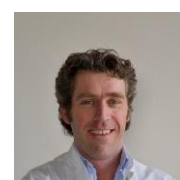
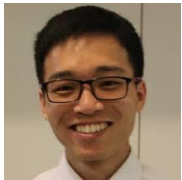


Microbes, microbiota and microbiomes; their role in humans, animals, plants and the environment.

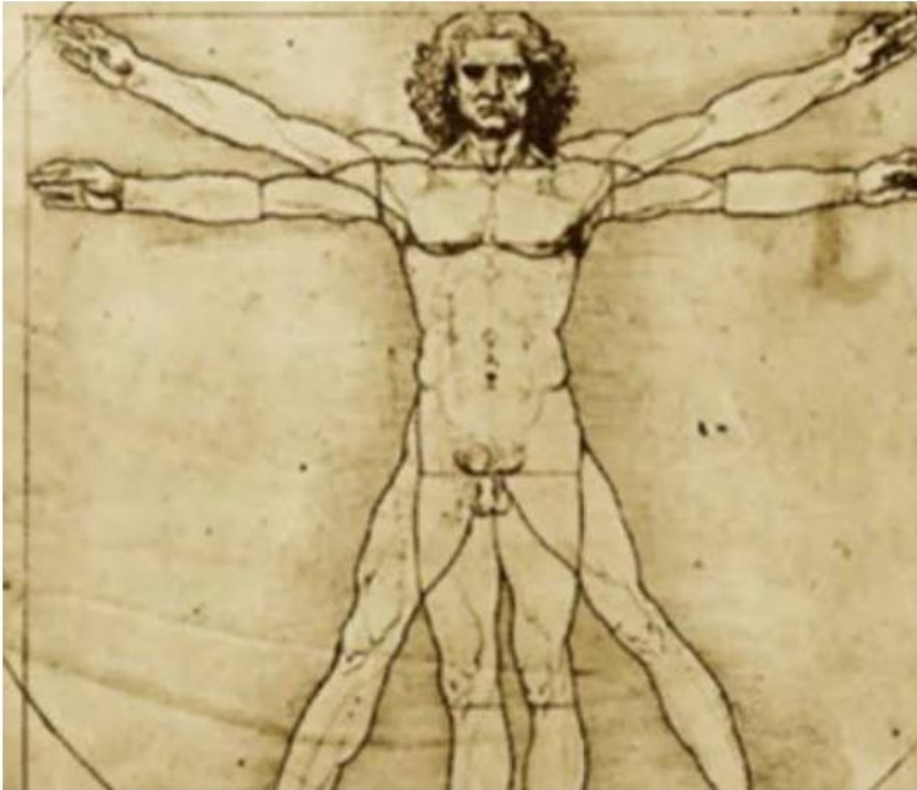


Stanley Brul @ Swammerdam Institute for Life Sciences; University of Amsterdam
Kennislezing NVWA 30 Juni 2022 <https://sils.uva.nl/> <https://systemsbiology.amsterdam/>

Acknowledgements: Jianbo Zhang, Meike Wortel, Age Smilde, Marten Smidt (Science Faculty UvA), Hilde Herrema, Max Nieuwdorp, Wouter de Jonge, Anja Lok (Amsterdam UMC), Hauke Smidt (WUR)



Human host more bacterial cells than human cells?



Vitruvian Man depicted by Leonardo da Vinci

- Human body is composed of ten trillion (10^{13}) cells
- There are hundreds of trillion (10^{14}) bacterial cells in and on our bodies
- Collectively, these bacteria have 100X more genes than all the genes in the human genome (~ 25000)

Open questions:

Where are the microbes and what do they do?

Are there common elements between Human, animal, Plant and environmental consortia?

How do we analyse the complex microbial consortia?

Where are the microbes and what do they do?

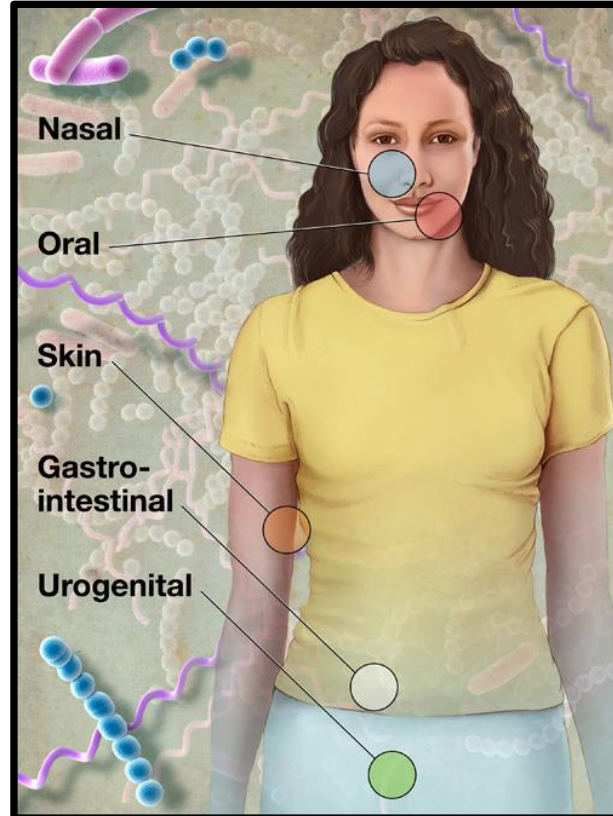
Are there common elements between Human, animal, Plant and environmental consortia?

How do we analyse the complex microbial consortia?

Where are microbes in and on our body?

Some microbes are **native**, normally found in the body

Some microbes are **introduced**, suddenly arriving at a new residence in the body



Nose
Mouth
Skin
Gastrointestinal
Urogenital

Throughout your life, microbes secrete compounds that regulate immune cells (T cells)

All these trillions of bacteria in the human gut are together with the other microorganisms (including viruses) called our microbiota.

Joshua Lederberg (Nobel Prize Medicine, 1958) first introduces the term 'microbiome' in 2001.

'collection of genomes of microbiota living in a specific niche'

Humans consist of multiple organisms

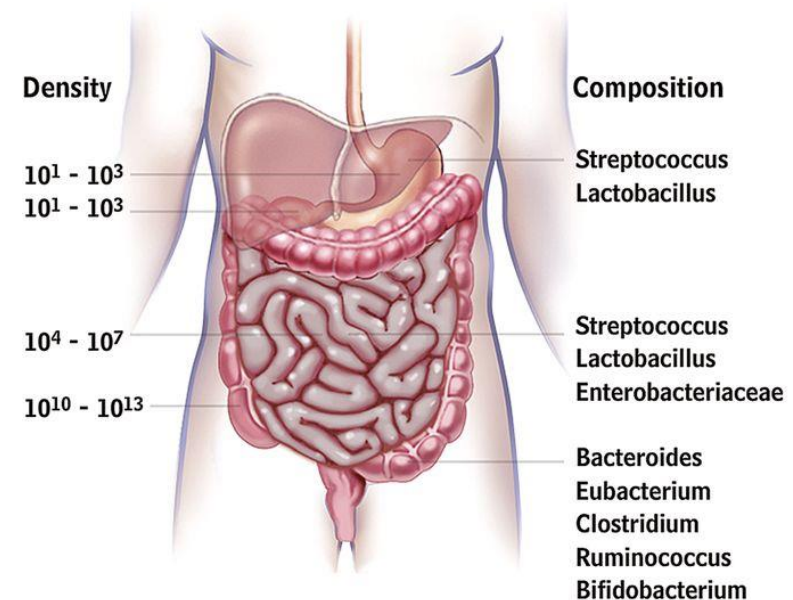
Up to 2kg per person!

For an 80kg person, this is 2,5% of total body weight

At least 1000 different bacterial species currently known

Many are yet to be identified
Interindividual differences are large

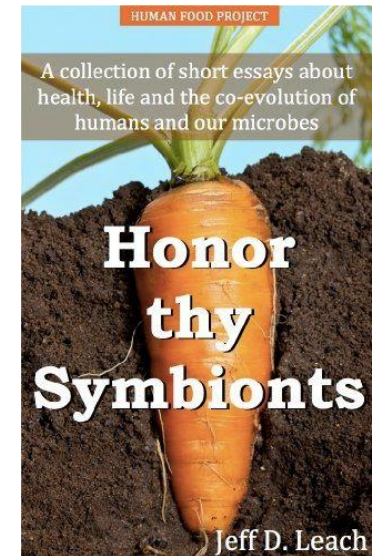
Gut bacteria express over 2,5 million genes
100 times more than human genes



Based on DNA content, we are as much (or more?) microbial as human

Gut microbiota: crucial symbionts that constitute an endocrine organ

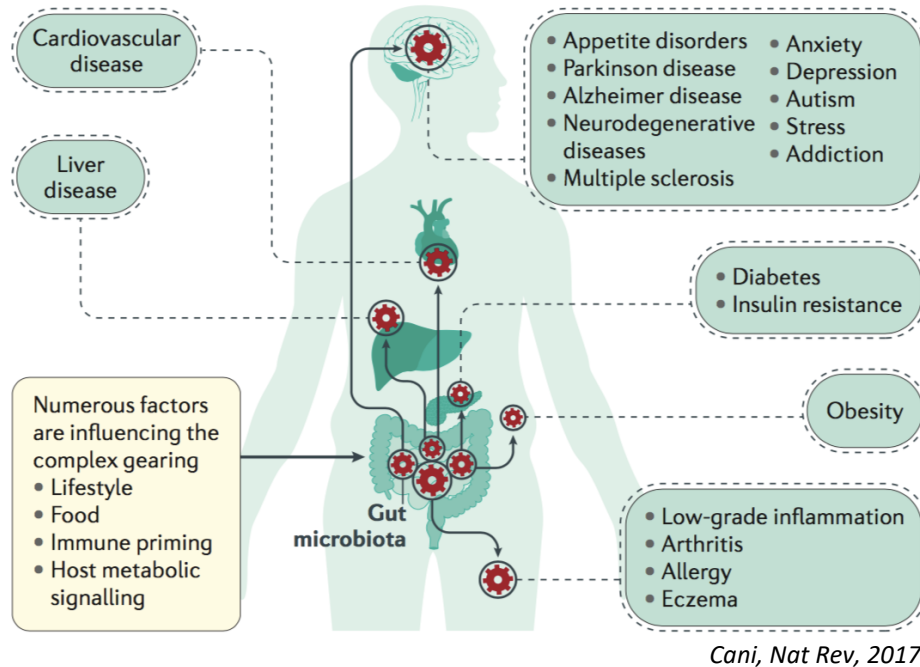
- **Increase energy harvest from diet**
 - Secrete carbohydrate degrading enzymes
- **Produce metabolites with host metabolic effects**
 - Short-chain fatty acids (SCFA's) → Regulate gut hormones
 - Trimethylamine (→ TMAoxide in liver with pro-atherosclerotic effects)
- **Produce vitamins**
 - (biotin, B12 and vitamin K)
- **Metabolize bile acids, sterols and xenobiotics***
 - * Drugs such as antidiabetic drug metformin
- **Train host immune system**
 - Protect from pathogen invasion
 - Maintain healthy gut barrier function



Paradigm Shift in Medicine: No Bacteria or Not The Right Consortium May Cause Disease.

Potential for Diagnostics & Therapy.

Gut microbiota in human health and disease



Gut microbiota implicated in host health and development of disease

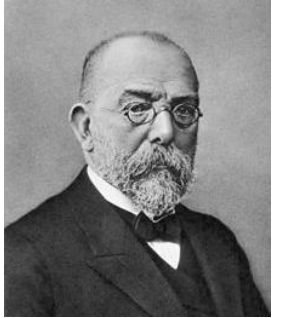
Microbiota research is moving from an associative to a translational/ causative science (*C. diff.* is the best proven case)

Multidisciplinary endeavor

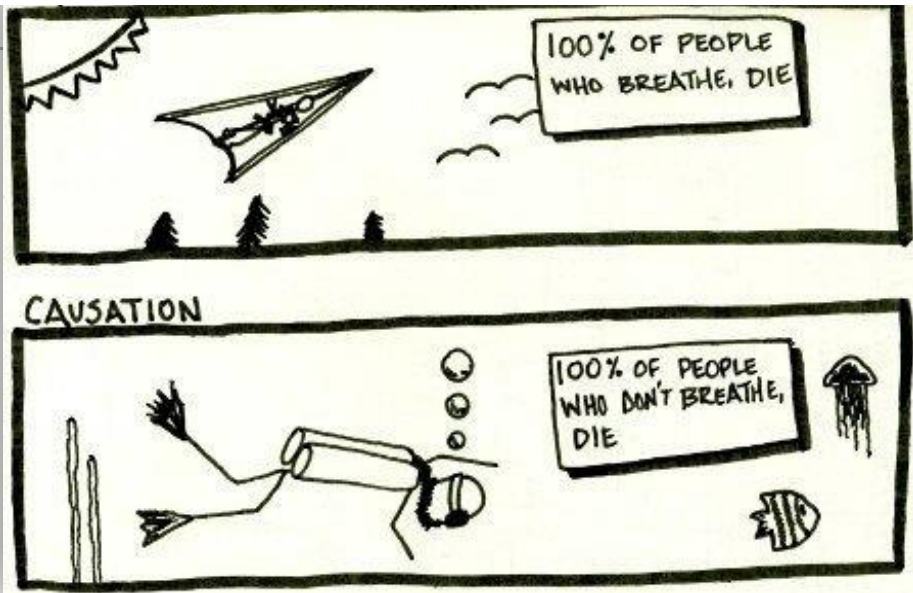
-Wide range of expertise and skill sets (Big Omics Data Analysis!)



Gut microbiota and human disease; Association or Causality?



Robert Hermann Koch
(1843 –1910)

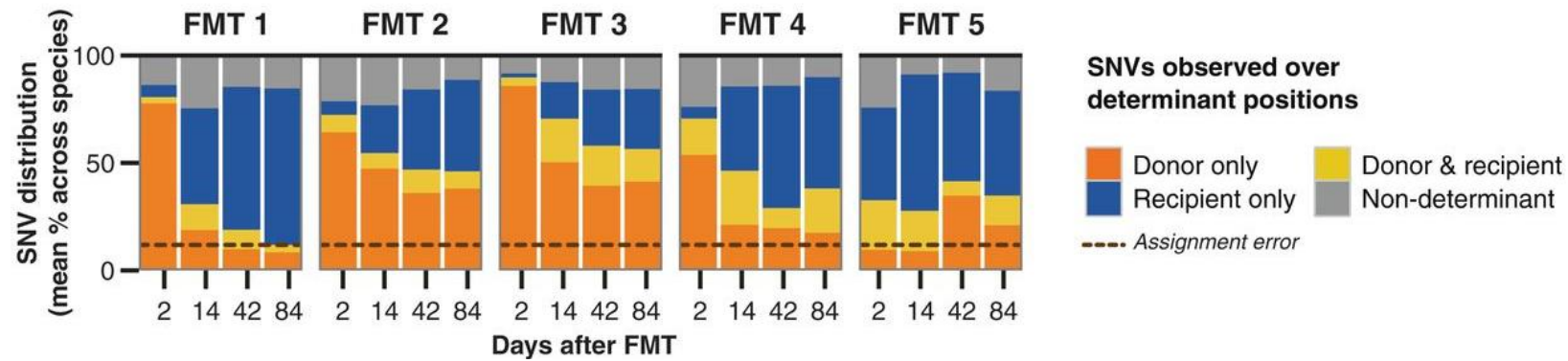


Causality in infectious diseases are described by Koch's postulates:

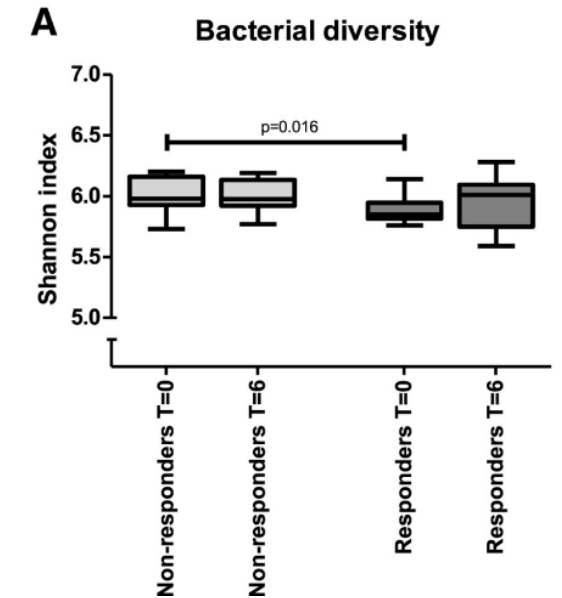
- Micro-organism should be associated with disease(s)
- Micro-organism should be found in a sick person
- Cultured micro-organism introduced in animal drives disease
 - or eradication prevents disease

Fecal microbiota transplantation (FMT) as tool to study causality of gut microbiomes

Insulin sensitivity response and bacterial colonization after FMT

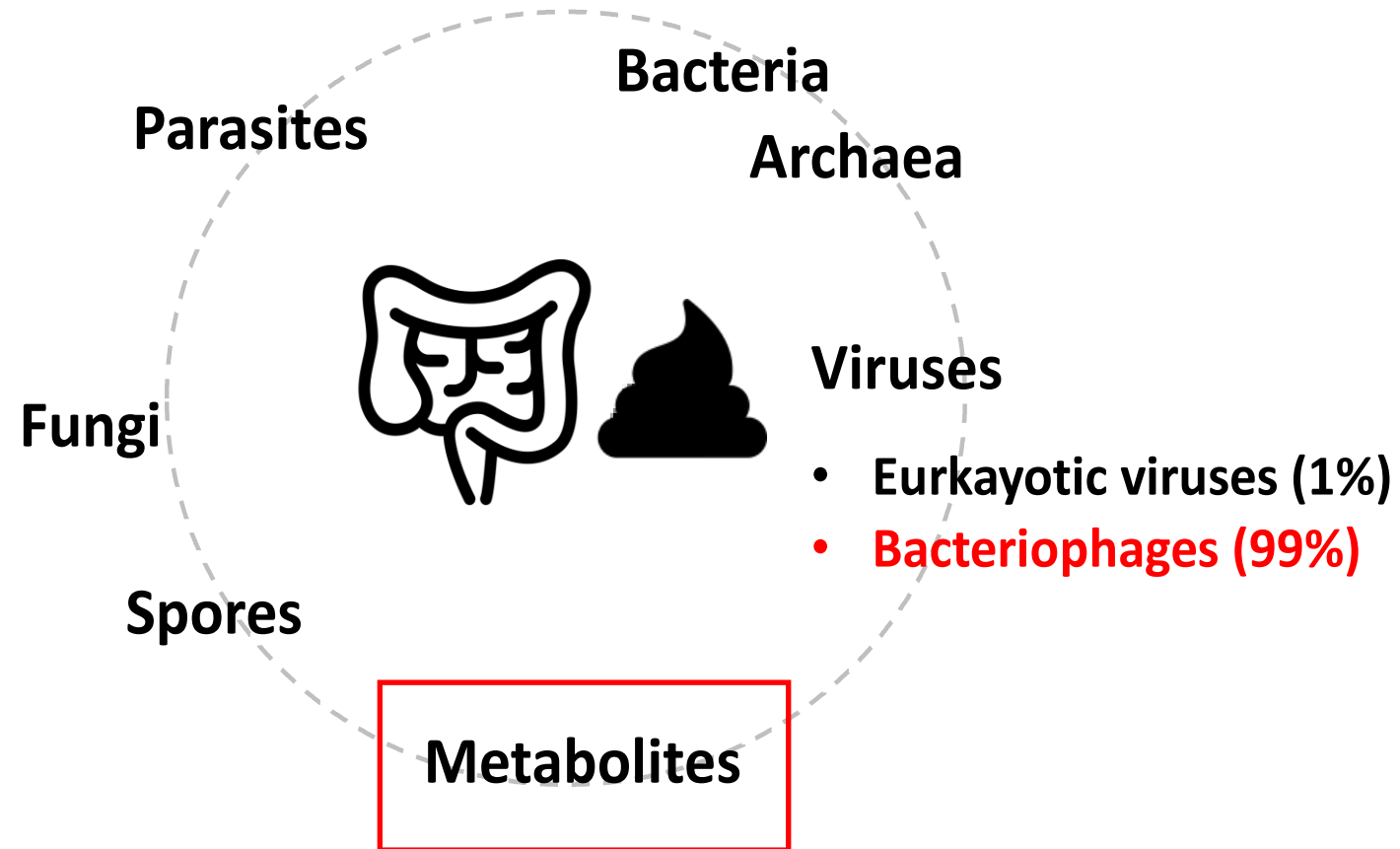


SNV (single-nucleotide analysis) = method to distinguish and trace donor- and recipient-specific strain populations

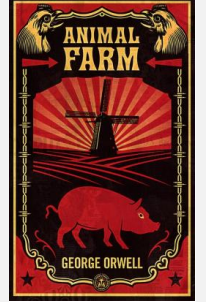


- No 'super-donors'
- Enhance colonization?
- Lower diversity at baseline more likely to benefit
- Predict success of FMT using computational approaches
- Note that the small intestine is exposed to fecal/colonic microbiota that it normally never sees!

Better understanding of the gut ecosystem microbial class diversity might increase FMT efficacy
(and other microbiome-targeted interventions)



“All Disease Begins in The Gut” (?) A statement by Hippocrates 460-377 bc.



**Microbiome not
equally important
in all disease**

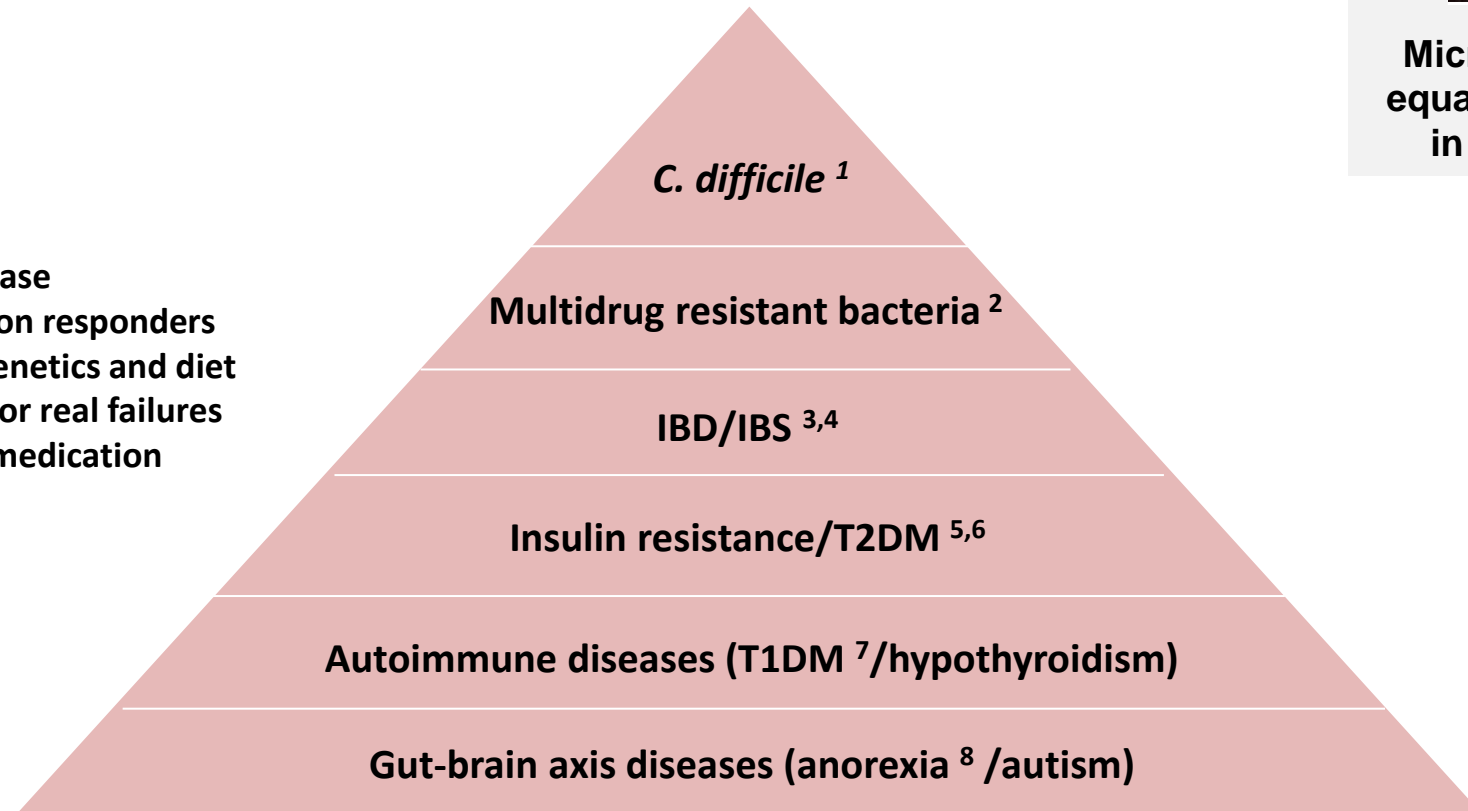
Role microbiome:

Causal

- Course of disease
- Responders-non responders
- Influence of genetics and diet
- Multiple FMT or real failures
- Concomitant medication



***Disease modifier
or...consequence of disease?***



Longitudinal integrated cohort studies needed to get clues towards temporal events in health perturbation.

In Amsterdam the HELIUS cohort exists which was started from a multiethnic perspective on health.

<http://www.heliusstudy.nl/>

Special acknowledgements research Hilde Herrema go to:



Torsten Scheithauer
(almost) PhD



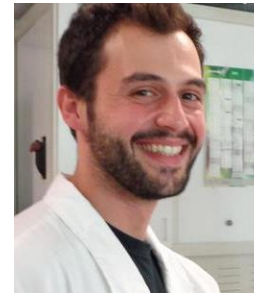
Patrick de Jonge, PhD



Koen Wortelboer,
PharmD



Kirby Dick Frank
(intern)



Franklin Nóbrega, PhD
Uni Southampton, UK



Bas Dutilh, PhD
University Utrecht, NL



Stan Brouns, PhD
TU Delft, NL



Max Nieuwdorp, MD PhD **Bert Groen, PhD**



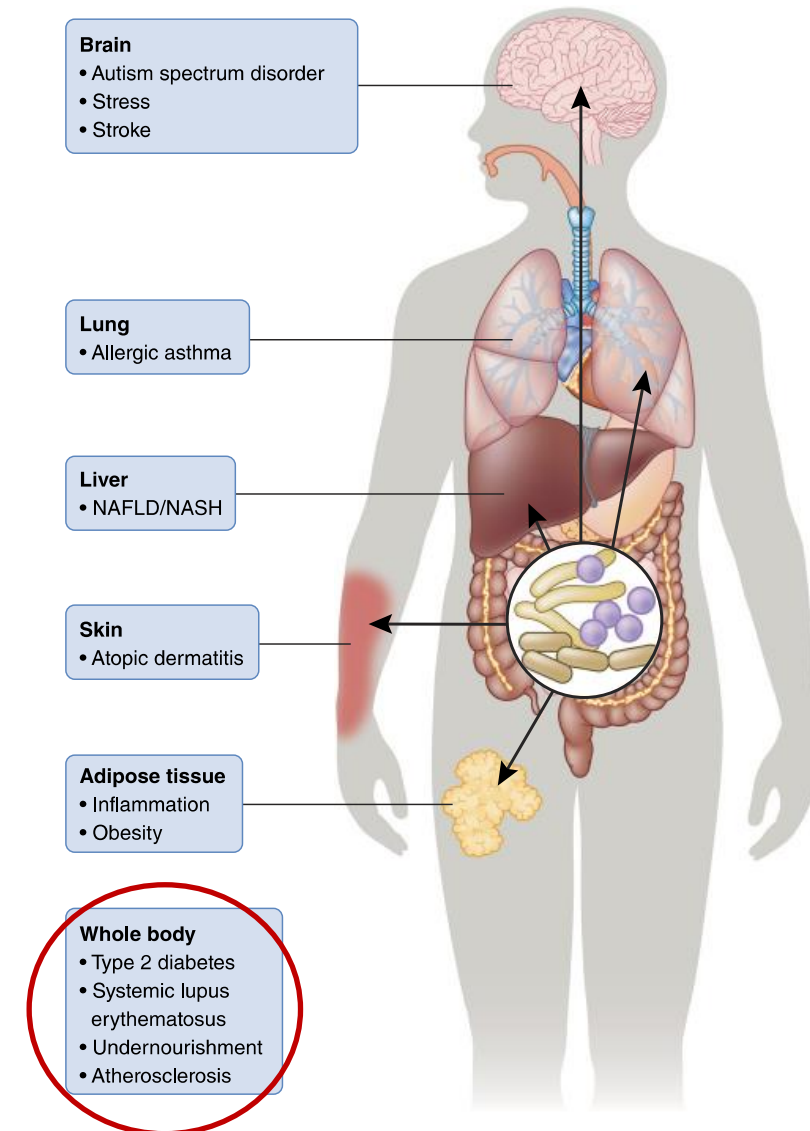
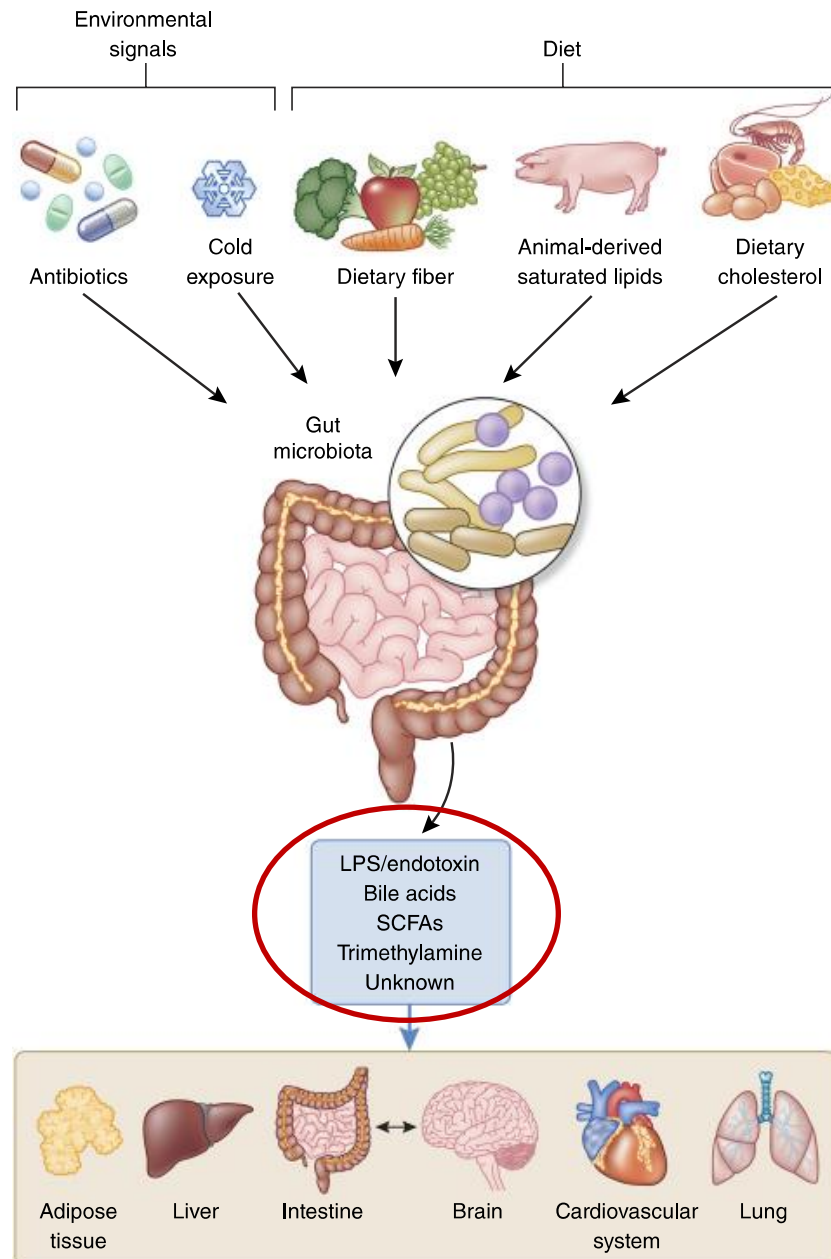
h.j.herrema@amsterdamumc.nl

Where are the microbes and what do they do?

**Are there common elements between Human, animal,
Plant and environmental consortia?**

How do we analyse the complex microbial consortia?

Intestinal microbiota are influenced by a broad range of diet & environmental factors!



Schroeder and Backhed, Nature Medicine 2016

Are there common elements among the different microbes?
Look at us and our environments as ONE system, ONE health!

A Growth fund proposal in the making:
The HoloMicrobiome

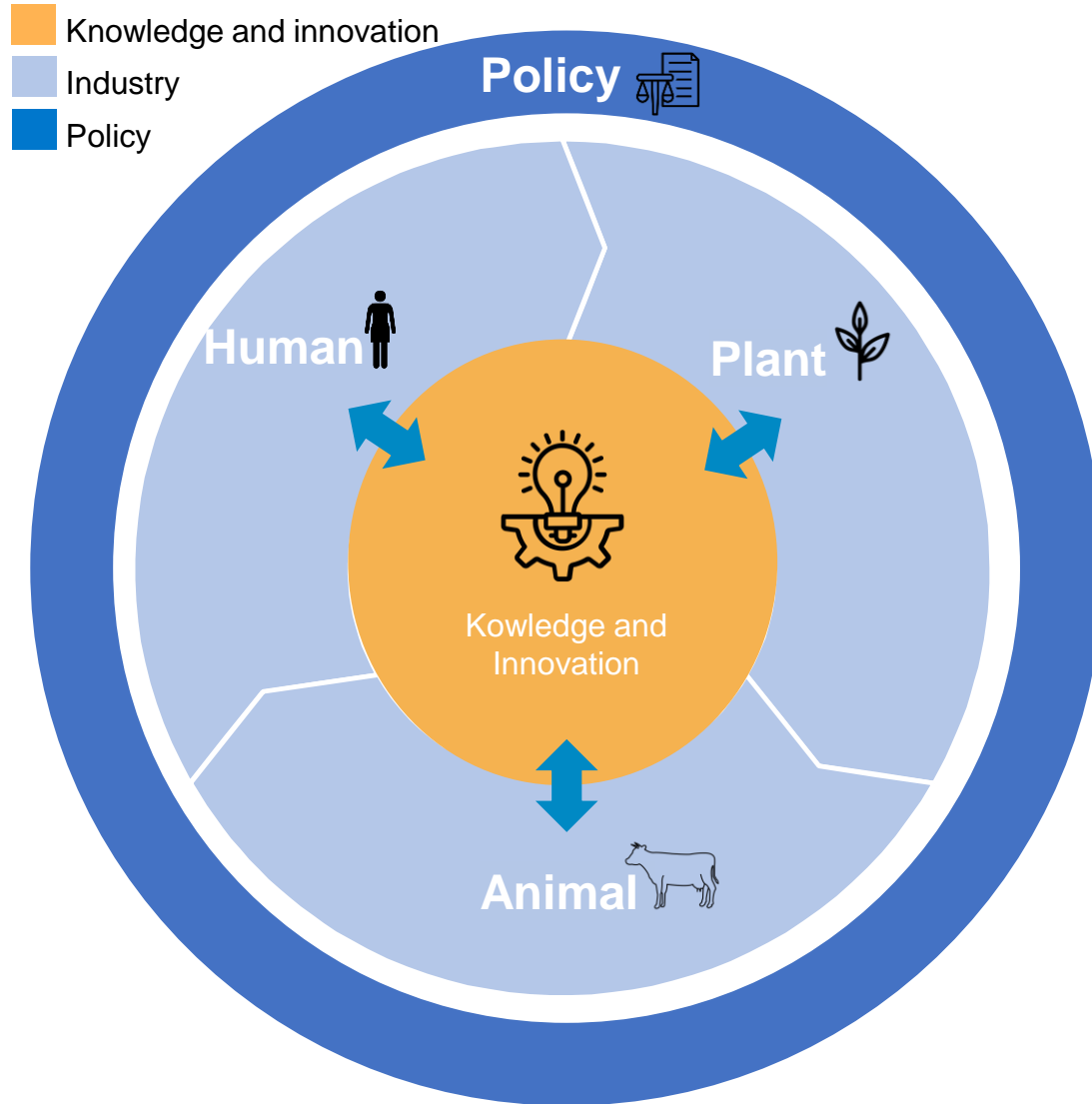
Leveraging the microbiome for economic growth

[Home-en | Holomicrobiome \(holomicrobiome.nl\)](https://holomicrobiome.nl)

Joining forces between existing research groups and research programs
in the Netherlands (UvA, WUR, RUG, UMCs TNO, Companies etc.....)

The HoloMicrobiome

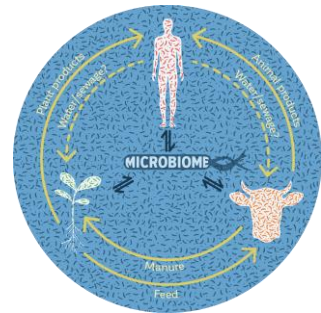
Leveraging the microbiome for sustainable growth



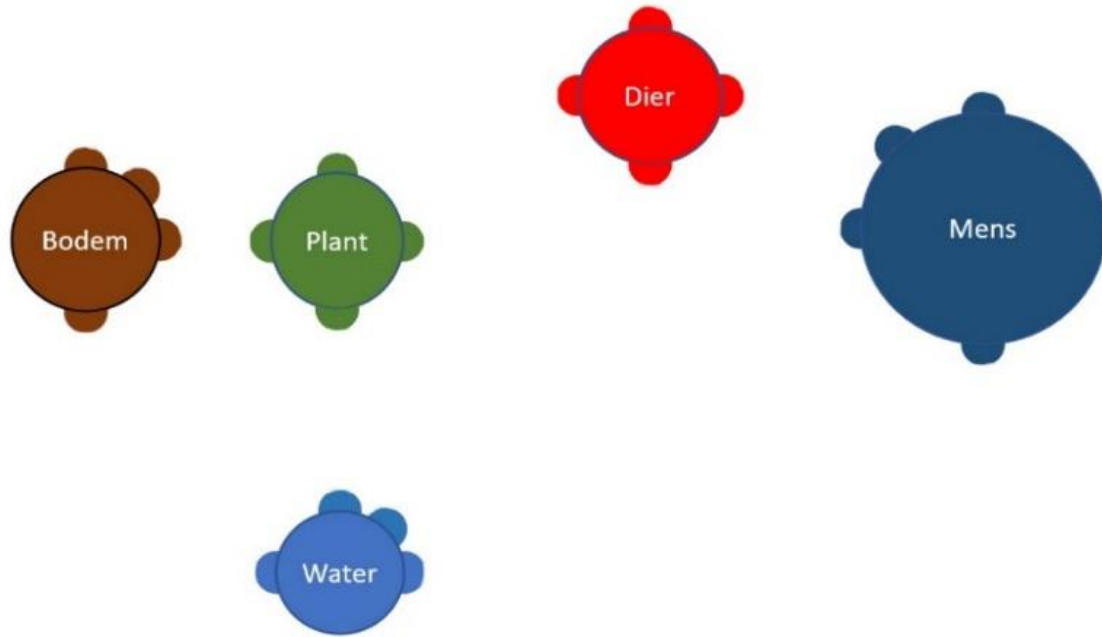
Knowledge and Innovation are the connecting flywheel for the realization of our mission and is an overlapping activity for all domains.

Partnership Industry is crucial for creating impact, valorization and realization from Knowledge and Innovation.

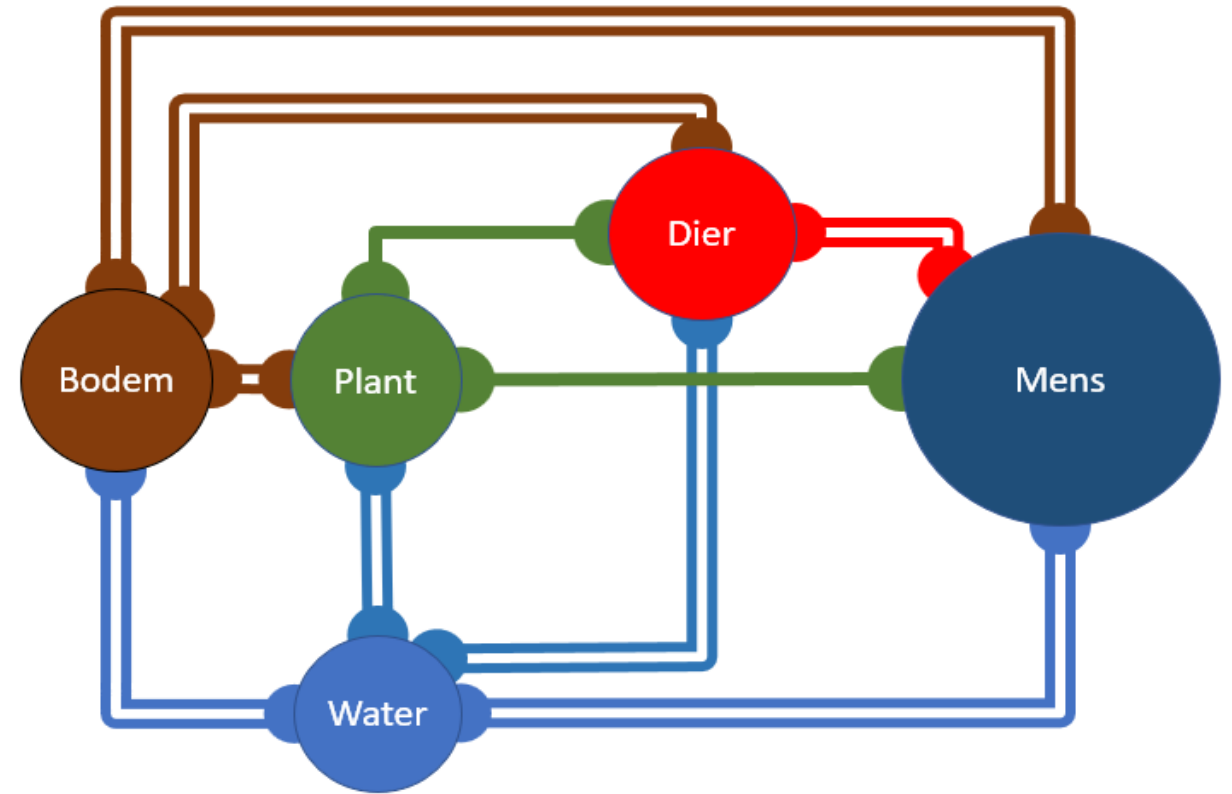
Partnership Policy guarantees the implementation of a policy regarding the realization of a healthy, safe and sustainable food chain for the Netherlands.



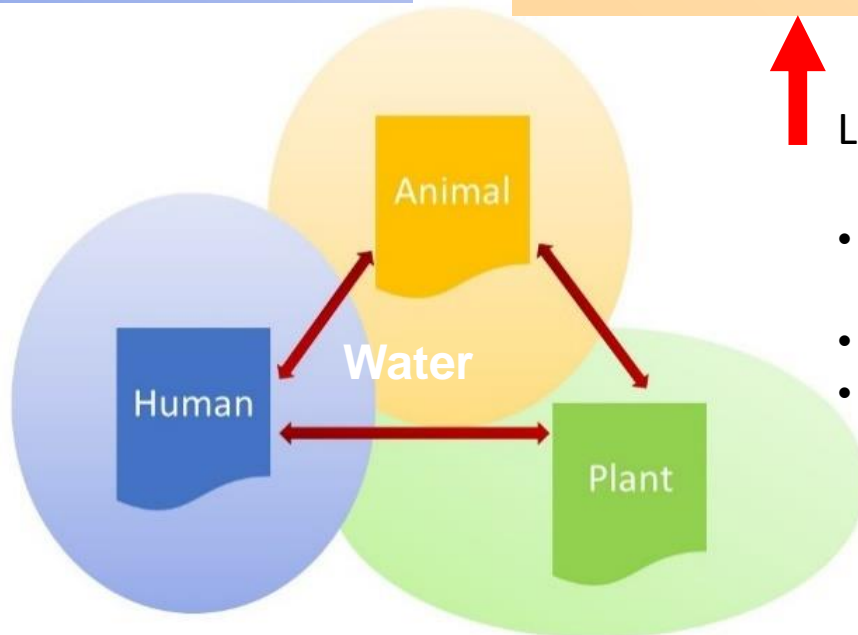
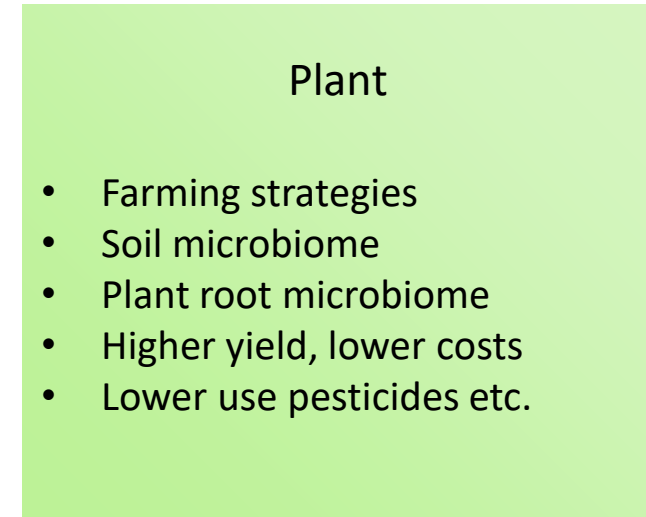
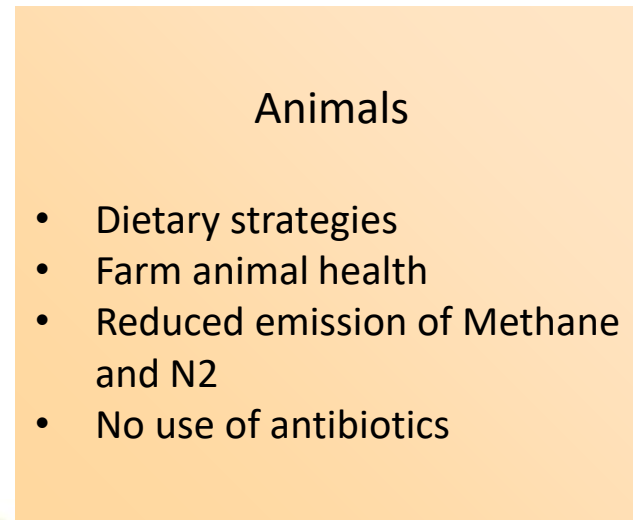
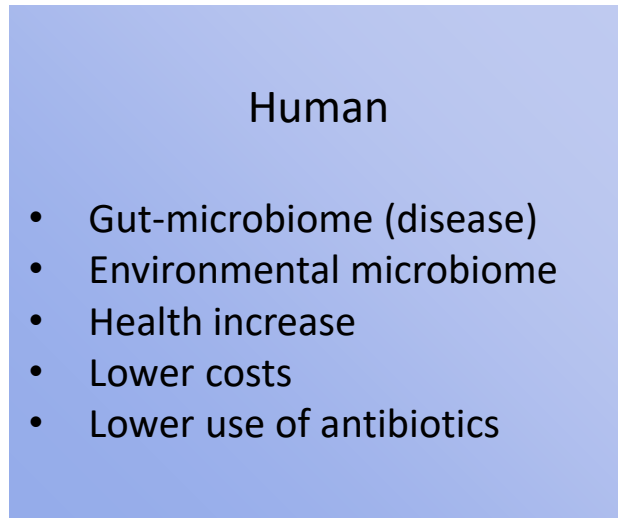
Separate
microbiomes



The Holomicrobiome

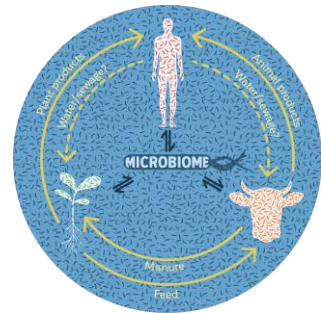


Four linked example projects



Linking the domains:

- **Building a new supercohort with stored information on nutrition and food related microbes in all different domains**
- Transfer of microbiome (and related chemicals)
- Causal Models for strategic interventions



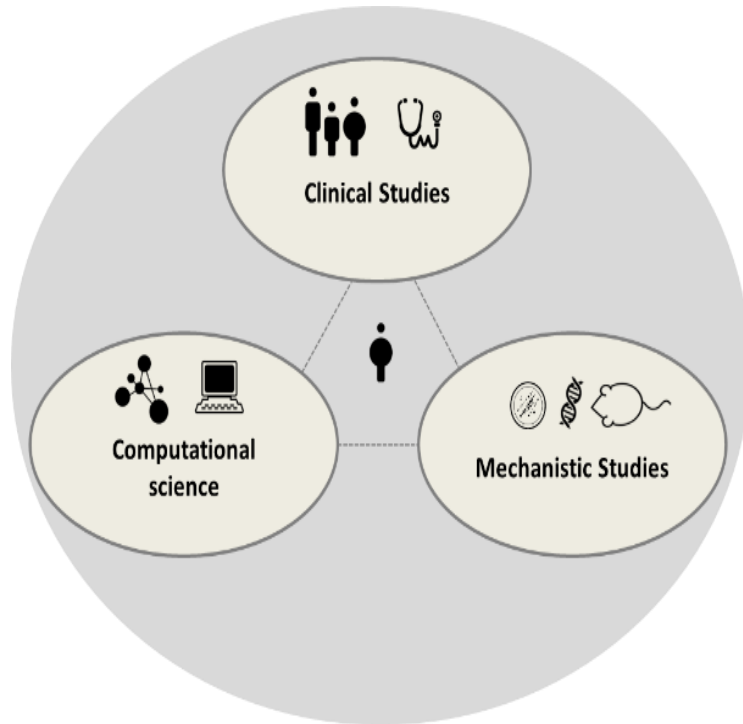
PIG-PARADIGM International research team to combat antibiotic resistance in pigs.

Where are the microbes and what do they do?

Are there common elements between Human, animal, Plant and environmental consortia?

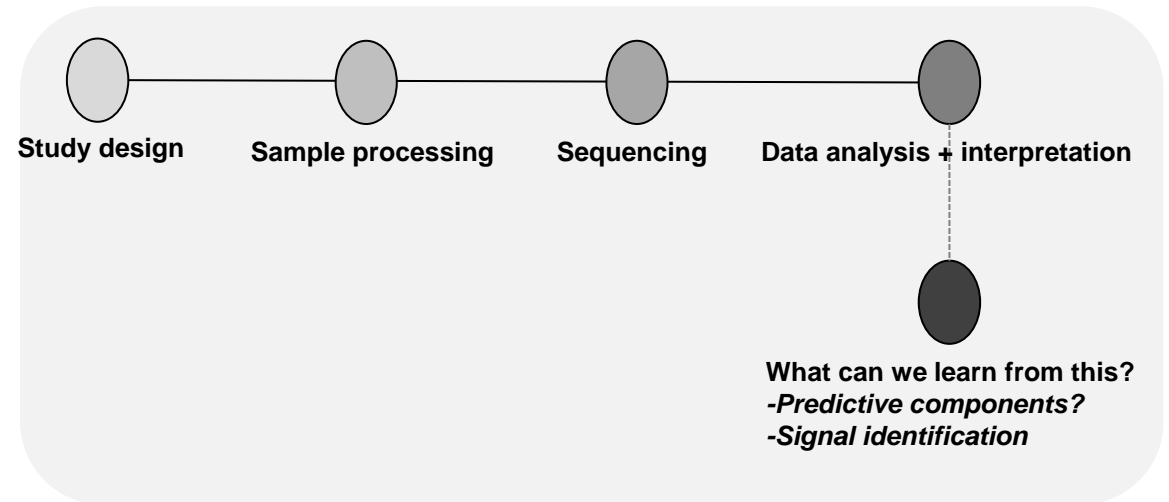
How do we analyse the complex microbial consortia?

Gut microbiome from association to mechanisms associated with health and disease



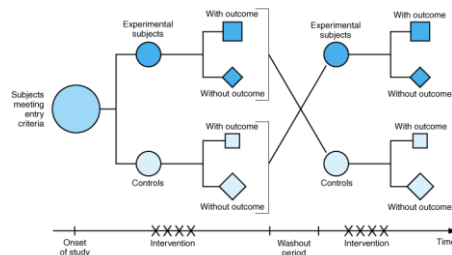
Combine forces, share knowledge

How? – Microbiota Center Amsterdam

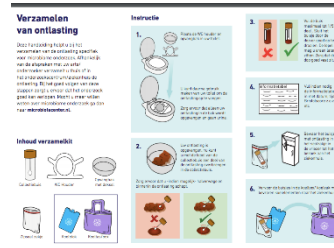


Microbiota Center Amsterdam (MiCA)

Expertise and equipment in-house



Research question/study design



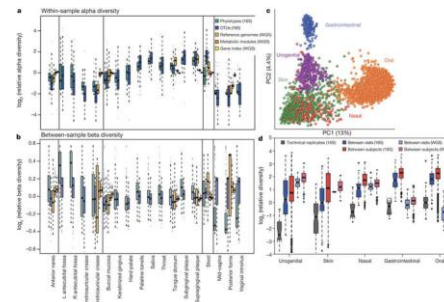
Patient folders



Sample processing
(Equipment located at EVG, CEMM, Tytgat and LVGA)



Sequencing
(MiSeq EVG, located at LVGA)



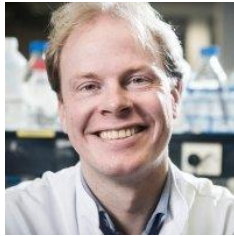
Data processing, analysis, interpretation
(EVG)



Anaerobic chamber
(Located CEMM tower)

Microbiota Center Amsterdam (MiCA)

“powered by Amsterdam UMC location AMC”



Joost Wiersinga



Wouter de Jonge



Max Nieuwdorp



Hilde Herrema

Wet lab



Theo Hakvoort



Jorn Hartman

Computation



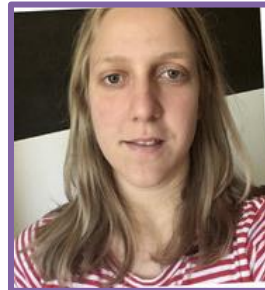
Mark Davids



Evgeni Levin



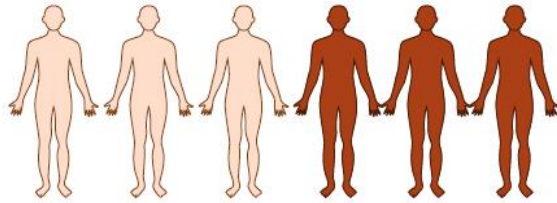
Iris Admiraal



Xanthe Verdoes

Host-Microbiome Interactions in the laboratory and beyond

How to study their influence?



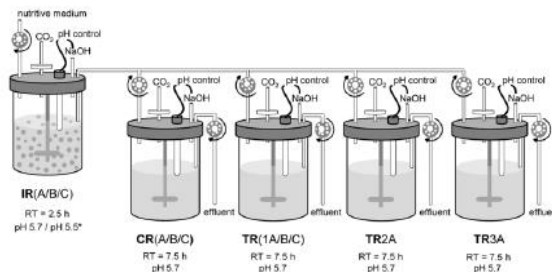
Clinical studies

(e.g. case-ctrl, FMT)



Animal models

(e.g. Germ-free mice)



Simulator of fermentation

(e.g. PolyFermS; SHIME)

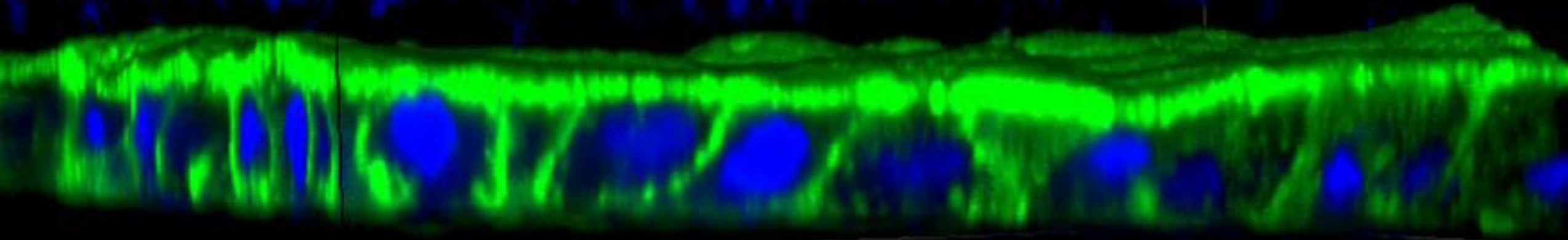


Physiometric systems

(e.g. gut-on-a-chip; HMI; GuMI)

Understanding by recreating Host-Microbiome (Microbiota) interactions in a miniature human gut

Dr. Jianbo Zhang (SILS-UvA formerly ETH and MIT)



The Wish List (Roadmap)

Controlled
ANAEROBIC
apical flow

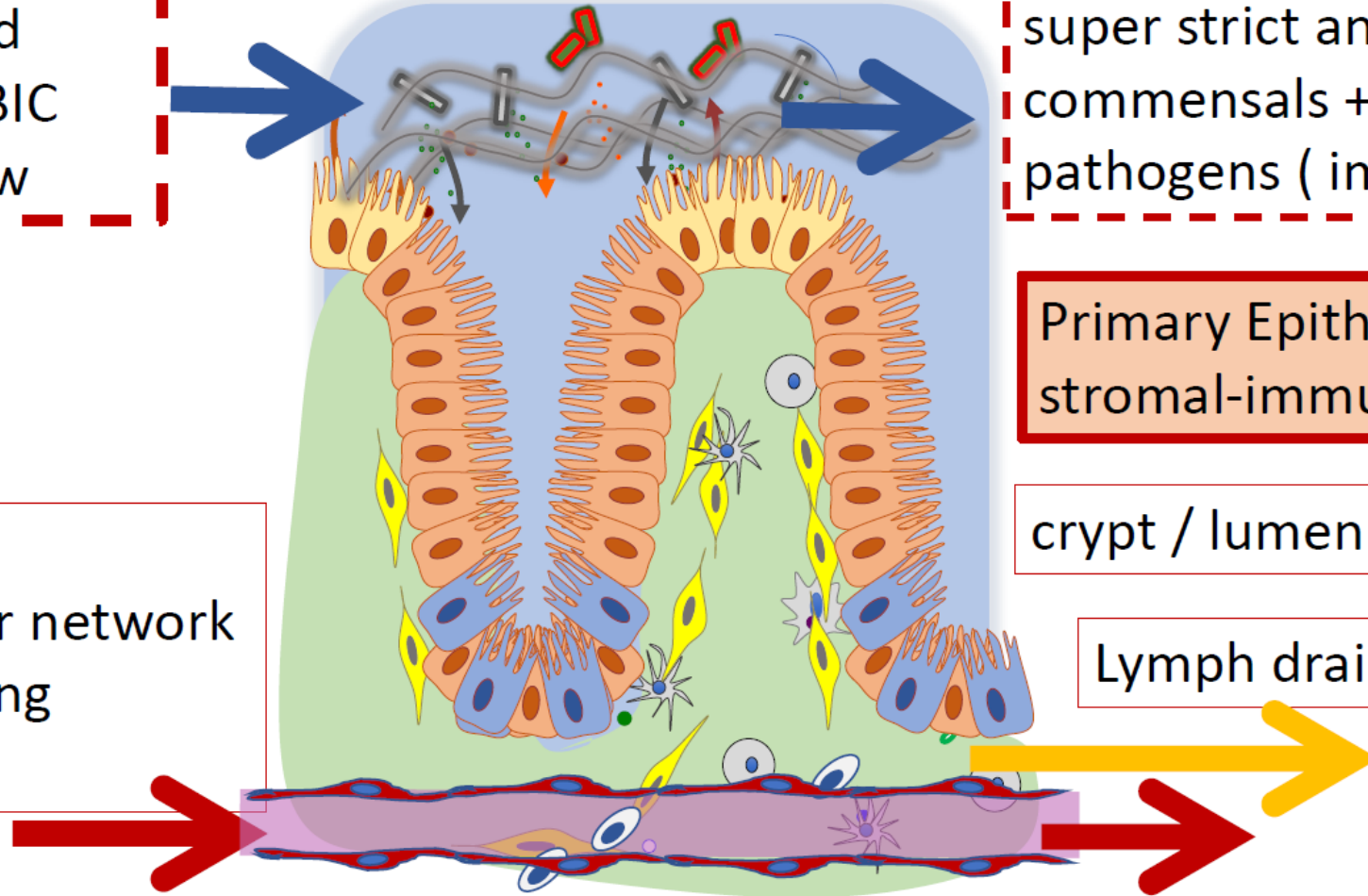
microbiome =
super strict anaerobic /
commensals +
pathogens (imaging)

Primary Epithelial –
stromal-immune tissue

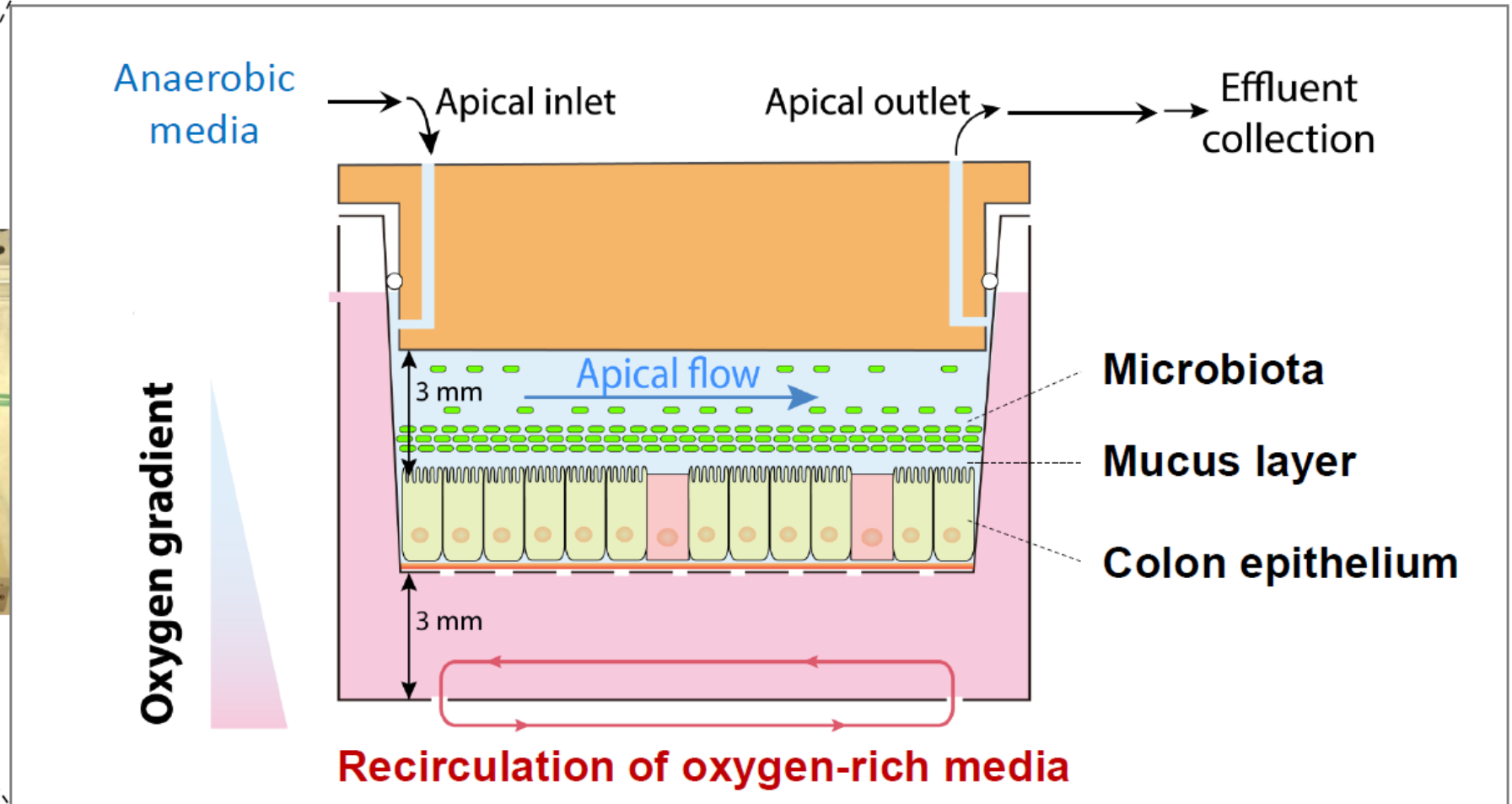
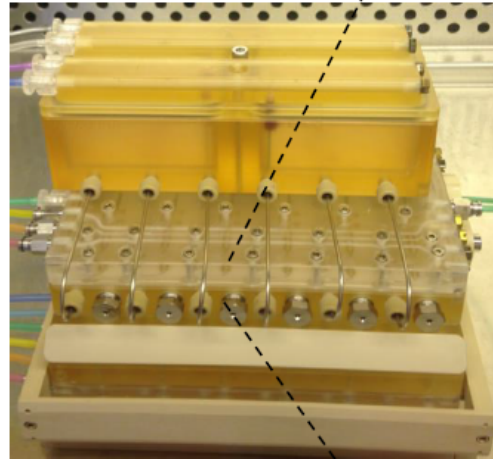
crypt / lumen structure

Lymph drainage

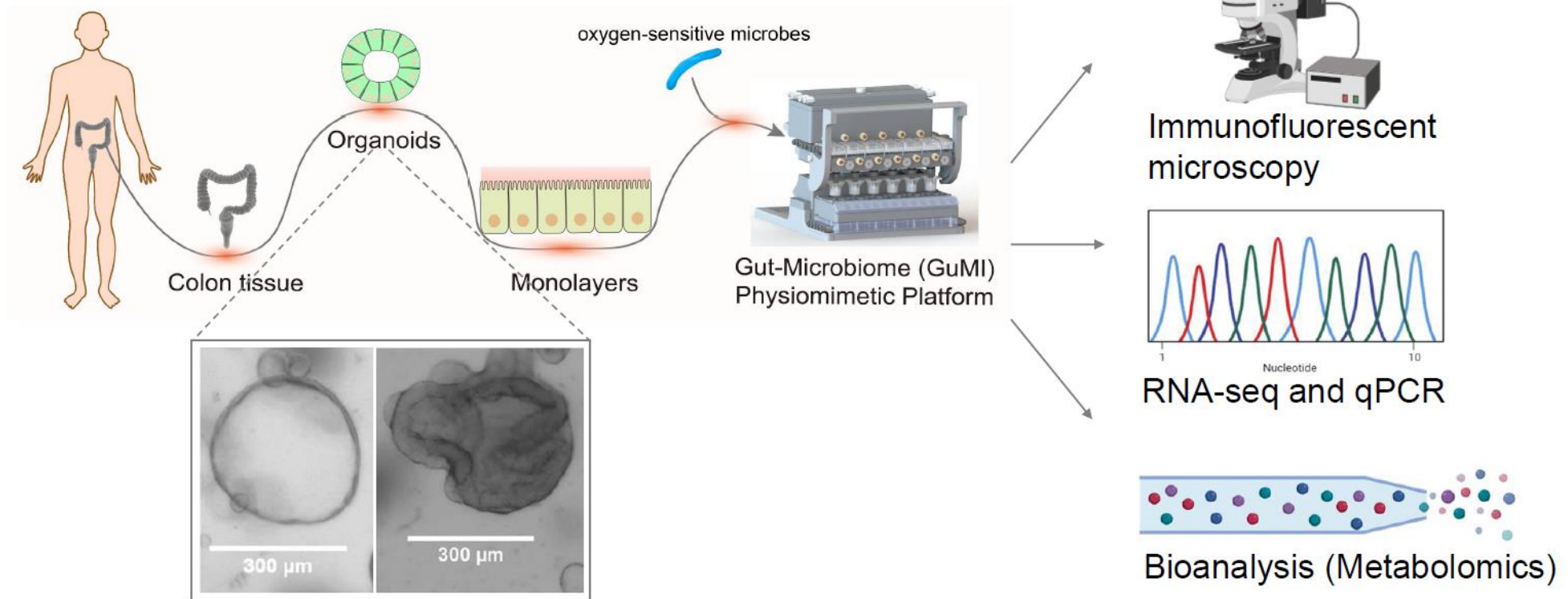
Perfusable
microvascular network
with circulating
immune cells



Gut-Microbe (GuMI) physiomimetic system

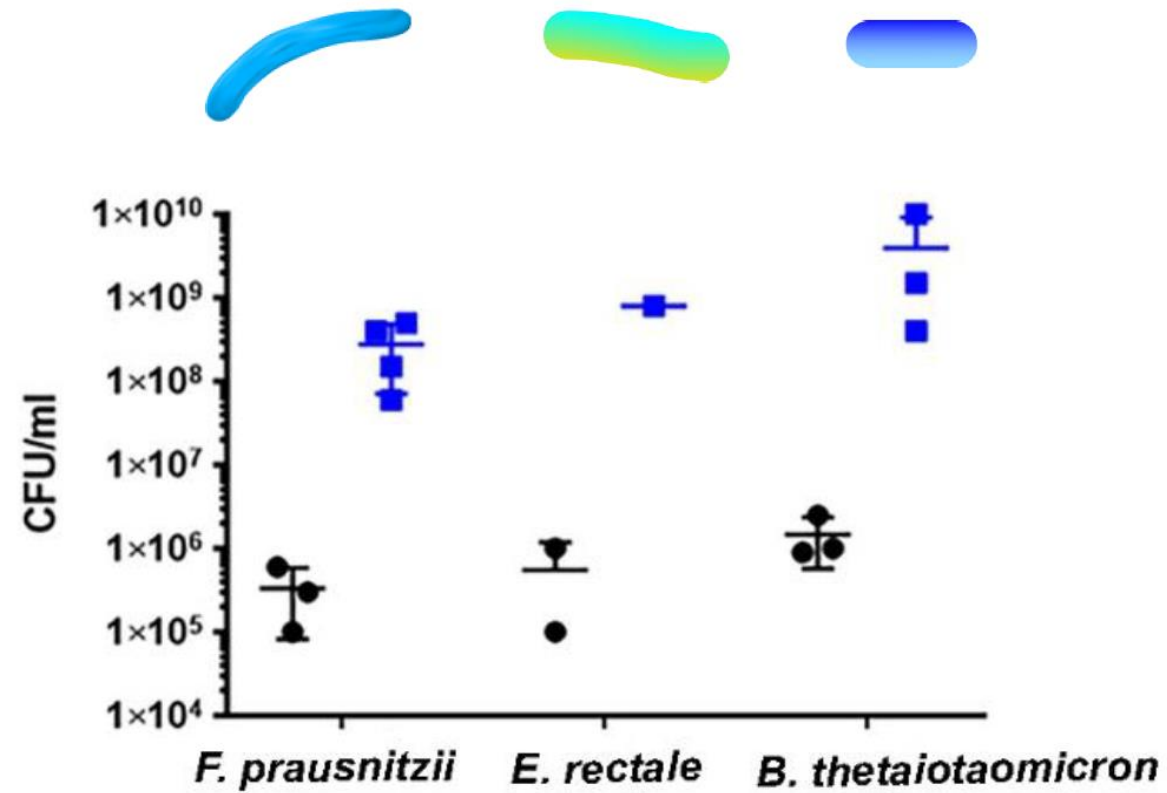


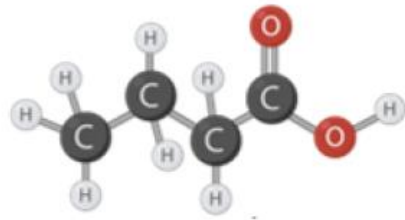
Workflow to study microbial impact on gut inflammation



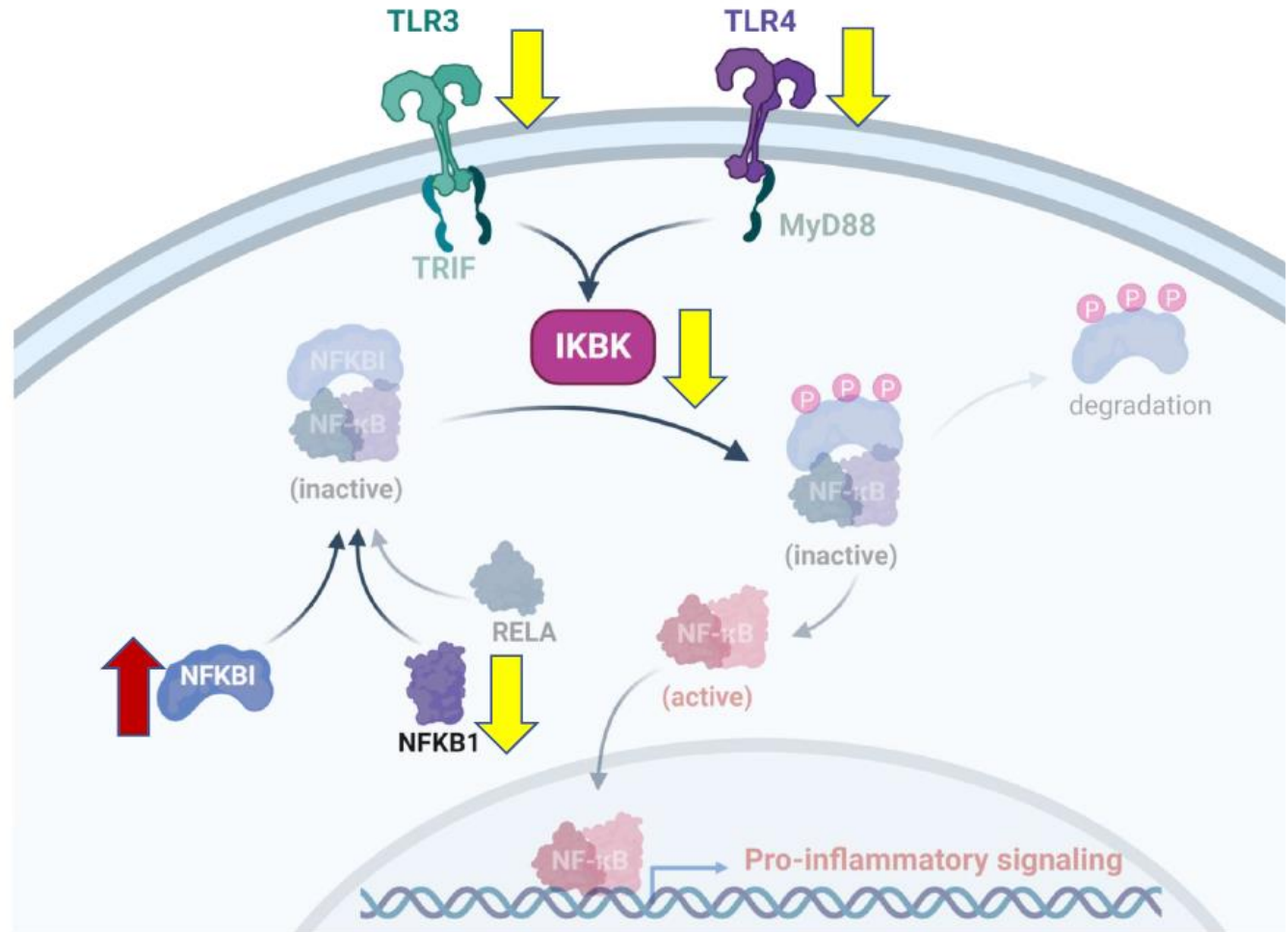
Bacterial growth in the GuMi model system

Super oxygen-sensitive bacteria grew

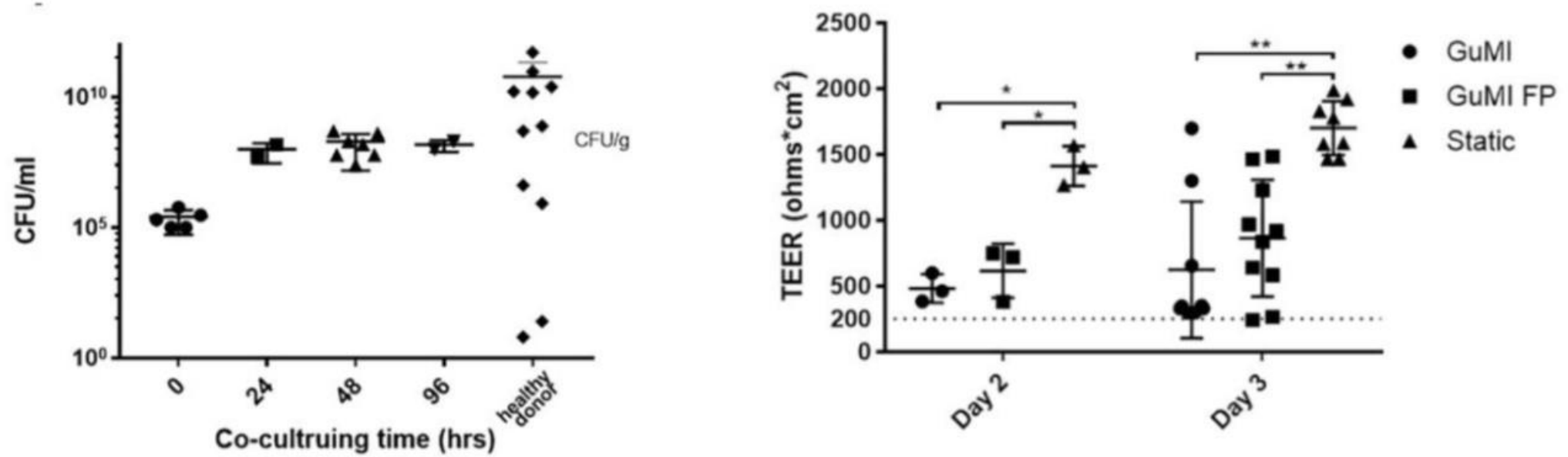




Butyrate



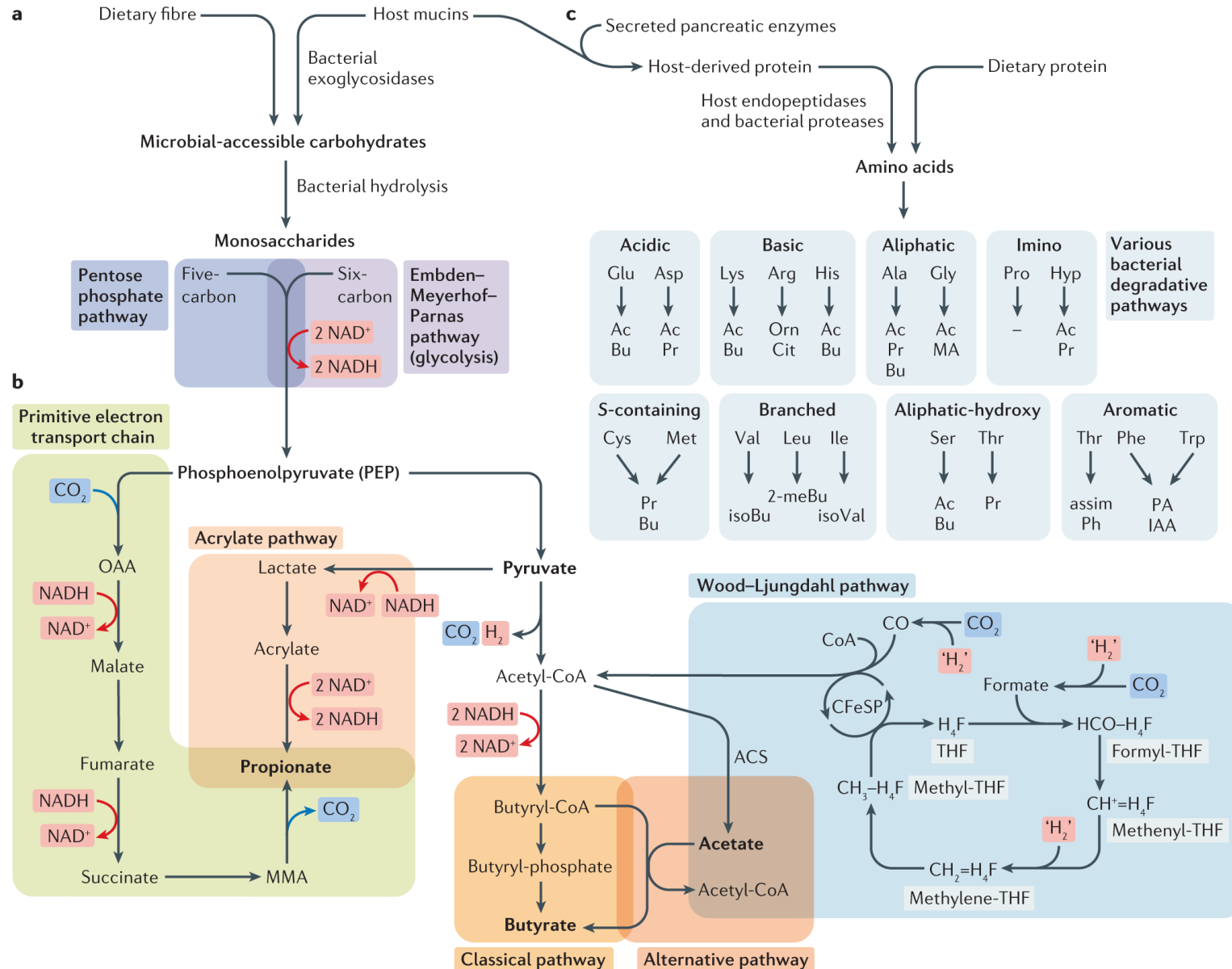
GuMI maintains barrier function and supports bacterial growth



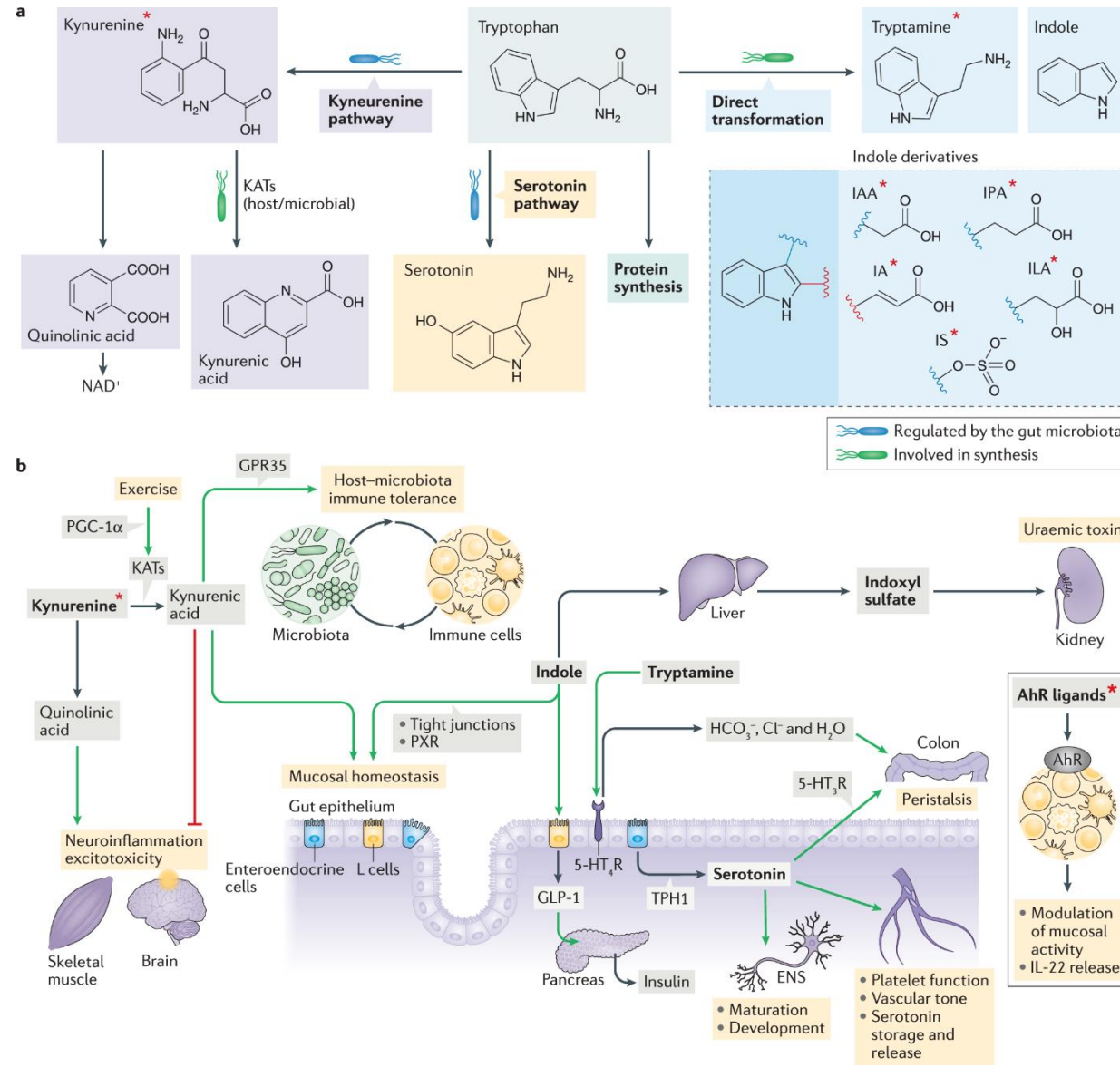
Faecalibacterium prausnitzii growth reached the plateau after 24 h.

Epithelial barrier function is maintained despite the presence of highly dense bacterial cells.

Progress in understanding the molecular basis of host-microbe interaction: Short chain fatty acids/ amino acids

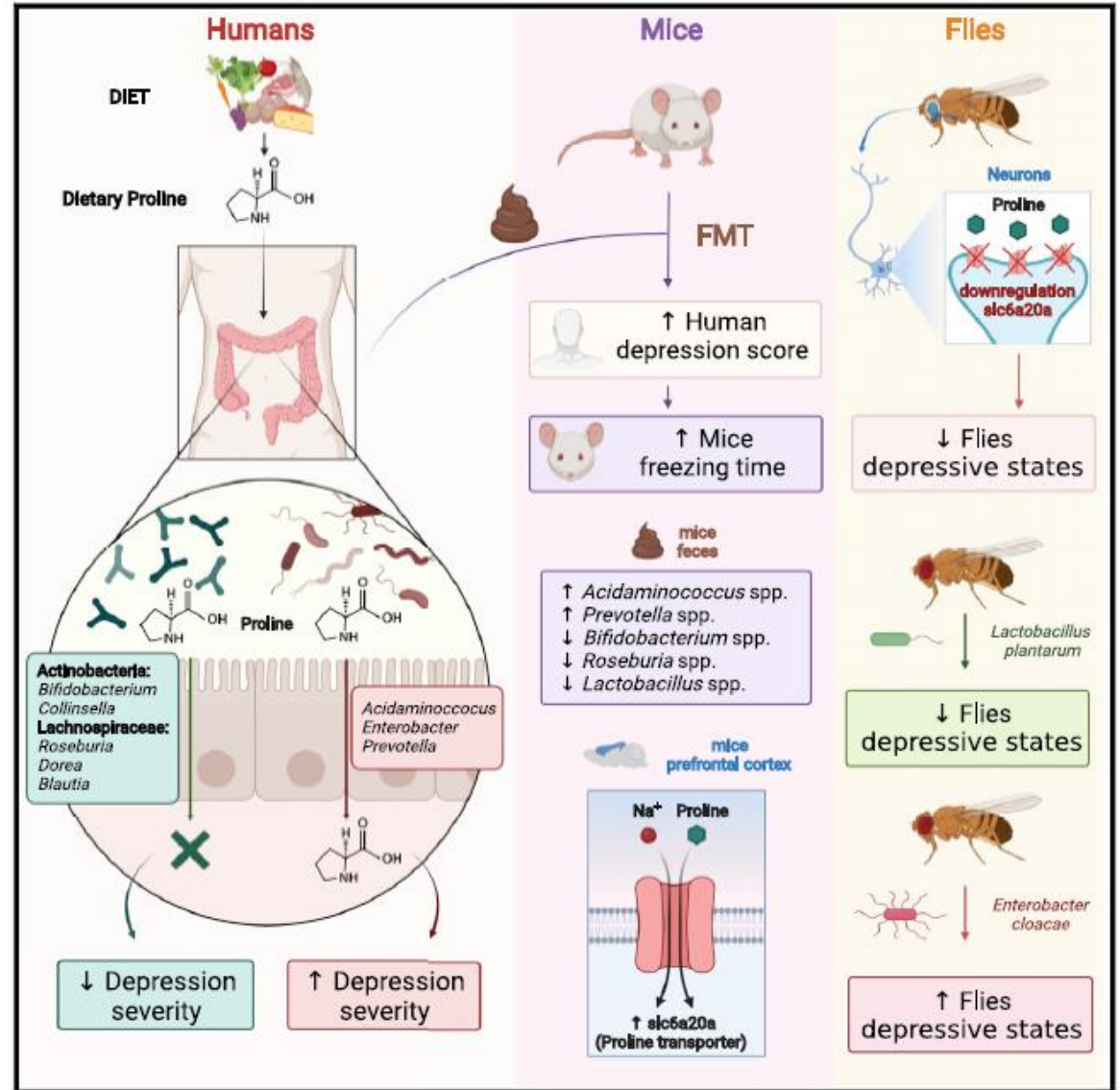
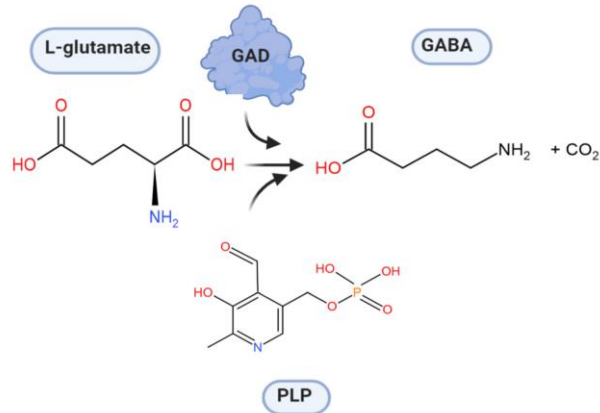
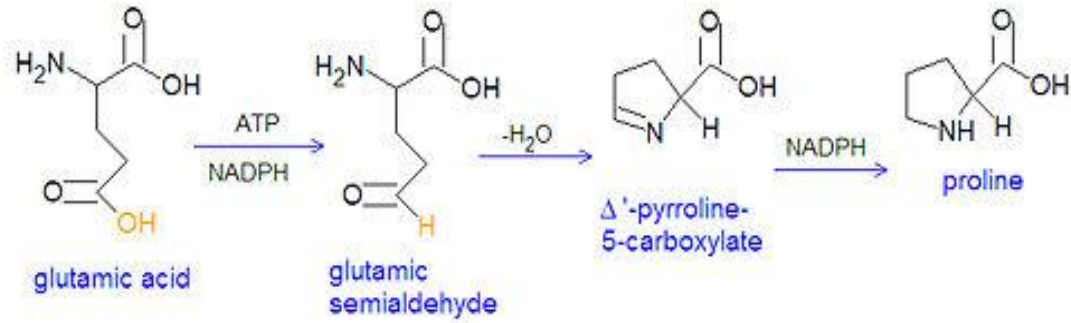


Progress in understanding the molecular basis of host-microbe interaction; tryptophan metabolism and serotonin



Progress in understanding the molecular basis of host-microbe interaction; proline metab., glutamate and GABA

<https://doi.org/10.1016/j.cmet.2022.04.001> (Cell Metabolism)



Bacterial spores; the good.....& the bad

LETTER

OPEN

doi:10.1038/nature17645

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

Hilary P. Browne^{1*}, Samuel C. Forster^{1,2,3*}, Blessing O. Anonye¹, Nitin Kumar¹, B. Anne Neville¹, Mark D. Stares¹, David Goulding⁴ & Trevor D. Lawley¹

www.nature.com/scientificreports



RESEARCH ARTICLE



Visualization of SpoVAEa Protein Dynamics in Dormant Spores of *Bacillus cereus* and Dynamic Changes in Their Germinosomes and SpoVAEa during Germination

Yan Wang,^a Norbert O. E. Vischer,^a Demi Wekking,^a Alessandra Boggian,^a Peter Setlow,^b Stanley Brul^a

^aMolecular Biology and Microbial Food Safety, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands

^bDepartment of Molecular Biology and Biophysics, UConn Health, Farmington, Connecticut, USA

scientific reports



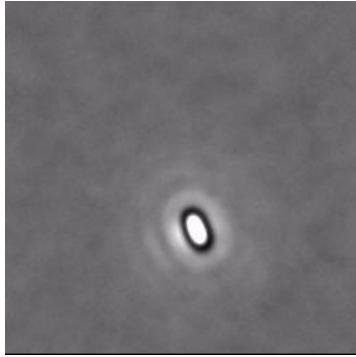
OPEN Organization and dynamics of the SpoVAEa protein and its surrounding inner membrane lipids, upon germination of *Bacillus subtilis* spores

Juan Wen¹, Norbert O. E. Vischer¹, Arend L. de Vos¹, Erik. M. M. Manders², Peter Setlow³ & Stanley Brul¹

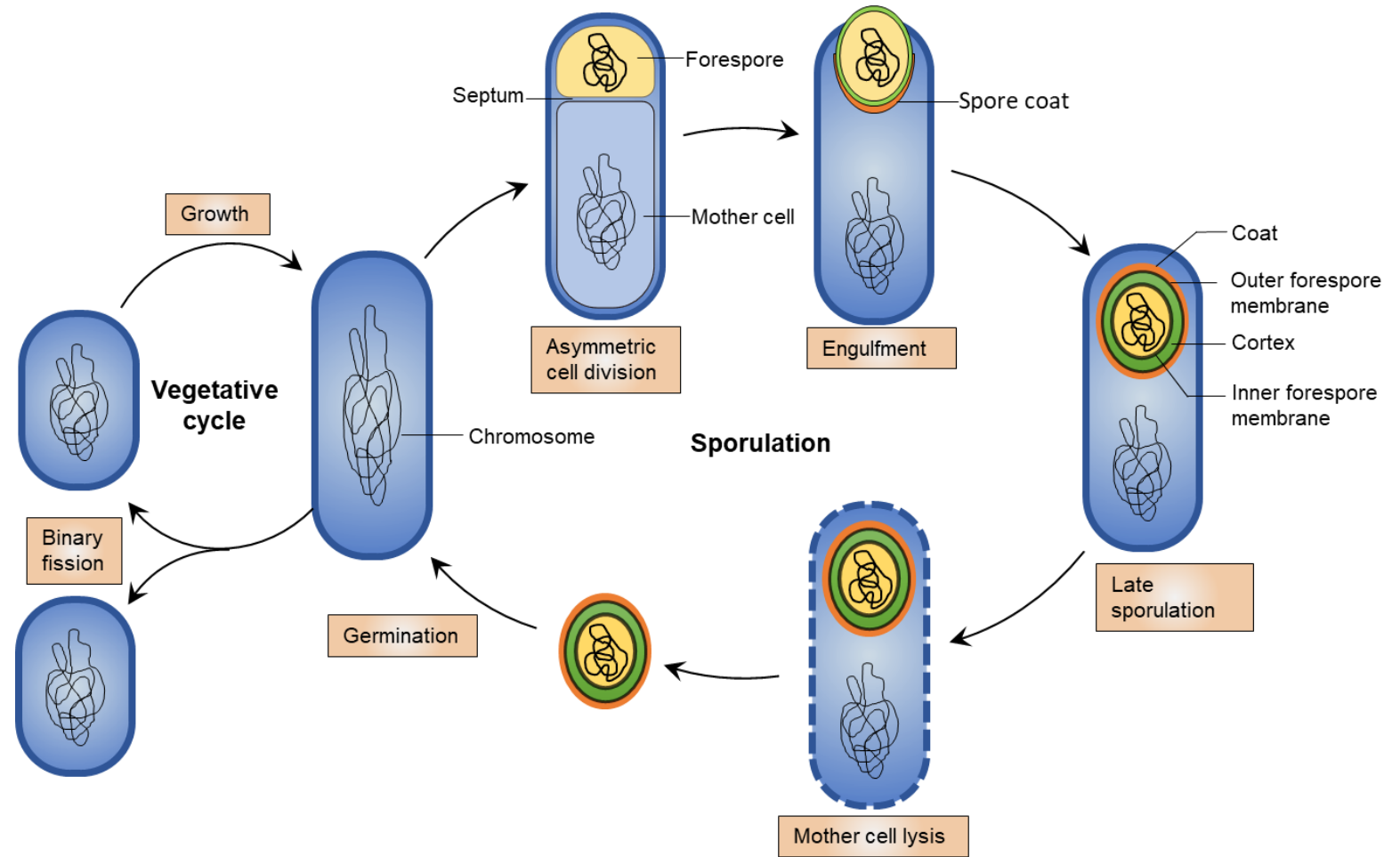
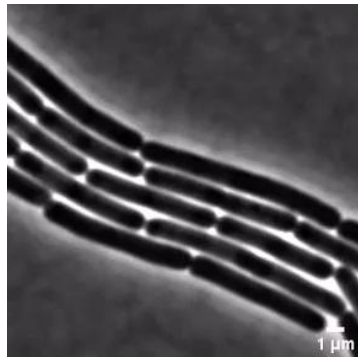
<https://systemsbiology.amsterdam/>

Sporulation cycle of *Bacillus cereus*

Germination and outgrowth:



Sporulation:

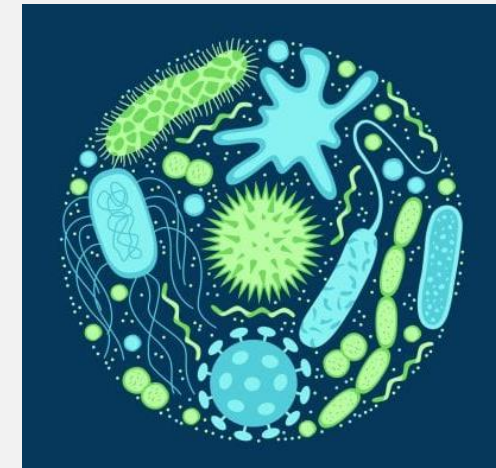


ANTIMICROBIAL RESISTANCE (AMR)

The group linked to the NVWA chair @ SILS-UvA (Benno Ter Kuile) works on:

- Plasmid-mediated → transfer of antibiotic resistance genes carried on plasmids (horizontal gene transfer)
- Antibiotic-induced → sub-lethal antibiotics exposure leads to mutagenesis with acquisition of resistance (vertical gene transfer)

Can be extended to real life (microbiome/ microbiota) settings!



Factors responsible

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.



Over-prescribing
of antibiotics



Patients not finishing
their treatment



Over-use of antibiotics in
livestock and fish farming



Poor infection control
in hospitals and clinics



Lack of hygiene and poor
sanitation



Lack of new antibiotics
being developed

Model development on individual level and its impact on a biological system; example @ the Centre for Urban Mental Health @ UvA (Van der Wal et al. Lancet 11, 991, 2021)

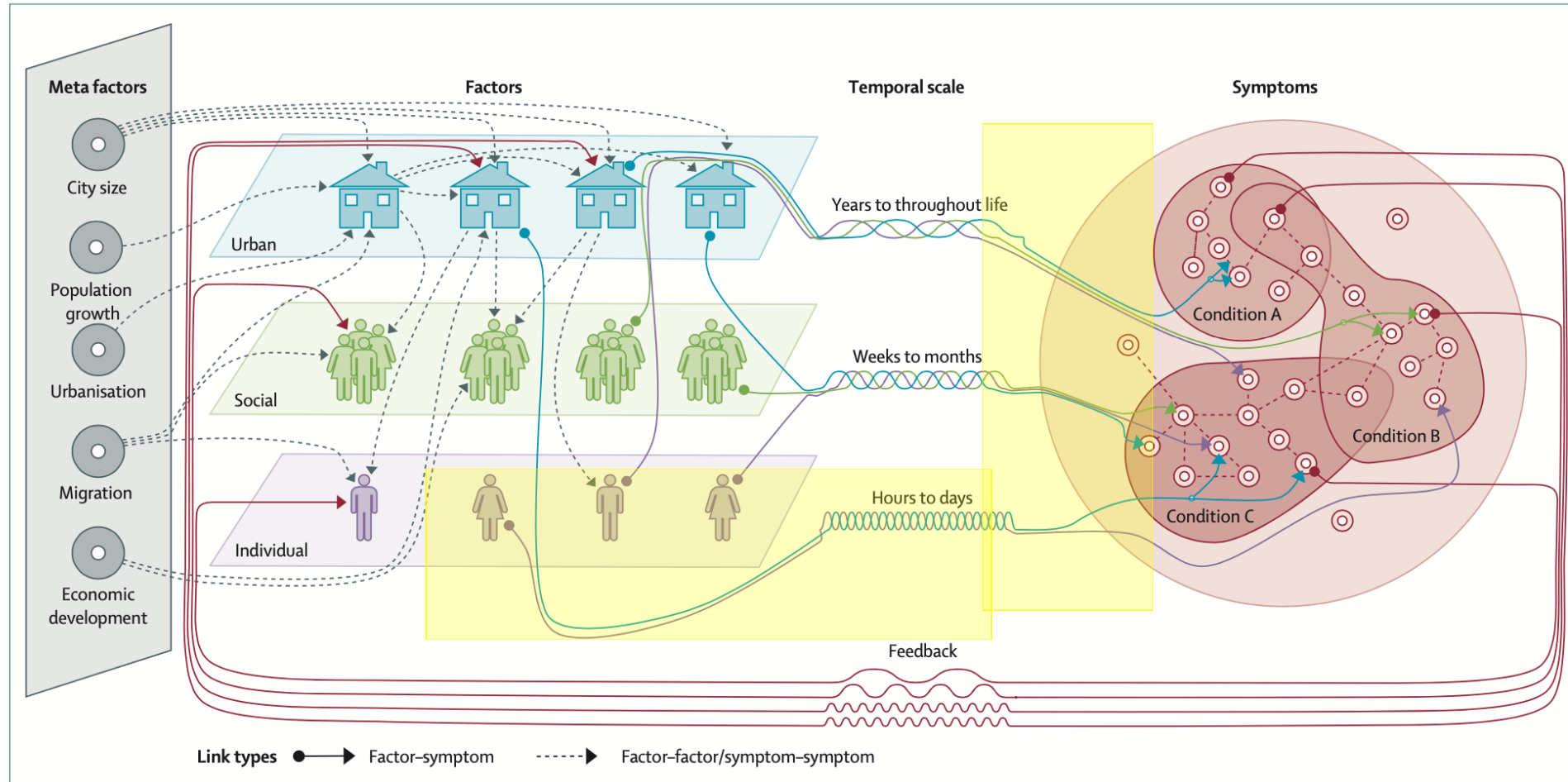


Figure 3: Conceptual framework of the relationship between factors in the urban environment and CMD outcomes

This framework conceptualises urban mental health from a complex systems perspective. Meta factors (grey box) are considered to have a dynamic effect on the urban environment and its inhabitants. Factors are categorised as urban factors (eg, air pollution or built environment), social factors (eg, social cohesion), or individual factors (eg, individual demographic, psychological, or neurobiological characteristics). Arrows between the factors and CMD symptoms represent the different temporal scales across which factors can assert their effect. CMDs are represented as symptom clusters connected by overlapping symptoms. Feedback arrows represent the possibility of feedback from CMD symptoms to explanatory factors, which can also occur over different timescales. CMD=common mental disorder.

Final conclusions

- Causality of gut microbiota in many human (autoimmune) diseases is not known.
- Fecal microbiota transplantation studies suggest a role for specific bacterial strains in disease including diabetes, inflammatory bowel disease and under- or overweight
- *Future*: personalized diet (based on gut microbiota composition) in combination with novel probiotic-medication (synergy) to improve human (autoimmune) diseases.
- The gut harbors an ecosystem with (spore forming) adapted microbes! Study of (transkingdom) interaction between its members is important to understand microbiota-related pathologies and to design effective interventions.
- Miniature Gut models can recreate important physiologically relevant environments to help understand the function of gut microbiota.
- Unique and extensive physiological knowledge on AMR and bacterial spore formers, prime inhabitants of the Gut and highly represented in the gut microbiota is available.
- Extensive modelling knowledge infrastructure needed at different time and length scales. @UvA an example is available at the Centre for Urban Mental Health.

Discussion and queries

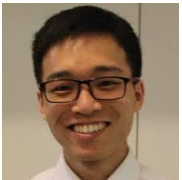
Microbes, microbiota and microbiomes;
their role in humans, animals, plant and environment.



[Home-en | Holomicrobiome \(holomicrobiome.nl\)](https://home-en.holomicrobiome.nl)

Stanley Brul @ Swammerdam Institute for Life Sciences; University of Amsterdam
Kennislezing NVWA 30 Juni 2022 <https://sils.uva.nl/> <https://systemsbiology.amsterdam/>

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Hilde Herrema, Max Nieuwdorp, Wouter de Jonge, Anja Lok (Amsterdam UMC), Hauke Smidt (WUR)

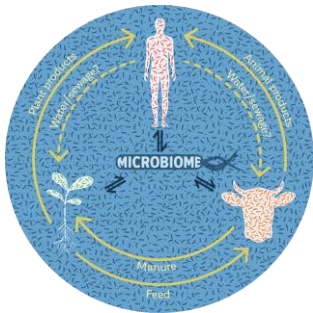


Timeline-planning



Timeline as of april 2022:

Preproposal oktober 2022, Full application January 2023



Task Force; Consortium core; Extended consortium

Marten Smidt (UvA, FNWI, SILS):

Harro Bouwmeester (UvA, FNWI, SILS):

Hauke Smidt (WUR):

Age Smilde (UvA, FNWI, SILS):

Stanley Brul (UvA, FNWI, SILS):

Gerard Muijzer (UvA, FNWI, IBED):

Max Nieuwdorp (AUMC):

Hilde Herrema (AUMC):

Project leader

Plant/root domain

Animal microbiome

Modeling, data analysis

General microbiology and fermentation

Environmental microbiology

Human Microbiome, health

Human Microbiome, health

“External”

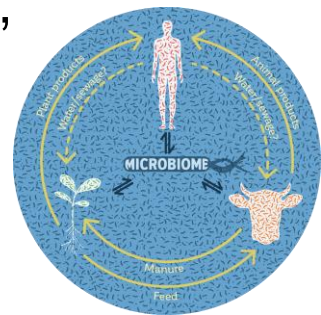
Helen Bergman

Quartermaster

Peter Vermij

Scientific writer

Extended Consortium has a great number of representatives from UMCs, universities, Knowledge Institutes, industries, Ministries.



Task Force; Consortium core; Extended consortium

Universiteiten/academische ziekenhuizen:

RUG (JF Salles), UvA (oa AmsterdamUMC, FNWI(SILS, IVI), FGW), VU (oa B. Teusink), UM (oa N. Bocken), Erasmus (J. Samson), UL (T. Hamkemeijer), UU (A. Stegeman), WUR (oa H. Smidt), TUD (M. van Loosdrecht), RU (L. van Niftrik)

Organisaties

TIFN (A. Kardinaal), NIOZ (L. Villanueva/C. Brussaard), NIOO (E. Kuramae) , KWR (P. van de Wielen/ T. ter Laak), Plantum (M. van Vegchel), NIZO (A. Kardinaal), TNO (R. Montijn), Sanquin (M. van Ham). Topsector health, Topsector T&U (J. Vogelenzang), RIVM (S. Fuentes)

Bedrijven (onder constructie)

BASF (Plantum, J. van den Berg), TIFN geassocieerde bedrijven, Danone (J. Knol en via TiFN), Trouw/Nutreco (L. den Hartog), Baseclear (B. Reichert), ...

Ministries

LNV (P.P. Mertens, M.J.M..Latijnhouwers, M.S, Plantinga), VWS (..), EZ (directie Strategie, kennis, Innovatie)

