RESEARCH ON TAP

Cancer & Microbiome

Thursday, February 4, 2021

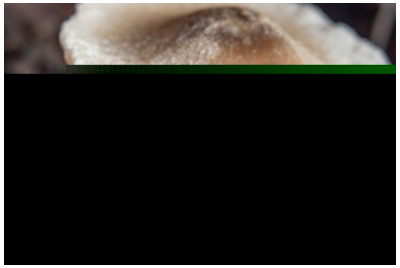
bu.edu/research/events

BOSTON UNIVERSITY

Boston University Office of Research

ROT NAME Agenda

- Welcome Remarks
- Presentations
  - Evan Johnson
  - Daniel Segre
  - Matthew Kulke
  - Jennifer Bhatnagar
  - Julie Palmer
  - Jessica Petrick
  - Stefano Monti
  - Gerald Denis
  - Andrew Emili
  - Xiaowei Ge
- Q&A
- Closing Remarks



many microbiomes

common processes,
quantitative tools
and principles

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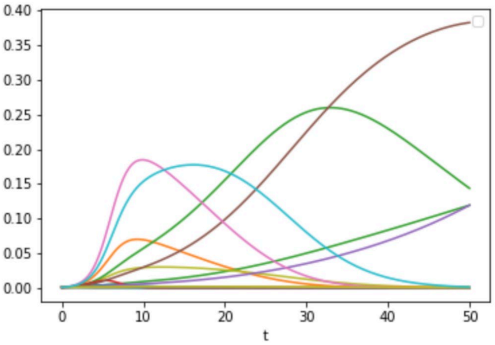
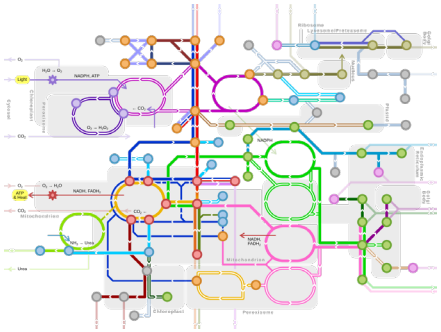
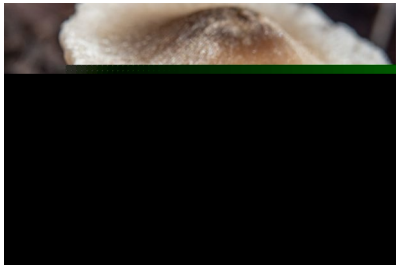
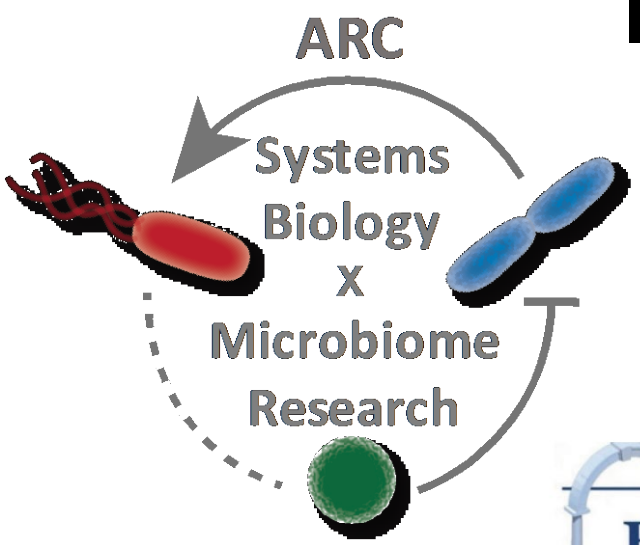
GTCGGTTACTCT
TACGTAGTACAC
CATGGGTATCGG





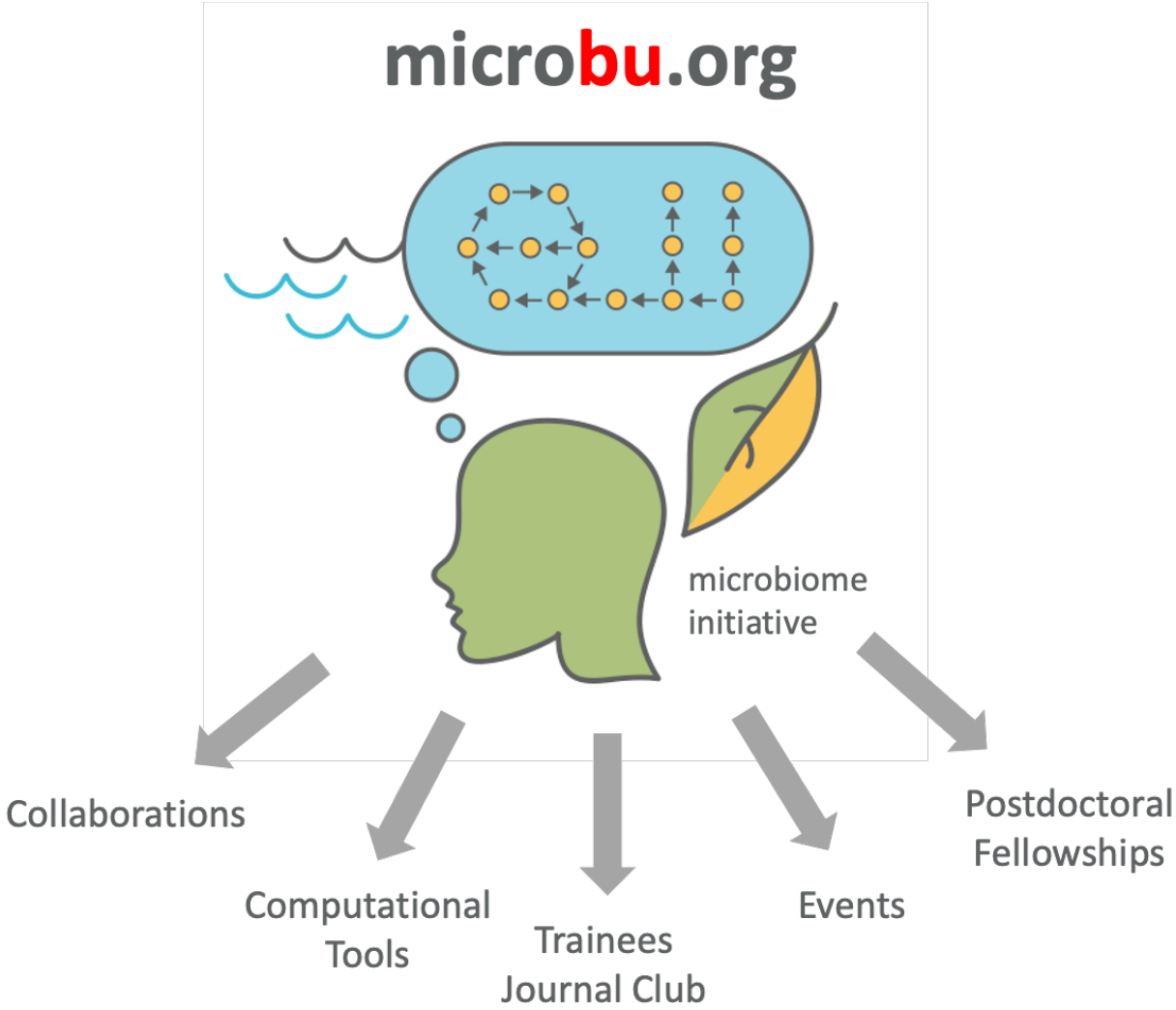


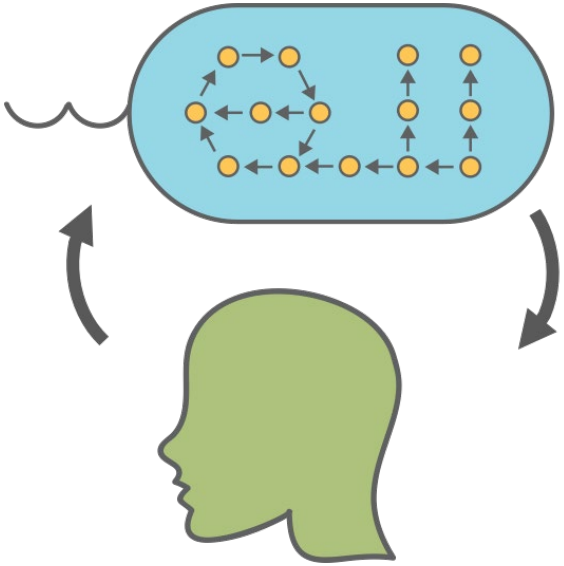


BU

Boston University Research
Interdisciplinary Biomedical Research Office

Evans Center
For Interdisciplinary
Biomedical Research


microbu.org
microbiome initiative
Collaborations
Computational Tools
Trainees Journal Club
Events
Postdoctoral Fellowships



Trends in Cancer

CellPress REVIEWS

Opinion

The Cancer Microbiome: Distinguishing Direct and

Joao B. X
Alexander
Keith A. C
Heather H
Tal Korem
Christian
Jennifer A

The collec
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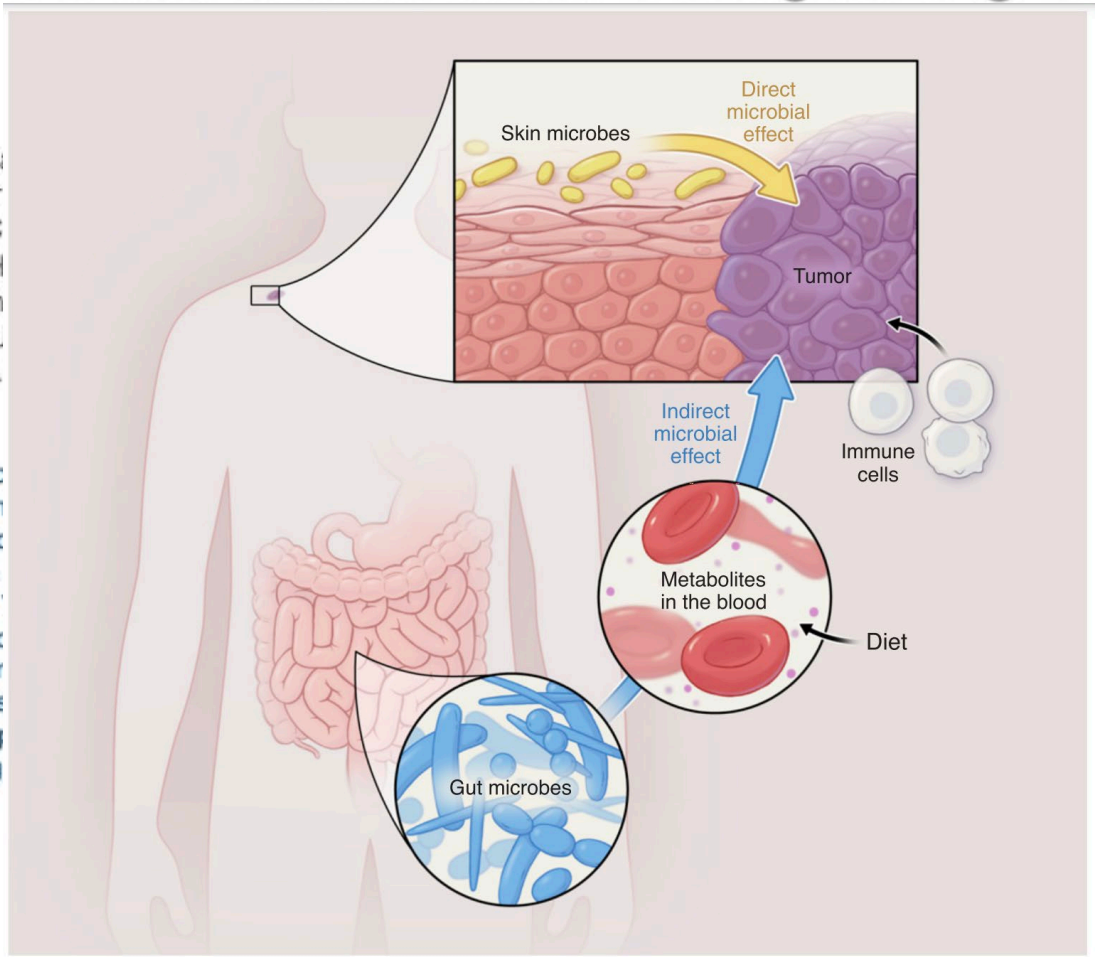


Opportunities:

Systems Biology approach is needed!

- Methods, both experimental and computational

Local/remote microbiomes likely relevant

- Example: colorectal cancers and *Fusobacterium*
- Gut microbes regulate metabolites and immunity

Circulating metabolites

- Metabolize bile acids, estrogen, androgens
- Antibiotics impact metabolite levels in distant tissues
- Brain, mood, and reward system and cancer

Opportunities:

Systemic or local immunity

- Microbes increase/decrease local inflammation
- Gut microbes and immunotherapy:
  - Agreement on microbes and mechanisms?
  - Use of antibiotics or probiotics?

Oncogenic Viruses and the Microbiome

- First genetic origin of cancer was a viral discovery
- Microbiome studies bias for bacteria!

Impact of treatment on the microbiome?

- Chemotherapy and radiation and the microbiome
- How to maintain or restore the microbiome?

Funding Opportunities:

Dept. of Defense - CDMRP -

Congressionally Directed Medical Research Programs

Cancer Grand Challenges UK:

https://www.cancerresearchuk.org/

"Improve treatment responses by manipulating the composition and status of the microbiota"

NCI Programs interested in funding microbiome research:

- CSBC: Cancer Systems Biology Consortium
  - U01, U54
- ITCR: Informatics Technology for Cancer Research
  - R21, U01, U24
- Physical Sciences In Oncology
  - U01, R01, U54
- IMAT: Innovative Molecular Analysis Technologies
  - R21, R33

Computational Methods and Tools for Meta-omic Analysis with Application in Multiple Cancers

W. Evan Johnson

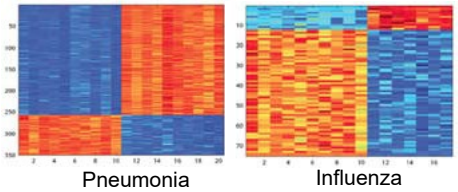
Associate Professor of Medicine & Biostatistics
Division of Computational Biomedicine
BU School of Medicine

Johnson Lab
c b m
BOSTON UNIVERSITY

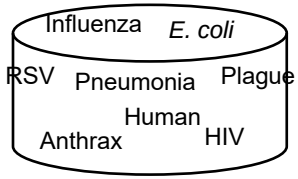
Collect specimen

DNA/RNA Sequencing

Host Response Pathways

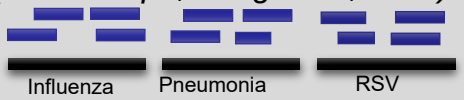


Genome Sequence Library



Microbiome Profiling

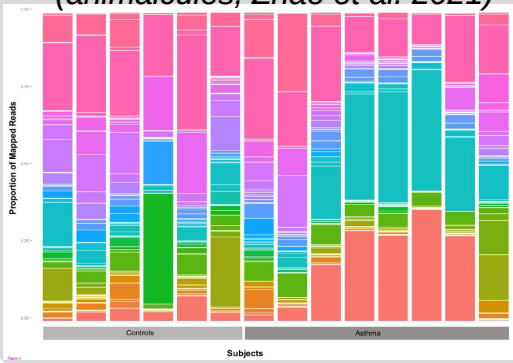
Align to Microbial Genomes
(PathoScope; Hong et al., 2014)



Bayesian Mixture Modeling
(PahoID; Francis et al., 2013)

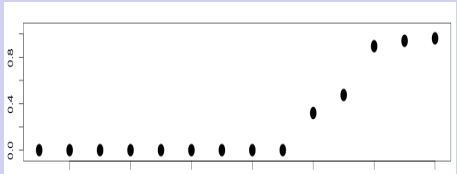
$$\mathcal{L}(\pi,\theta,\eta) = \prod_{i=1}^{R}\prod_{j=1}^{G} q_{ij}\,\pi_j^{x_{ij}}\,\theta_j^{(1-y_i)x_{ij}}$$

Microbial Abundance
(animalcules; Zhao et al. 2021)

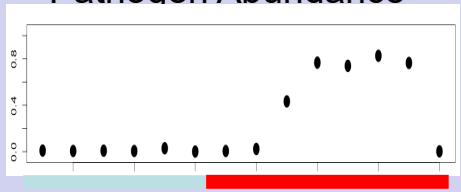


Integrate Results
(animalcules; Zhao et al. 2021)

Pathway Activation



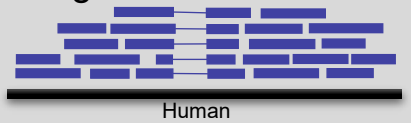
Pathogen Abundance



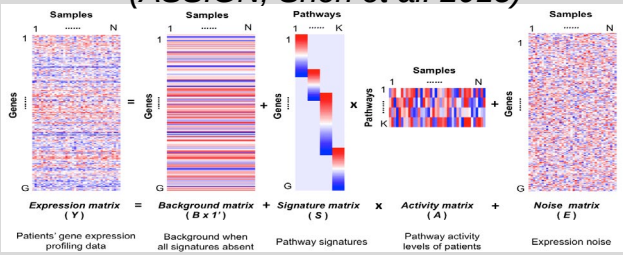
Control Asthma
Castro-Nallar et al., 2015

Host Profiling

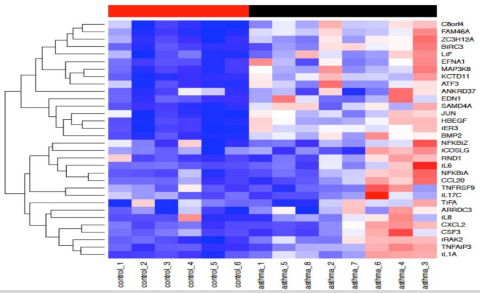
Align to Human Genome



Sparse Baysian Factor Analysis
(ASSIGN; Shen et al. 2015)



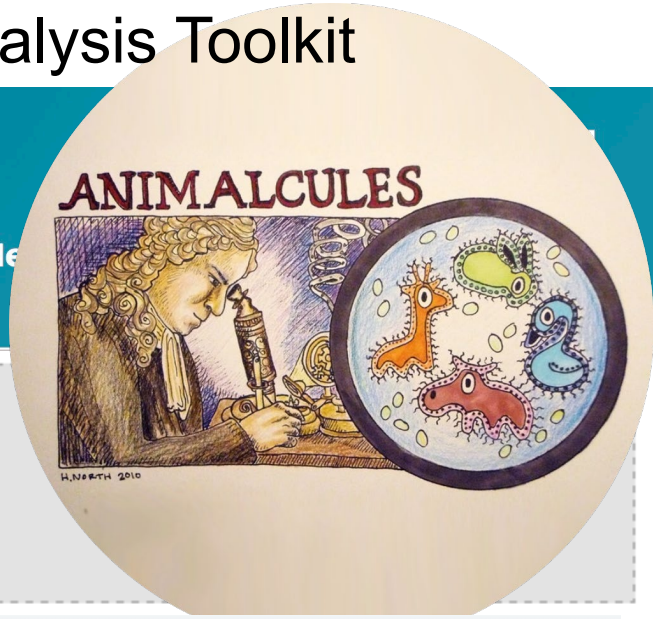
Immune Pathway Activity
(Johnson et al., 2021)



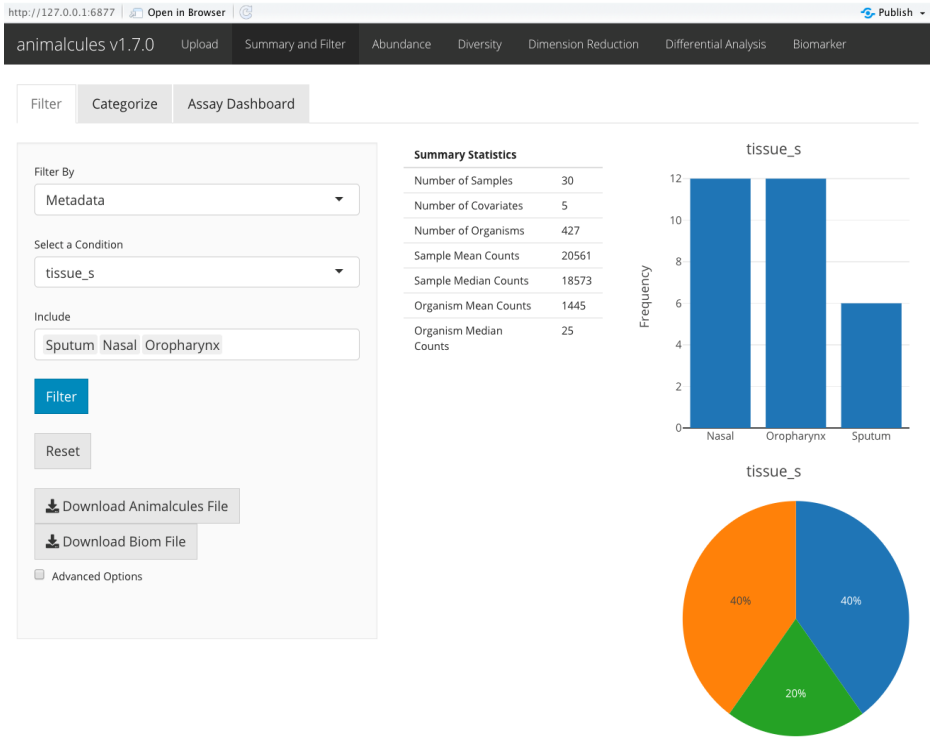
Animalcules: Interactive Microbiome Analysis Toolkit

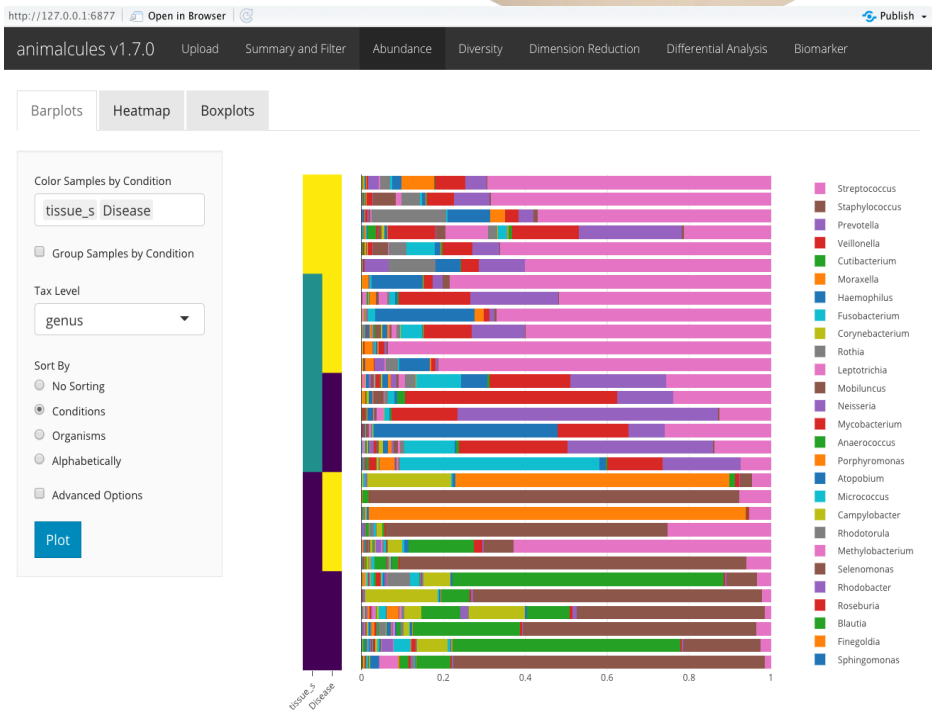
Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS

Home Install He



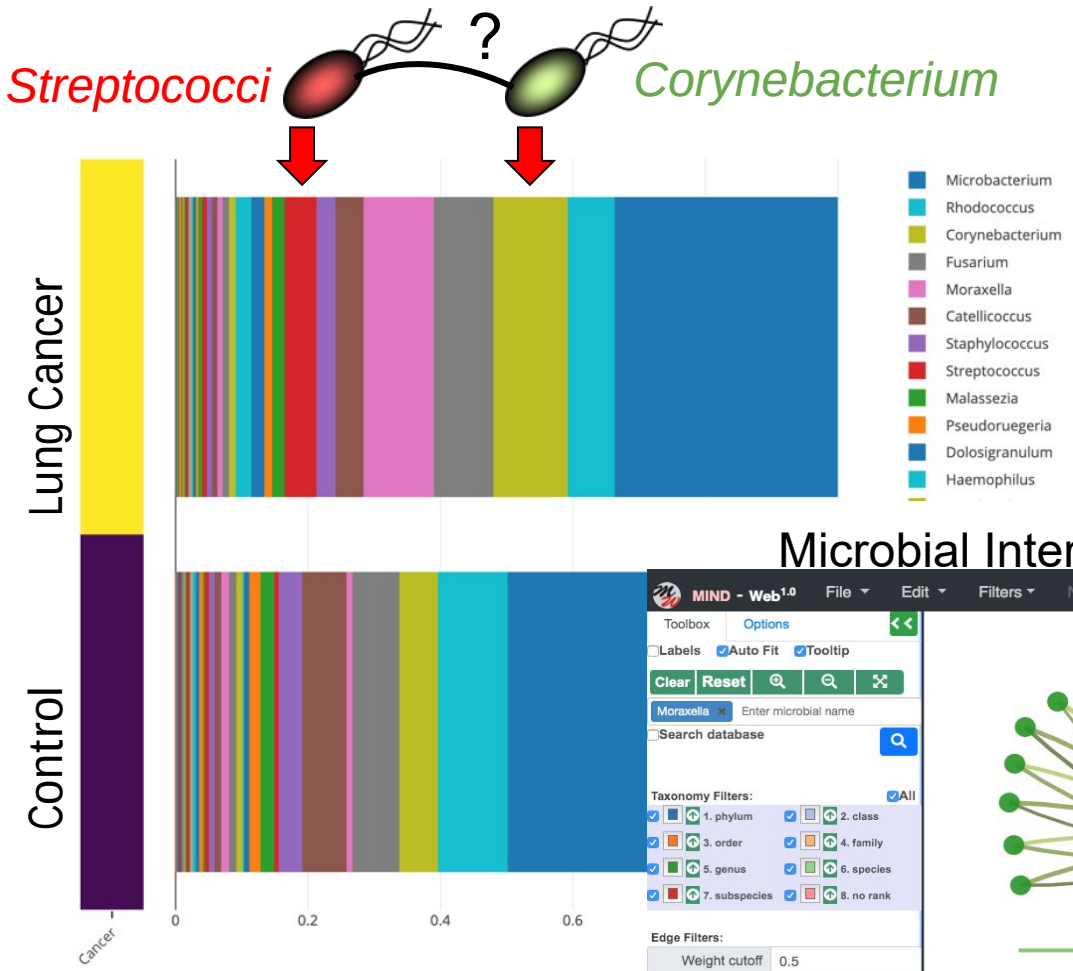

```
if (!requireNamespace("BiocManager", quietly = TRUE))
    install.packages("BiocManager")

BiocManager::install("animalcules")
```

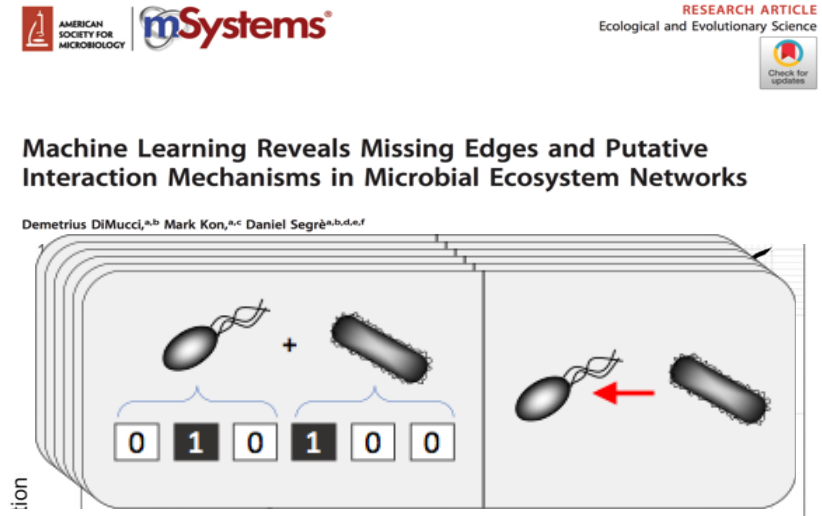




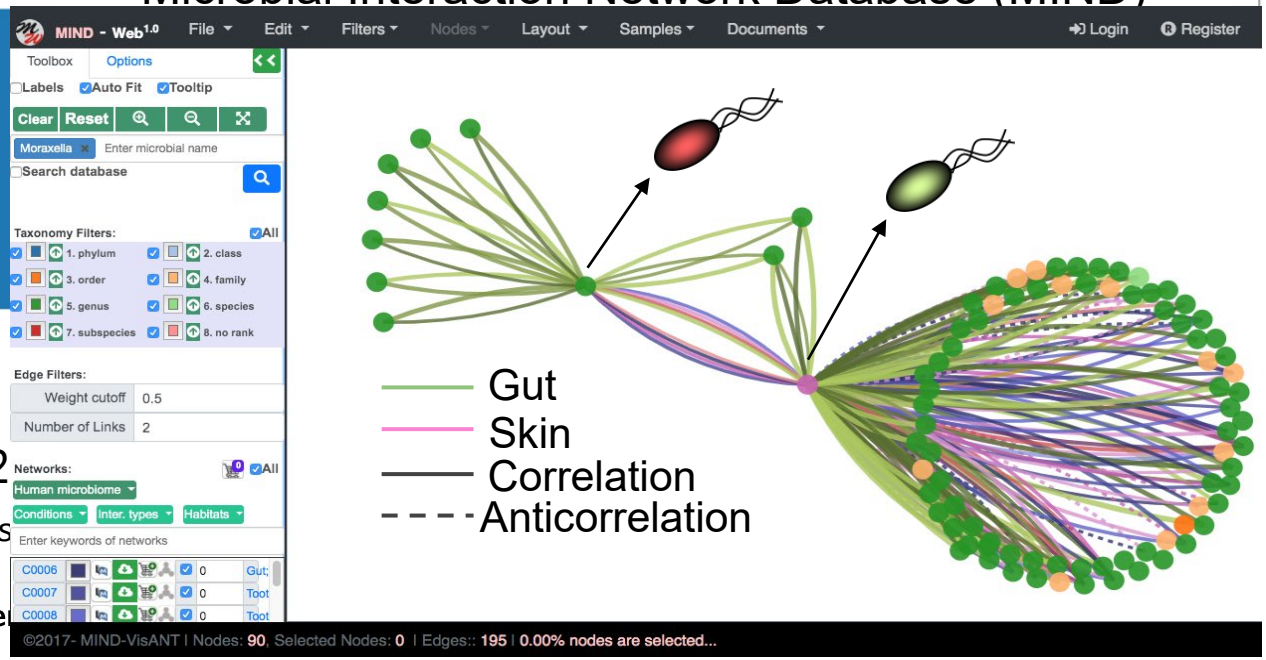
(animalcules: Interactive Microbiome Analytics and Visualization in R, Zhao et al., Microbiome, in press)

Microbiome-based Nasal Biomarker for Lung Cancer





Microbial Interaction Network Database (MIND)



Trained on *n*=35 cancer, *n*=2

(Research in progres

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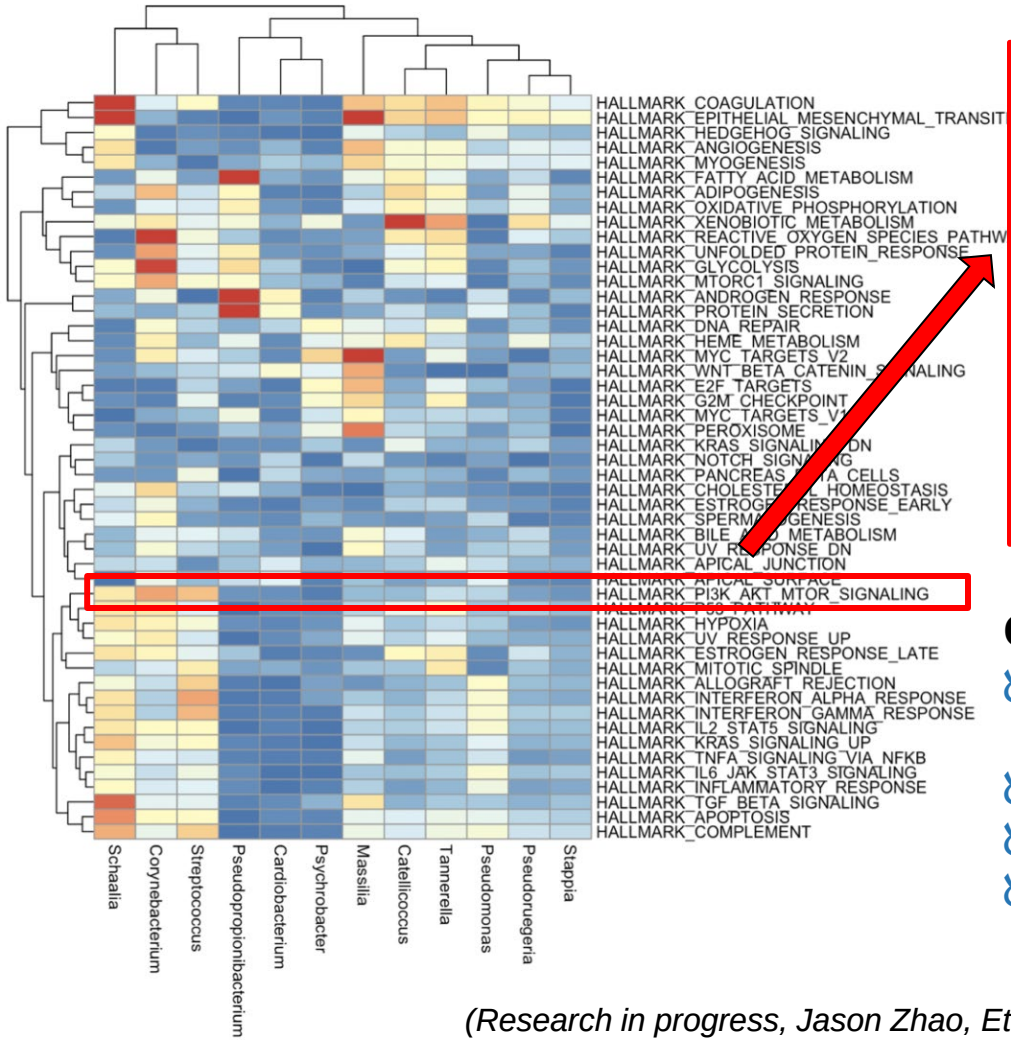
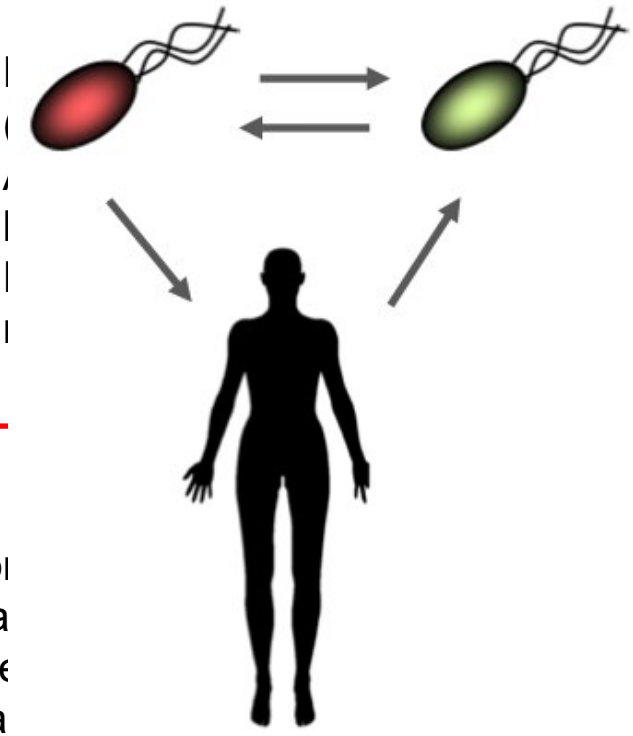
Boston Univer

(Research in progress, Zhenjun Hu and Dileep Kishore)

Microbiome and Host interactions



PI3K_AKT_MTOR Signaling:



- ... nent
- ...
- ... sing
  ...)

Other ... ions:

- Co... and rea...
- Pse... nse
- Ma...
- Catellicoccus: Oxidative phosphorylation

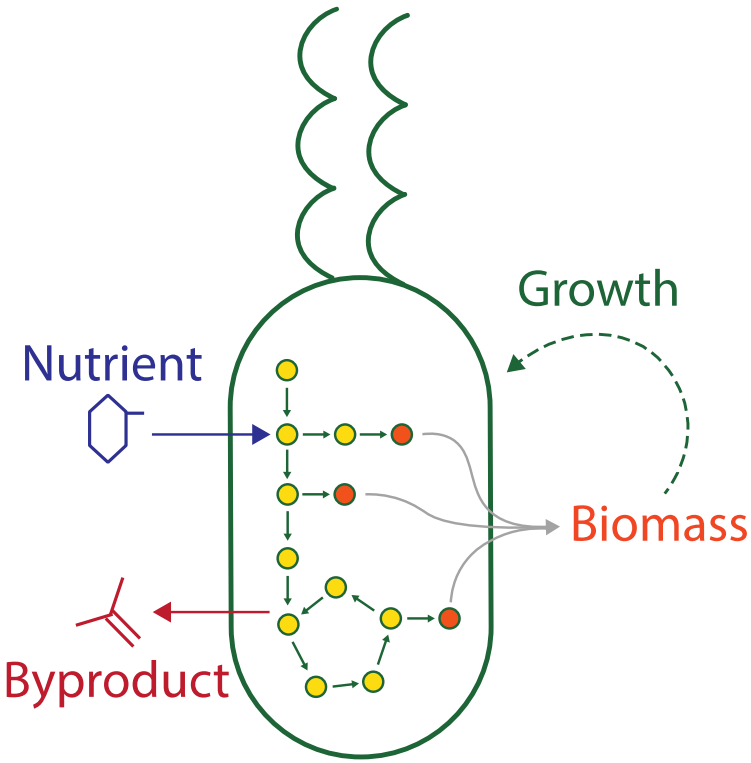
(Research in progress, Jason Zhao, Ethel Nankya, Saket Pandit)

Spatio-temporal Modeling of Multicellular Metabolism

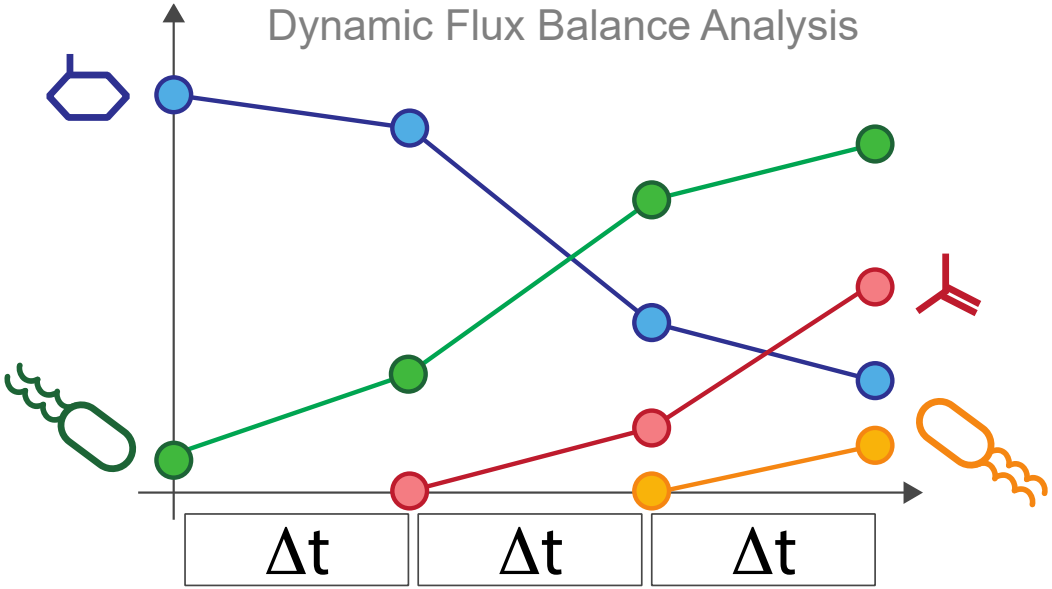
Daniel Segrè

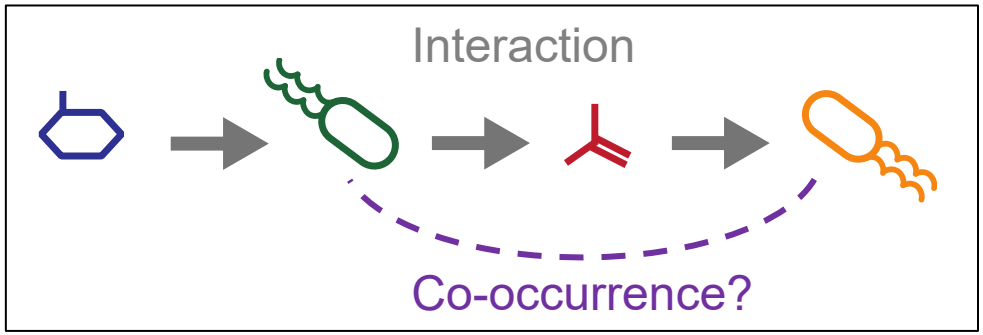
Professor of Biology, Director of the Microbiome Initiative
Dept. of Biology, Physics (CAS), Biomedical Engineering (ENG)
Bioinformatics Program, Biological Design Center, CNSB

From metabolic networks to mechanistic predictions



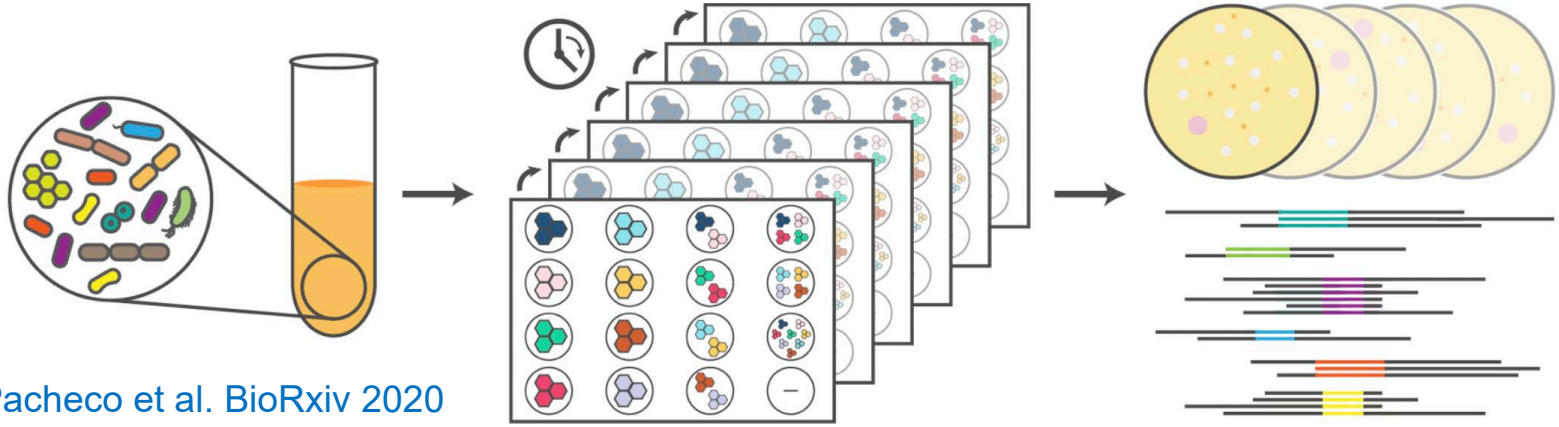
~1500 reactions



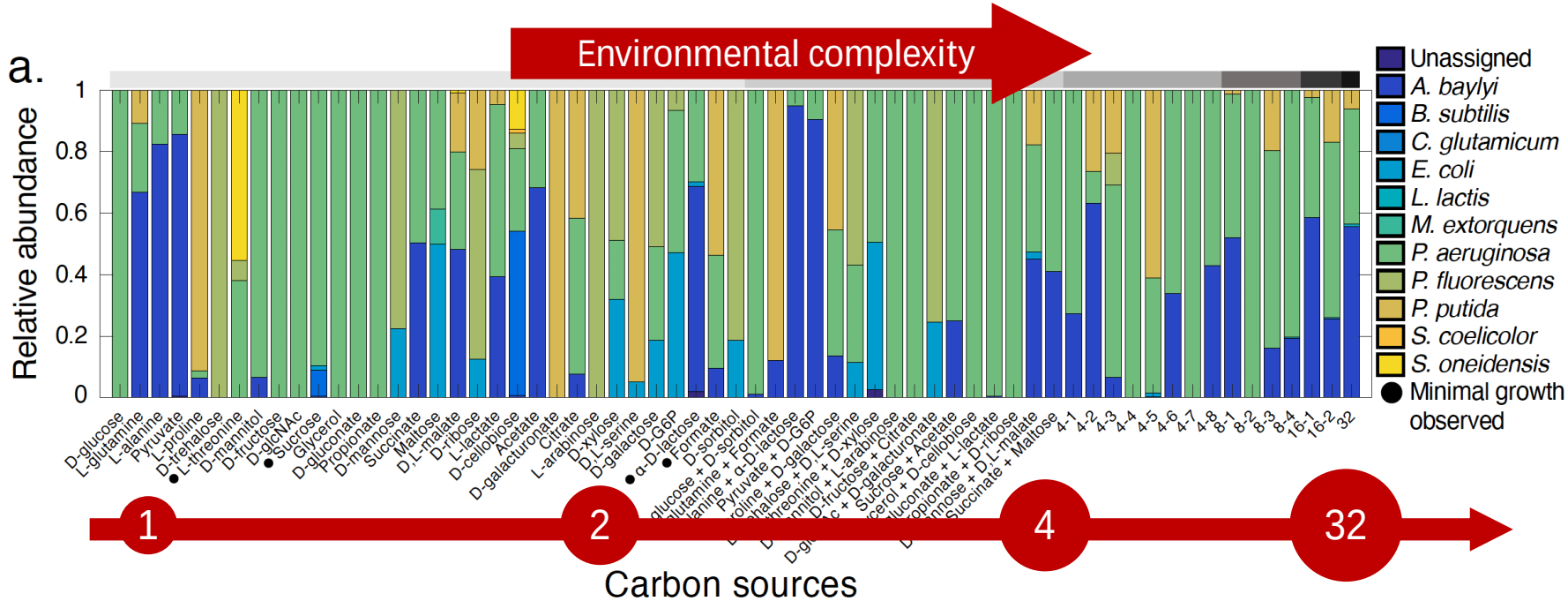


Kishore et al. BioRxiv 2020

Testing models through combinatorial synthetic ecology: Can we design communities with desired properties?

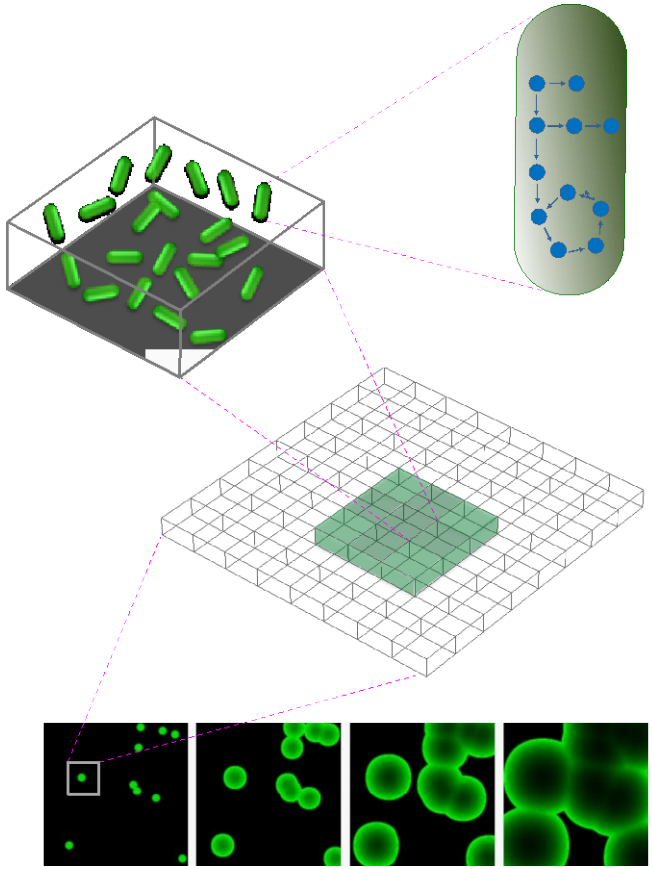


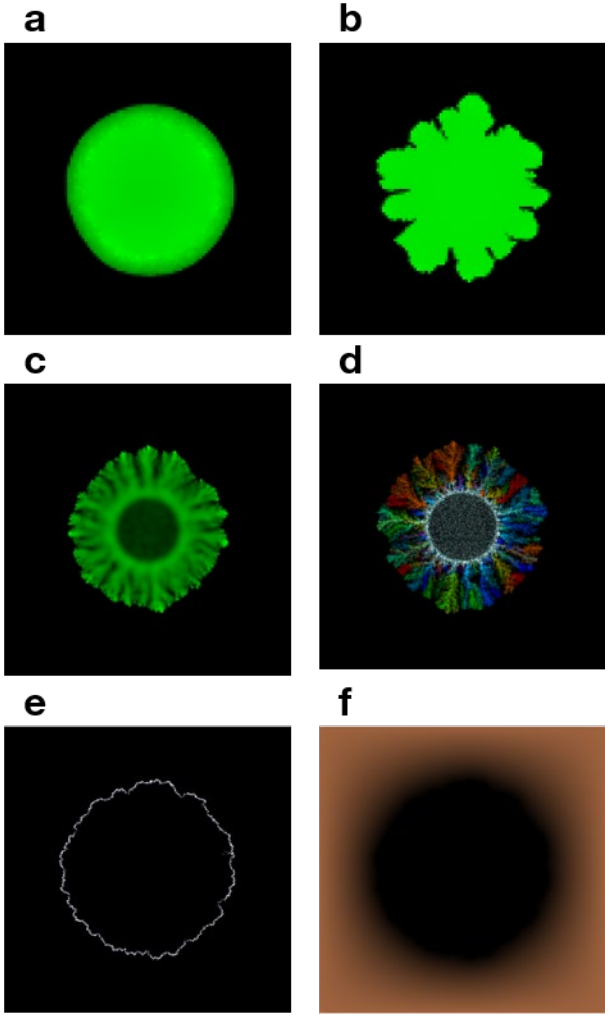
Alan Pacheco et al. BioRxiv 2020



Adding the spatial dimension: Computation Of Microbial Ecosystems in Time and Space (COMETS)

runcomets.org





Ilija Dukovski et al. arXiv 2020

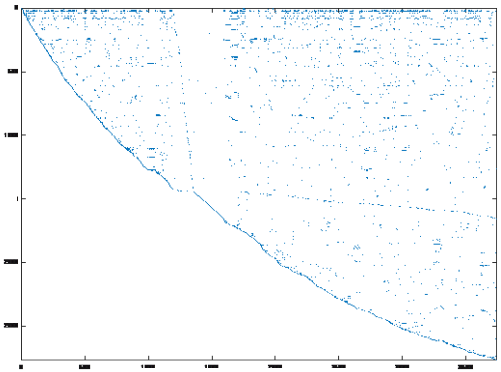
Collab. with Kirill Korolev, Jenny Bhatnagar, …

Bridging microbiome & human

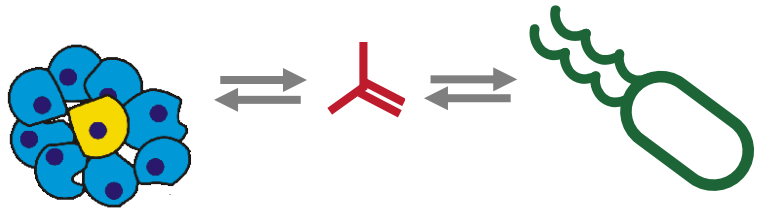
1

The known human metabolism

~3000 metabolites



~4,000 reactions



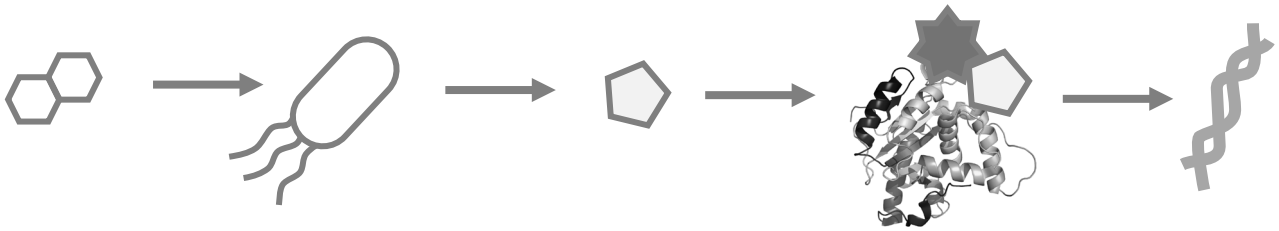
4D COMETS modeling of cancer

human-microbe interactions

(I. Dukovski, D. Shah, Z. Huang)

2

Diet → Microbiome → Byproducts → Human proteins → Human regulation



Collab. with David Sherr, Andrew Emili, Trevor Siggers and others

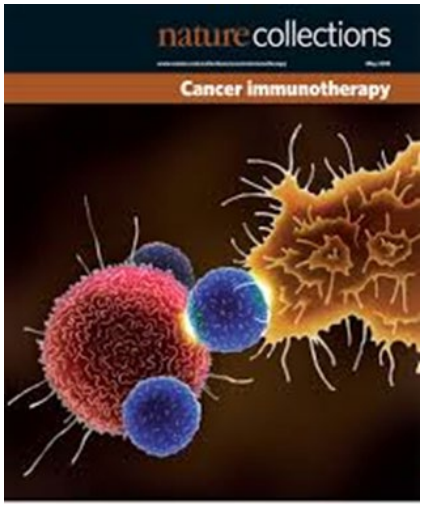
Prospective Evaluation of the Microbiome and Treatment Response in Cancer Patients Receiving Treatment with Checkpoint Inhibitors

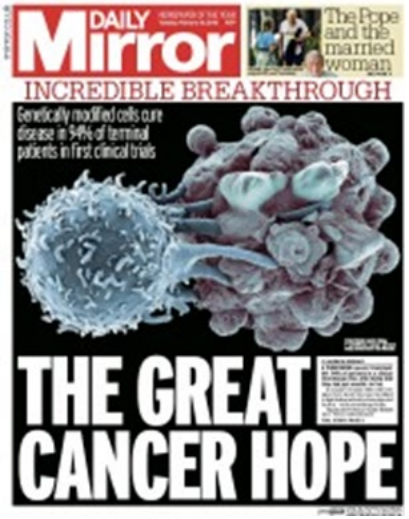
Matthew Kulke, MD

Kiana Mahdaviani PhD, David Li, Nina Modanlo, Lucas Schiffer PhD, Evan Johnson PhD

Section of Hematology and Medical Oncology, Boston University and Boston Medical Center
Section of Computational Biomedicine, Boston University School of Medicine

Immunotherapy using immune checkpoint inhibitors has revolutionized cancer therapy…and is impacted by the host microbiome





CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,2,3] Caroline Flament,[1,2,3] Vichnou Poirier-Colame,[1,2,3] Paule Opolon,[6] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[18] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[8,21,22] Bernard Escudier,[1,14,23] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,3,14] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28*] Laurence Zitvogel[1,2,3,5*]

CANCER IMMUNOTHERAPY

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients

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CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients

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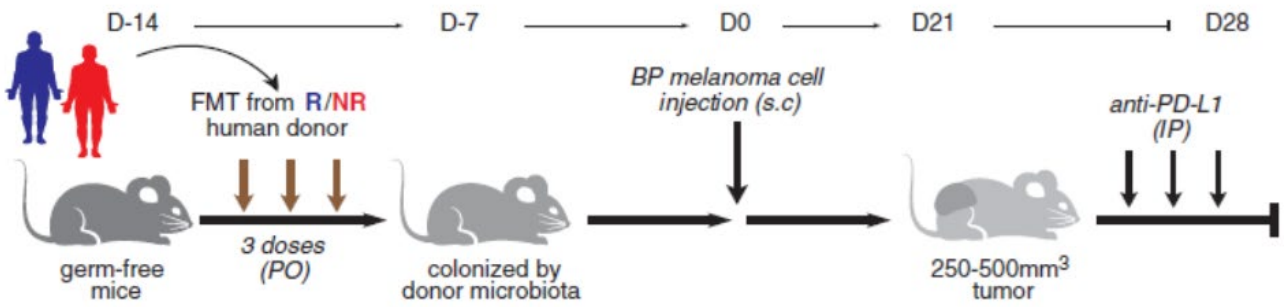
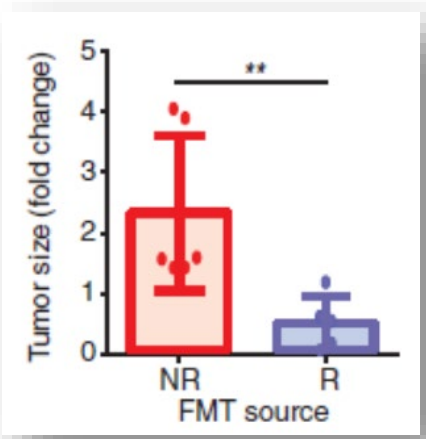
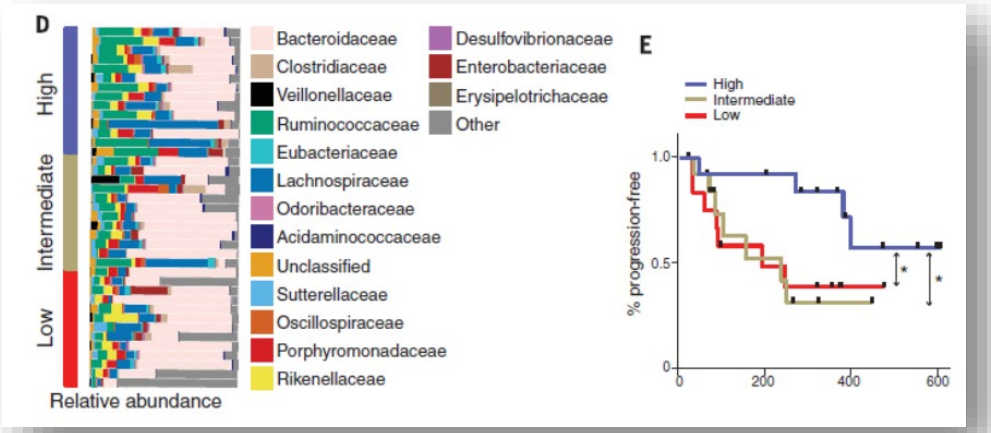
Science 2018; 359: 91-97, 97-103, 104-108

The host microbiome can alter response to checkpoint inhibitors in mouse models; microbiome composition is also associated with treatment response in the clinical setting



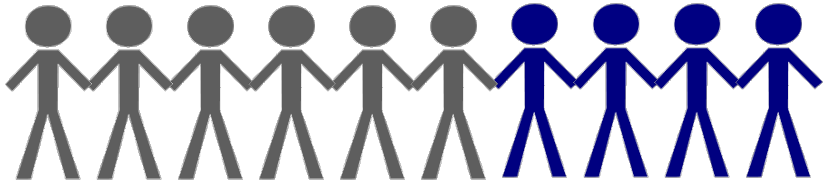




Gopalakrishnan et al, Science 2018; 359: 97-103

Cancer clinical trials evaluating the effect of the host microbiome on treatment response in diverse patient populations are limited

- **5 – 7%** of cancer clinical trial enrollees are **underrepresented minorities nationally**
- **< 4%** of enrollees in trials of immune checkpoint inhibitors are from minority populations

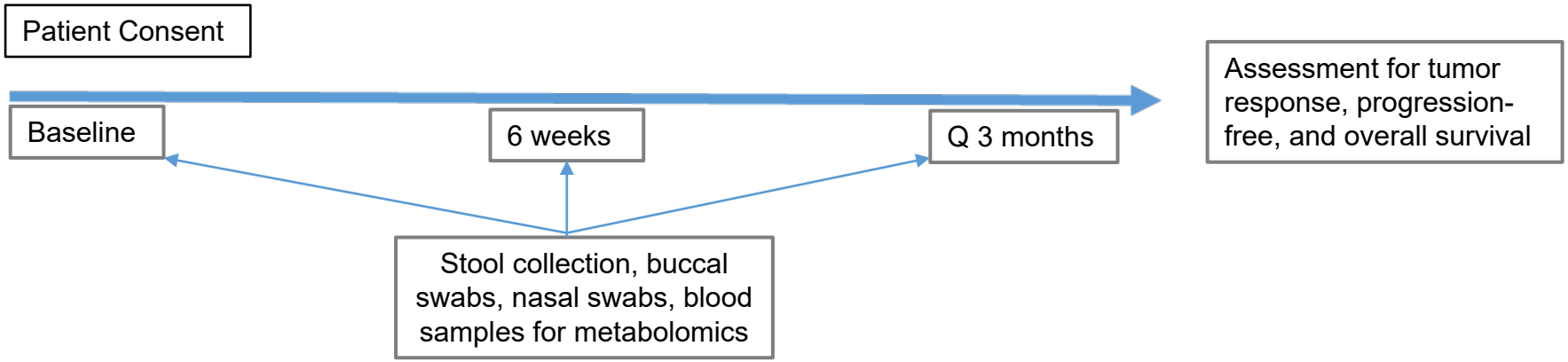


- **Over 50%** of cancer clinical trial enrollees at **BMC are from underrepresented minority populations**

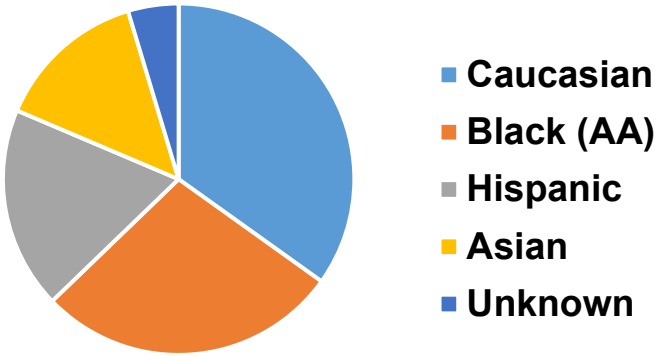
- *Our overarching hypothesis is that the host microbiome in BMC patients from diverse backgrounds and socioeconomic strata will vary, and that this variation will be associated with response to immune checkpoint inhibitors*

- *The host microbiome is modifiable, and our findings may therefore have therapeutic implications*

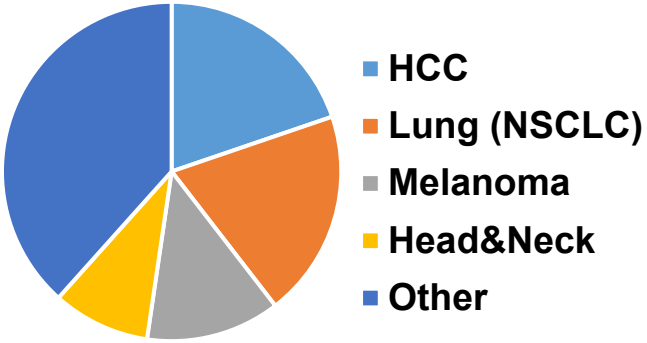
We are Undertaking a Prospective Evaluation of the Microbiome and Treatment Response in Patients Receiving Checkpoint Inhibitors at BMC



Ethnicity/ Race



Cancer Type



N=86 patients consented to date

Cancer and the Environmental Microbiome

Jenny Bhatnagar

Assistant Professor
Department of Biology, CAS

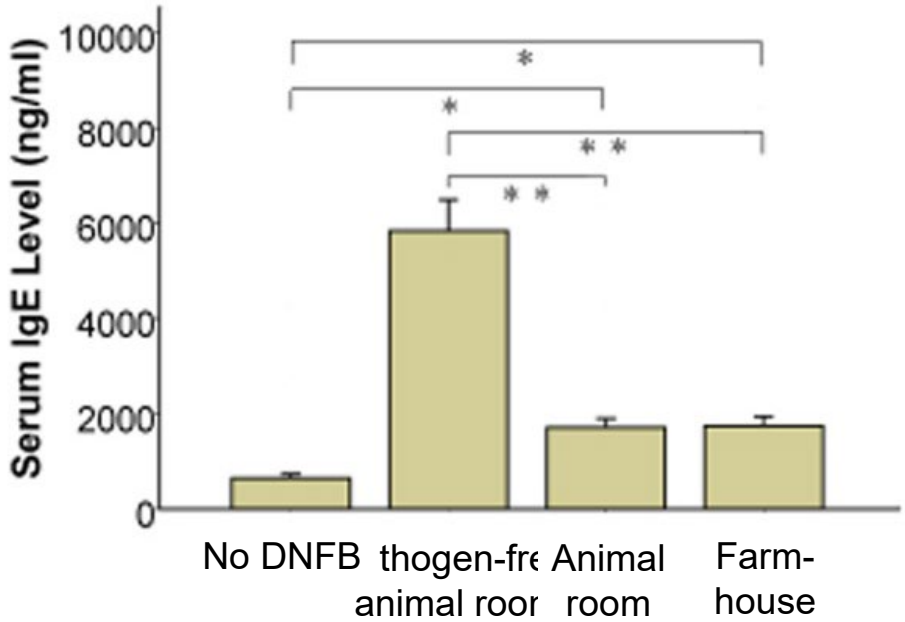
Who we are depends on “who” is around us

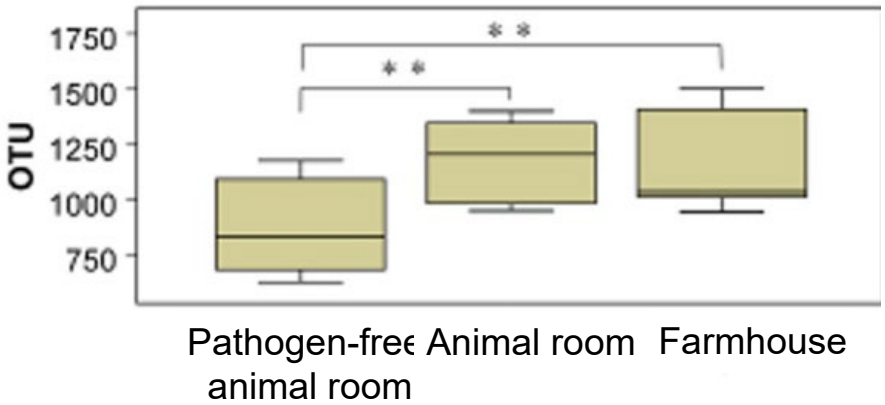
Diversity of Proteobacteria

Variation in Land Use Types
~ forests, agricultural land

Hanski et al. 2012 PNAS

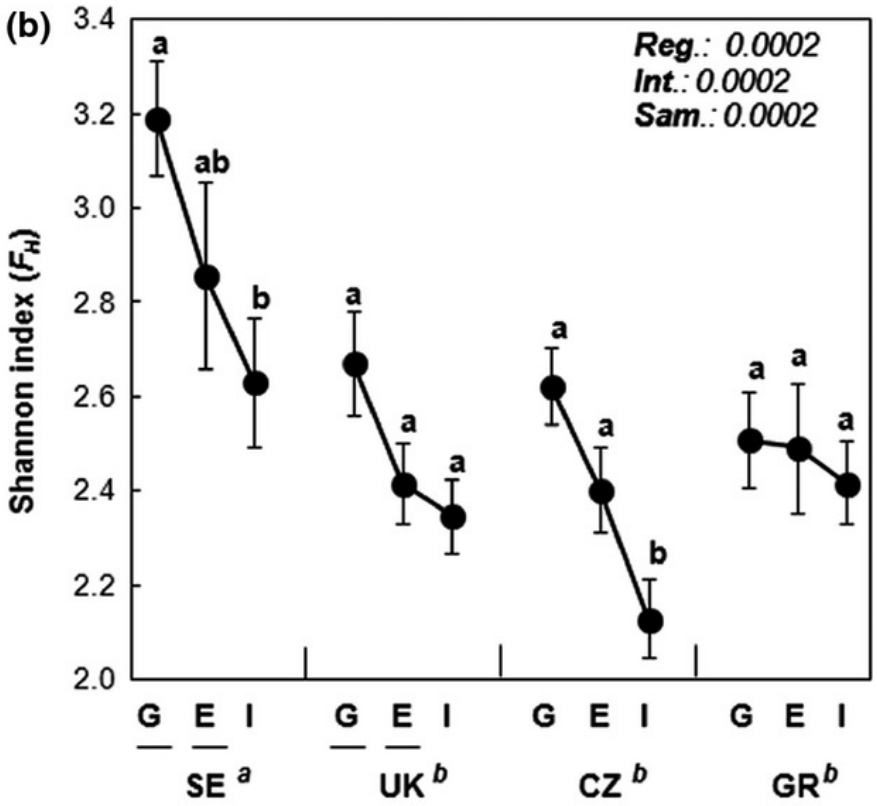
Who we are depends on “who” is around us





Zhou et al.2015 Environ. Microbiol.

”Biodiversity hypothesis”: rise in colorectal cancer linked to declines in exposure to a diverse environmental microbiome



Arnold M, et al. 2017. Gut

Tsiafouli et al. 2014. Global Change Biology

Diversity of Proteobacteria

Host/Microbiome Cross-Talk in Oral (Pre)Malignant Lesions (PML)

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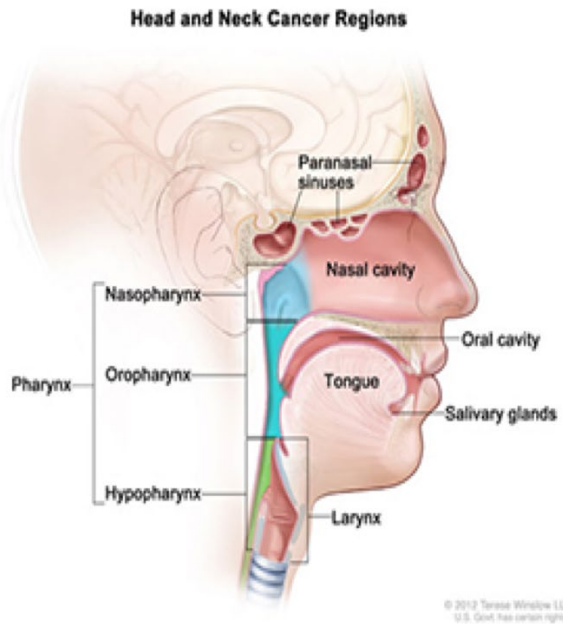
Division of Computational BioMedicine, School of Medicine

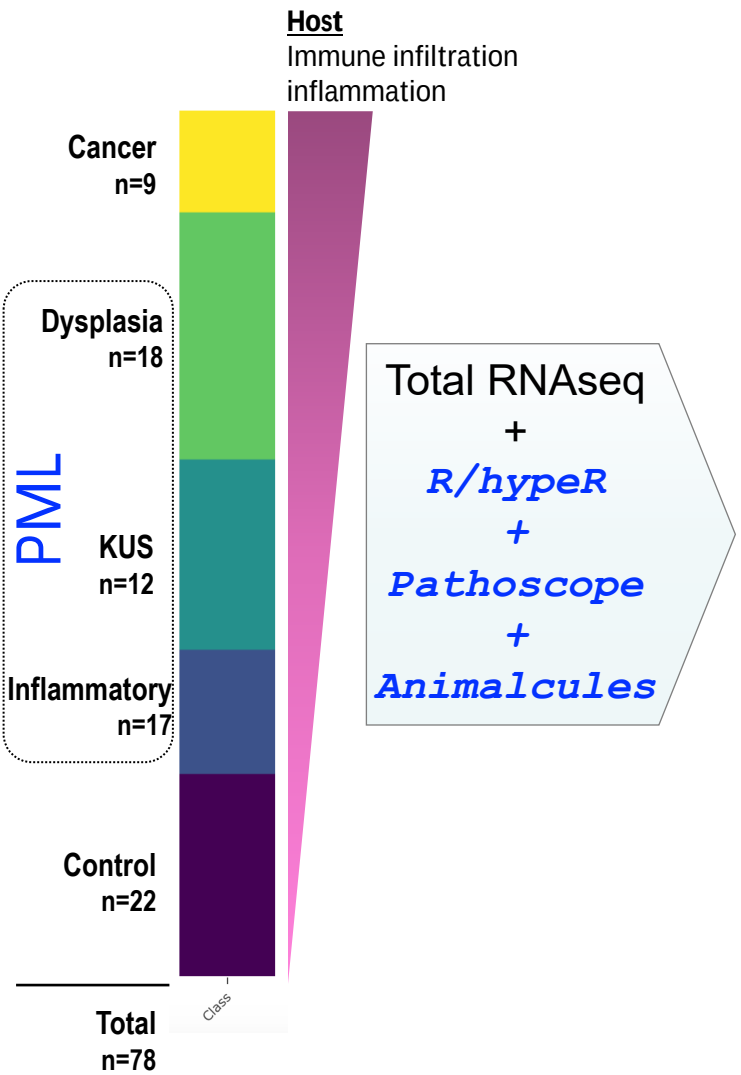
Maria Kukuruzinska
Bob Varelas
Manish Bais
Muzamil Khan
Evan Johnson
Alessandro Villa @ UCSF
Jennifer Frustino @ ECMC

Background:
Head & Neck Squamous Cell Carcinoma (HNSCC)

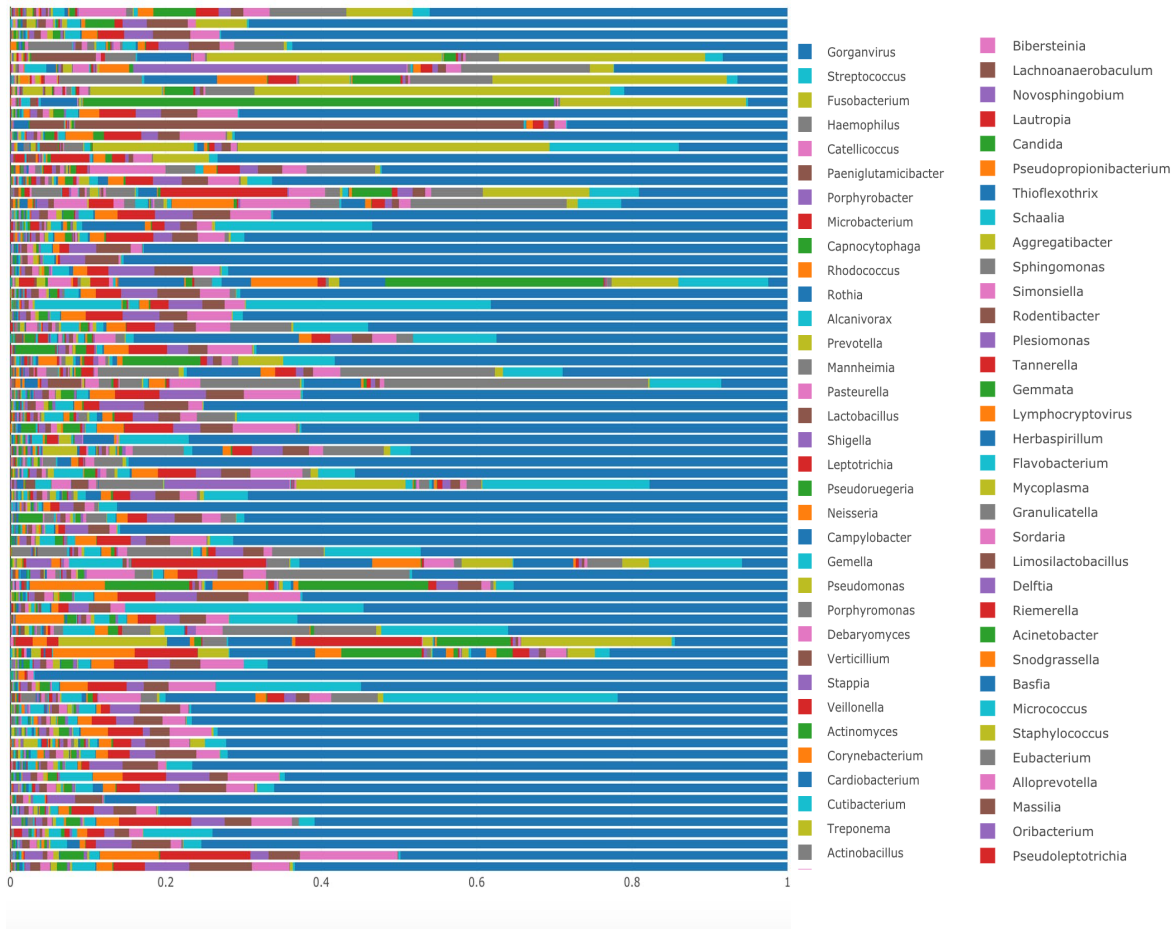


- ✓ ***HNSCC***: malignancies arising in the upper aerodigestive tract
  - ❑ Survival rate <60% at five years from diagnosis
  - ❑ HPV(-) Oral Squamous Cell Carcinoma (OSCC) most common
- ✓ ***Oral microbiome*** 2nd largest & diverse microbiota in human body
  - ❑ Oral cancer associated with changes to the oral microbiome
  - ❑ Urgent need for research on the role of the microbiome in oral cancer
  - ❑ Host/microbes imbalance → Oral/systemic disease →Inflammation → Cancer?

Relative Abundance of Genera by Class

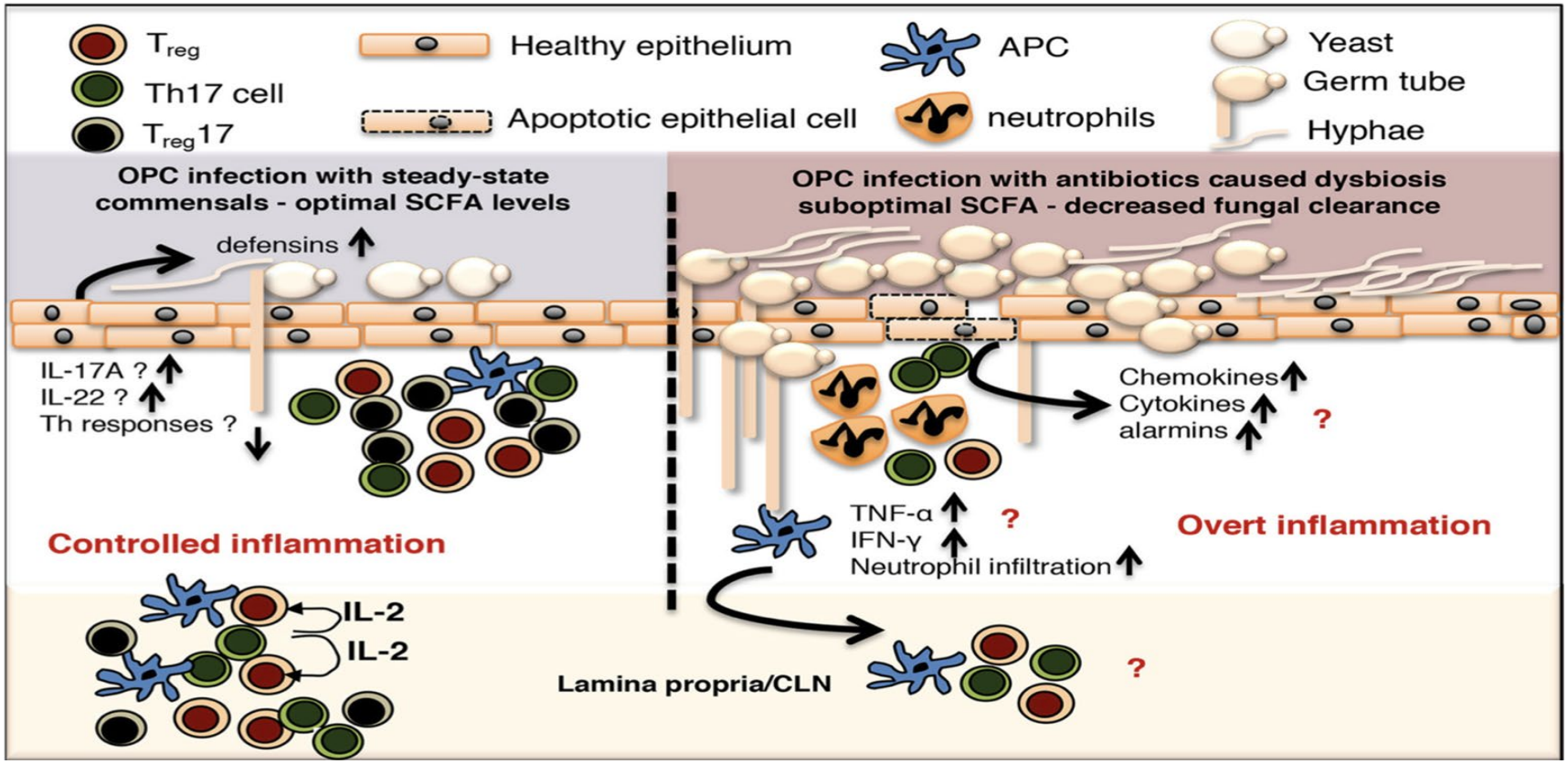


Total RNAseq
+
R/hypeR
+
Pathoscope
+
Animalcules



Muzamil Khan

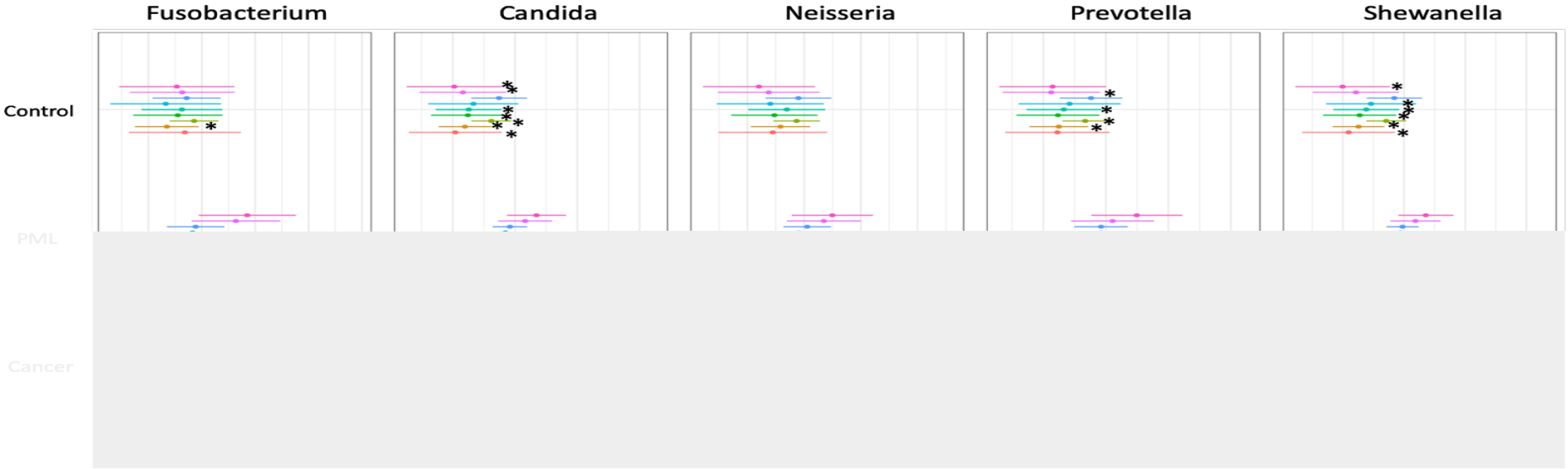
Dysbiosis *vs.* Immune Response



OPC (oropharyngeal candidiasis) - fungal infections; common manifestations among cancer patients

Microbiome Dependent Regulation of Tregs and Th17 Cells in Mucosa Pandiyan et al, Frontiers in Immunology, 2019

Immune/inflammation activity is associated with lesion type …

INFα TNF TGF Neutrophils IL6 Apoptosis Necrosis IL10 T-regs

… and with microbes' abundance across lesion types