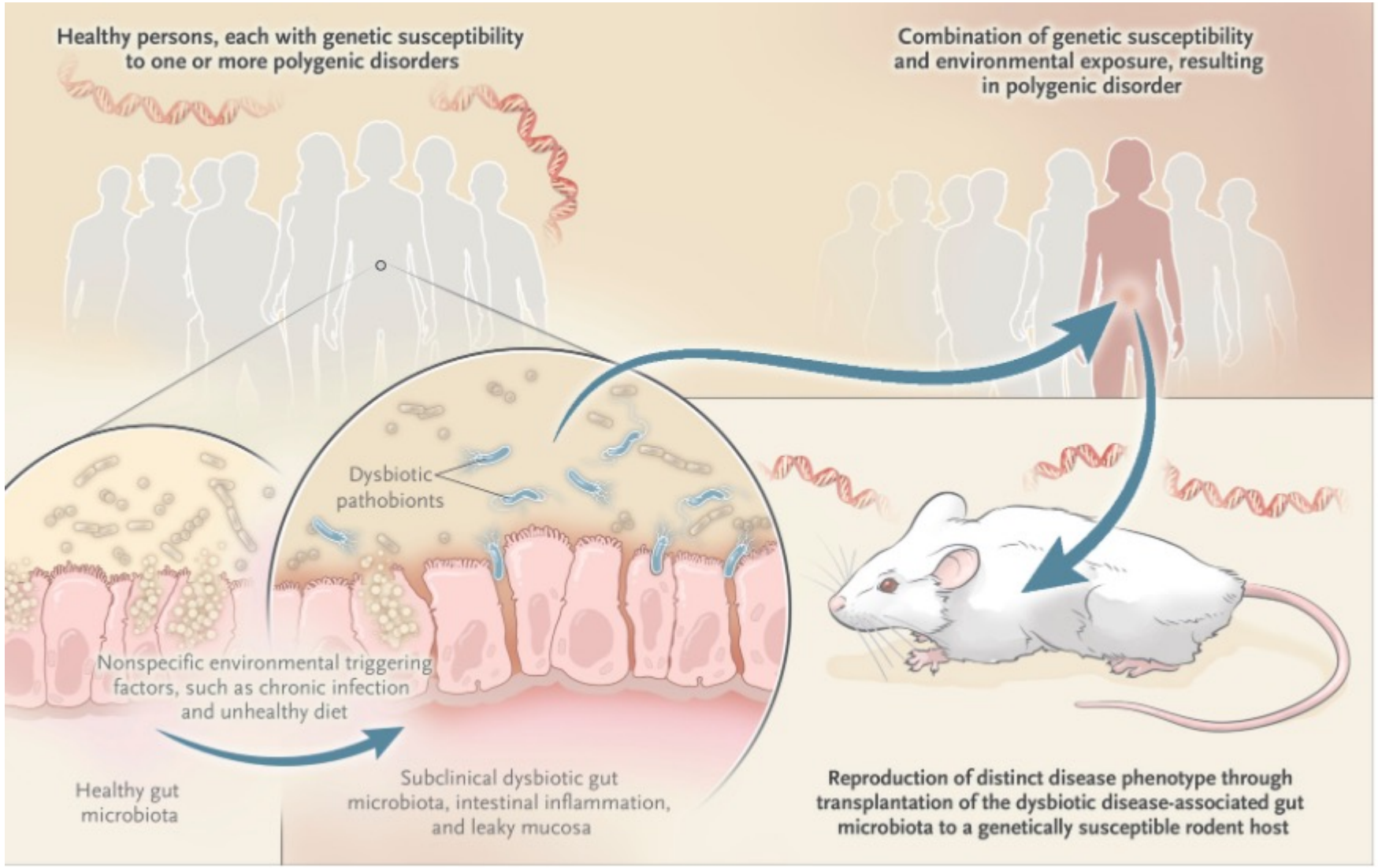


Lynch et al, NEJM 2016

DIG-CLL

- Collaboration with ElGamal Lab to profile microbiome
  - Adoptive CLL transfer model
    - Effect of antibiotic ablation on CLL progression
  - Eu-TCL Transgenic Model
- Prospective sampling of CLL patients and cohabitating controls
  - Diet
  - Serum cytokines
  - Microbiome samples
    - BTK inhibit
    - Rai stage 2-4 Untreated

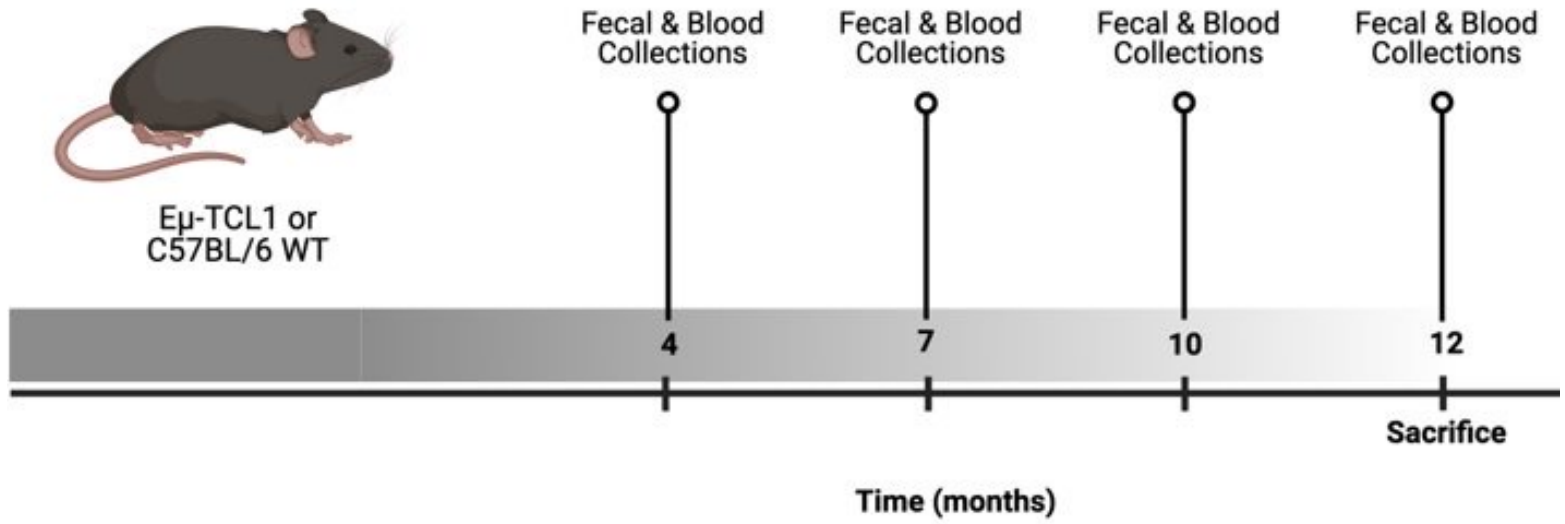
Common Ground Hypothesis



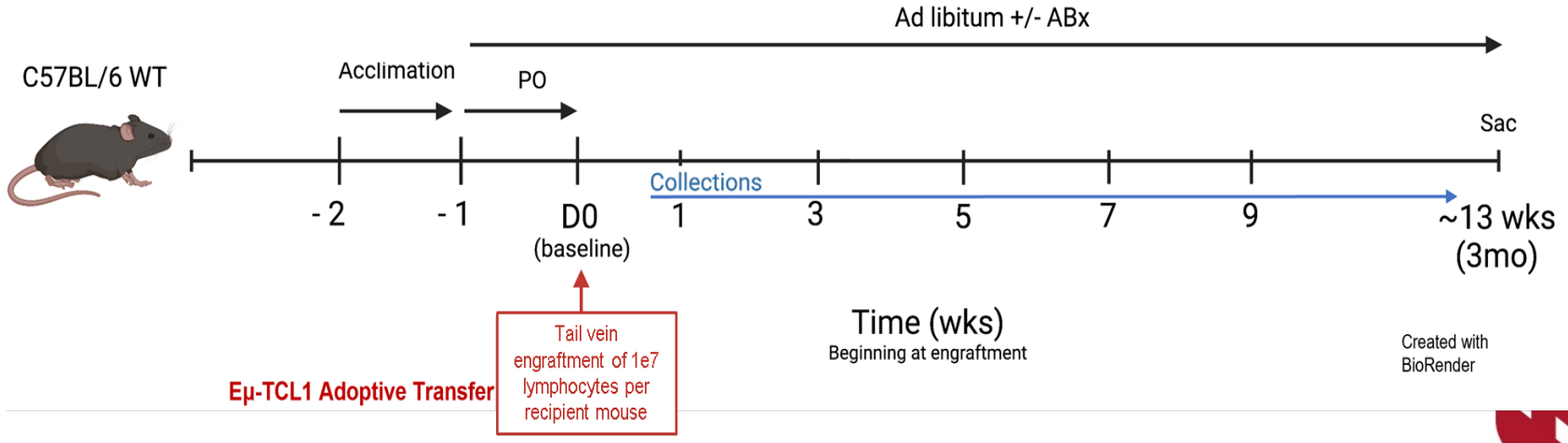
Lynch et al, NEJM 2016

DIG-CLL

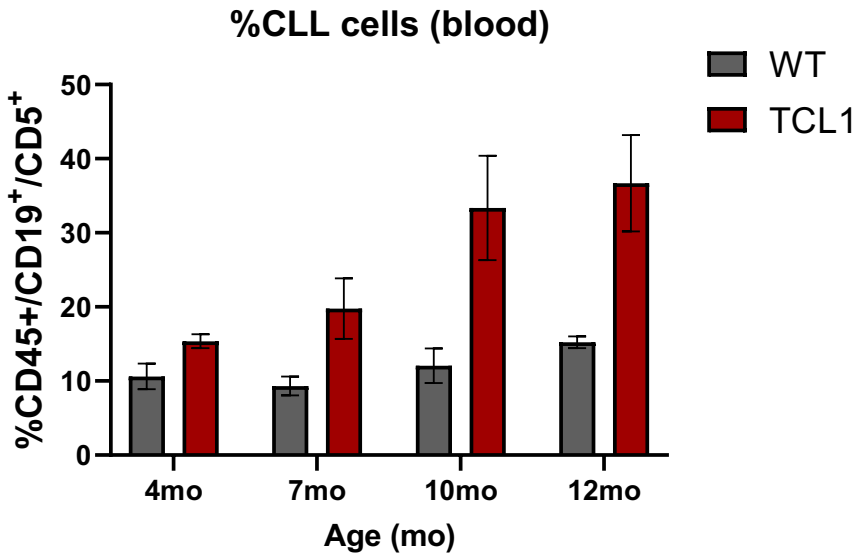
Progression Model (CLL vs WT mouse)

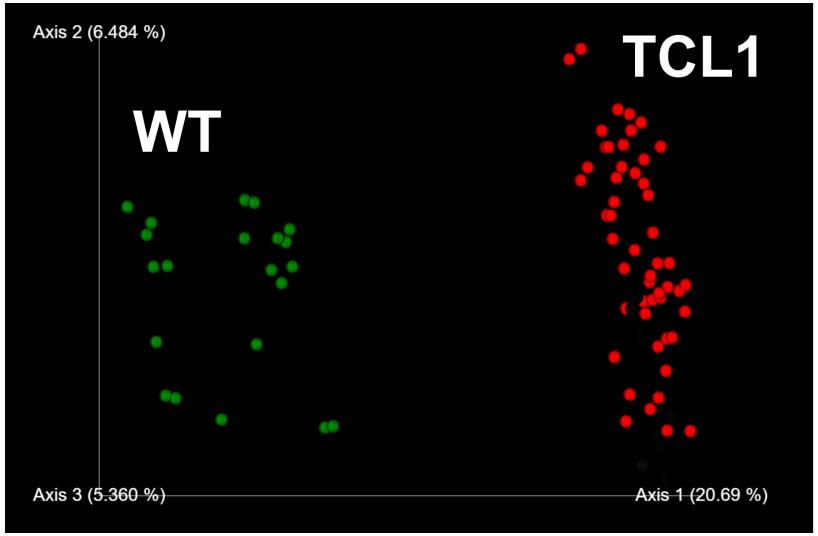


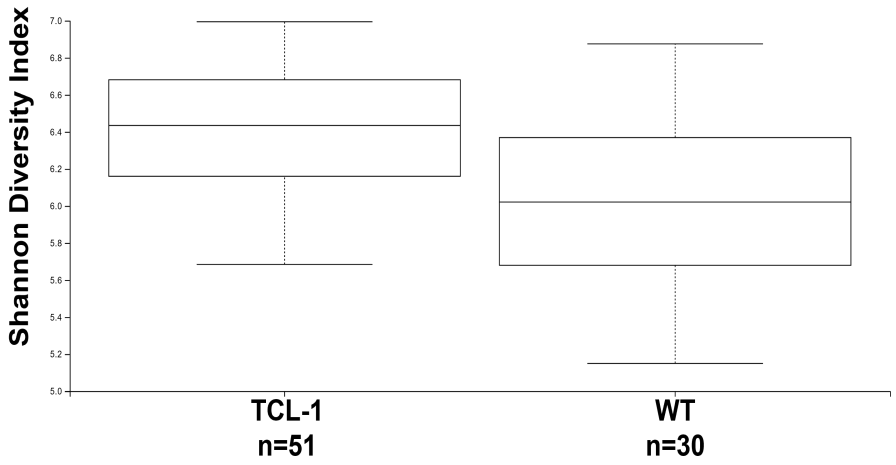
Antibiotic-Treated vs Control (CLL transfer)

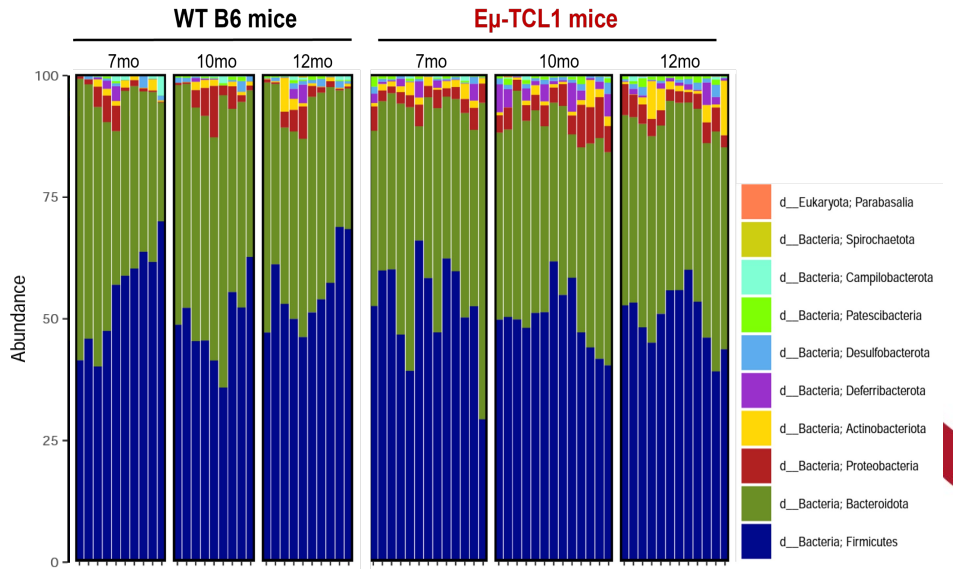


Eμ-TCL1 Mice Harbor a Unique and Dysbiotic Gut Microbiome

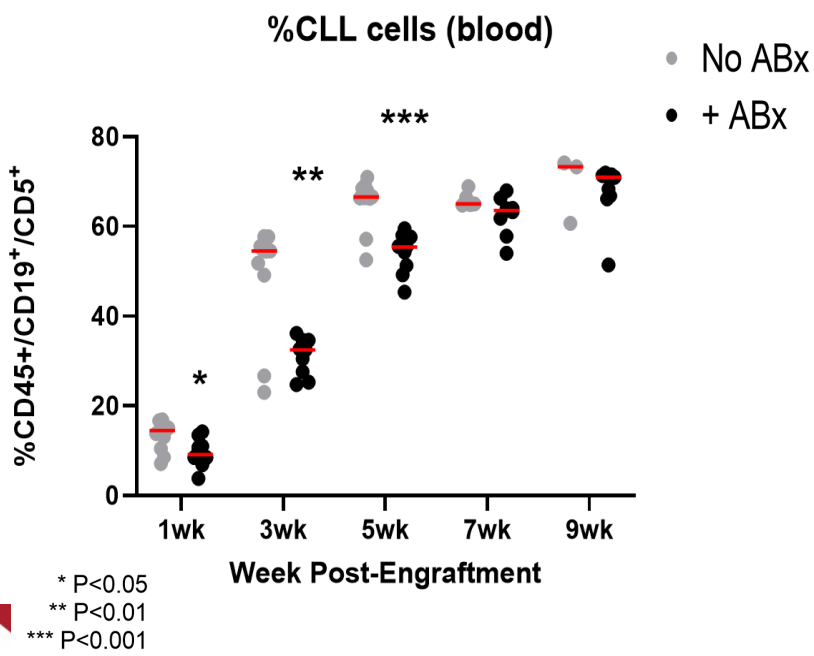


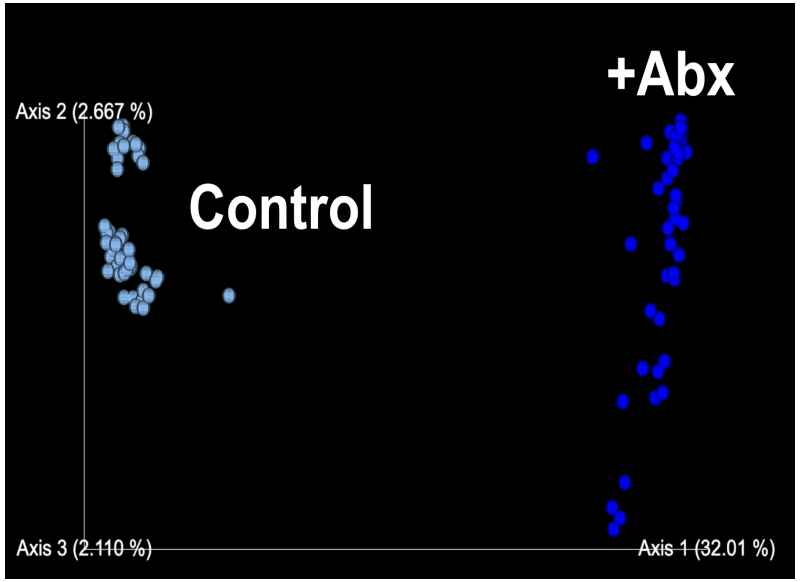


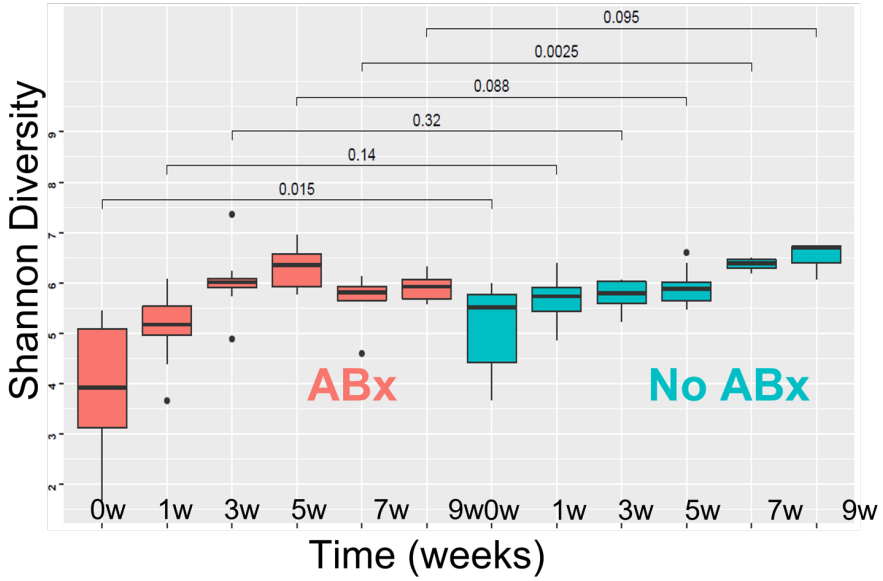




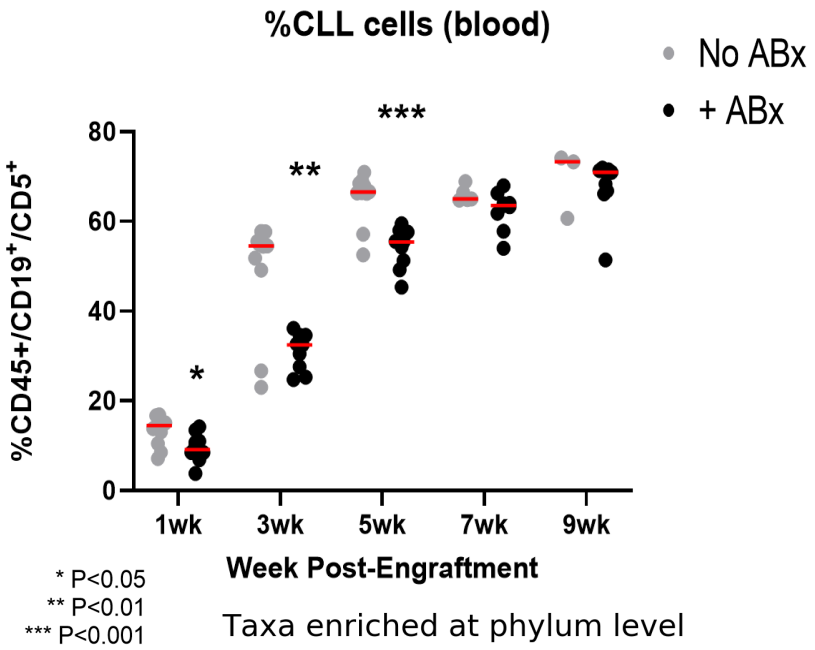
Antibiotic Ablation Impacts CLL Pathogenesis and Forms Unique Gut Microbial Communities

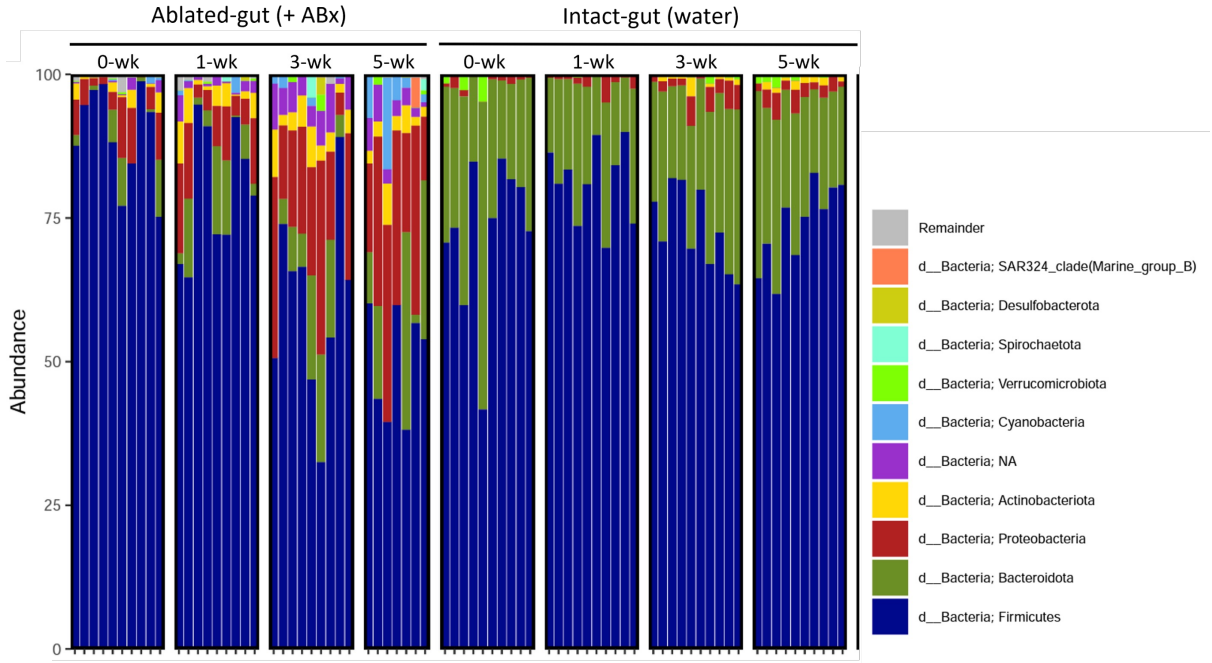


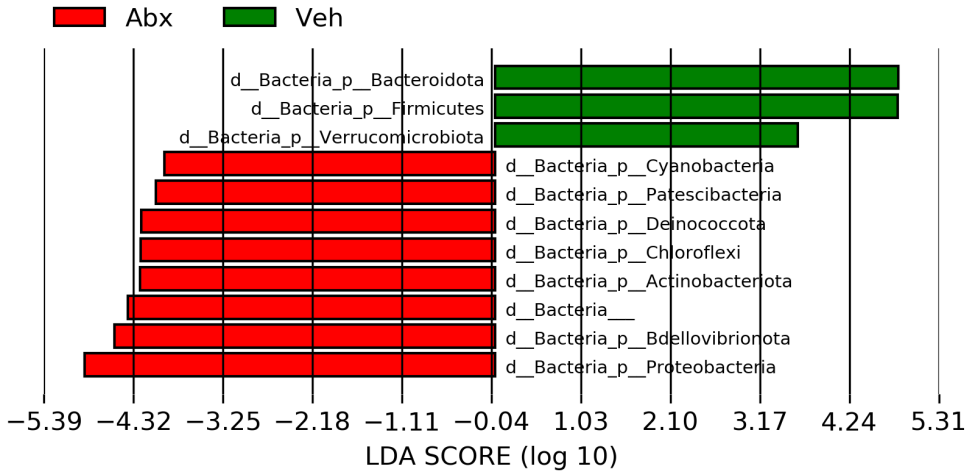


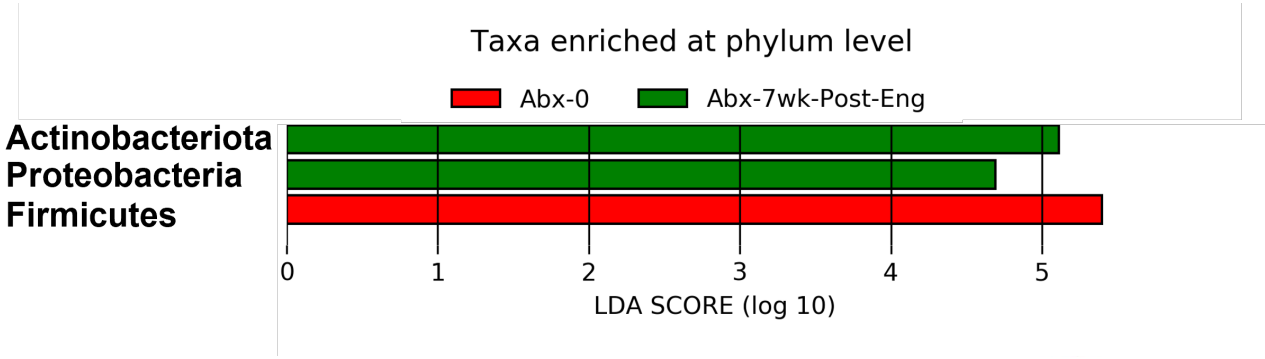


Antibiotics Produce a Progressively Dysbiotic Microbiome









Clinical Studies

- Alpha diversity as a biomarker
- Microbiome and CAR-T cell therapy in lymphoma
- Microbiome and myeloma

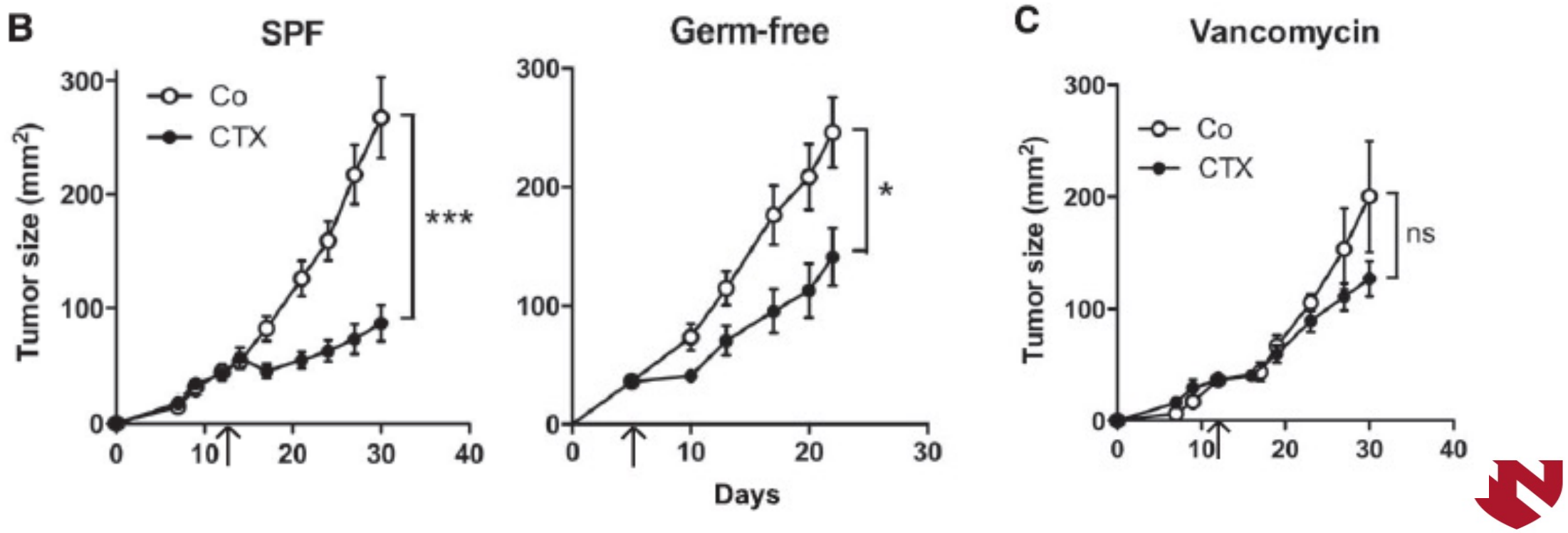
Gut Microbiota Diversity

- **Diversity is emerging as a key microbiome trait increasingly linked to outcomes in oncologic disease**
  - **Allogeneic transplant** (Peled et al, NEJM, 2020)
  - **Autologous transplant** (Khan et al, Blood, 2020)
  - **Melanoma and PD-1 inhibition** (Gopalakrishnan et al Science 2018)

Why microbial diversity may matter

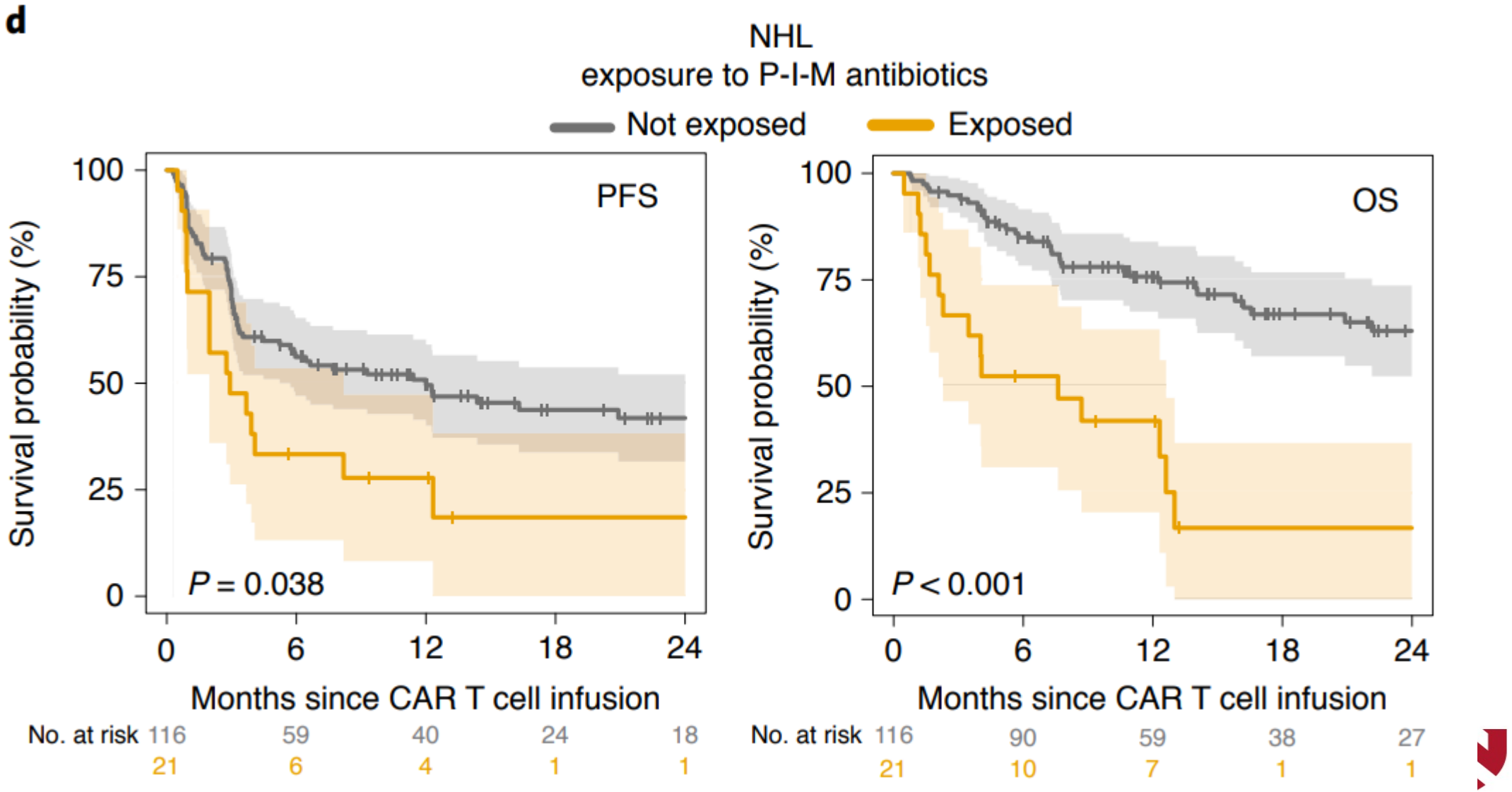
Cyclophosphamide: Viaud et al revealed that the gut microbiota is involved in the anti-neoplastic activity of cyclophosphamide

- traced to gut translocation of gram-positive species into nearby lymphoid organs, stimulating T-cell responses
- Similar observation for platinum agents



Viaud et al, *Science*, 2013

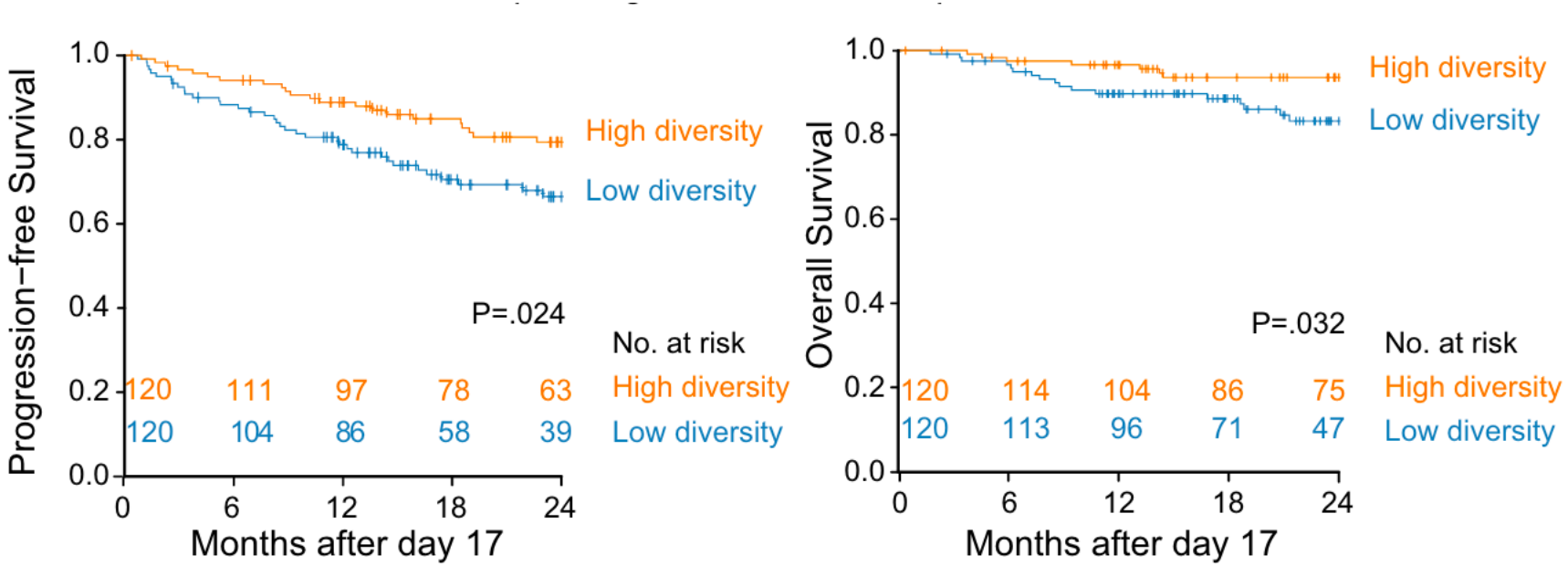
CAR-T and Antibiotics



Smith et al, Nature Medicine, 2022

Autologous Stem Cell Transplantation in Multiple Myeloma

Microbiome diversity at time of engraftment associated with PFS and OS

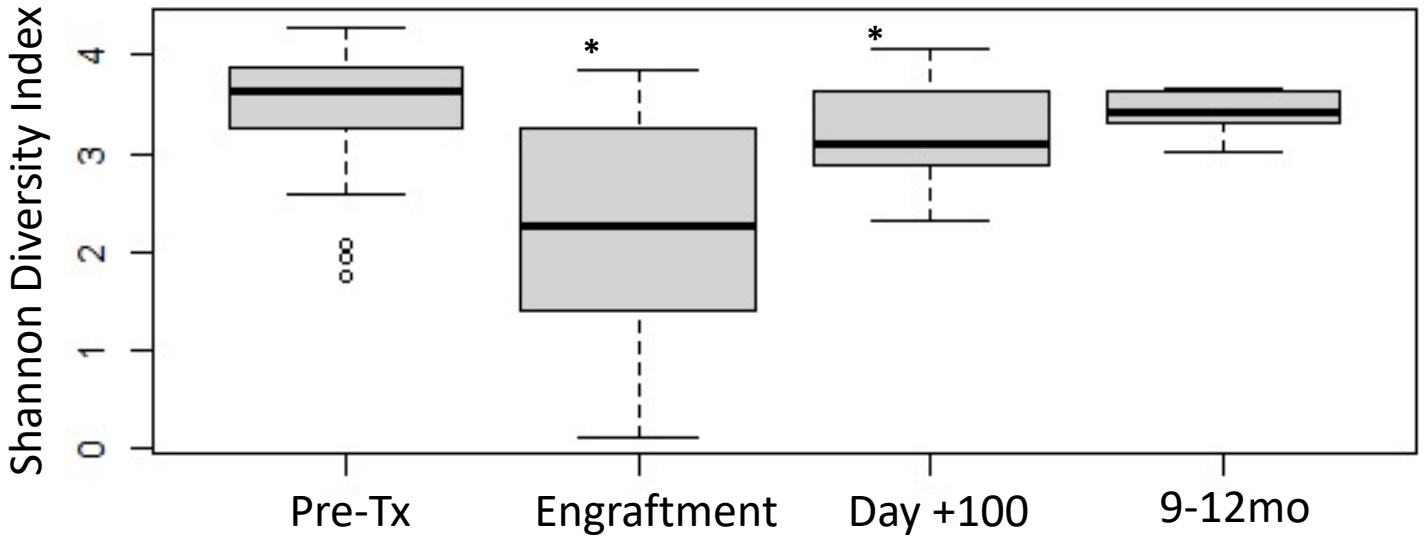


Khan et al, *Blood*, 2020

- **What contributes to low diversity at engraftment?**
- **Why/How does microbial diversity at *this* timepoint matter?**

Autologous Stem Cell Transplant in Multiple Myeloma

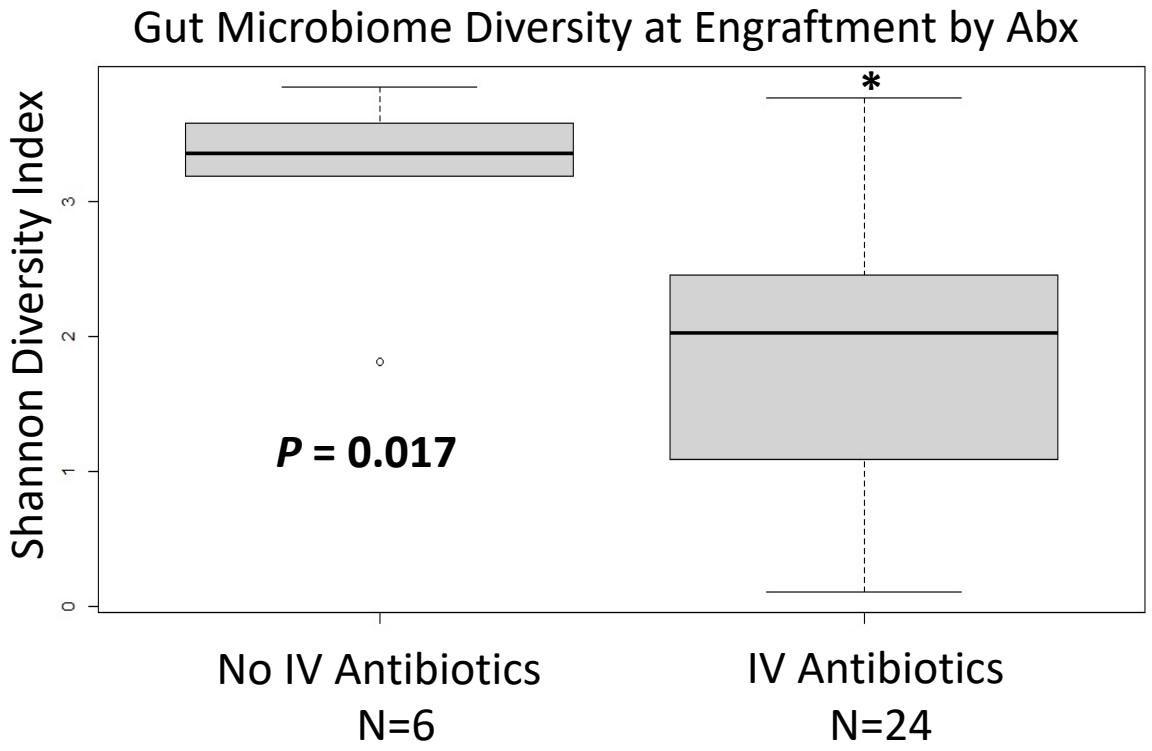
- 30 patients with myeloma
- Loss of microbial diversity observed immediately post-transplant
- Suggests this engraftment period is a key timepoint for the microbiome



D'Angelo et al, Leukemia Lymphoma 2022

IV Antibiotic Influence on Post-transplant Diversity

- Alpha diversity at time of engraftment was measured according to IV antibiotic exposure
- IV = cefepime/piperacillin/tazobactam + vancomycin
- Antibiotic exposure had the largest effect on post-transplant gut microbial diversity
- Corroborate findings from El Jurdi et al *BBMT* 2019

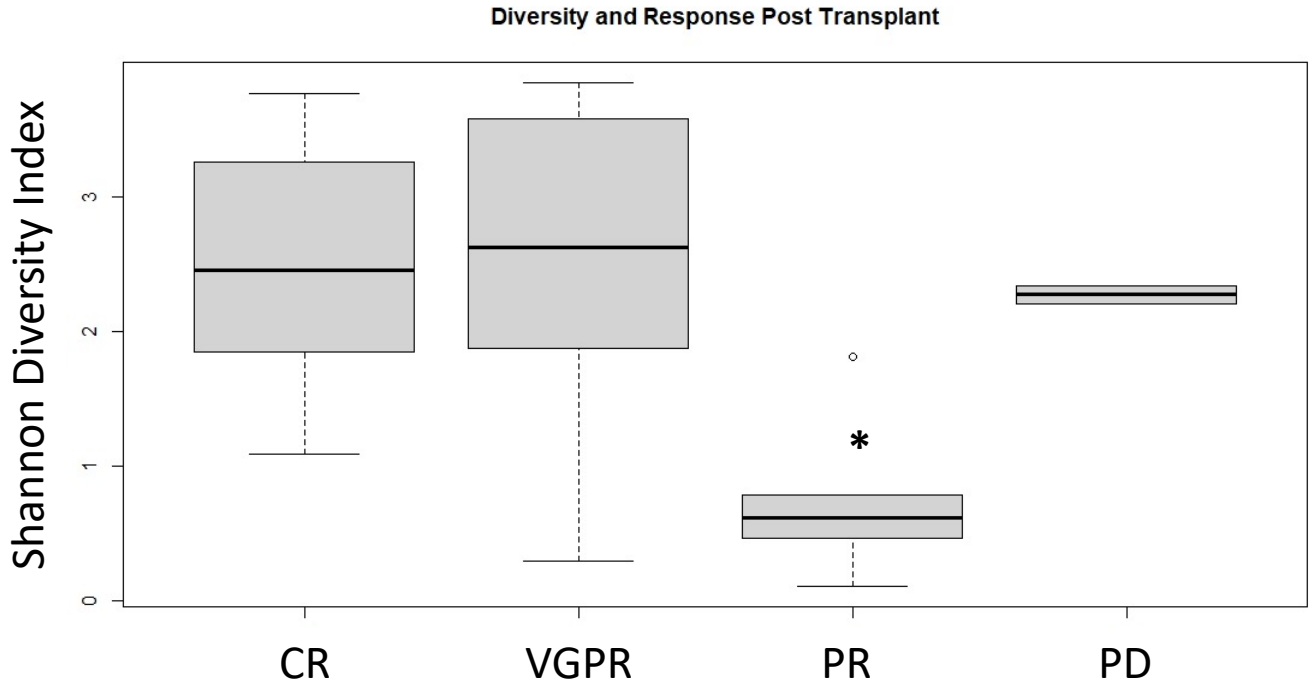


Summary: microbial diversity is lost in the peri-transplant period and predominantly driven by broad-spectrum abx

D'Angelo et al, Leukemia Lymphoma, 2021

Engraftment Diversity is associated with D+100 response to ASCT

- Response assessed at D+100 per IMWG response criteria
- 29/30 subjects available for response
- Higher diversity was associated with CR/VGPR compared to PR
- * denotes *P* <0.05 in pairwise comparison to CR and VGPR



Maybe a link is forming -> antibiotic exposure -> microbiome loss during transplant -> impaired response -> reduced PFS -> reduced OS

D'Angelo et al, Leukemia Lymphoma 2022

But questions remain:

- Confounding? -> how do we know the microbiome is indeed an independent trait

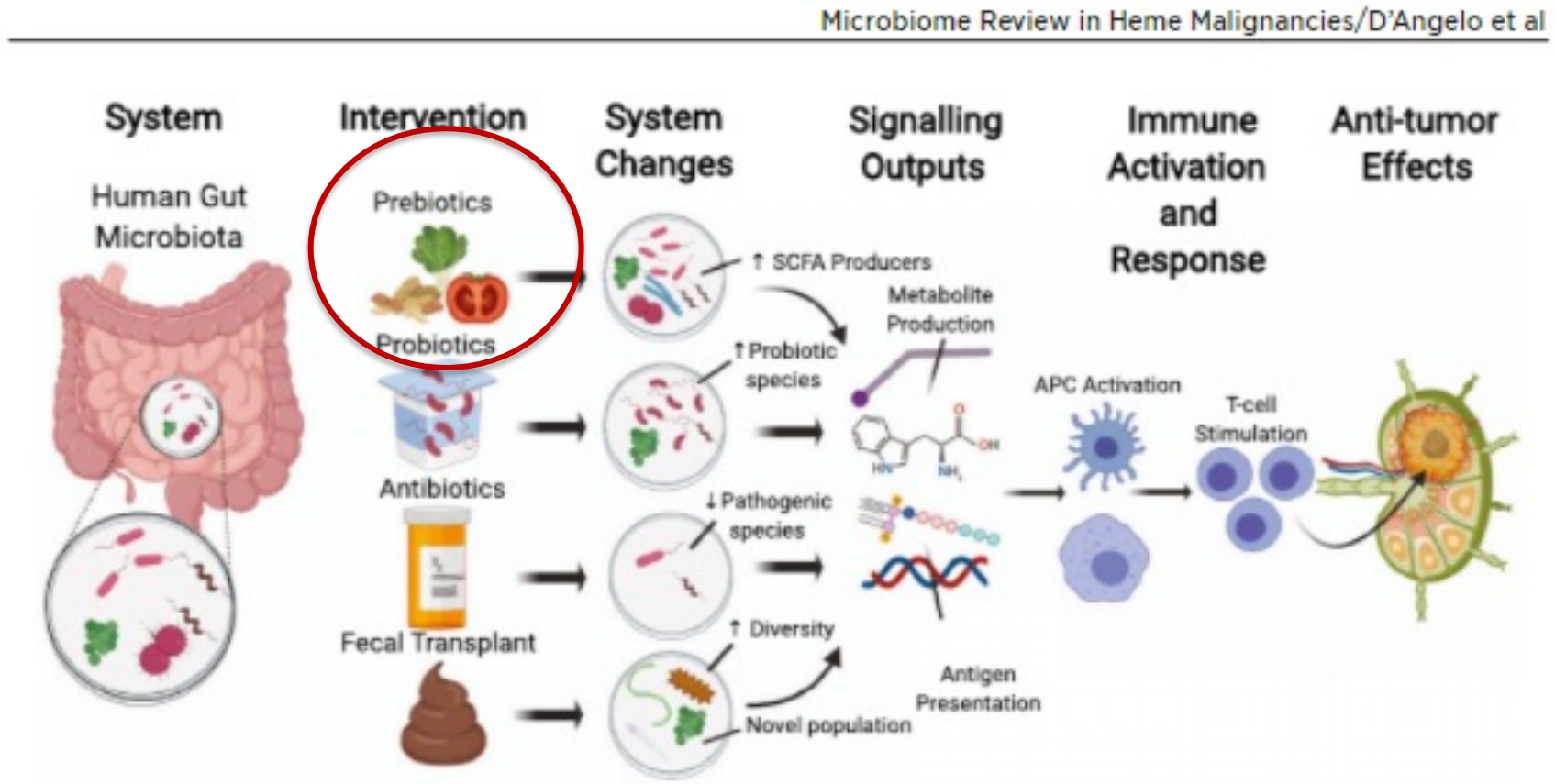
- Can we use this data to guide a therapeutic strategy targeting gut microbiota in this setting?

Prebiotics ~ Microbiome ~ Transplant Outcomes

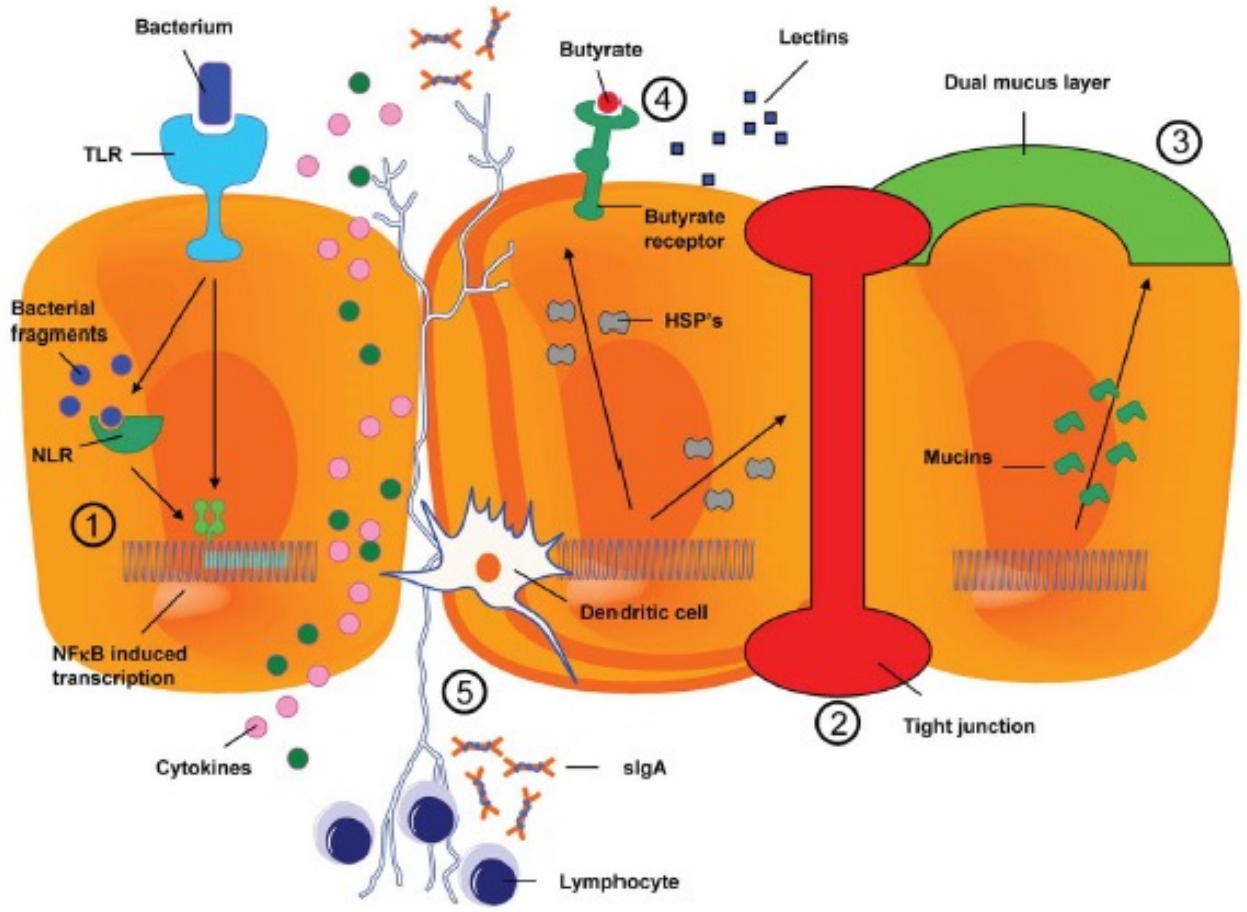
- Antibiotics are necessary for neutropenic fever management
- Main source of neutropenic fever is gut translocation
- Can we target and re-program the gut microbiome to prevent neutropenic fever?

- Hypothesis: prebiotic supplementation peri-transplant can reinforce the integrity of the gut lumen -> reduce the need for antibiotics -> improve diversity

Targeting Gut Microbiota



Prebiotics/Microbiome/Intestinal Barrier

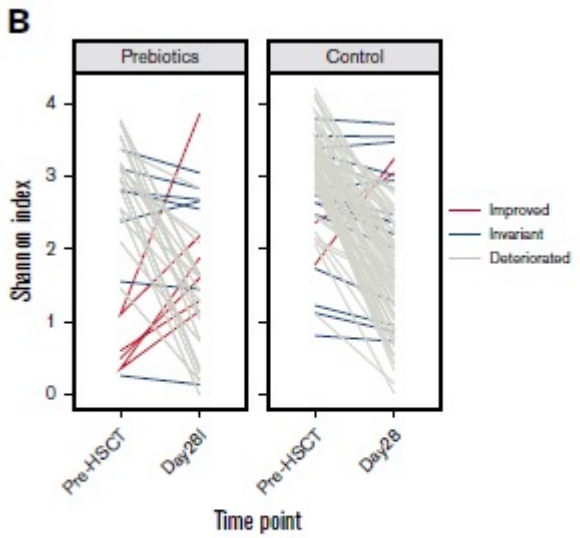


Van Vliet et al, PLoS Pathogens 2010

- Well tolerated
- Pair well with toxic therapies
- Simple to store/deliver
- *Patient interest*
- Target multiple species/niche
- Demonstrated activity in intestinal barrier/SCFA/etc

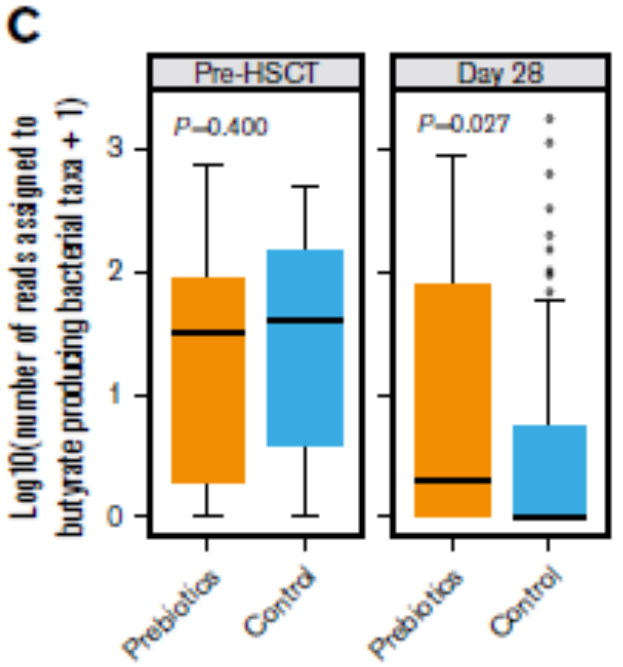
What prebiotic?: Resistant Starch

- Traits: inc butryate, inc probiotic populations (bifidobacterium)
- Improve diversity possibly, possible reduce abx need
- Readily available: Bob's Red Mill potato starch
- studies in allogeneic transplant confirm feasibility at doses planned here



	Increased	Invariant	Decreased	Total	*P* value
Prebiotics	6 (20.0)	7 (23.3)	17 (56.7)	30 (100)	0.0042
Control	2 (2.8)	15 (20.8)	55 (76.4)	72 (100)	

(%)



Yoshifuji et al, Blood Advances 2020

*Pr*ebiotics to *I*mprove Gut *M*icrobiome Diversity After *A*utologous Stem Cell Transplantation in Multiple Myeloma and *L*ymphoma: The PRIMAL Trial

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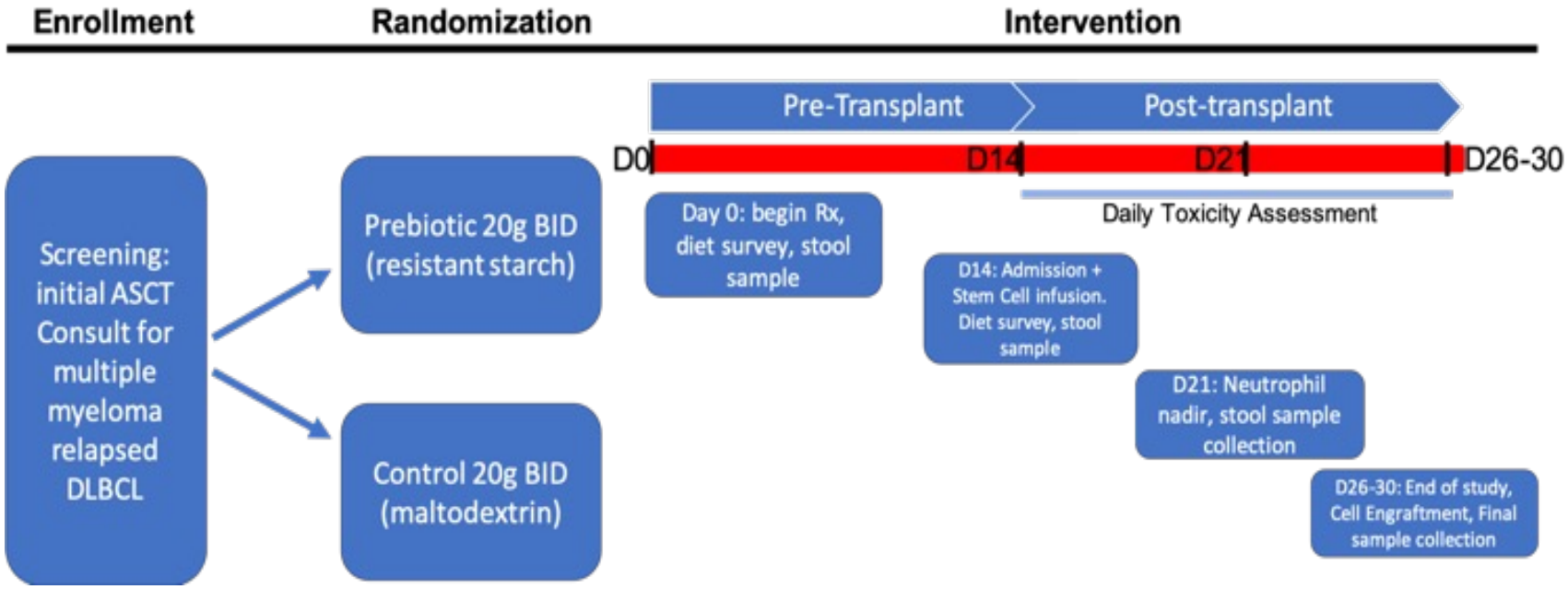
Protocol Number: 821-21

Principal Investigator: Christopher D'Angelo, MD

Overall Design: RCT 1:1



Primary Objective

- To determine the impact of a prebiotic intervention on gut microbiome diversity post-transplant. The primary endpoint will be a measure of gut microbiome diversity recorded at the time of post-transplant engraftment.

Secondary Objectives:

- **Diet impact:** diversity changes according to dietary intake by DHQ-3 survey, stratified by fiber intake
    - Correlatives with nutritional science group at UNMC/UNL
    - Mariah Jackson, Dr. Heather Rasmussen, and Dr. Corrine Hanson
- **Infectious complications:** neutropenic fever, bacteremia
- **Intestinal permeability:** measured with serial blood testing of serum markers associated with permeability
- **Patient Reported Outcomes:** regarding GI tolerability to the intervention

Study Status

- Open 4/2022
- 13/30 patients recruited
- General observations:
  - Well tolerated in setting of mucositis
  - Significant patient interest re: recruitment
  - Difficulty with diet tool ASA-24

Impact

- The pilot data taken from this study could demonstrate that prebiotic interventions:
  - Are feasible during auto transplant
  - Affect intestinal permeability
  - Impact antibiotic exposure
  - Improve diversity
- Provide a key proof of concept that microbiota directed therapy as an adjunctive measure may help improve therapeutic outcomes in autologous stem cell transplant

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