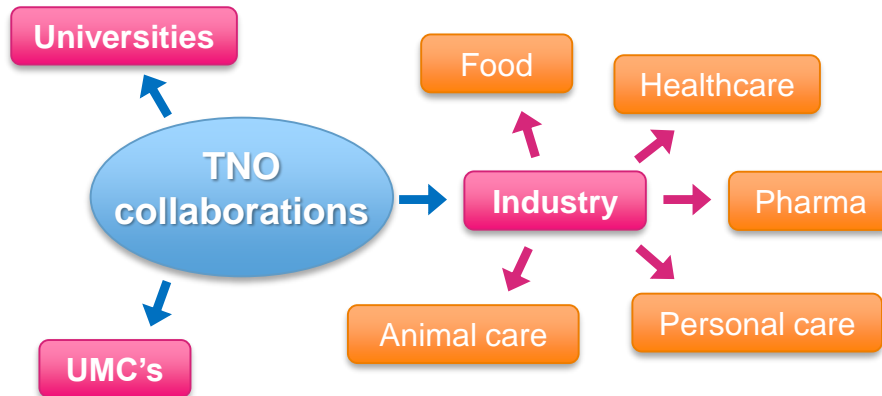# MICROBIOME FOR HEALTH

Microbiology & Systems Biology

Contact: Edwin Abeln

TNO innovation for life

TNO MICROBIOLOGY

> TNO is an <u>independent research institute</u>

> Many collaborators

> National and international

> Industry and academy

> High expertise on microbiology ➔

> Applied research

> TNO has over **15 years of experience** in microbiome research

> High quality data

> Publications, peer-reviewed

> Integrated, systems biology approach

> Functional tests to link microbiome to physiology

Early Respiratory Microbiota Composition Determines Bacterial Succession Patterns and Respiratory Health in Children

Giske Biesbroek[1]*, Evgeni Tsivtsivadze[2]*, Elisabeth A. M. Sanders[1], Roy Montijn[2], Reinier H. Veenhoven[3†], Bart J. F. Keijser[2], and Debby Bogaert[1]

In Vitro **Fermentation of Selected Prebiotics and Their Effects on the Composition and Activity of the Adult Gut Microbiota**

Sophie Fehlbaum[1,]*, Kevin Prudence[1], Jasper Kieboom[2], Margreet Heerikhuisen[2], Tim van den Broek[2], Frank H. J. Schuren[2], Robert E. Steinert[1] and Daniel Raederstorff[1]

VISION

› We believe that a healthy microbiome is essential to optimize health.

› TNO therefore aims to develop better research tools that enable the development of microbiome-directed health products.

   › Our application areas:
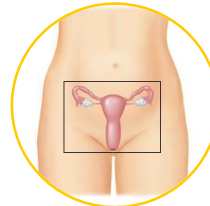

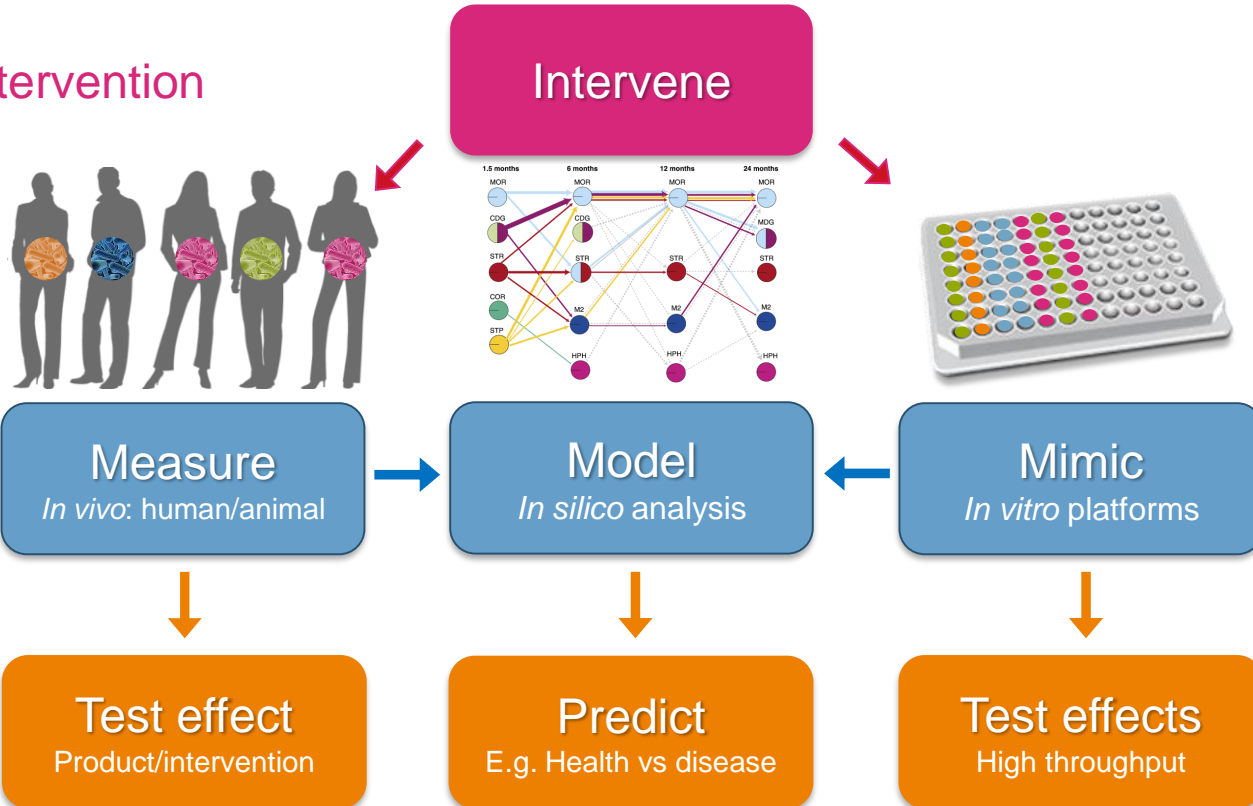| Gut health | Oral health | Respiratory health | Vaginal health | Skin health | Systemic health |

TYPES OF RESEARCH

Product or intervention

Intervene

Study type

Measure
In vivo: human/animal

Model
In silico analysis

Mimic
In vitro platforms

Outcome

Test effect
Product/intervention

Predict
E.g. Health vs disease
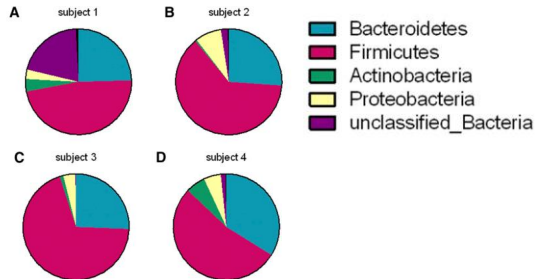
Test effects
High throughput
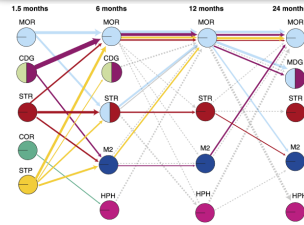
WHAT WE Measure

Microbiome composition
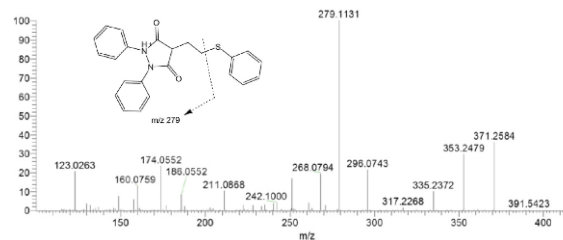
- Microbiome composition
  - 16S or metagenome
  - ITS Fungal composition
  - Anti-biotic resistance
  - Viability

Microbial composition of individual and pooled fecal samples.[1]
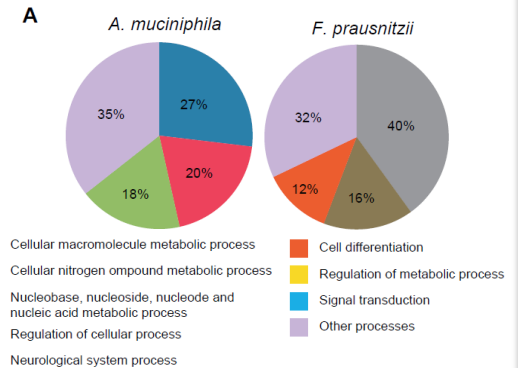
Microbiome function

- Microbiome function
  - Metagenome
  - Transcriptome
  - Metabolome
    - SCFA analysis
    - Microbiome metabolites
    - Drug metabolites
  - Microscopy (fluorescence)


High-resolution mass spectra of deoxysulfinpyrazone metabolite.[1]

Physiology of host

- Physiology of host
  - Blood biomarkers
  - Metabolites
  - Host-microbiome interactions

The distribution of affected genes in organoids in relation to *A. muciniphila* and *F. prausnitzii*.[2]

1. Van de Steeg et al. An Ex Vivo Fermentation Screening Platform to Study Drug Metabolism by Human Gut Microbiota. (2018)
2. Lukovac et al. Differential Modulation by Akkermansia muciniphila and Faecalibacterium prausnitzii of Host Peripheral Lipid Metabolism and Histone Acetylation in Mouse Gut Organoids. (2014)

Relationship between the composition of the gut microbiota and the levels of short-chain fatty acids (SCFAs).[3]
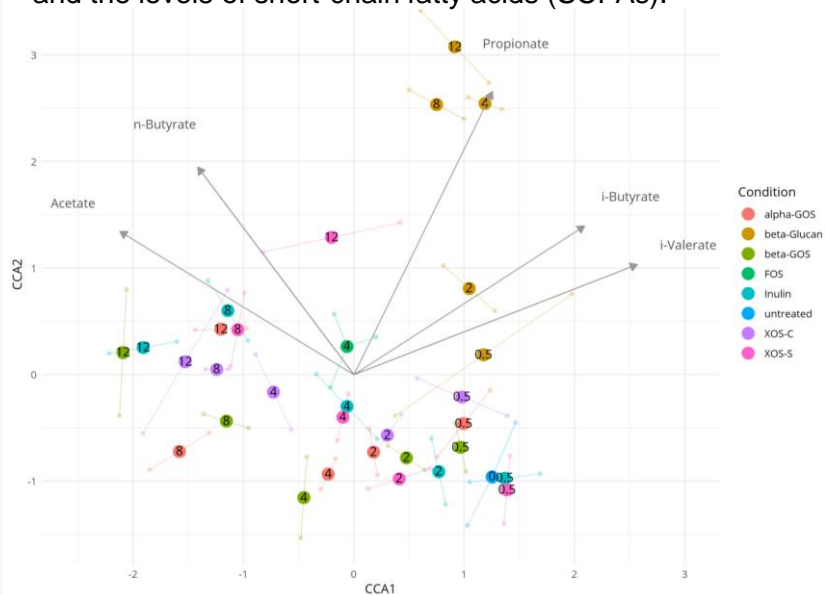
The larger dots represent microbiome composition and show the centroid values for each of the samples. Arrows represent the direction of the association of microbiome composition with specific SCFA levels.

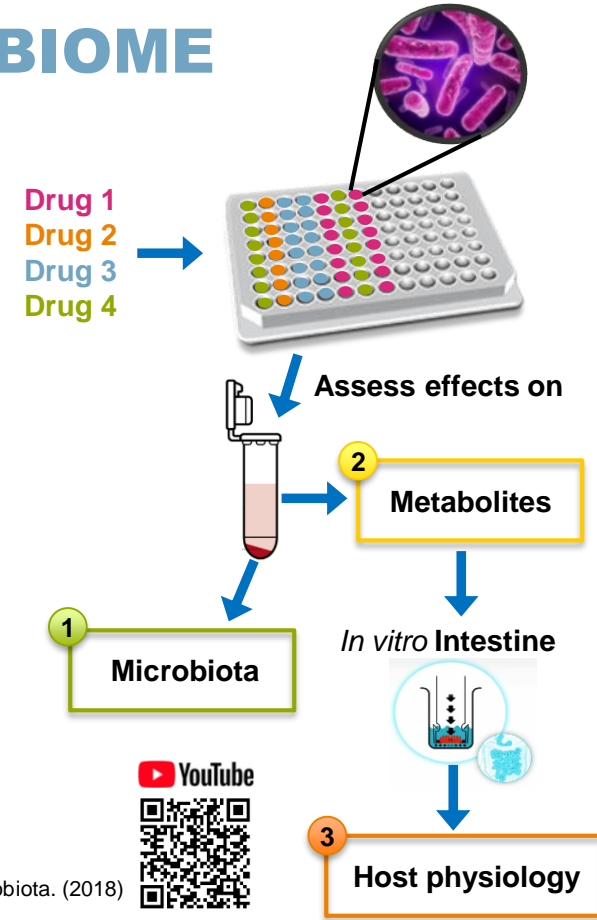Nasopharynx microbiota colonization patterns in healthy children over time.[4]
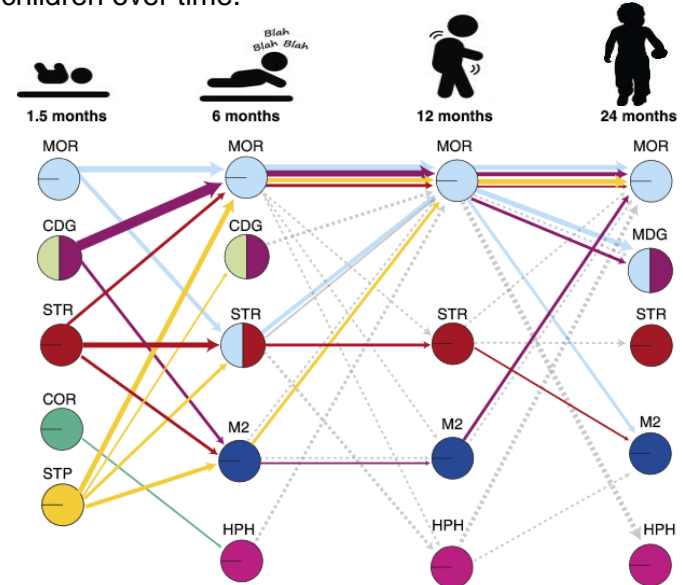
CDG = Corynebacterium and Dolosigranulum; COR = Corynebacterium; HPH = Haemophilus; M2=Moraxella lincolnii; MDG= Moraxella- and Dolosigranulum-dominated clusters; MOR = Moraxella; STP = Staphylococcus; STR = Streptococcus.

3.   Fehlbaum et al. In Vitro Fermentation of Selected Prebiotics and Their Effects on the Composition and Activity of the Adult Gut Microbiota. (2018)
4.   Biesbroek et al. Early Respiratory Microbiota Composition Determines Bacterial Succession Patterns and Respiratory Health in Children. Am J Respir Crit Care Med (2014)
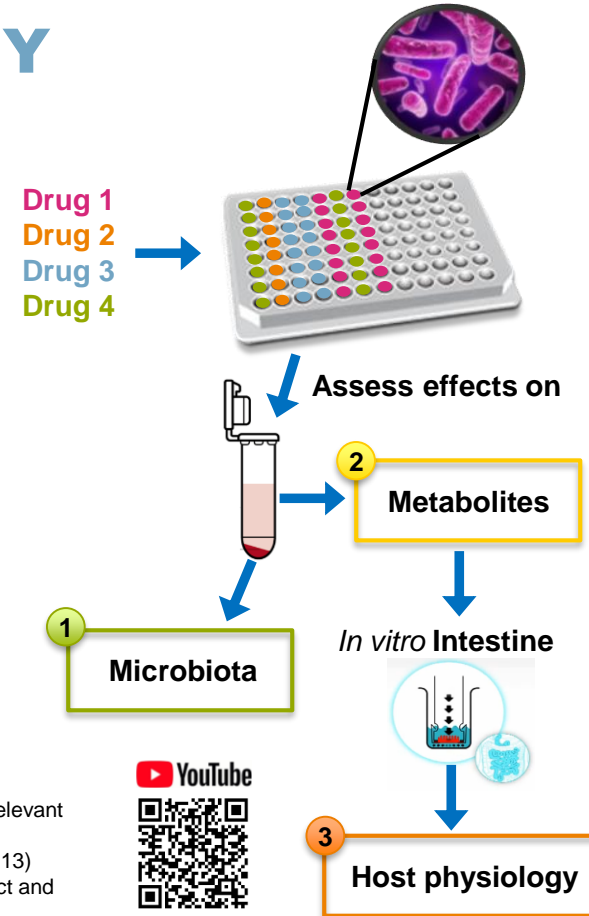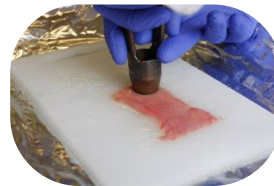
Mimicking THE *IN VIVO* GUT MICROBIOME

I-SCREEN

› I-Screen: an *in vitro* human gut microbiome model[1,3,5]

› **Test your product:**
  › Cost efficient set up allows for screening of compounds
  › Proven benefit for food, ingredient and drug testing
  › Evaluate effects of compounds on
    1. **Gut microbiota**
    2. **Compound metabolism**
  › Full analytical omics toolbox → see measure

› Validated in comparative study[1]

Drug 1
Drug 2
Drug 3
Drug 4

Assess effects on

2 **Metabolites**

1 **Microbiota**

In vitro **Intestine**

▶ YouTube

3 **Host physiology**

1. Van de Steeg et al. An Ex Vivo Fermentation Screening Platform to Study Drug Metabolism by Human Gut Microbiota. (2018)
3. Fehlbaum et al. In Vitro Fermentation of Selected Prebiotics and Their Effects on the Composition and Activity of the Adult Gut Microbiota. (2018)
5. Ladirat et al. High-throughput analysis of the impact of antibiotics on the human intestinal microbiota composition. (2013)

Mimicking *IN VIVO* GUT PHYSIOLOGY
INTESTINE™

› InTESTine™: an *in vitro* human intestinal tissue model[6,7,8]

› **Test your product:**
  › Effect of **microbiome metabolites** on gut health/absorption
  › Gut absorption (of drugs, nutrients, metabolites)
  › Epithelial barrier function
  › Detection of early immune response
  › Reduce *in vivo* studies

› Model is based on human intestinal tissue

Drug 1
Drug 2
Drug 3
Drug 4

Assess effects on

2 **Metabolites**

1 **Microbiota**

In vitro **Intestine**

YouTube

3 **Host physiology**

6. Westerhout et al. Prediction of Oral Absorption of Nanoparticles from Biorelevant Matrices Using a Combination of Physiologically Relevant In Vitro and Ex Vivo Models. (2017)
7. Westerhout et al. A new approach to predict human intestinal absorption using porcine intestinal tissue and biorelevant matrices. (2013)
8. Vaessen et al. Regional Expression Levels of Drug Transporters and Metabolizing Enzymes along the Pig and Human Intestinal Tract and Comparison with Caco-2 Cells. (2017)
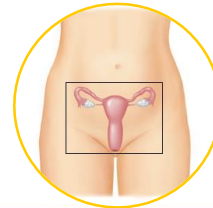
MICROBIOME FIELDS WE WORK IN

Gut health   **Oral health**   **Respiratory health**   **Vaginal health**   **Skin health**   **Systemic health**

› We have established multiple research tools, but we are looking to expand our toolbox further. Therefore, we are looking for co-development partners.

Co-development Opportunities

Academic partners: joint exploration

Business partners: joint exploitation

GUT HEALTH

| Measure (*In vivo*) | Model (*In silico*) | Mimic (*In vitro*) |

Technology readiness:
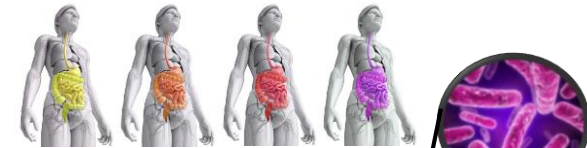
Exploration
Early development
Late development
Exploitation

› What we have:

  › *In vitro* platform I-screen based on colon microbiota from healthy people[1,3,5]

› What we would like:

  › Disease specific and personalized *in vitro* platforms I-screen
  › *In vitro* platforms I-screen based on small-intestinal microbiota
  › Quantitative microbiome drug metabolism system

Co-development Opportunities

▶ YouTube

1. Van de Steeg et al. An Ex Vivo Fermentation Screening Platform to Study Drug Metabolism by Human Gut Microbiota. (2018)
3. Fehlbaum et al. In Vitro Fermentation of Selected Prebiotics and Their Effects on the Composition and Activity of the Adult Gut Microbiota. (2018)
5. Ladirat et al. High-throughput analysis of the impact of antibiotics on the human intestinal microbiota composition. (2013)
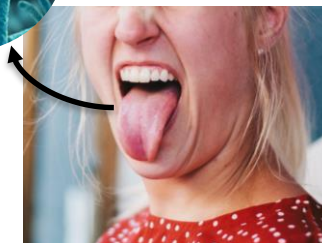
ORAL HEALTH

Technology readiness:

Exploration
Early development
Late development
Exploitation

| Measure (*In vivo*) | Model (*In silico*) | Mimic (*In vitro*) |

› What we have:

  › Knowledge and *in vivo* studies on the microbiome of the healthy mouth

› What we would like:

  › *In vitro* model for dental biofilms and tongue (halitosis)
  › Develop a sensor toothbrush for oral (microbiome) health

Co-development Opportunities

RESPIRATORY HEALTH

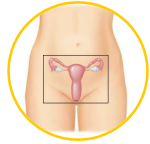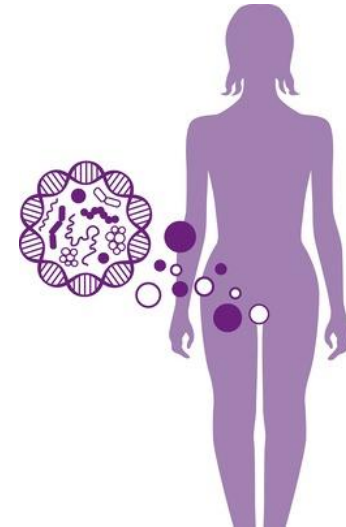| Measure (*In vivo*) | Model (*In silico*) | Mimic (*In vitro*) |

Technology readiness:
- Exploration
- Early development
- Late development
- Exploitation

› What we have:
  › Knowledge and *in vivo* studies e.g. on early life development of microbiome in relation to health[4]

› What we would like:
  › *In vitro* microbiology model
  › Preventive personalized healthcare strategies

Co-development Opportunities

4. Biesbroek et al. Early Respiratory Microbiota Composition Determines Bacterial Succession Patterns and Respiratory Health in Children. Am J Respir Crit Care Med (2014)

VAGINAL HEALTH

Measure (*In vivo*)	Model (*In silico*)	Mimic (*In vitro*)

Technology readiness:

- Exploration
- Early development
- Late development
- Exploitation

› What we have:
  › Extensive knowledge on the vaginal microbiome
  › Experimental set-up to mimic the vaginal microbiome, in healthy and disease

› What we would like:
  › Develop a personalized screening system for identifying non-antibiotic treatments for Bacterial Vaginosis and other health problems

Co-development Opportunities

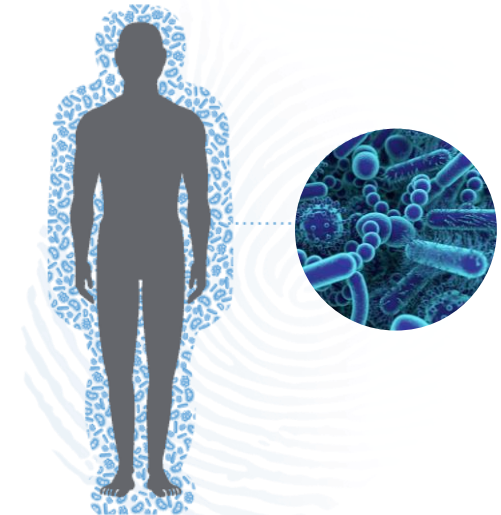# SKIN HEALTH

| Measure (*In vivo*) | Model (*In silico*) | Mimic (*In vitro*) |

Technology readiness:

- Exploration
- Early development
- Late development
- Exploitation

› What we have:

  › Exploratory research on *in vitro* microbiome model
  › Generic toolbox for microbiome research and skin sampling protocol

› What we would like:

  › Translational healthy skin microbiome model
  › Develop in-depth knowledge on relation microbiome and health
  › Translational skin disease microbiome model e.g. atopic dermatitis

Co-development Opportunities

SYSTEMIC HEALTH

| Measure (*In vivo*) | Model (*In silico*) | Mimic (*In vitro*) |

Technology readiness:
- Exploration
- Early development
- Late development
- Exploitation

› What we have:
  › *In vivo* studies to evaluate metabolic and immune health status
  › Systems biology expertise

› What we would like:
  › Identify specific roles of microbiome in systemic health
  › Identify microbiome-targeting interventions to stimulate specific health aspects
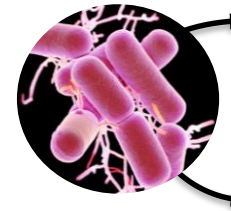
Co-development Opportunities

TNO COLLABORATION
FLEXIBILITY TO CHOOSE MODEL OF COLLABORATION

Co-development Opportunities

› Fit in goals of TNO
› Together with industry
› Translate knowledge into applicable models / readouts

Contract Research

› Tailor made study designs making use of existing models
› Making use of broad knowledge and expertise available
› Excellent project management and reporting

IP deals

› License agreements

Public Private Partnerships

› E.g. EU projects
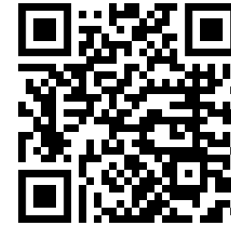
PEOPLE & CONTACT

Edwin Abeln
Sr. Business Development Manager

Email: edwin.abeln-at-tno.nl
Location: TNO Zeist
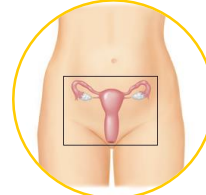Utrechtseweg 48

Gut health

Oral health

Respiratory health

Vaginal health

Skin health

Systemic health

LITERATURE

1. Van de Steeg et al. An Ex Vivo Fermentation Screening Platform to Study Drug Metabolism by Human Gut Microbiota. (2018)
2. Lukovac et al. Differential Modulation by Akkermansia muciniphila and Faecalibacterium prausnitzii of Host Peripheral Lipid Metabolism and Histone Acetylation in Mouse Gut Organoids. (2014)
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Further reading:

Google scholar:

▶ YouTube

TNO website:

THANK YOU FOR YOUR ATTENTION

Take a look at

Presentation by Dide Reijmer, *MSc*