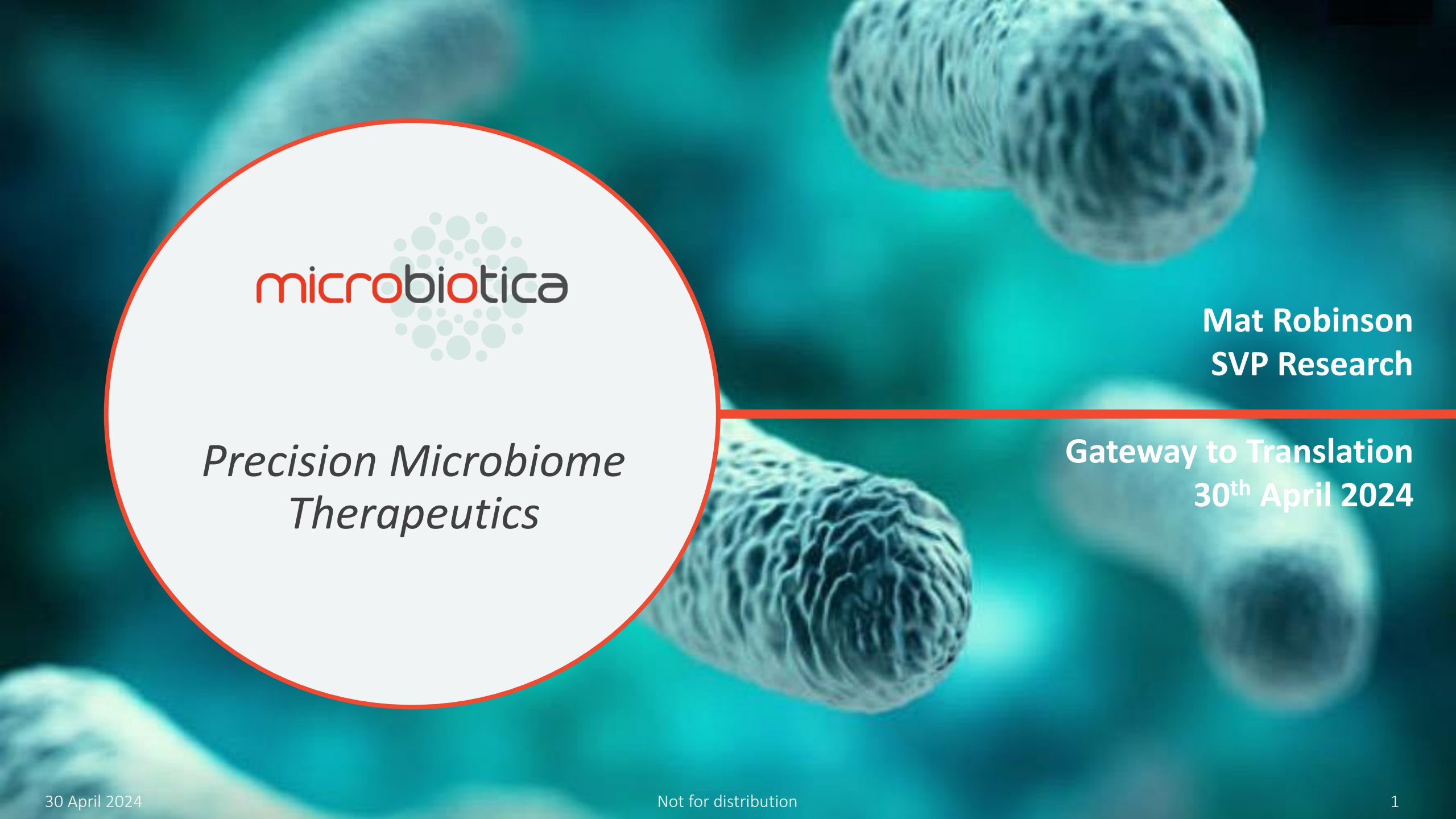


microbiotica

Precision Microbiome Therapeutics

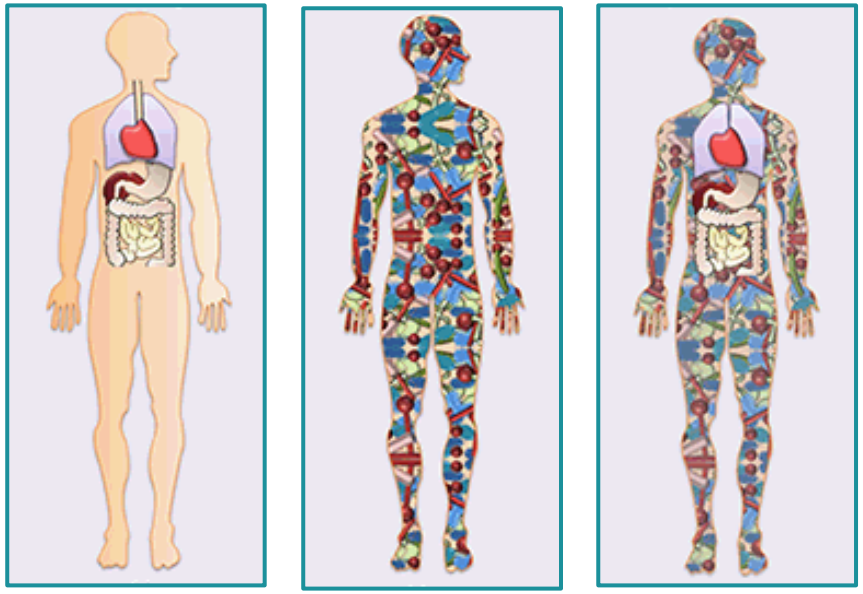
Mat Robinson
SVP Research

Gateway to Translation
30th April 2024

Microbiome: Central in human biology … increasing recognition

The Human-Microbiome Symbiont

Human + Microbiome = Complete Human

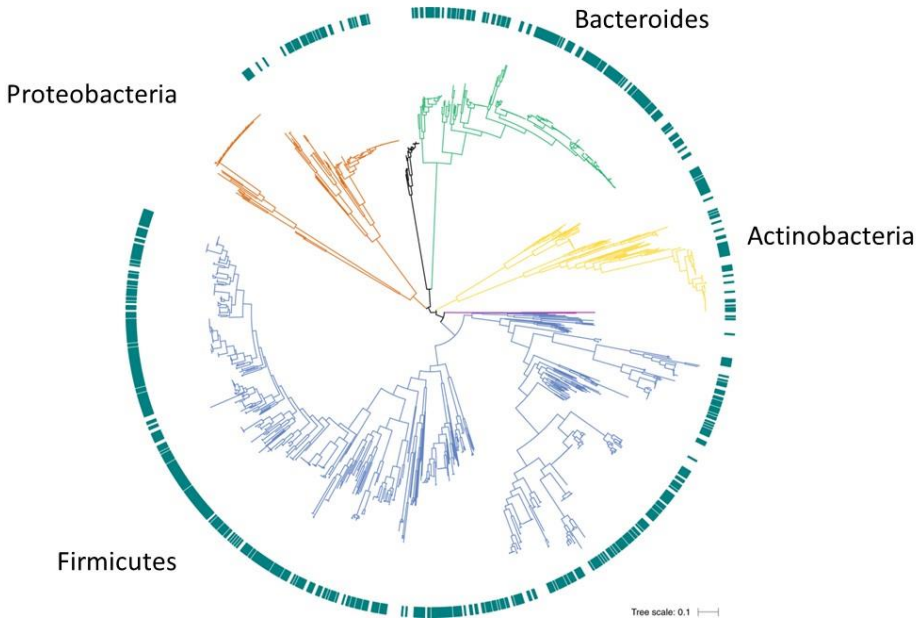


10^{14} cells
23,000 genes

10^{14} microbes
9m genes

Normal functioning body

Human Gastro-Intestinal Microbiome: Role in Health

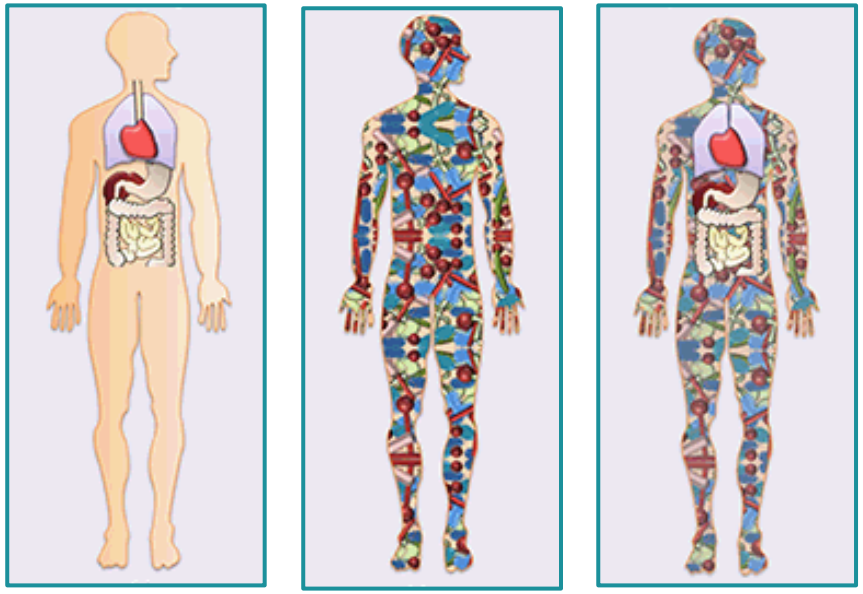


- Prevent infection
- Break down food
- Synthesize vitamins
- Protect & regulate gut function
- Modulate the immune system
- Regulate brain function

Microbiome: Central in human biology … increasing recognition

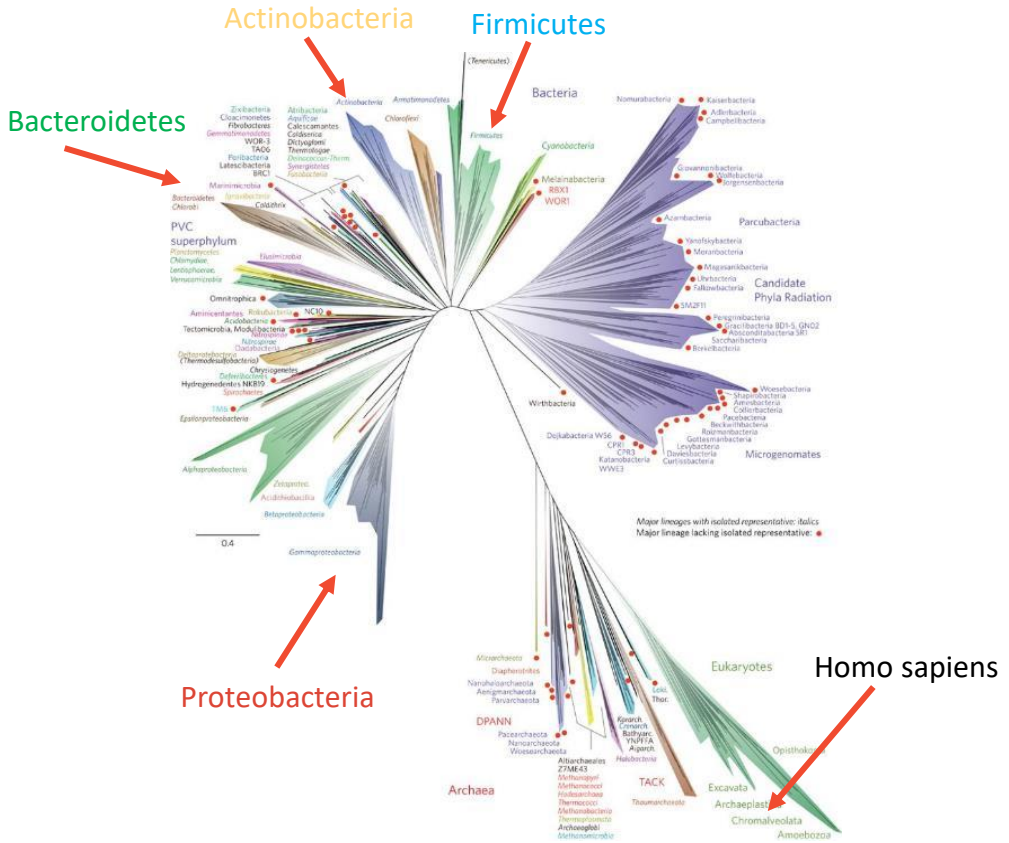
The Human-Microbiome Symbiont

Human + Microbiome = Complete Human



10^{14} cells 23,000 genes	10^{14} microbes 9m genes	Normal functioning body

Highly diverse: 4 Gut Phyla Mapped to Tree of Life



Hug et al. 2016. Nat Microbiol. 1:16048

The Human Microbiome is a Major Factor in Many Diseases

The predictive power of the microbiome exceeds that of genome-wide association studies in the discrimination of complex human disease

Braden T Tierney[1,2,3,4], Yixuan He[1], George M Church[5,6], Eran Segal[7,8], Aleksandar D Kostic[2,3,4+], Chirag J Patel[1+]

[1]Department of Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA
[2]Section on Pathophysiology and Molecular Pharmacology, Joslin Diabetes Center, Boston, MA 02215, USA
[3]Section on Islet Cell and Regenerative Biology, Joslin Diabetes Center, Boston, MA 02215, USA
[4]Department of Microbiology and Immunobiology, Harvard Medical School, Boston, MA 02115, USA
[5]Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, USA
[6]Department of Genetics, Harvard Medical School, Boston, MA, USA
[7]Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot 7610001, Israel
[8]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 7610001, Israel

bioRxiv preprint doi: https://doi.org/10.1101/2019.12.31.891978; this version posted January 2, 2020.

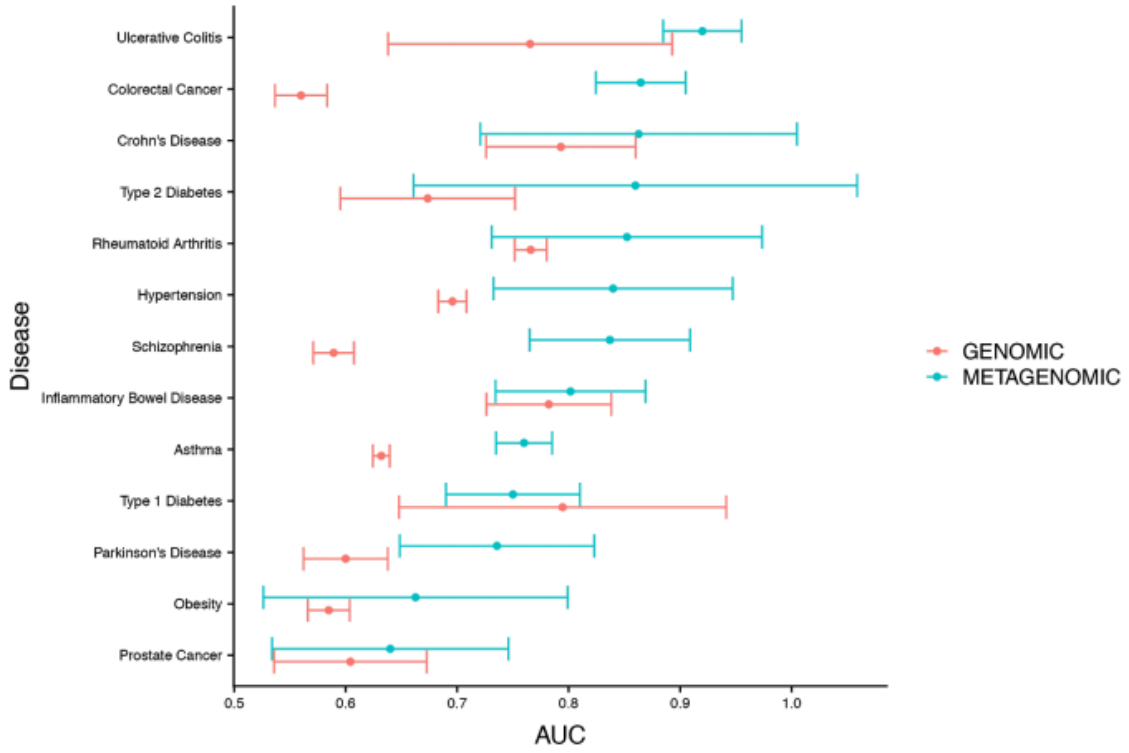
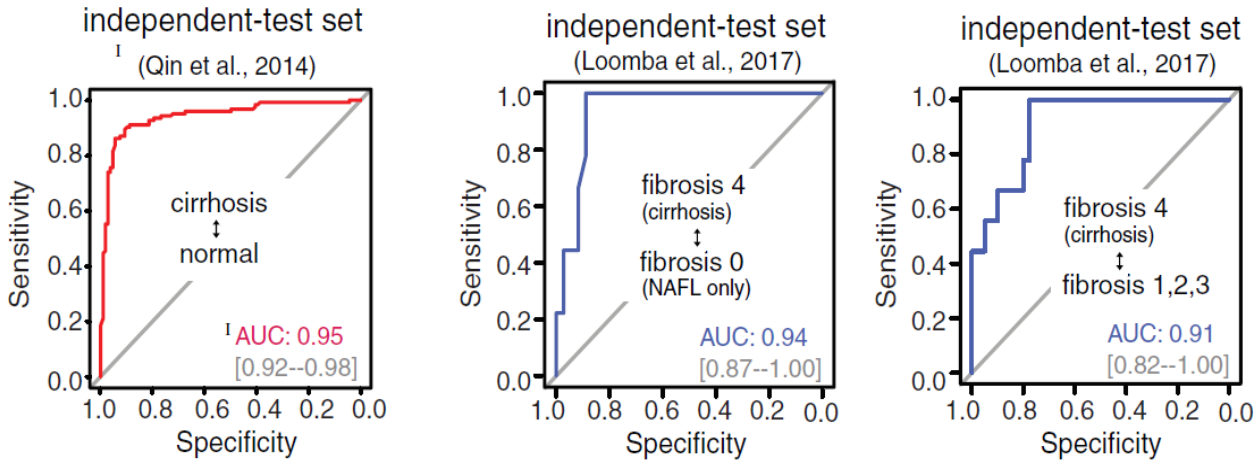


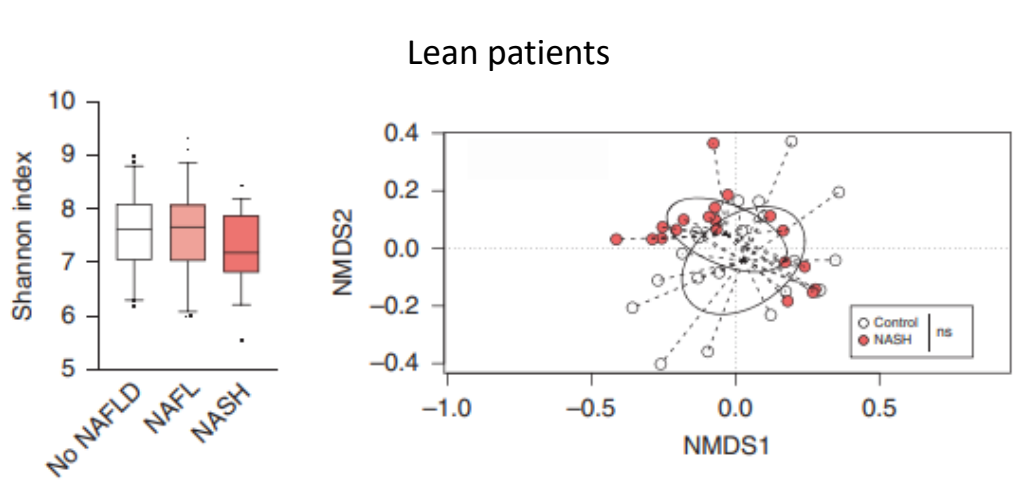
Figure 2: Results from literature-review-based meta-analysis of genomic vs. metagenomic predictors.

Microbiome is changed in many diseases

- Change in the intestinal microbiome is associated with many indications including several immune-mediated diseases, neurological conditions and metabolic diseases
- Microbiome is altered in multiple liver diseases, including viral hepatitis and alcohol associated cirrhosis, and late-stage complications eg acute-on-chronic liver failure and hepatic encephalopathy
  - Progressive changes in microbiome as progress from NAFLD through to cirrhosis
  - Microbiome signatures are link to metabolite changes including bile acid metabolism and SCFA
- Cause-effect relationship is complicated



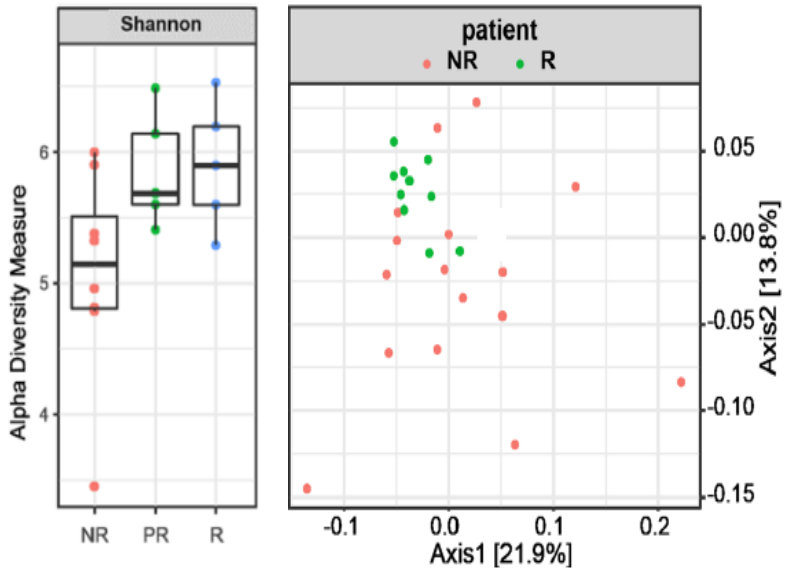
Oh et al *Cell metabolism* (2020) **32**:878



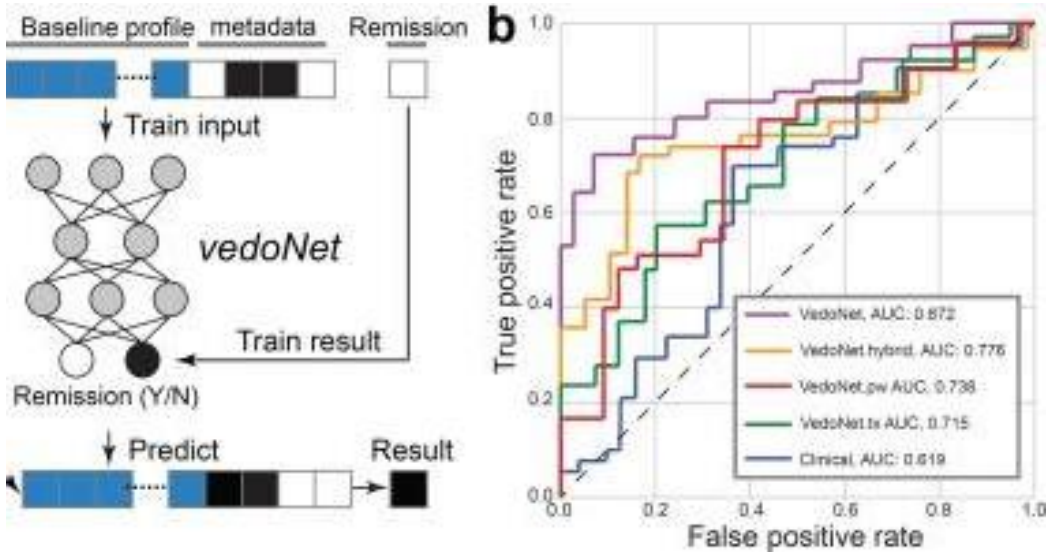
Lee et al *Nat Comm* (2020) **11**:4982

Microbiome is associated with drug response

- Pre-treatment microbiome of ankylosing spondylitis patients is linked to anti-TNF response
- Baseline microbiome linked to vedolizumab response in IBD



Bazin et al *Scientific Reports* (2018) **8**:5446

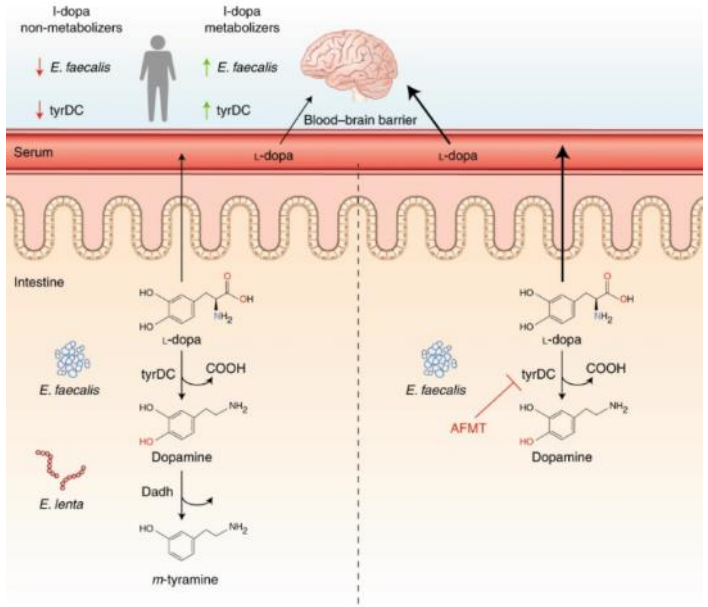


Ananthankrishnan et al Cell Host Microbe (2017) **21**:603

Drug Metabolism by the Microbiome

L-Dopa Metabolism in Parkinson's

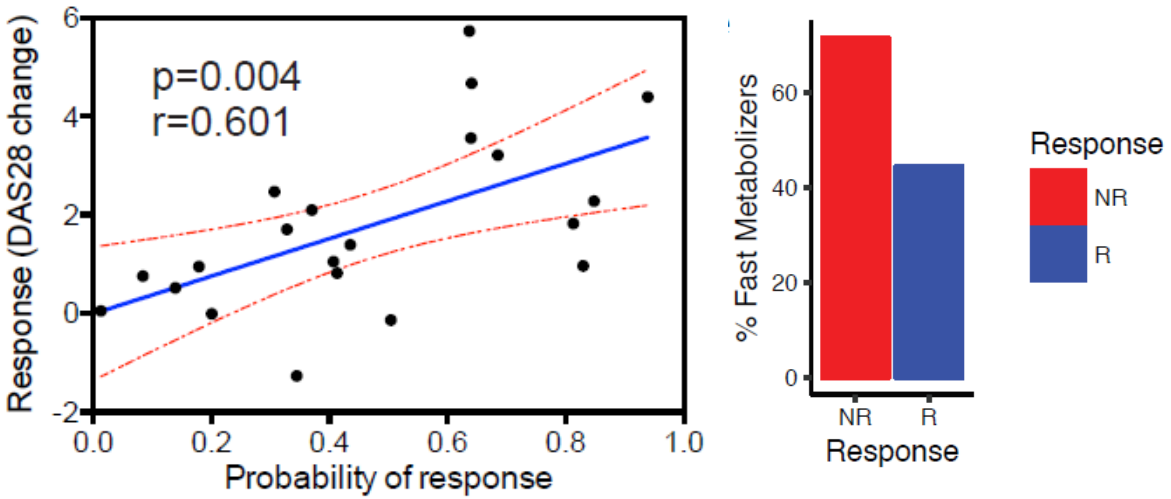
- Interspecies pathway for gut bacterial l-dopa metabolism
- Pathway leads to metabolism of L-Dopa to *m*-tyramine



Rekdal et al *Science* (2019) **364**: eaau6323

Methotrexate Response in RA

- Response of treatment naïve RA patients to methotrexate can be predicted by gene function analysis of gut microbiome
- Many key pathways could be linked to MTX metabolism
- Microbiome of NRs typically fast metabolisers of MTX



Artacho et al *Arthritis Rheumatol* (2020) 10.1002/art.41622

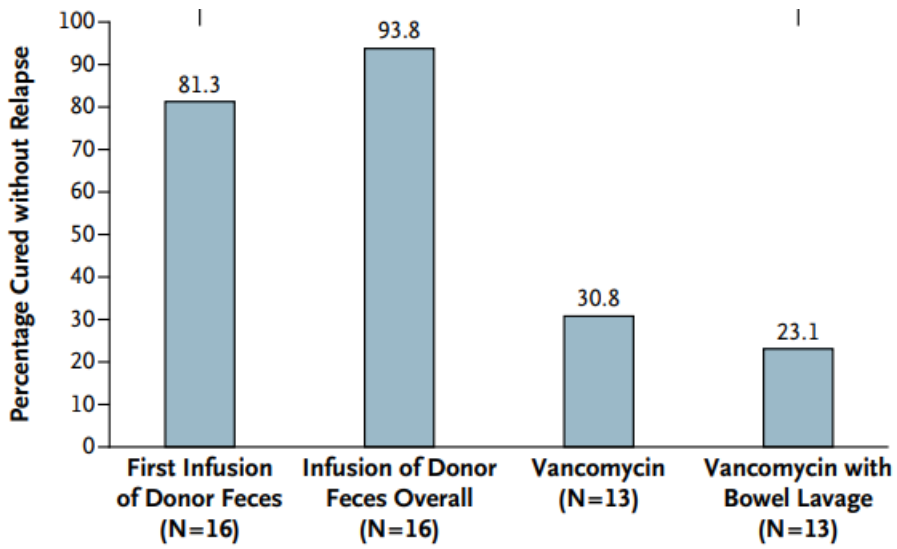
Therapeutic Forerunner: Faecal Microbiota Transplantation (FMT)

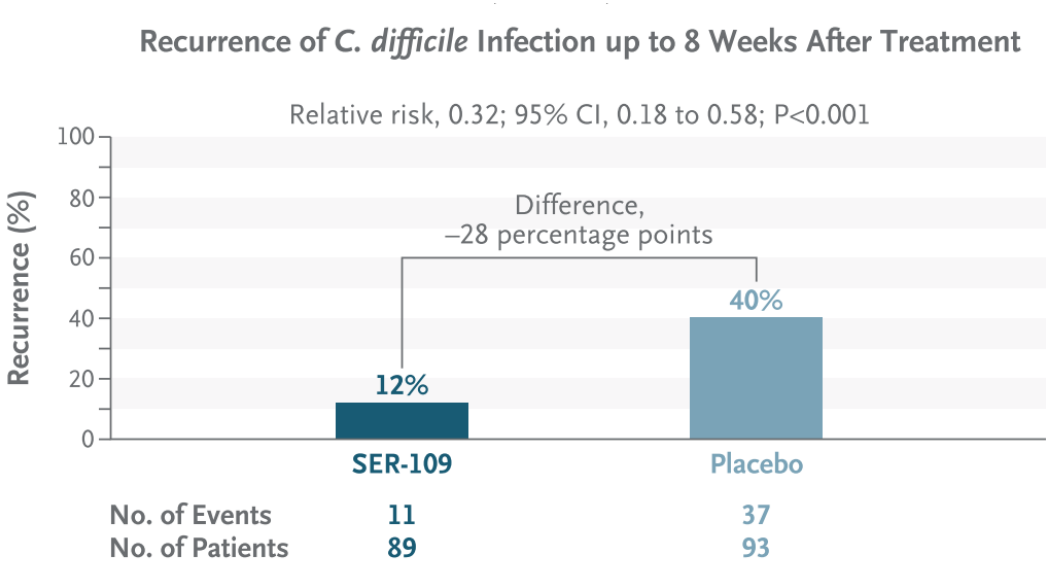
- Resets dysbiotic microbiome eg after antibiotic treatment

Yellow Soup
Li Shizhen李時珍
1518-1593

Faecal Transplant
Eiseman et al
1958

FMT/donor-derived products in recurrent *C. difficile* infection





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection

Broader use of FMT/donor-derived products

- FMT efficacious in a wide range of conditions including IBD, IBS, cancer immunotherapy, autism and GvHD
  - Mostly dysbiotic conditions
- Challenges
  - Infection risk
  - Reproducibility (super donor effect)
  - Non-dysbiotic/endotype conditions
  - Supply of donor material
    - especially “special donors”
  - Unregulated use

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- Challenges
  - Infection risk
  - Reproducibility (super donor effect)
  - Non-dysbiotic/endotype conditions
  - Supply of donor material
    - especially “special donors”
  - Unregulated use

Silicon gloves “if you are squeamish”
A big-brown towel or bath

Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

June 13, 2019

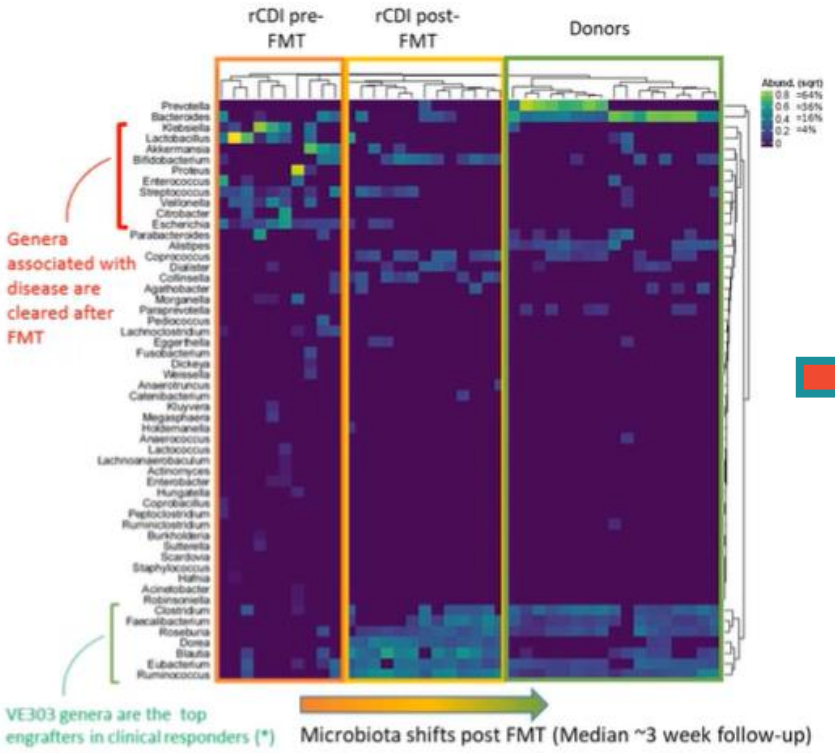
Content current as of:

frontiers in Cellular and Infection Microbiology

REVIEW
published: 21 January 2019
doi: 10.3389/fcimb.2019.00002

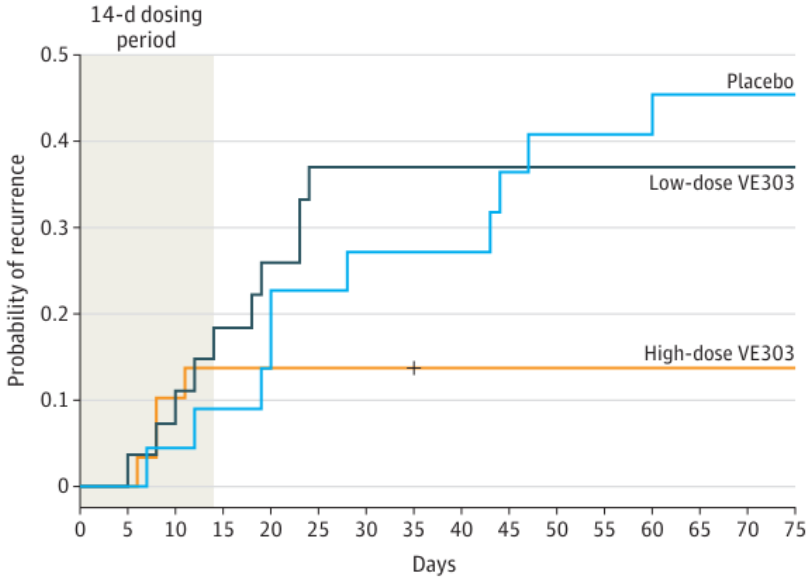
The Super-Donor Phenomenon in Fecal Microbiota Transplantation

Defined consortia offer a more “pharmaceutical-like” alternative



VEDANTA BIOSCIENCES

VE303
Defined 8 strain consortium



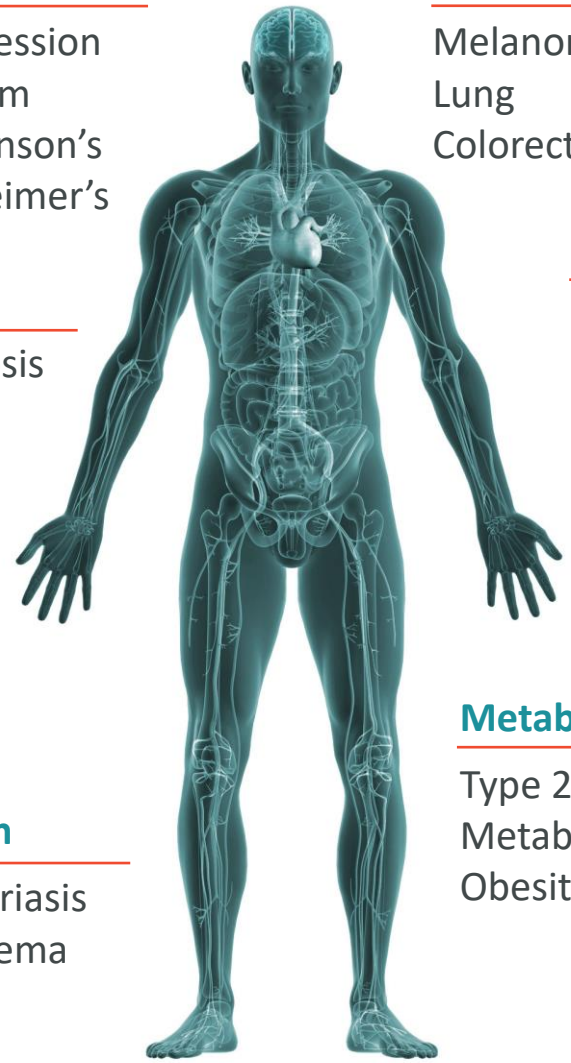
JAMA | Preliminary Communication

VE303, a Defined Bacterial Consortium, for Prevention of Recurrent *Clostridioides difficile* Infection
A Randomized Clinical Trial

Microbiome Progressing Towards Defined Live Therapeutics

- Recognised driver of health and disease, key role in drug response
- Emerging therapeutic interventions in many diseases
- Clinical validation
  - 3 donor-derived live bacterial product are licensed for *C. difficile*
  - FMT studies show efficacy in ulcerative colitis, IBS, immuno-oncology, autism and GvHD
  - Positive Phase 2 data with oral defined products in ulcerative colitis, immuno-oncology, psoriasis and *C. difficile*
  - Several oral defined live bacterial products shown to consistently colonise gut in clinic

Poised to become a new modality



CNS
Depression
Autism
Parkinson's
Alzheimer's

Oncology
Melanoma
Lung
Colorectal

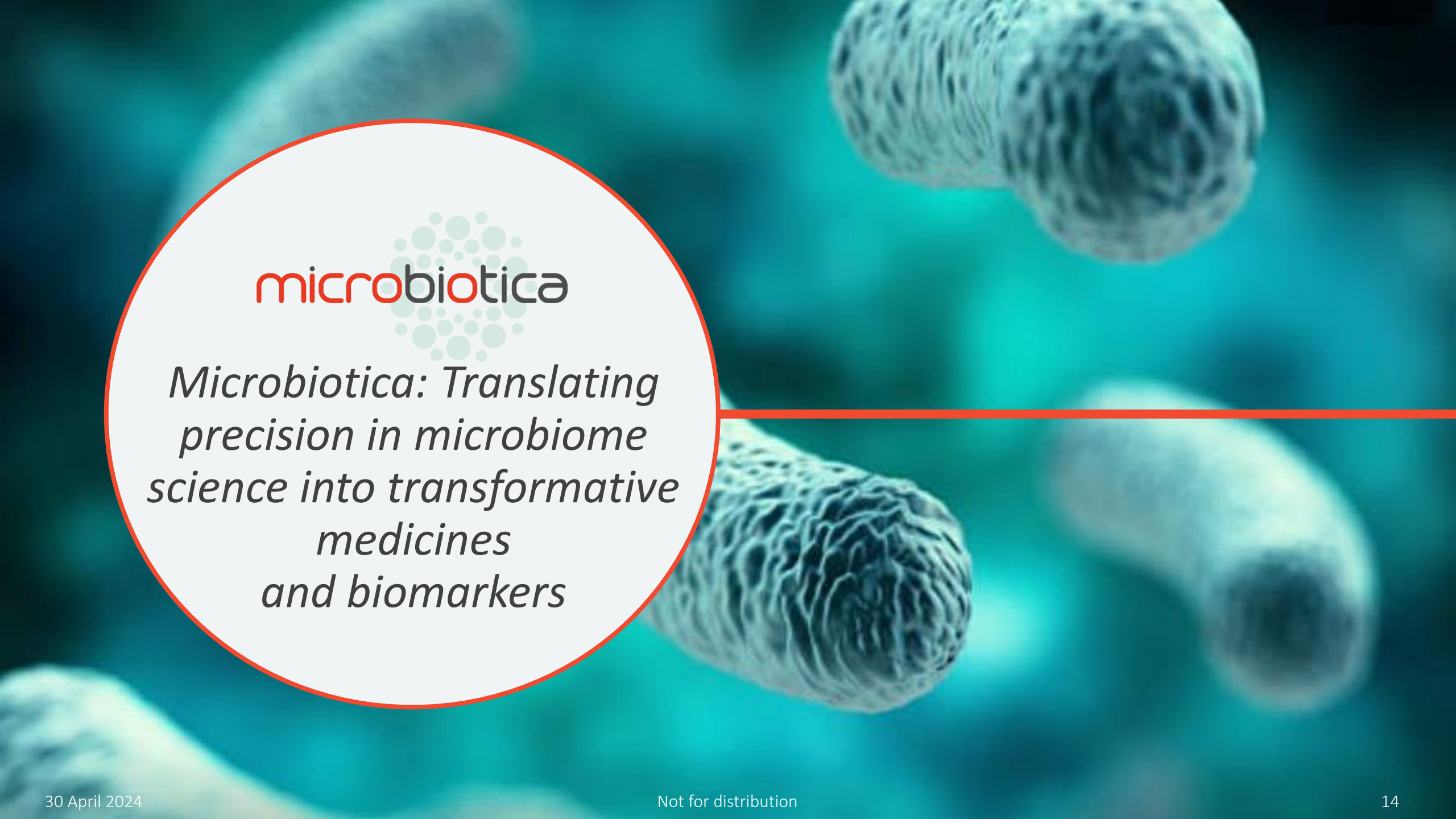
Hepatic
Liver cirrhosis
NASH

Autoimmunity
Asthma
Lupus
Multiple sclerosis
Type 1 Diabetes
Food Allergy

GI
Infection
IBD
IBS
Coeliac

Metabolic
Type 2 Diabetes
Metabolic syndrome
Obesity

Skin
Psoriasis
Eczema


microbiotica
Microbiotica: Translating precision in microbiome science into transformative medicines and biomarkers

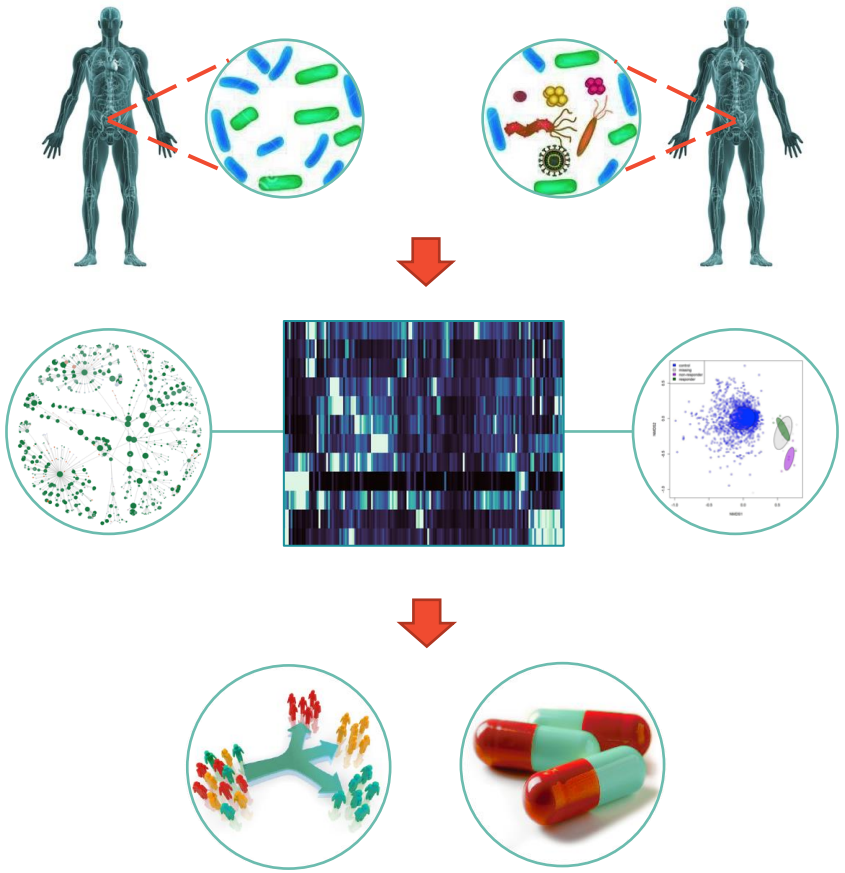
Rationale for Clinic-First Discovery in the Microbiome Field

Human-microbiome interactions

Known mechanisms by which the microbiome impacts human homeostasis and diseases

Unknown mechanisms by which the microbiome impacts human homeostasis and diseases

Microbiotica Links Bacteria to Clinical Outcome for Discovery of Medicines, Biomarkers and Targets



Best in class microbiome profiling

Bacterial composition determined in large patient groups with unparalleled comprehensiveness and precision

Identifying signature linked to phenotype

Leading bioinformatic tools identify microbiome signatures linked to different patient outcomes missed by other groups

Biomarker, Target and Therapeutic candidates

Microbiome signatures stratify patients for personalised drug treatment and identify Live Bacterial Therapeutics and drug targets for testing in defined patient groups

Underpinned by unprecedented precision in microbiome clinical analysis

Underpinned by Leading Science

microbiotica

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Targeted Restoration of the Intestinal Microbiota with a Simple, Defined Bacteriotherapy Resolves Relapsing *Clostridium difficile* Disease in Mice

RESOURCE

https://doi.org/10.1038/s41587-018-0009-7

nature biotechnology

OPEN

A human gut bacterial genome and culture collection for improved metagenomic analyses

Peggy Lillis Foundation

Fighting C. diff through Education and Advocacy

Innovator Award: Dr. Trevor Lawley

nature

International journal of science

OPEN

https://doi.org/10.1038/s41586-019-0965-1

A new genomic blueprint of the human gut microbiota

Alexandre Almeida[1,2*], Alex L. Mitchell[1], Miguel Boland[1], Samuel C. Forster[2,3,4], Gregory B. Gloor[5], Aleksandra Tarkowska[1], Trevor D. Lawley[2] & Robert D. Finn[1*]

nature

International journal of science

OPEN

doi:10.1038/nature17645

Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation

The Economist

Treating disease with microbes

Bugs in the system

Bacterial medicine is starting to emerge

Nov 3rd 2012 | From the print edition

nature

International journal of science

https://doi.org/10.1038/s41586-019-1560-1

Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth

Yan Shao[1], Samuel C. Forster[1,2,3], Evdokia Tsaliki[4], Kevin Vervier[1], Angela Strang[4], Nandi Simpson[4], Nitin Kumar[1], Mark D. Stares[1], Alison Rodger[4], Peter Brocklehurst[5], Nigel Field[4*] & Trevor D. Lawley[1*]

wellcome sanger institute

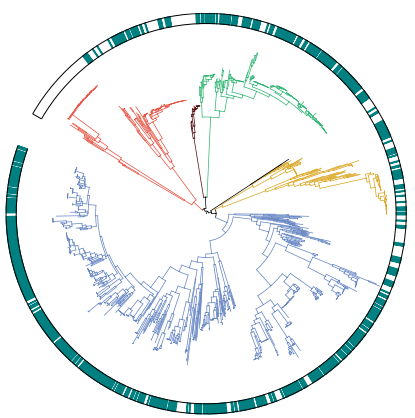
Cell

Massive expansion of human gut bacteriophage diversity

Luis F. Camarillo-Guerrero,
Alexandre Almeida,
Guillermo Rangel-Pineros, Robert D. Finn,
Trevor D. Lawley

World Leading Microbiome Discovery Platform

- First comprehensive bacterial isolation from patients: **Personalised Bacterial Bank**
- **Microbiotica Culture Collection** (100,000s of strains)
  - Library of potential therapeutics
- **Microbiotica Reference Genome Database**
  - Identifies previously unknown microbiome “dark matter”
  - Essential for high precision bacterial ID in patients
  - Dwarfs the others and is growing rapidly to maintain a lead
- **Microbiotica Analytics** – leading Bioinformatics and ML tools



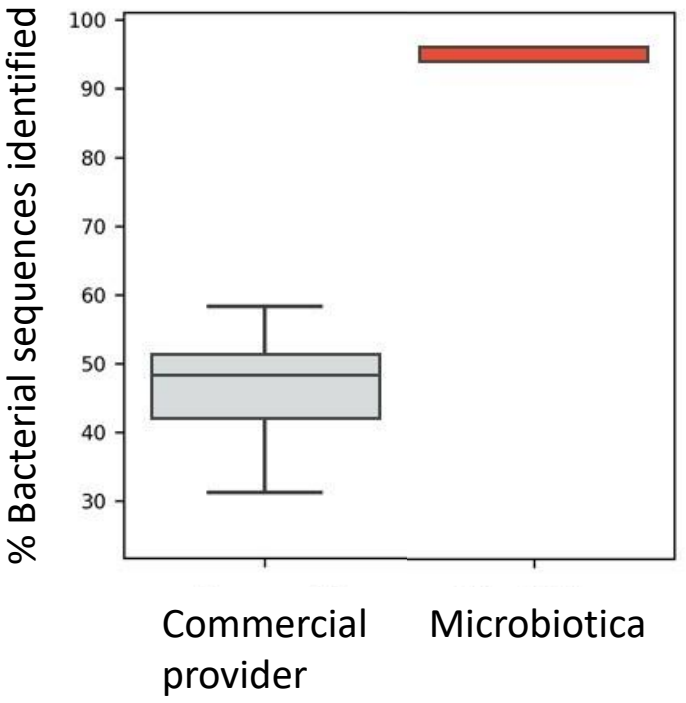
Microbiotica Reference Genome Database

Microbiotica Culture Collection

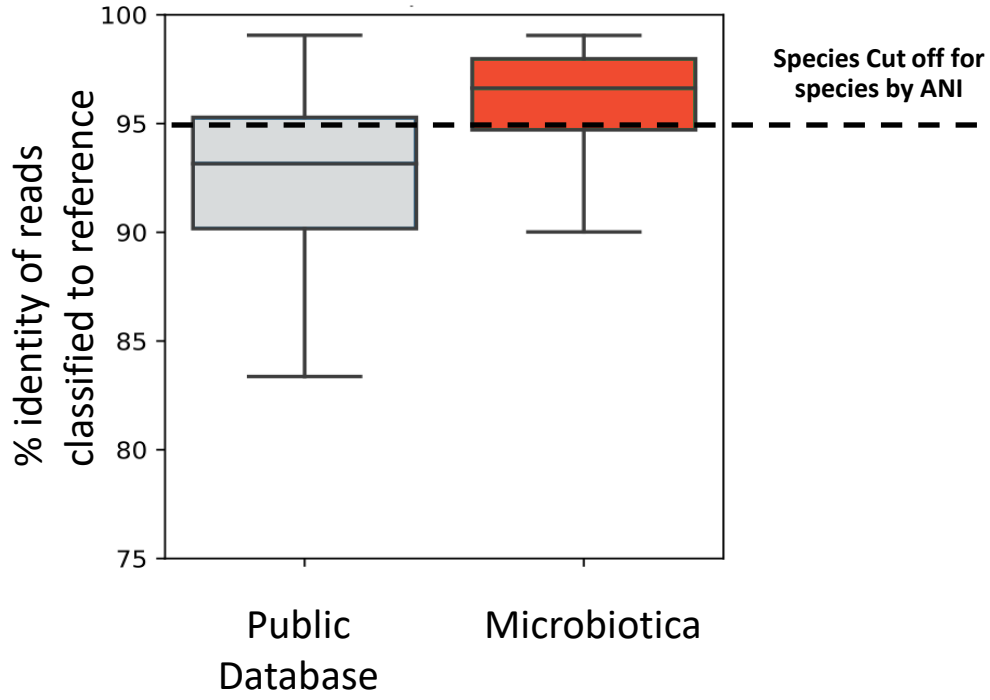
A unique asset: “global microbiome blueprint”

Microbiotica Platform Enables Precise Bacterial Identification

Comprehensive Profiling



Accuracy of Profiling

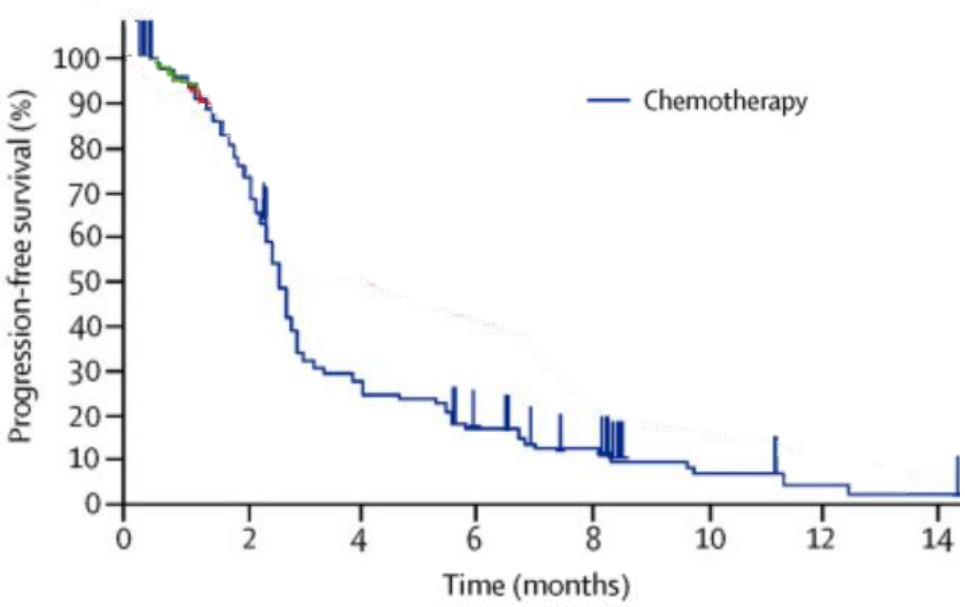


Benchmark comparison with Ulcerative Colitis FMT study Microbiotica dataset

Immuno-Oncology Program

Advanced Melanoma

- 91% of melanoma patients survive 5 years
- Chemotherapy not very effective, so surgery was (and still is) primary treatment
- Locally advanced and malignant melanoma had a very poor prognosis

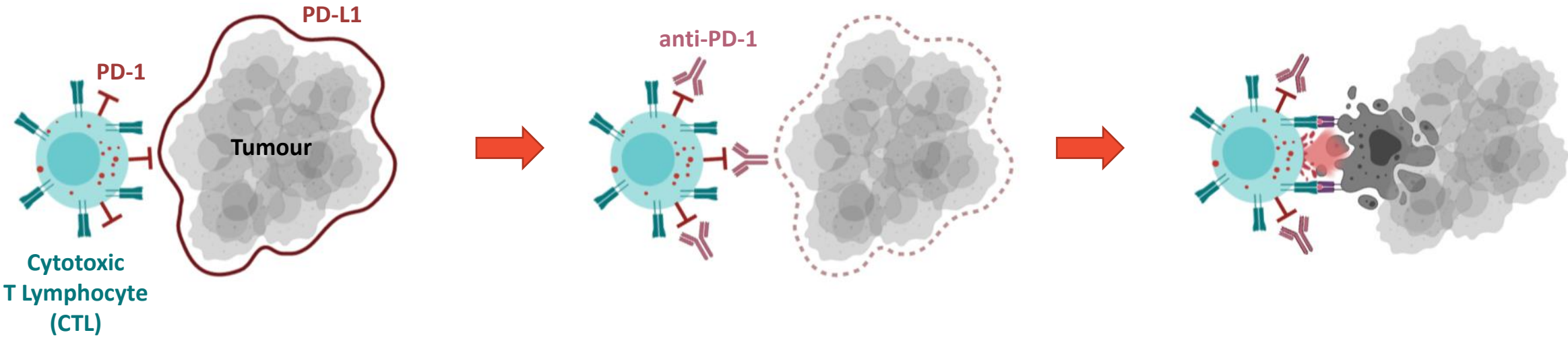


KEYNOTE-002

Ribas et al *Lancet Oncol.* (2015) **16**:908

Immune Checkpoint Inhibitors Transformative, but Response Rates Need to be Improved

- Melanoma typically carries many mutations, so looks foreign to the immune system
- ICIs have revolutionised treatment of multiple cancers including melanoma



Immune Checkpoint Inhibitors Transformative, but Response Rates Need to be Improved

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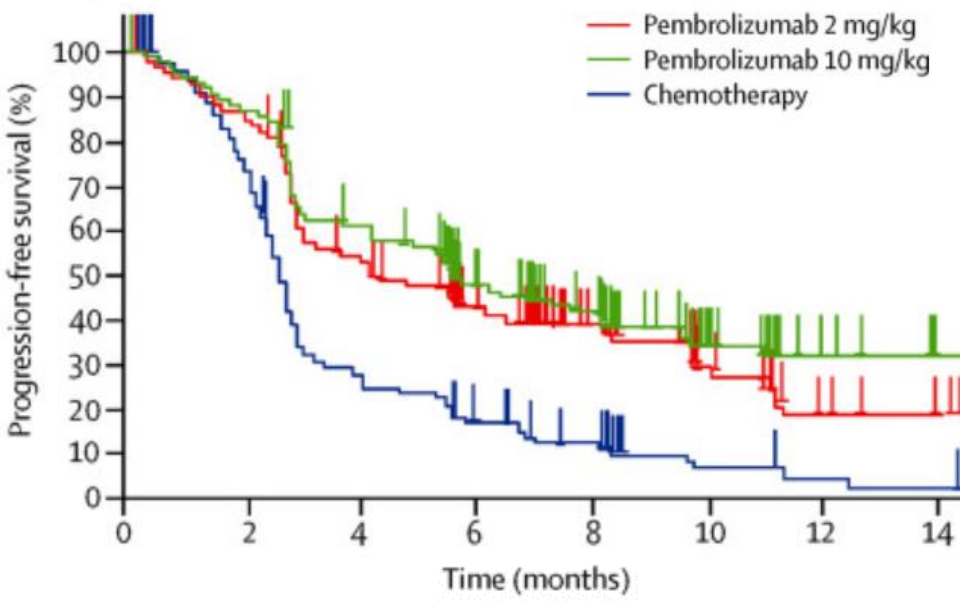

KEYNOTE-002

Ribas et al *Lancet Oncol.* (2015) **16**:908

Immune Checkpoint Inhibitors Transformative, but Response Rates Need to be Improved

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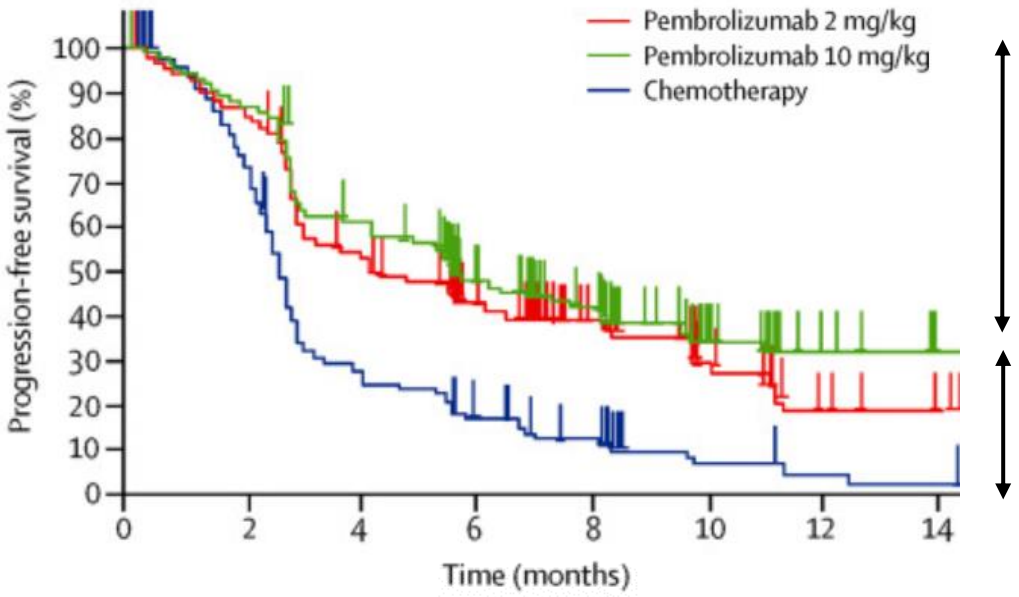
- ICIs have revolutionised treatment of multiple cancers including melanoma
- Long term survival 40-50% in advanced melanoma, lower in other indications
- Major need for a co-therapy that increases the response rates of ICIs



Non-responders

Responders

KEYNOTE-002

Ribas et al *Lancet Oncol.* (2015) **16**:908

Gut Microbiome is Associated with Response to anti-PD1 Therapy

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]

Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients[1]

Arthur E. Frankel*, Laura A. Coughlin†, Jiwoong Kim‡, Thomas W. Froehlich*, Yang Xie‡, Eugene P. Frenkel* and Andrew Y. Koh†,§

*Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX; †Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; ‡Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX; §Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX

CANCER IMMUNOTHERAPY

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

Vyara Matson,[1*] Jessica Fessler,[1*] Riyue Bao,[2,3*] Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4†]

CANCER IMMUNOTHERAPY

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

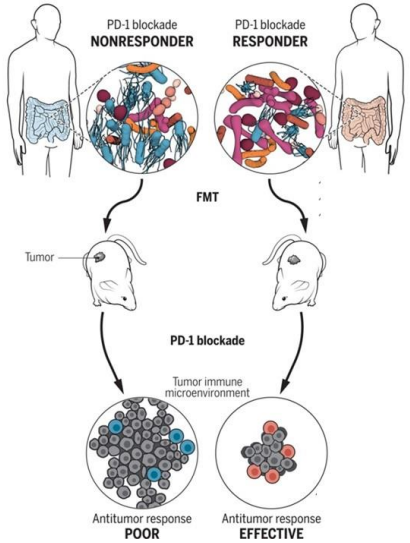
V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Reuben,[1] M. C. Andrews,[1]

Role of Microbiome in Immune Checkpoint Inhibitor Efficacy

- Multiple groups shown response to ICI linked to microbiome
- Causation established by human to mouse FMT and antibiotics reduce ICI efficacy
- Early data from FMT trial suggests modulating the microbiome can make patients responsive to ICIs

Causation from human to mouse FMT

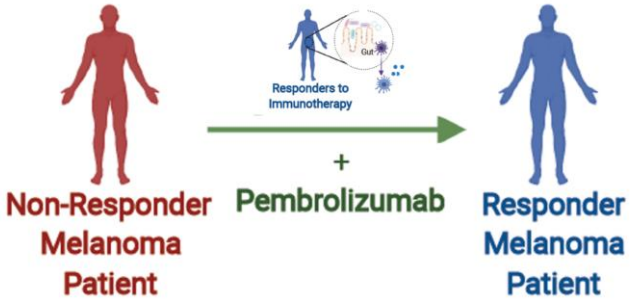
Response in mouse models transferred by FMT from responding patients



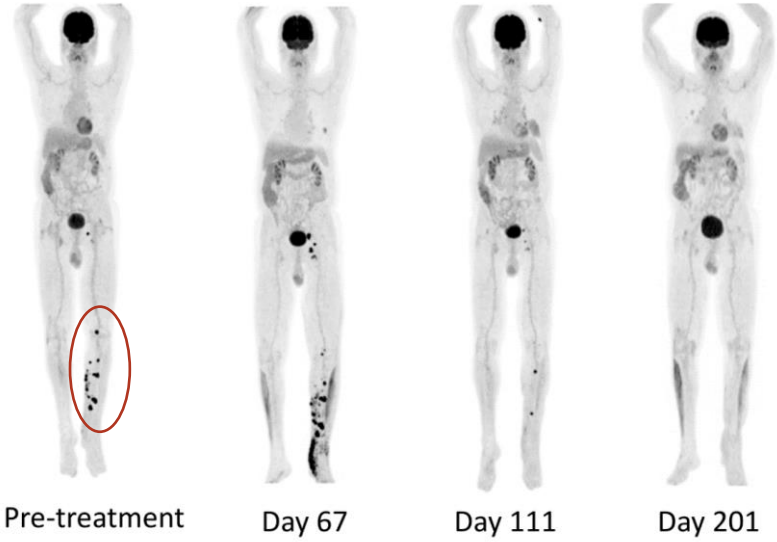
Science (2018) **359**:91, 97 & 104

FMT modulates ICI response in melanoma

FMT from responders made some patients that had progressed on anti-PD1 therapy responsive

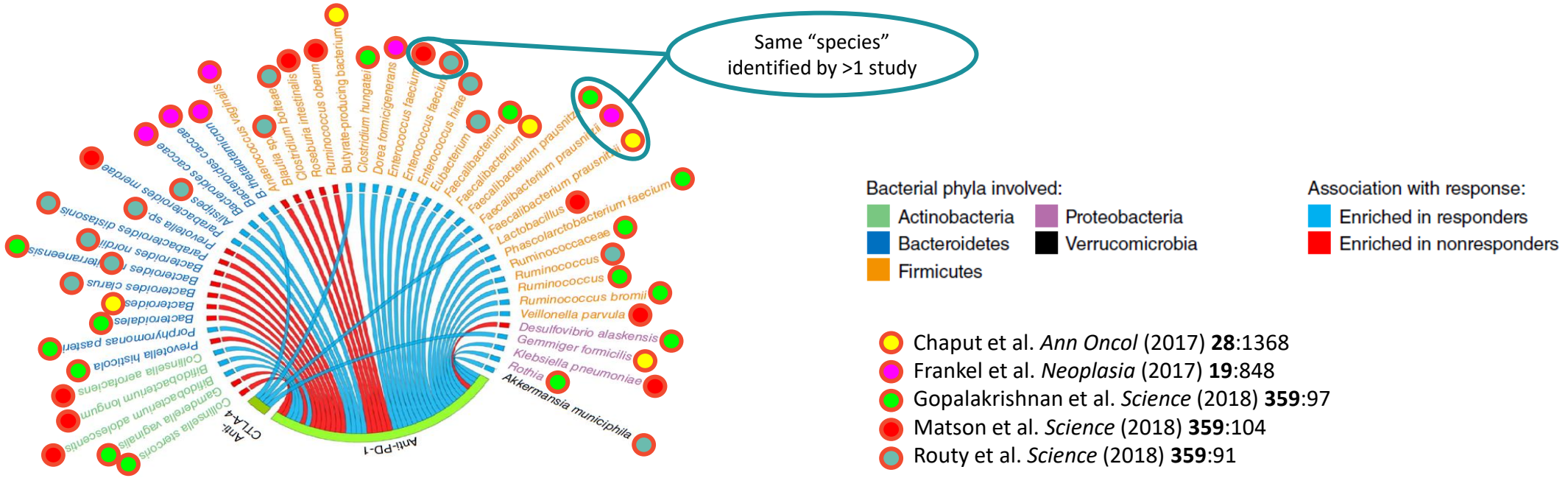


Baruch et al *Science* (2021) **371**:602
Davar et al *Science* (2021) **371**:595



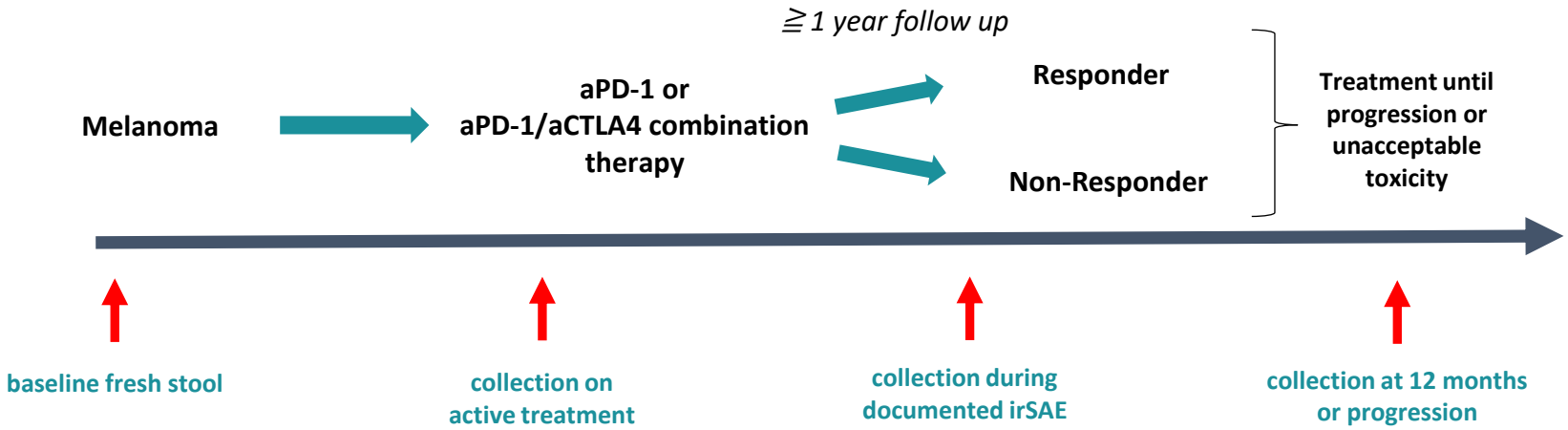
ICI Response:
Completely Different Bacteria Identified by Different Groups

- Five published clinical microbiome studies on checkpoint inhibitor response report different species associated with response
- Combined analysis of the public datasets also fails to identify a signal consistent across studies (eg Gharaibeh et al 2019)
- Conflicting signatures have been a major challenge in the field



Adapted from Helmink et al *Nat Med* (2019) **25**:377

MELRESIST: Novel Melanoma/Microbiome Study



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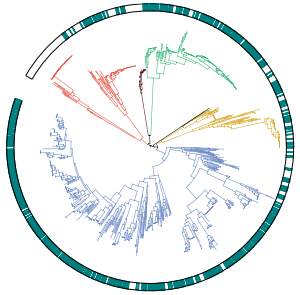
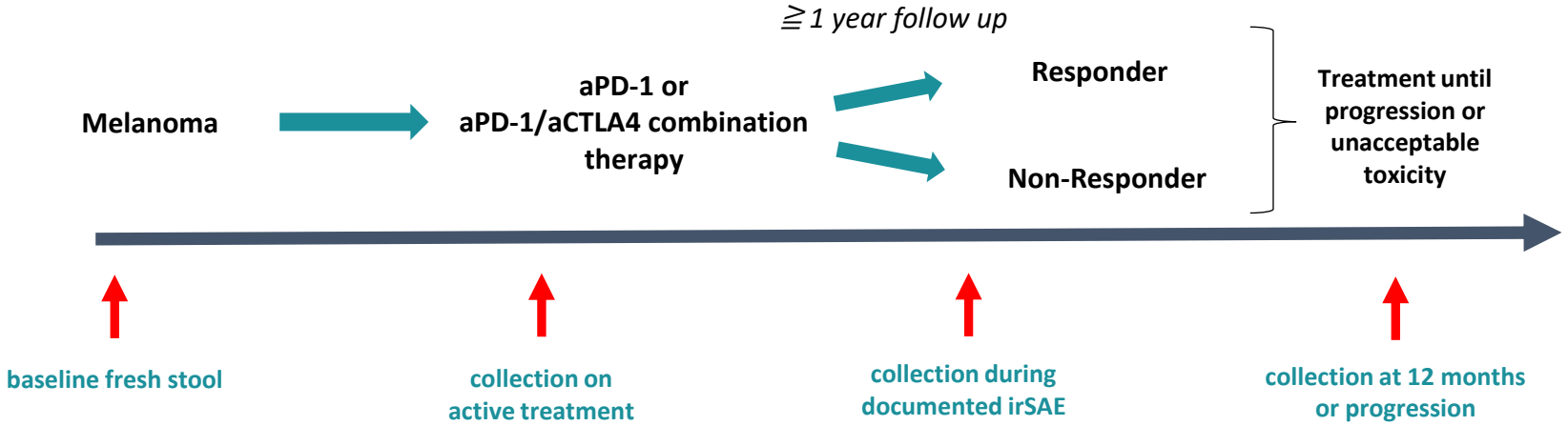
- The best standards in microbiome sample collection and storage
- Largest number of patient (69)
- Longitudinal sampling
- Detailed clinical metadata

Microbiotica's platform

- Microbiotica's Reference Genome Database
- Precise and comprehensive microbiome analysis



MELRESIST: Novel Melanoma/Microbiome Study



Cambridge University Hospitals
NHS Foundation Trust

CANCER IMMUNOTHERAPY

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

V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Reuben,[1] M. C. Andrews,[1]

CANCER IMMUNOTHERAPY

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

Vyara Matson,[1*] Jessica Fessler,[1*] Riyue Bao,[2,3*] Tara Chongsuwat,[4] Yuanyuan Zha,[4]

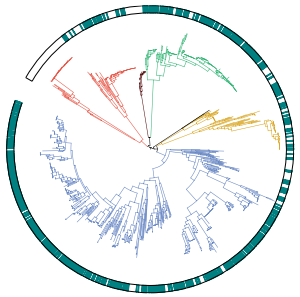
Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients[1]

Arthur E. Frankel*, Laura A. Coughlin†, Jiwoong Kim‡, Thomas W. Froehlich*, Yang Xie‡, Eugene P. Frenkel* and Andrew Y. Koh†,§

*Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX; †Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; ‡Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX; §Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX

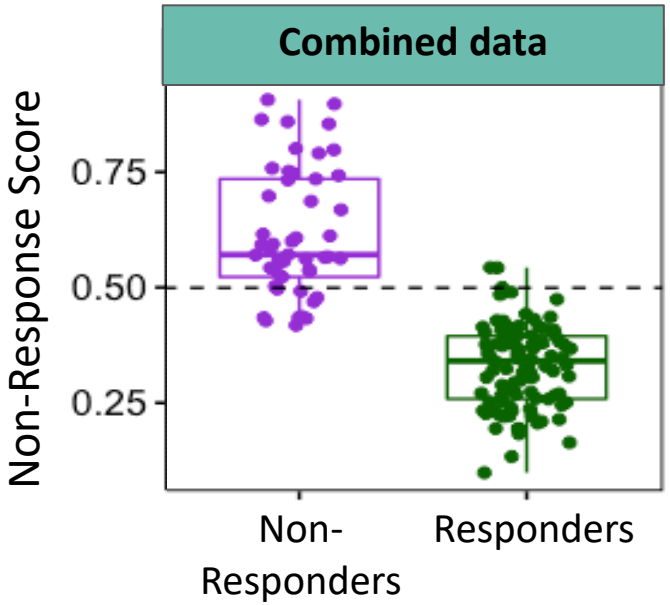
Microbiotica's platform

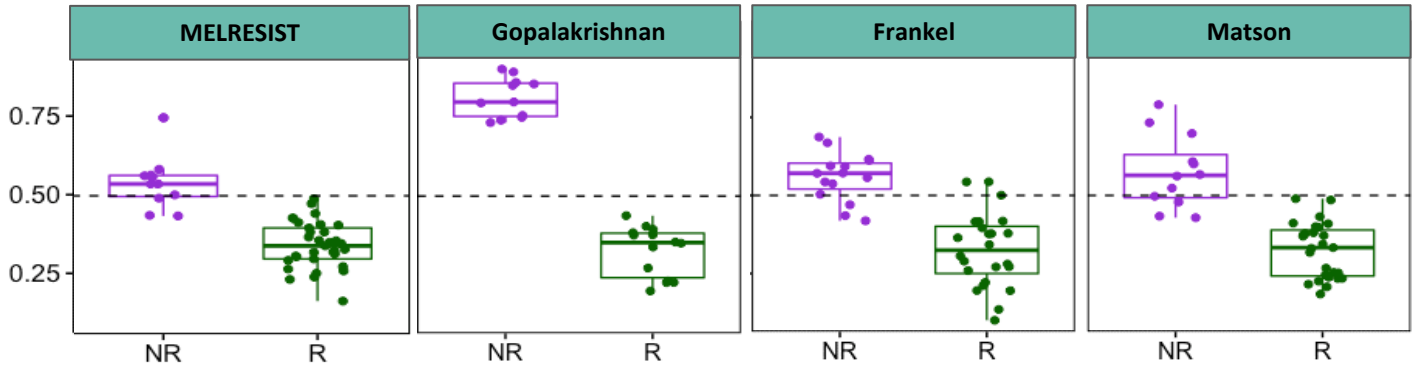
- Microbiotica's Reference Genome Database
- Precise and comprehensive microbiome analysis



Microbiome Signature Predictive Across Multiple Studies

- Common signal across all of 4 melanoma datasets that predicts response with 91% accuracy
- Microbiome signature is basis for development of biomarker and Live Bacterial Therapeutic

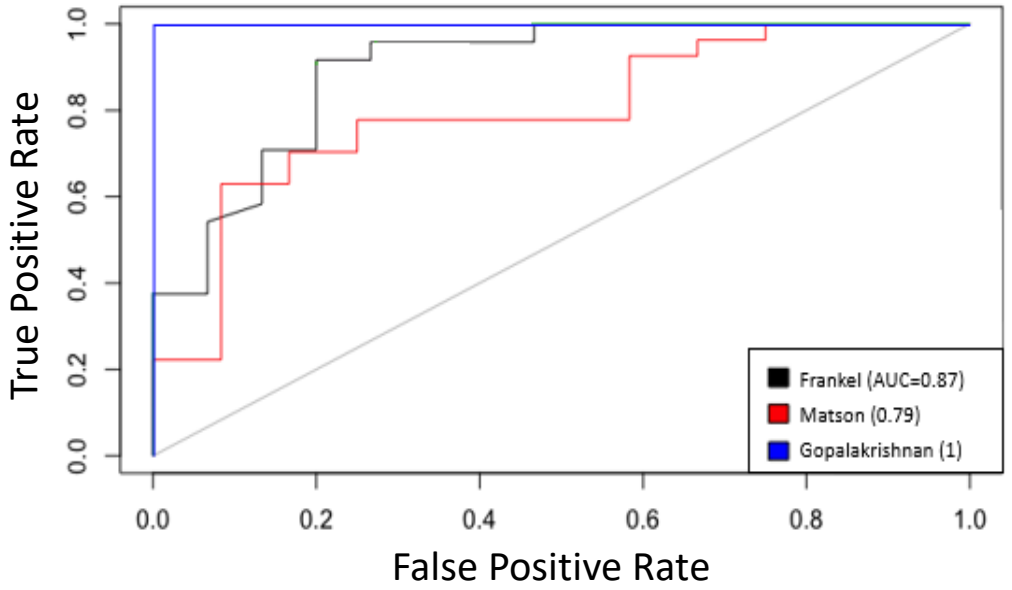




Validation of Predictive Biomarker of I-O response

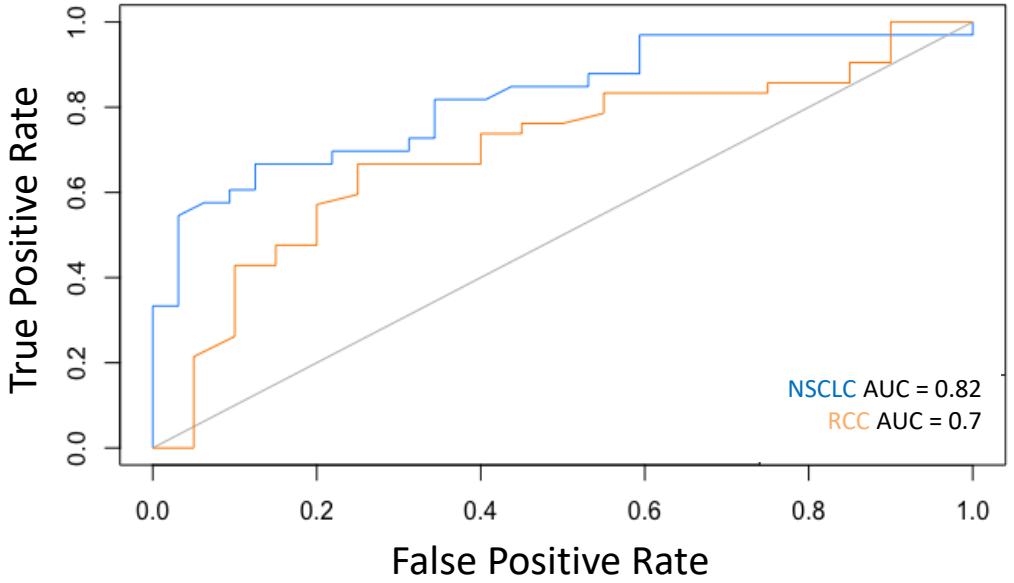
Melanoma

- Cross-validation of model by training on 3 cohorts and testing on 4th
- Prediction of response in independent cohorts validates the bioinformatic model



Other Indications

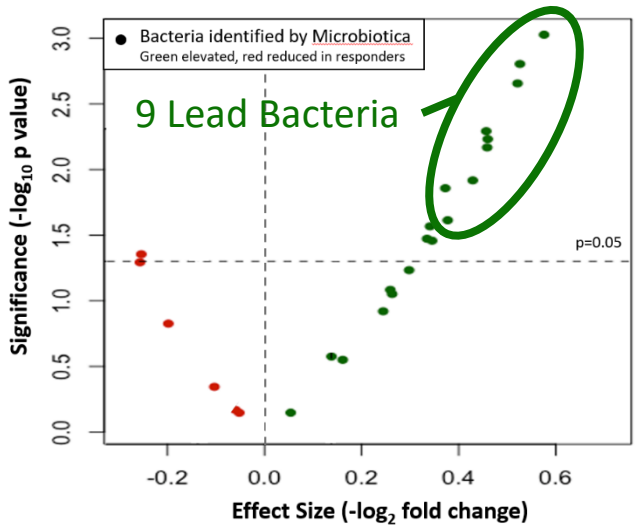
- Melanoma signature predictive in lung cancer (NSCLC)
- Less predictive in Renal Cancer (RCC)



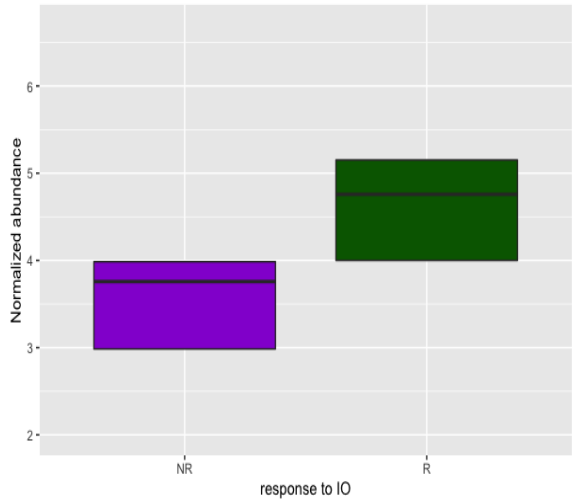
MB097: Candidate Consortium of Nine Bacteria Drives Response

- Top bacteria associated with response were all elevated in responders
  - This indicates the microbiome drive comes primarily from bacteria that have a positive impact on outcome as opposed to bacteria that inhibit response
- Nine lead bacteria identified, as a small defined consortium predictive of response in melanoma

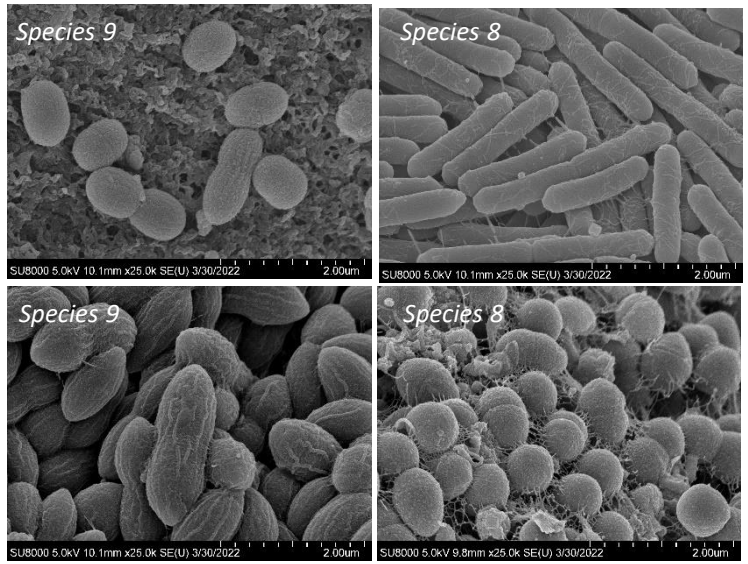
Lead candidates most associated with response in combined melanoma datasets



Association with response of the combined 9 species



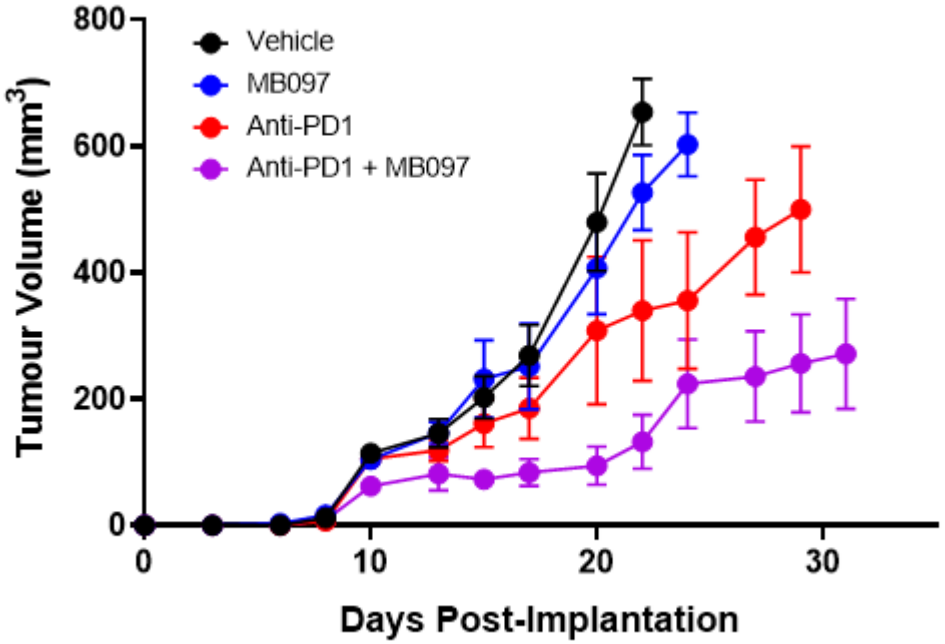
Four Novel Species



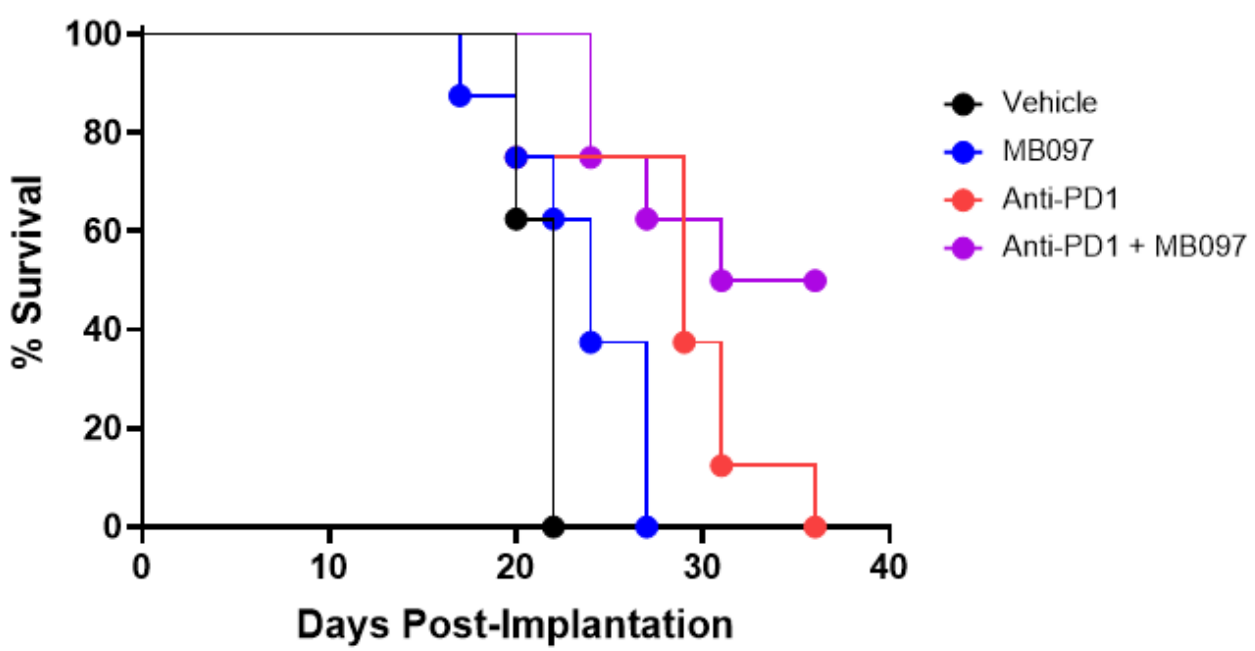
MB097 Synergises with Anti-PD1 in Syngeneic Tumour model

- MB097 synergistic efficacy with anti-PD1 in MCA205 mouse syngeneic tumour model
- Reproducible efficacy as monotherapy in same model following melanoma patient FMT

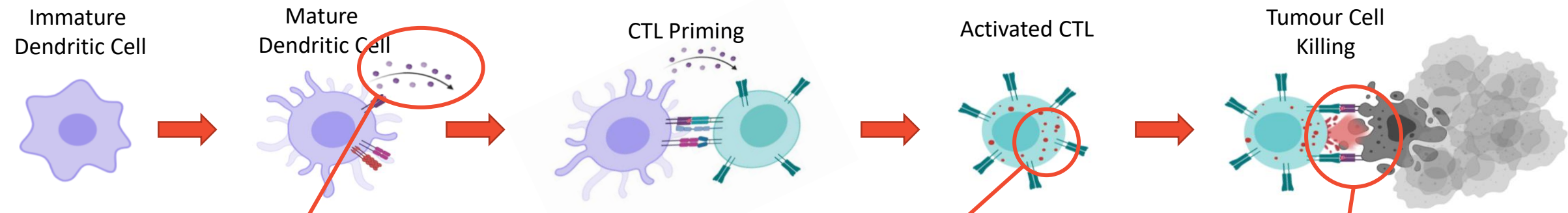
Tumour Volume

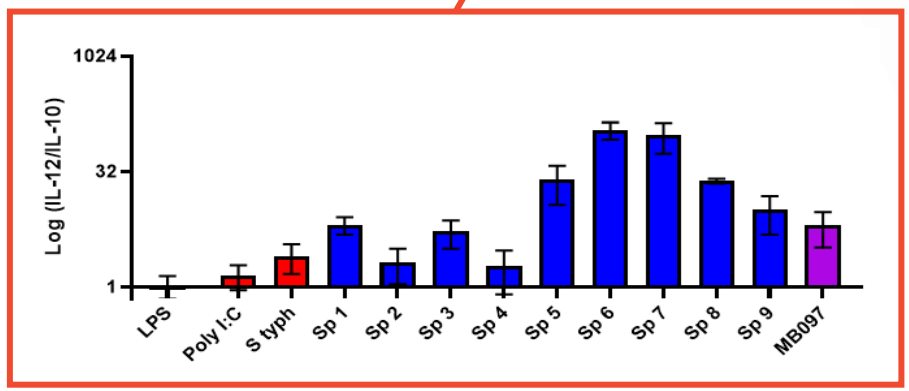


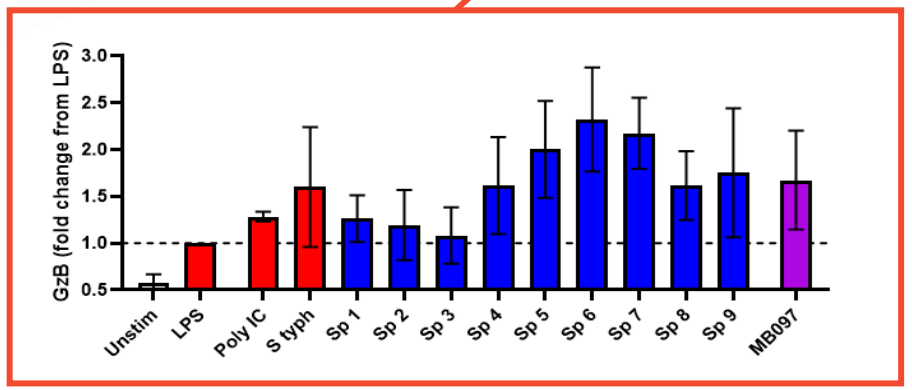
Survival

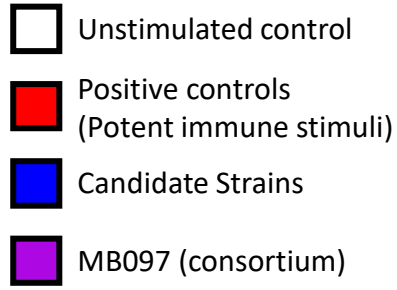


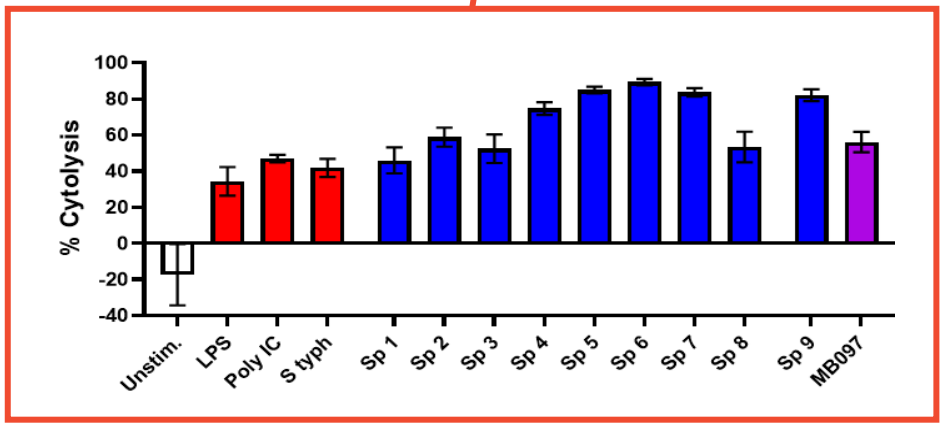
MB097 Bacteria Stimulate Multiple Steps in Tumour Killing





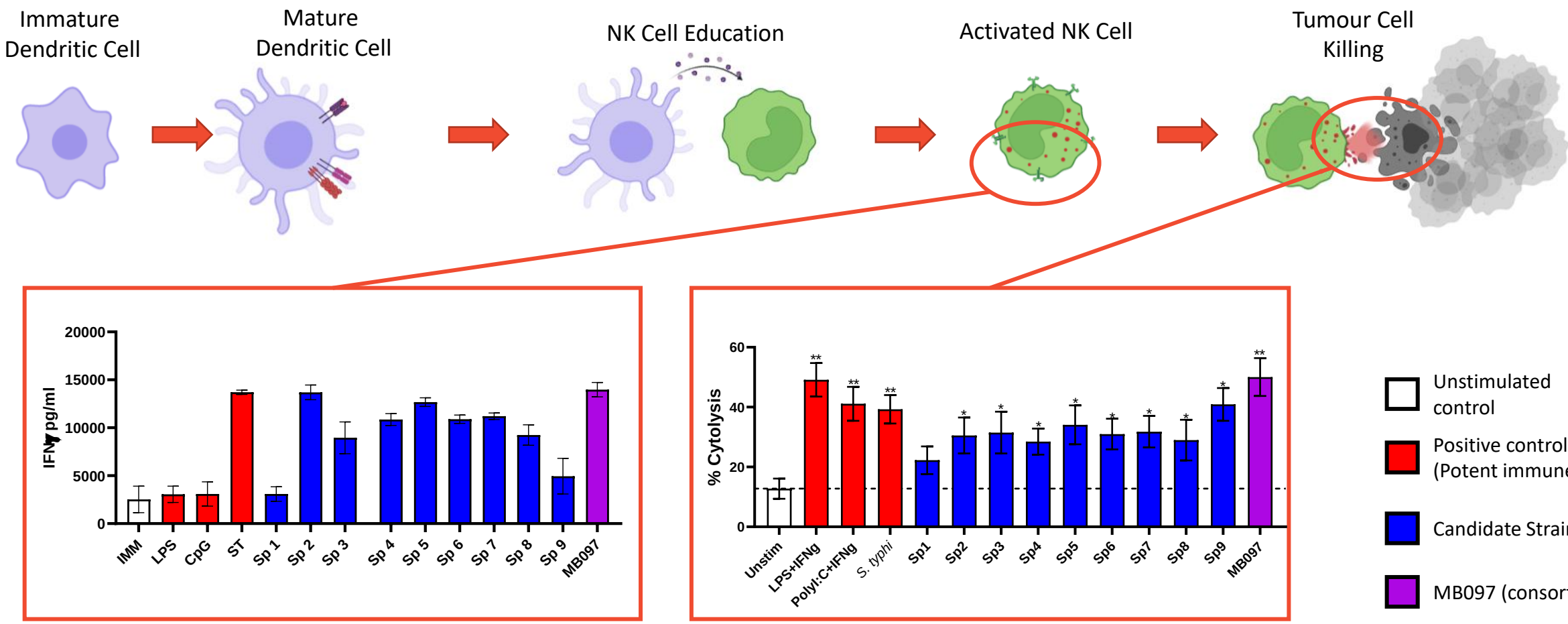






- MB097 and constituent strains tested for effect on all key steps in CTL-mediated tumour killing
- Primary human cell assays used due to poor physiological relevance of cell lines
- Potent stimulation of CTL activation and tumour killing seen

MB097 is a Potent Activator of NK Cells



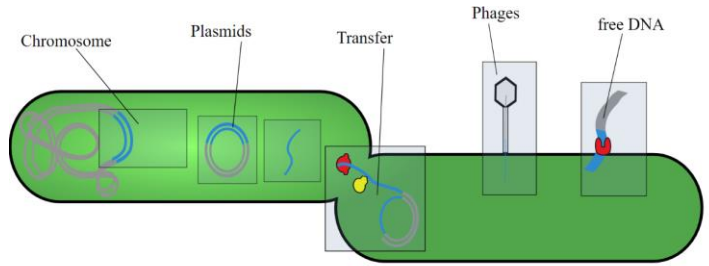
MB097 triggers NK cell activation and tumour cell killing

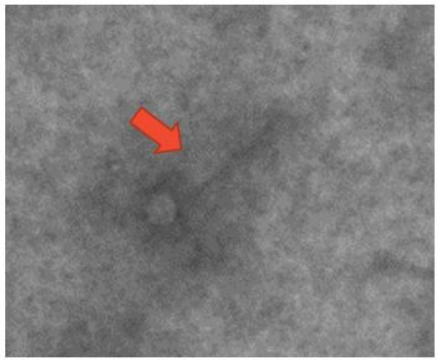
Pre-Clinical Development of MB097

- Safety
  - All strains highly pure (at least 3 rounds of isolation)
  - Good antibiotic resistance profile including 4 antibiotics that will be effective against the whole consortium
  - No antibiotic resistance on mobile elements
  - Low pathogenic potential (no virulence factors or toxins)
  - Profile consistent with a normal prevalent human commensal bacteria
- Developability
  - No detectable bacteriophage
  - Sporulation determined

Species	Moxifloxacin	Meropenem	Ceftriaxone	Clindamycin	Ampicillin	Cefoxitin	Chlor-amphenicol	Amocillin-clavulanate	Metronidazole	Tetracycline
Sp 1	R	S	S	S	S	S	S	S	S	S
Sp 2	S	S	S	S	I	I	S	S	S	S
Sp 3	S	S	S	S	R	S	I	S	S	S
Sp 4	S	S	I	S	I	S	S	S	S	S
Sp 5	S	S	S	S	S	S	S	S	S	S
Sp 6	R	S	S	S	S	S	S	S	S	S
Sp 7	S	S	S	S	R	S	S	S	S	R
Sp 8	S	S	S	S	S	S	S	S	S	S
Sp 9	S	S	S	S	S	S	S	S	S	S

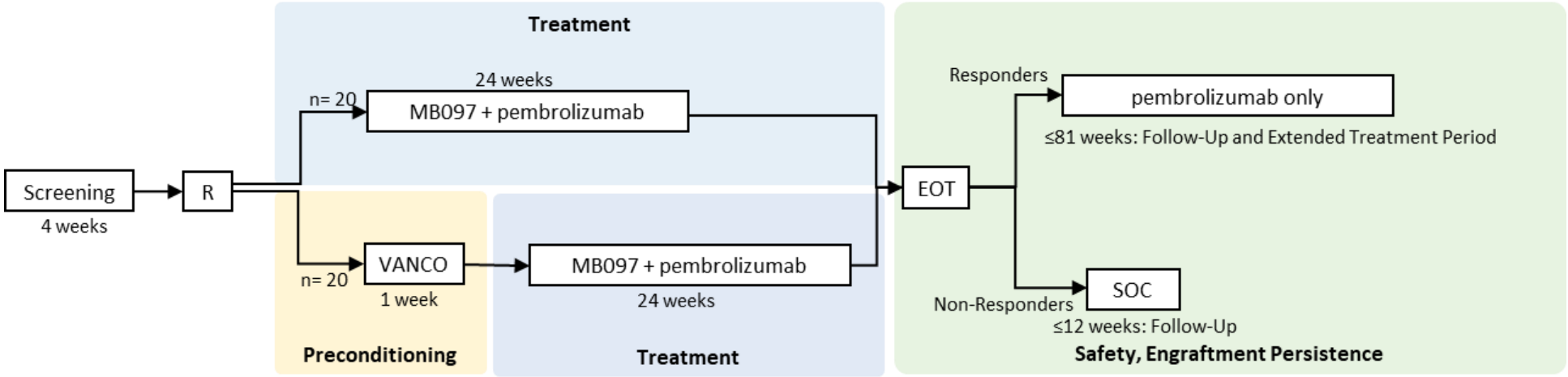
Sensitive
Intermediate
Resistant





All lead strains deemed safe and suitable for development as per guidance and endorsed by MHRA

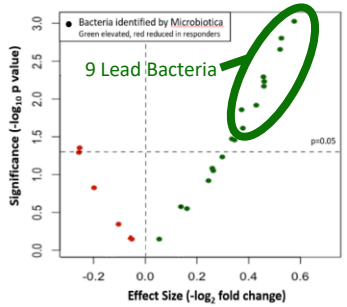
MB097 Development: A clinically-defined LBP



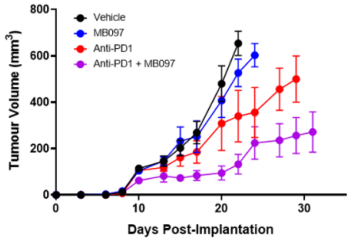
R: Randomization, VANCO: vancomycin oral capsules, EOT: End of Treatment, SOC: Standard of Care

Discovery in 4 advanced melanoma clinical trials

Microbiome signature



Consortium testing



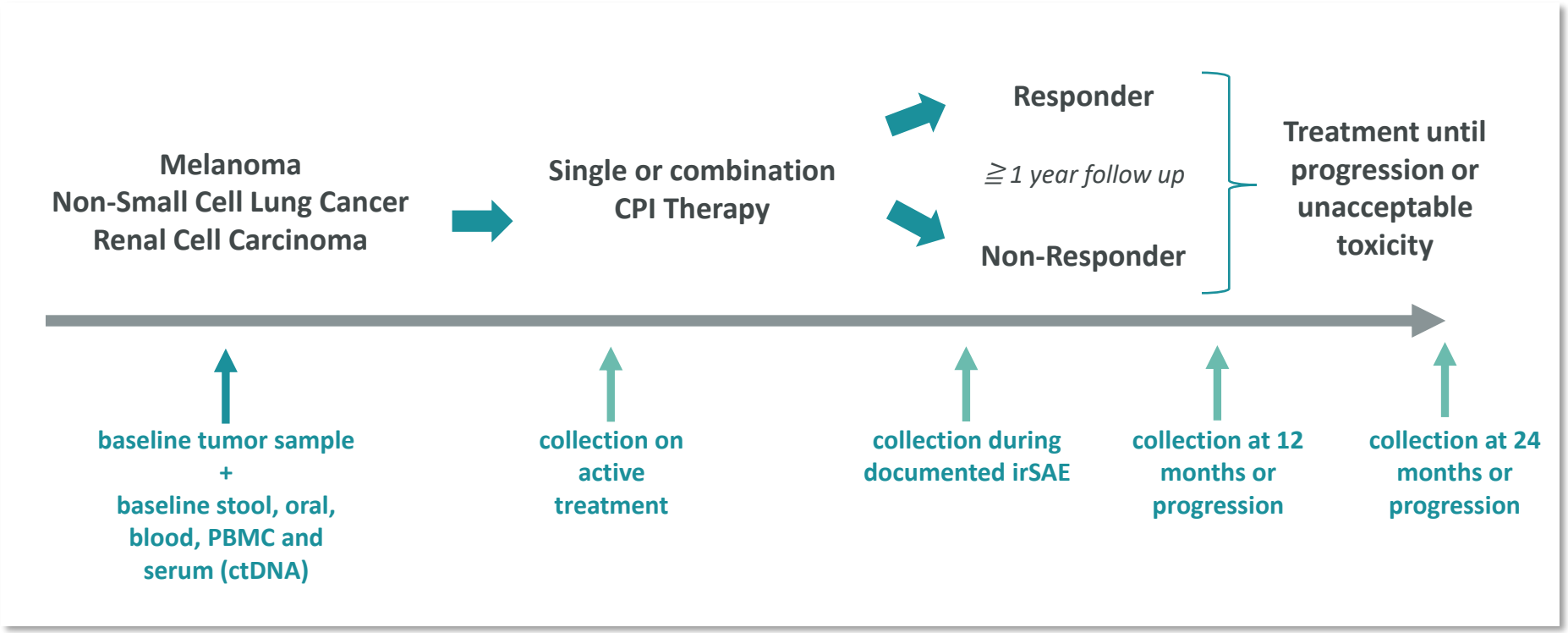
Manufacture

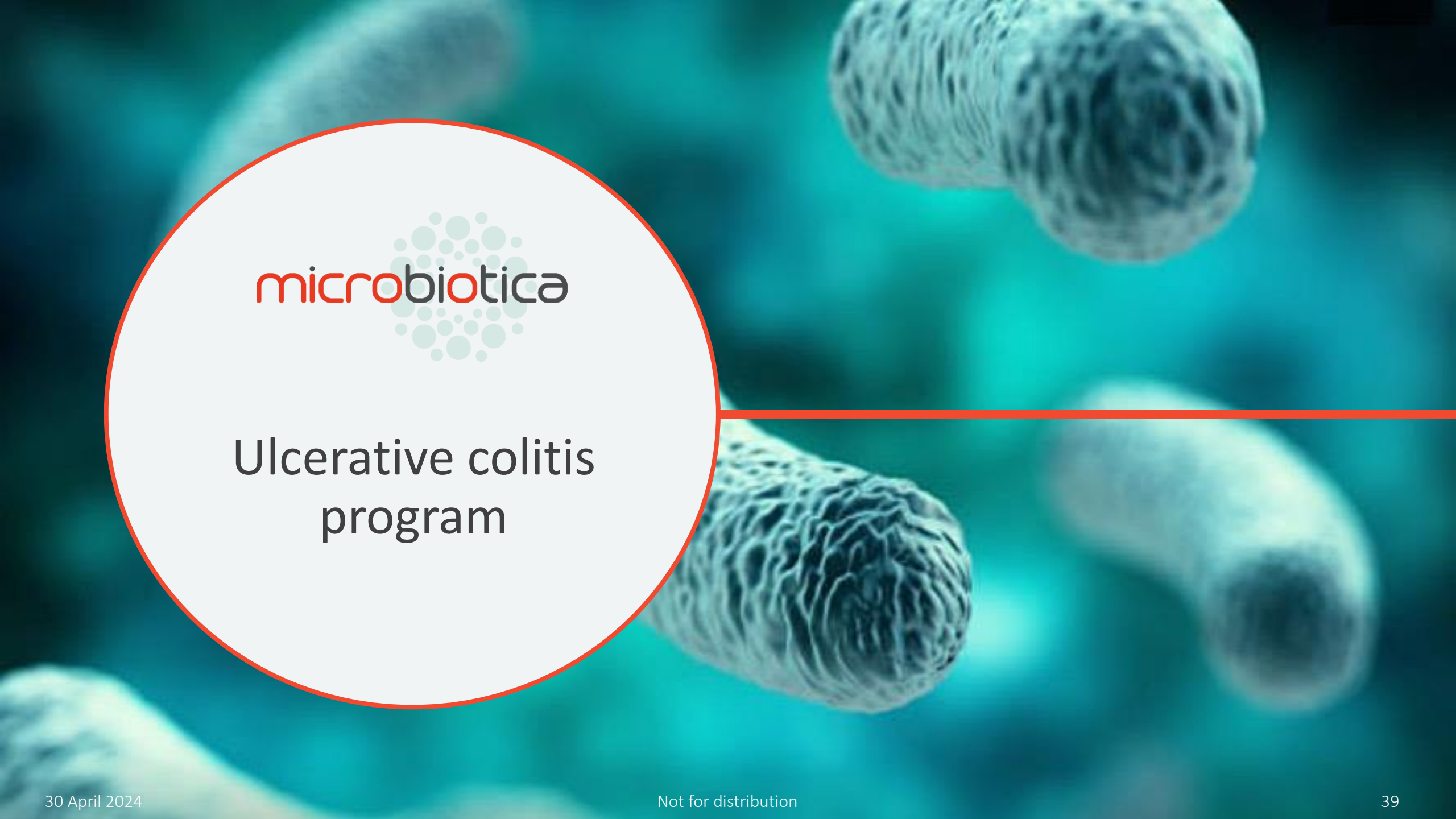
FIH clinical trial in advanced melanoma

MITRE: Landmark Study on Role of the Microbiome in Checkpoint Inhibitor Therapy in Multiple Cancers

- Major collaboration: CRUK and NHS funding
- Up to 1,800 patients receiving CPI
- Enrolment started July 2020 and likely to complete July 2025
- 12 sites open

MITRE: Microbiome Immunotherapy Response Evaluation





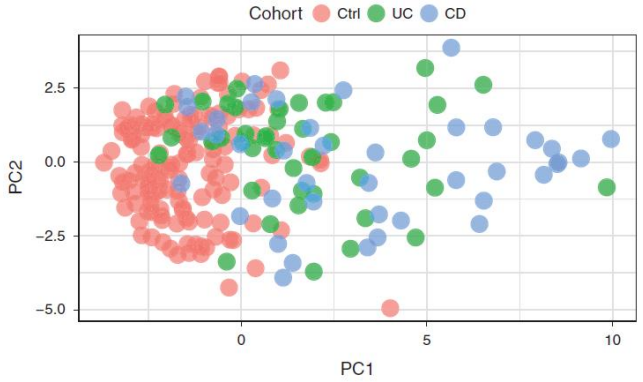
Ulcerative colitis program

Role of Microbiome in Ulcerative Colitis

- IBD is associated with an altered microbiome
- Microbiome in UC linked to clinical severity and drug response
- Human to mouse FMT from IBD patients increases susceptibility to colitis
- FMT induces remission in mild-moderate UC

Dysbiosis associated with UC

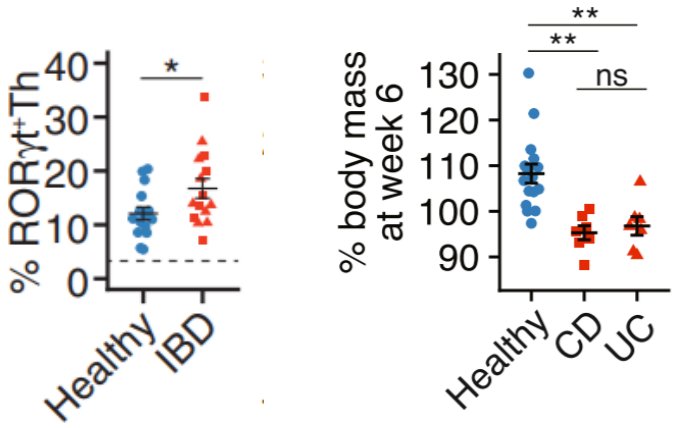
Numerous studies have demonstrated an altered microbiome profile in ulcerative colitis patients



Moustafa et al *Clin Trans Gastro* (2018) **9**:e132

Human to mouse FMT shows causation

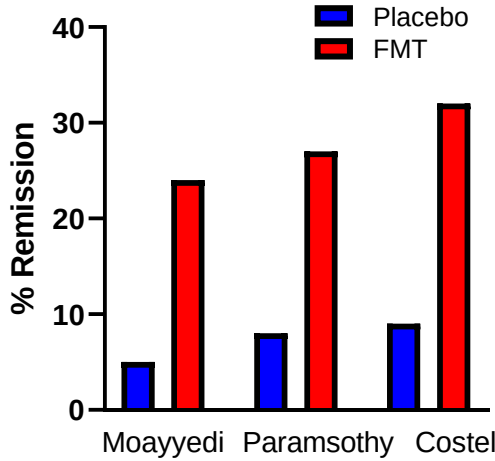
Transfer of IBD patient microbiome into germ-free mice drives increase in pathogenic T cells and confers susceptibility to colitis



Britton et al *Immunity* (2019) **50**:212

FMT has clinical benefit in UC

Correction of dysbiosis in UC by FMT from healthy donors induces clinical remission in multiple independent randomised clinical trials



Paramsothy et al *J Crohns Colitis* (2017) **11**:1180

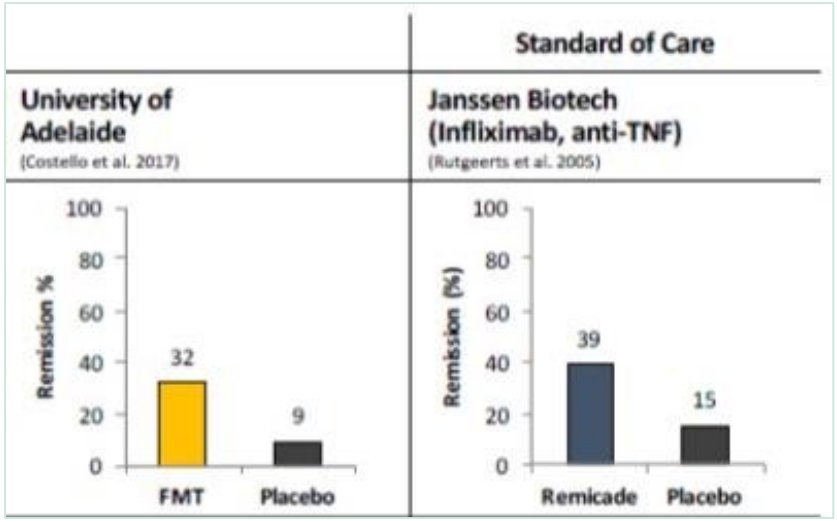
Adelaide Ulcerative Colitis FMT Study

- Randomised placebo controlled trial – patients given FMT by colonoscopy and enema, from healthy donors (active) and autologous (placebo)
- Steroid-free remission assessed at 8 weeks

JAMA | Preliminary Communication

Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis
A Randomized Clinical Trial

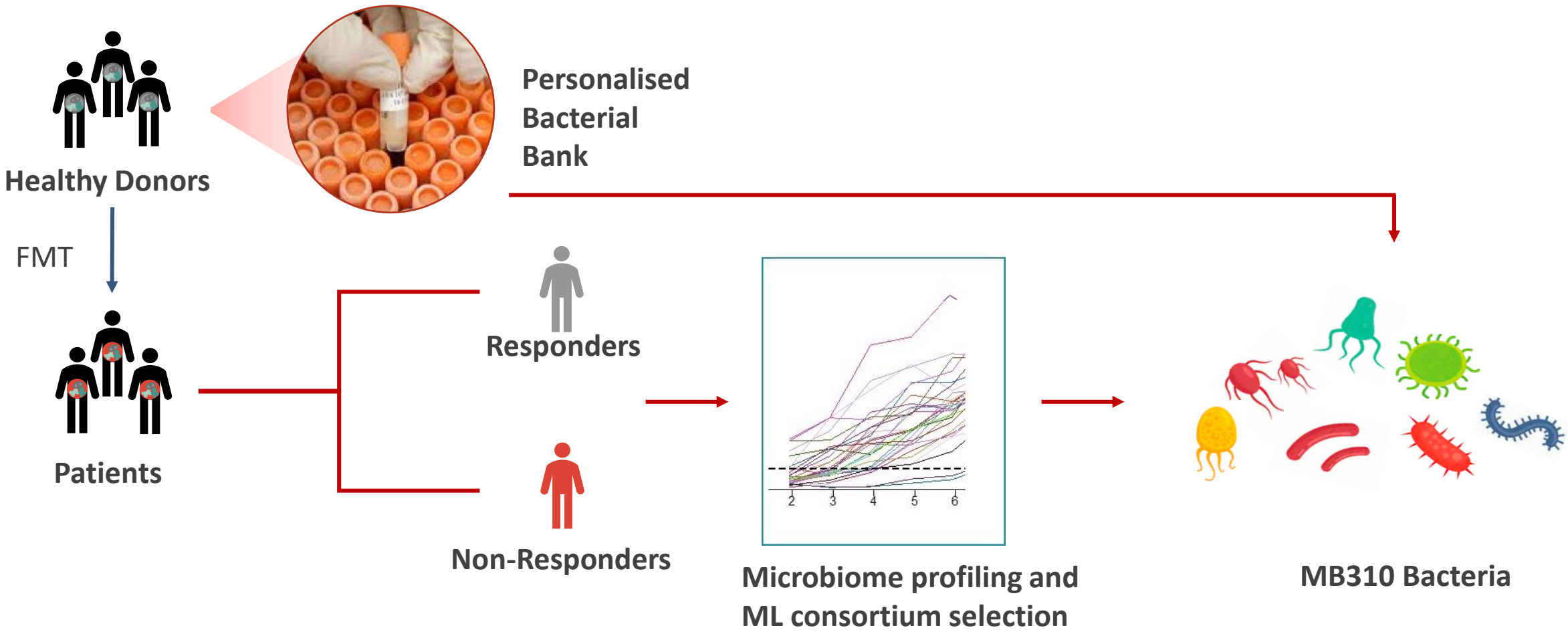
Samuel P. Costello, MBBS; Patrick A. Hughes, PhD; Oliver Waters, MBBS; Robert V. Bryant, MScR; Andrew D. Vincent, PhD; Paul Blatchford, PhD; Rosa Katsikeros, BSc; Jesica Makanyanga, MBChB; Melissa A. Campaniello, BSc; Chris Mavrangelos, BSc; Carly P. Rosewarne, PhD; Chelsea Bickley, BSc; Cian Peters, MS; Mark N. Schoeman, PhD; Michael A. Conlon, PhD; Ian C. Roberts-Thomson, PhD; Jane M. Andrews, PhD



THE UNIVERSITY of ADELAIDE

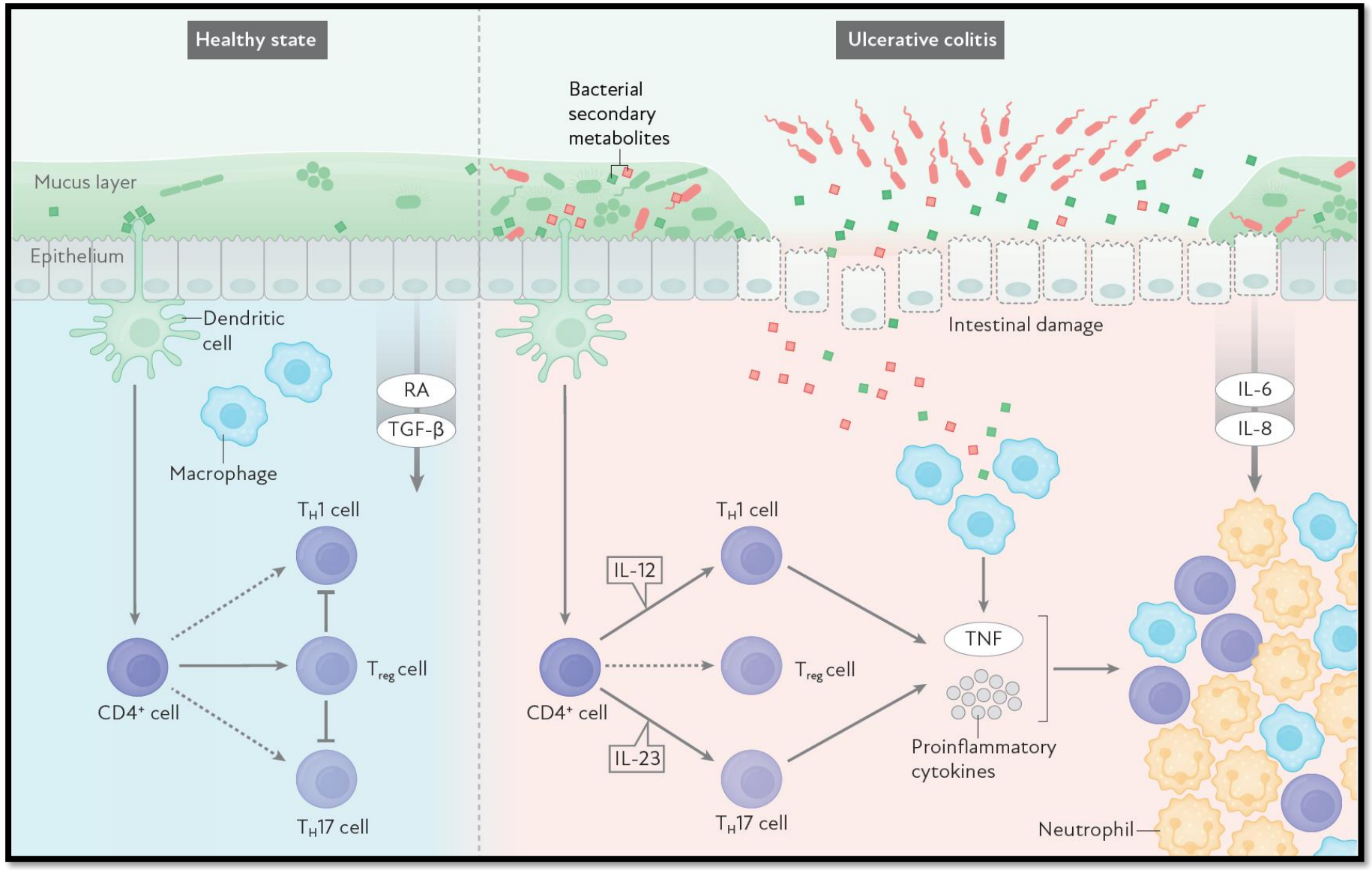
Dr Sam Costello
Queen Elizabeth Hospital, Adelaide

Precision Medicine Discovery Based on Ulcerative Colitis FMT

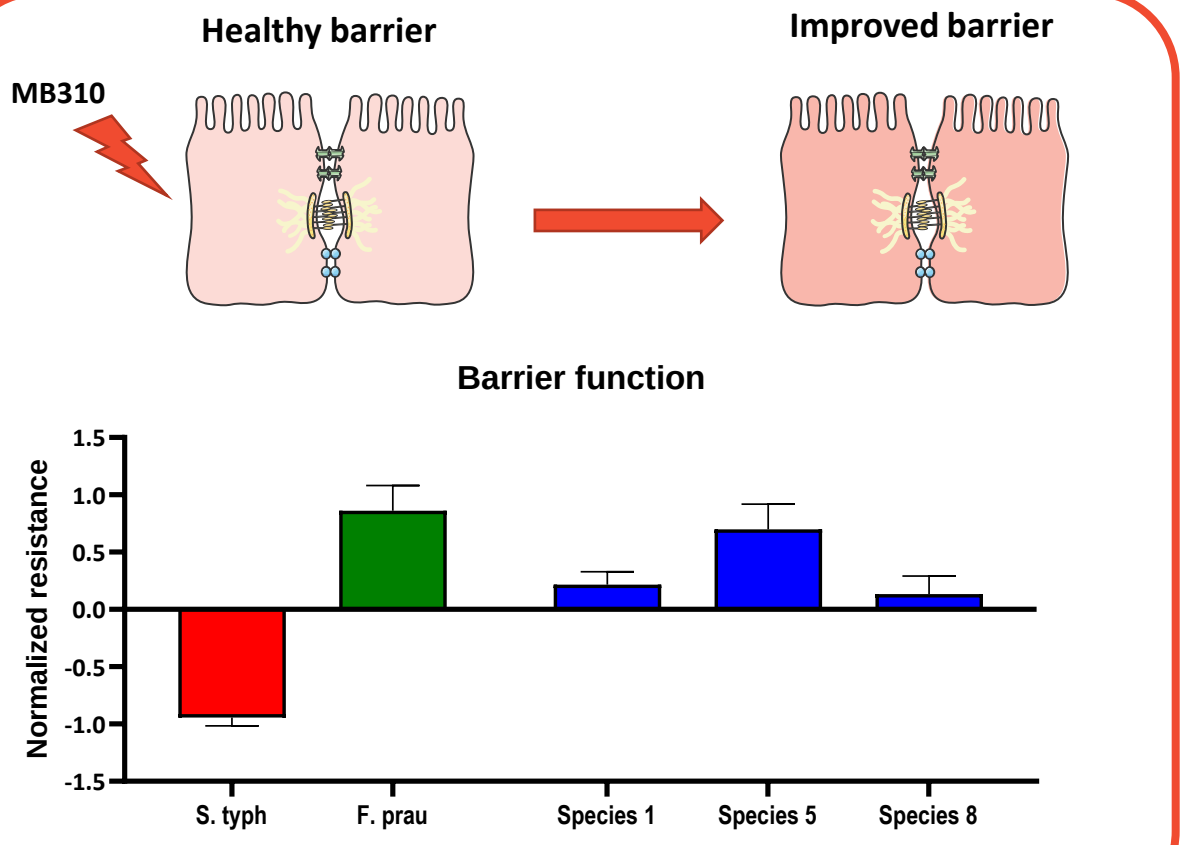


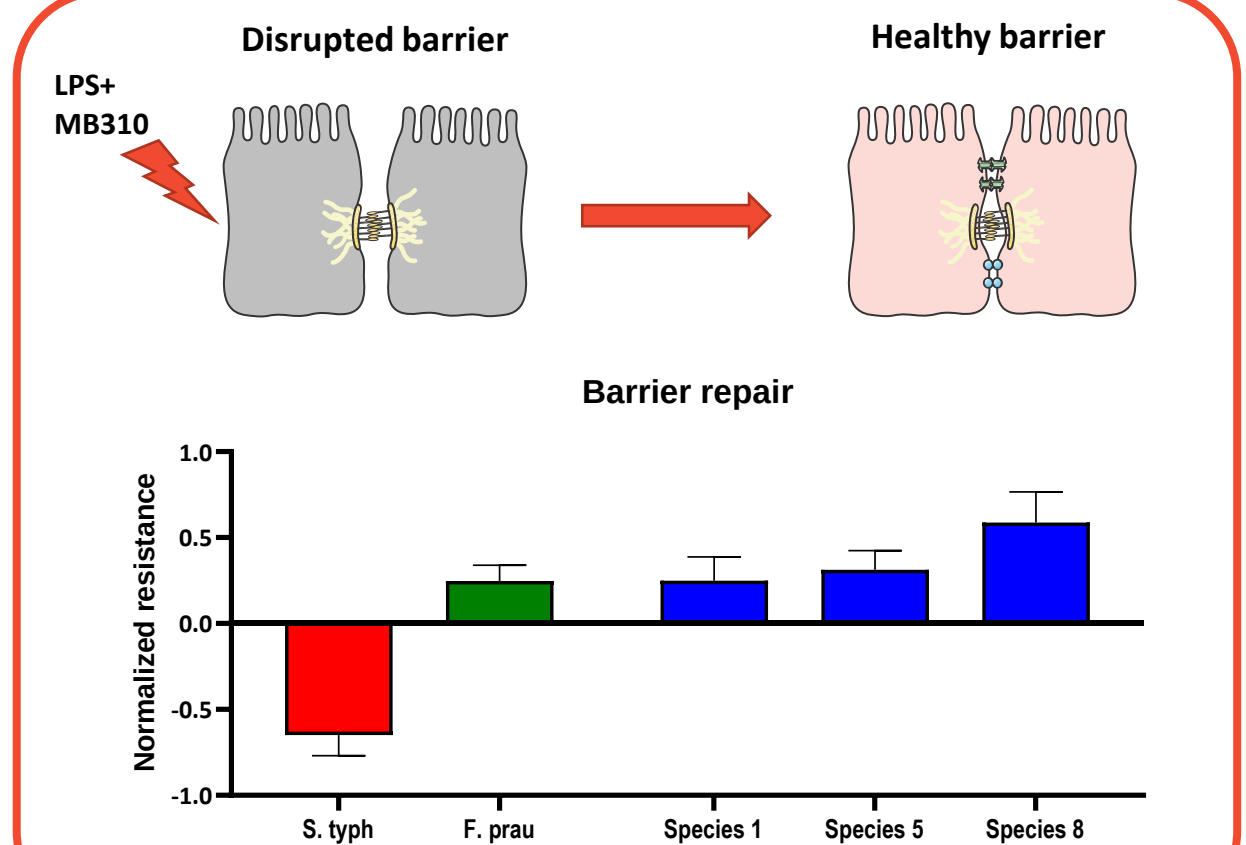
Best-in-Class FMT Trial + Best-in-Class Microbiome Platform

Cellular Responses in Ulcerative Colitis



MB310 Bacteria Enhance Gut Barrier Integrity

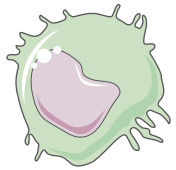


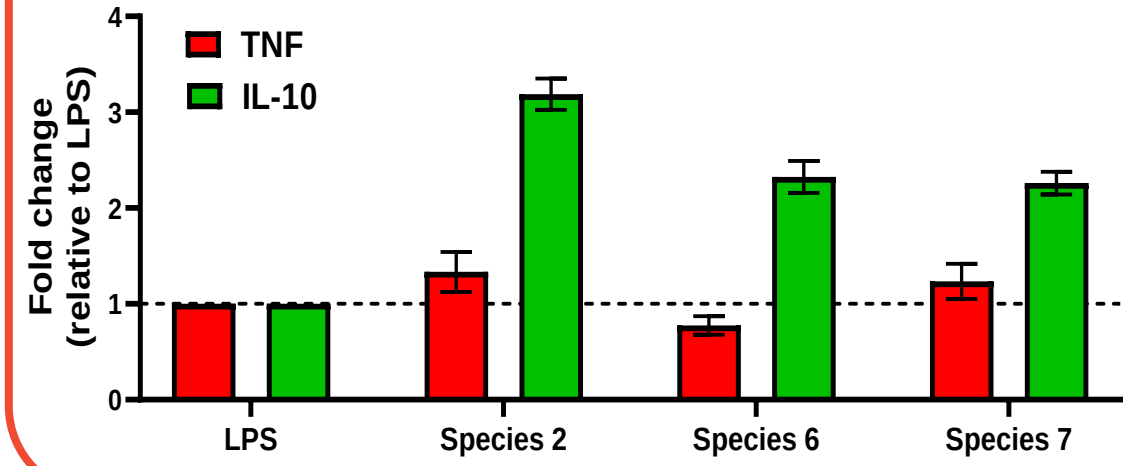


- 2 strains improve epithelium by releasing different metabolites known to support barrier function
- 1 strains expresses novel surface protein that enhances barrier function

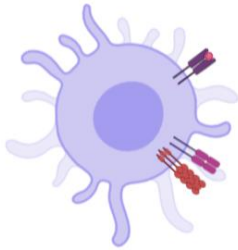
MB310 Promotes a Shift Towards Anti-Inflammatory Profile

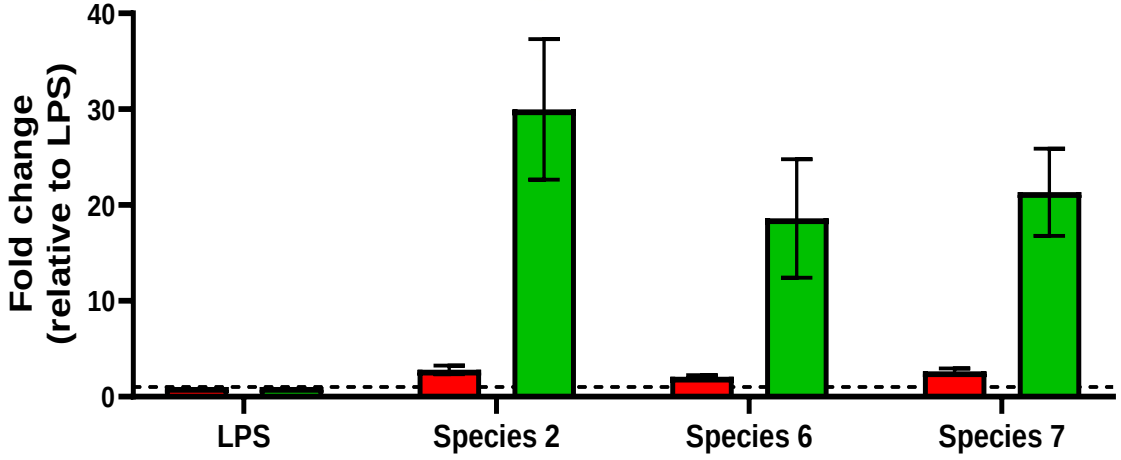
M1 Macrophages





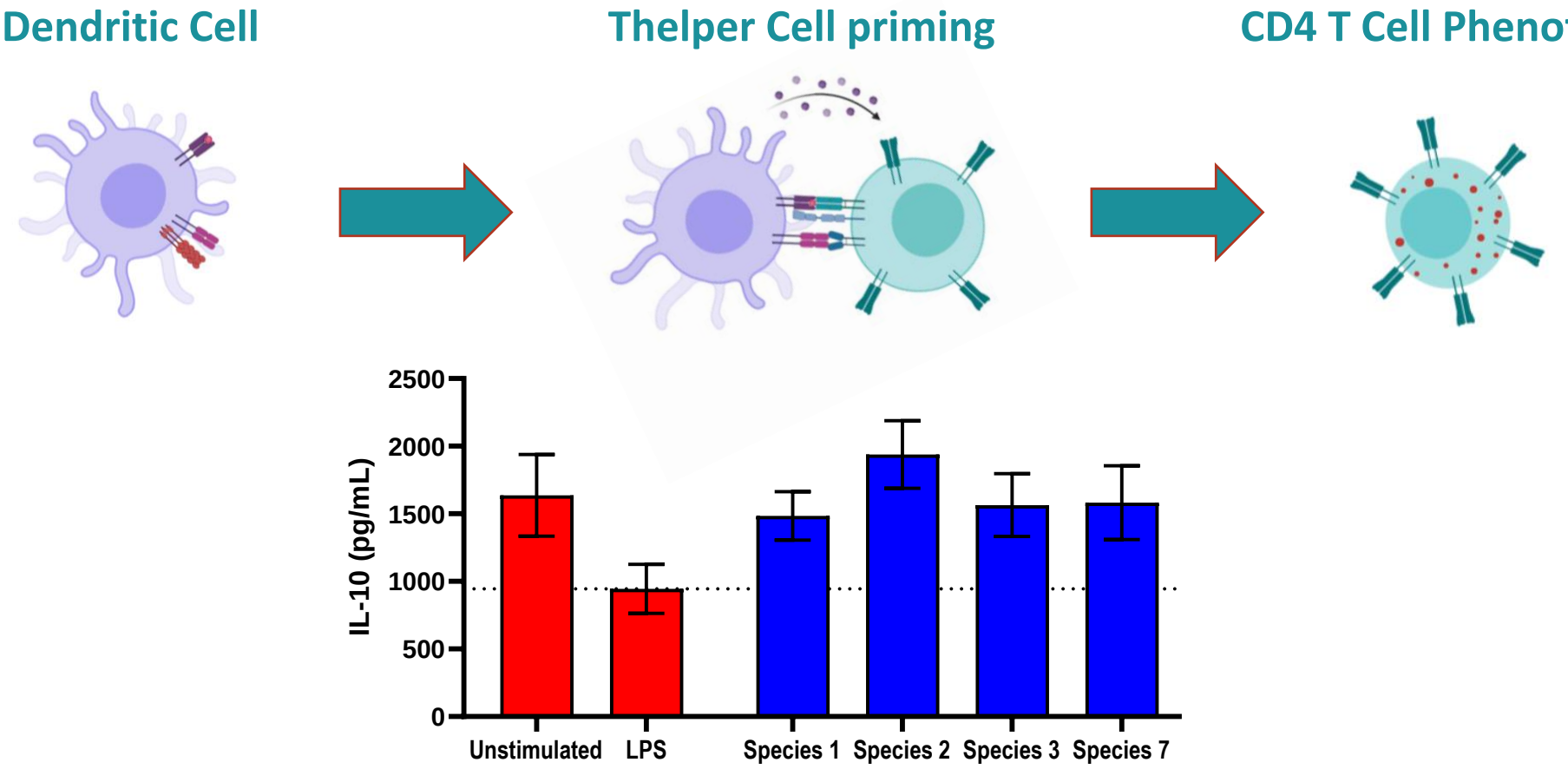
Dendritic Cells





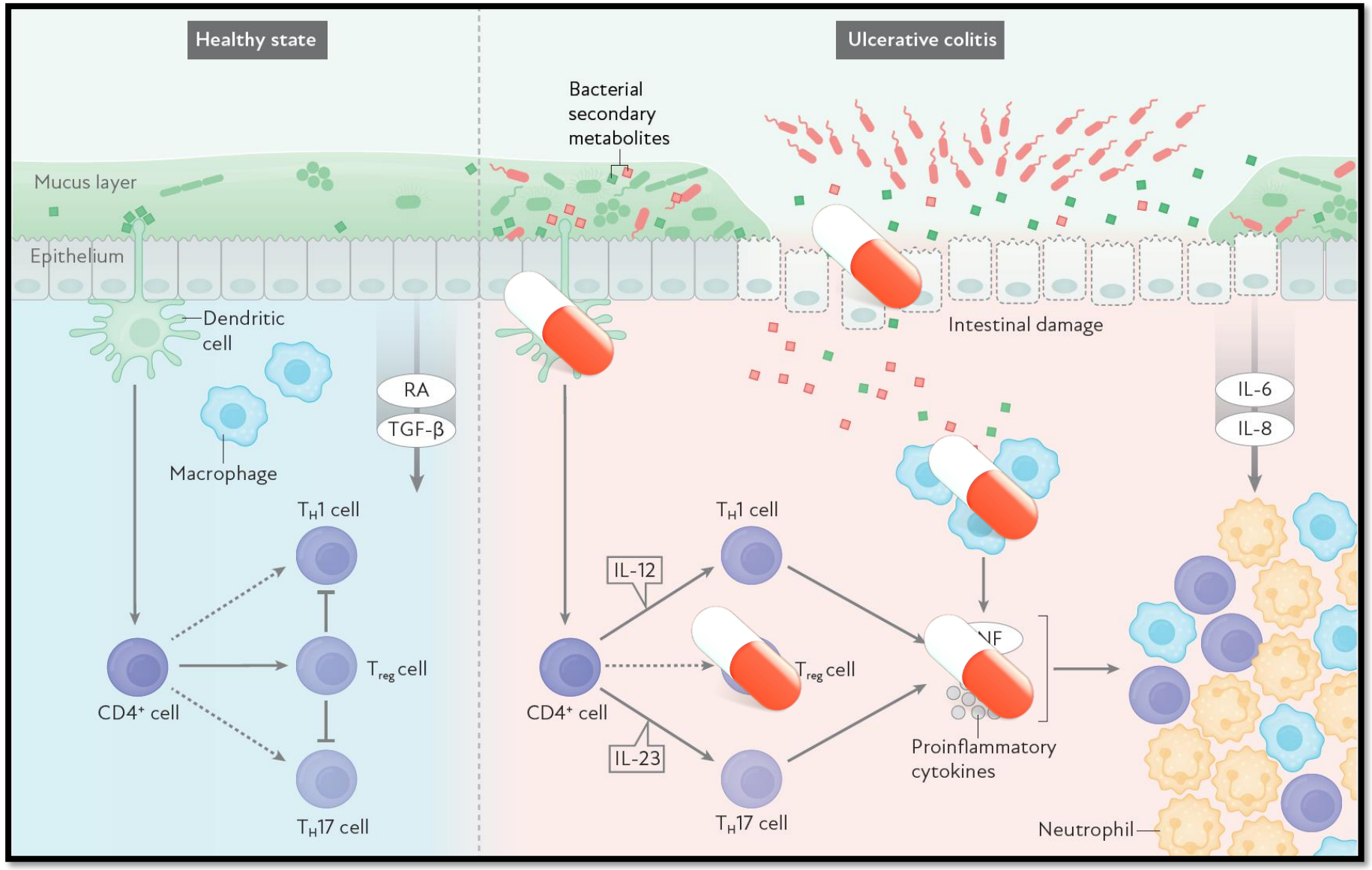
MB310 skews innate immune response to regulators profile (high IL-10)

MB310 Induces IL-10 Producing CD4^{+} T cells



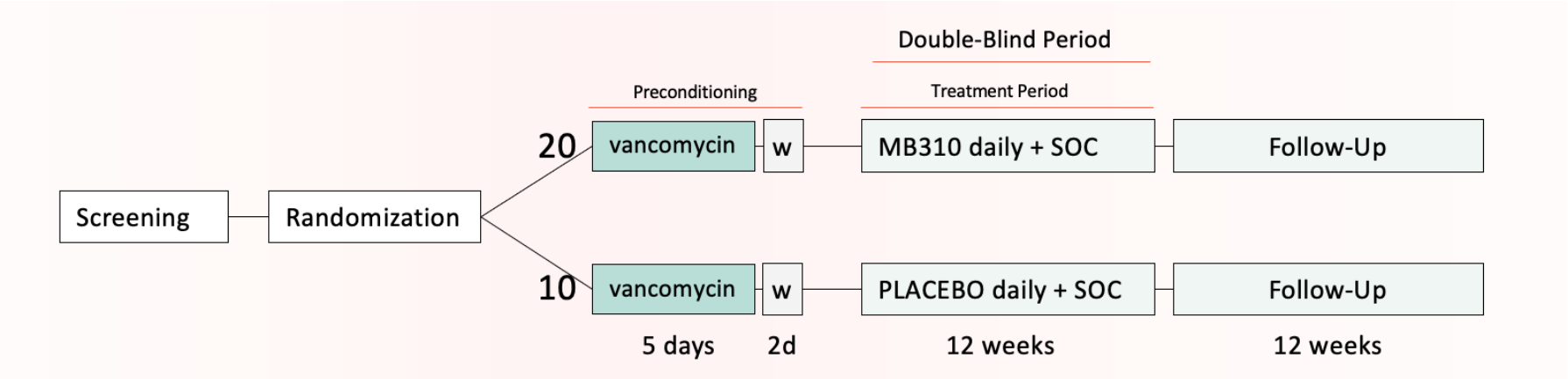
MB310 skews adaptive immune response to regulatory profile

MB310 Hits Multiple Key Pathologic Mechanisms in Ulcerative Colitis



MB310 – Phase Ib Clinical Trial in Ulcerative Colitis (UC)

Phase Ib, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Safety and Engraftment with Vancomycin Preconditioning, and Initial Signals of Clinical Activity of MB310 in Patients with Active, Mild-to-Moderate UC	
Study Population	• Patients ≥18 years of age with **active, mild-to-moderate ulcerative colitis**
Primary Objectives	• To evaluate the **safety and tolerability of MB310 vs. placebo** in adult subjects ≥18 years of age with active, mild-to-moderate ulcerative colitis
Secondary Objectives	• To determine the **engraftment of MB310 bacteria into the intestinal microbial community with vancomycin preconditioning**; and • To evaluate the **initial signals of efficacy** of MB310 in the treatment of active, mild to moderate UC with the use of clinical assessments, endoscopy, and histology.
Exploratory Objectives	• To determine the effect of MB310 treatment on the composition of the intestinal microbiome • To compare changes from baseline in exploratory biomarkers from stool samples, blood samples, and mucosal biopsies between the treatment groups throughout the Treatment Period.



Summary

- **Microbiome signature provides the basis for Live Biotherapeutic Products**
  - Unbiased and unrestricted by known mechanisms
- **MB097 is a precision medicine LBP that is clinically designed in patients and to be tested in the same patient cohort**
- **MB310 is a multi-modal consortium derived from ulcerative colitis FMT study**
- **Discovering known and novel microbiome-human interactions that impact disease pathology and drug response**
  - Supporting clinic-first discovery and broad consortia approach

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