

## Systems Ecology of the Human Microbiome



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Muller et al. (2018) Current Opinion in Systems Biology 8:73-80.



Muller et al. (2018) Current Opinion in Systems Biology 8:73-80.



Muller et al. (2018) Current Opinion in Systems Biology 8:73-80.



Muller et al. (2014) Nature Communications 5:5603.

Roume\*, Heintz-Buschart\* et al. (2015) npj Biofilms and Microbiomes 1:15007. Patents: PCT/EP2012/065178; PCT/EP2013/052134.

#### The biomolecular distillery









#### IMP **Integrated Meta-omics Pipeline**

Enhanced data usage

Reproducible

docker. M snakemake



Trezzi et al., unpublished.

#### http://r3lab.uni.lu/web/imp

Narayanasamy et al. (2016) Genome Biology 17:260.



## Why?



### **Chronic diseases**

- <u>Autoimmune</u>
- Cancer
- Metabolic
- Neurodegenerative



## Integrated omics of the gut microbiome in families with incidence of type 1 diabetes

## Comparison of previous study results

		Giongo / Brown <i>et al.</i> , 2011	Murri <i>et al.,</i> 2013	de Goffeau <i>et al.</i> , 2014	Davis- Richardson <i>et</i> <i>al.</i> , 2014	Endesfelder <i>et</i> <i>al.</i> , 2014	Kostic <i>et al.</i> , 2015
α-diversity		1	nd	1	?	=	•
functional diversity		•	=	nd	=	nd	=
Firmicutes/Bacteroidetes		•	•	•	¥	=	=
	B. dorei	=	nd	The human lineage Australopithecus afarensis	Pe Homo erectus Homo habilis	Homo neanderthalensis Homo s	sapiens 12 inches
abundances cases vs controls	other Bacteroides	<b>^</b>	1				
	Streptococcus	=	=				
	Prevotella	•	4				
	Veillonellaceae	1	1				
	butyrate-producers	•	?				
	others	Akkermansia <b>↓</b> Alistipes <b>∱</b>	Clostridium <b>∧</b> Lactobacillus ↓ Bifidobacterium ↓				

Giongo *et al.* (2011) *ISME J* **5**:82-91. Brown *et al.* (2011) *PLoS one* **6**:e25792. Murri *et al.* (2013) *BMC Med* **11**:46. de Goffeau *et al.* (2014) *Diabetologia* **57**:1569-77. Davis-Richardson *et al.* (2014) *Front Microbiol* **5**:678. Endesfelder *er al.* (2014) *Diabetes* **63**:2006-14. Kostic *et al.* (2015) *Cell Host Microbe* **17**:260-73.

## MuSt: <u>Multiplex Family Study in Type 1 Diabetes</u>

- Multi-omic measurements of gastrointestinal microbiota
- Deep phenotyping
- Sequencing of family genomes
- Nutritional information
- Partners:
  - Centre Hospitalier de Luxembourg
  - Integrated BioBank of Luxembourg





Heintz-Buschart et al. (2017) Nature Microbiology 16180:1-12.

#### Multi-omic data integration



Heintz-Buschart et al. (2017) Nature Microbiology 16180:1-12.

#### Taxonomic overviews 100-80abundance [%] 60-40-20-0- Alistipes putredinis Eubacterium eligens Prevotella other Prevotella copri Bacteroides dorei/vulgatus Bacteroides uniformis Frevolena Faecalibacterium prausnitzii unnamed Ruminococcus sp. 5\_1\_39BFAA Prevotella copri Alistipes sp. HGB5 Bacteroides ovatus Ruminococcus bromii Eubacterium rectale Clostridiales mOTU Bacteroidetes mOTU

• No generalisable taxonomic signature for TIDM

Heintz-Buschart et al. (2017) Nature Microbiology 16180:1-12.

## Systematically identifying the most discriminatory features





#### Decreased levels of enzymes from the exocrine pancreas

in faeces of individuals with  $\mathsf{TIDM}$ 

Heintz-Buschart et al. (2017) Nature Microbiology 16180:1-12.



Heintz-Buschart et al. (2017) Nature Microbiology 16180:1-12.

## Which taxa are involved? – integrated multi-omic view

- Glycolysis and thiamine biosynthesis: *Prevotella copri*, Bacteroides dorei / vulgatus, Alistipes putridinis
- Catalase and motility: *E. coli*
- Cellulose or hemi-cellulose degradation: Coprococcus eutactus
- Antioxidant synthesis, deamination of monoamines: Clostridiales mOTU\*
- Amino acid synthesis: Clostridiales mOTU\*

\*not identical.

- **Differentially expressed functions** can be co uted to the Ecosystem services elevant in chronic disease community phenotype by taxa whie' erentially abundant
- Function of interest by **distinct**
- Functional Join affected by different factors Heintz-Buschart et al. (2017) Nature Microbiology 16180:1-12.

Jommunity phenotype

#### Functional interactions between the microbiome and humans start at birth



• Qualitative and quantitative differences for bacteria, archaea and microeukaryotes

Wampach et al. (2017) Frontiers in Microbiology 8:738.

## Artefact-free high-resolution metagenomics





### Microbiome-conferred functions matter very early on

- Differential abundances of genes and pathways
- Functional profiles of vaginally delivered neonates resemble the maternal profiles





## Transfer of function-encoding strains



- Transfer of functionencoding strains from mother to vaginally delivered neonate
- Generally absent in neonates delivered by caesarian section

#### **Color key**

- Detected taxon without link
- Same taxon (P)
- Same phylogenetic markers Same species (S)
- Same species (S) Same strain based on reads (S)
- Same strain based on reconstructed genome (neonate) (S)
- Same strain based on reconstructed genome (neonate & mother) (S)

#### Earliest microbiome elicits distinct immune responses

(in monocyte-derived dendritic cells, MoDCs)





## Conceptualised experimental gut model



Fritz et al. (2013) Microbiome 1:14.

## HuMiX: Human-Microbial X-talk



Essential features							
M	Co-culture in close proximity						
	Incorporation of mucus layer						
Ø	Culture of strict and facultative anaerobes						
	Gradients (oxygen and nutrients)						
	Online monitoring						
	Compatible with high-throughput analytics						
M	Recapitulate in vivo data						
	Possibility to incorporate several cell types						
V	Integration of primary cells (iHuMiX)						

Fritz *et al.* (2013) *Microbiome* **1**:14. Shah *et al.* (2016) *Nature Communications* **7**:11535. Giolla Eain *et al.* (2017) *Engineering* **3**:60-65. Wilmes et al. (2018) *Current Opinion in Microbiology* **44**:28-33. & unpublished. 013/056607\_PCT/EP2016/062024\_EP2016/062024\_EP18206858.5

Patents: PCT/EP2013/055712, PCT/EP2013/065718, PCT/EP2013/056607, PCT/EP2016/062024, EP2016/062024, EP18206858.5



Patent: EP18206858.5

#### Synbiotic: anti-cancer effects and molecular cocktails



- Pathway enrichment analysis indicates that the synbiotic regimen downregulates colorectal cancer-associated pathways
- Metabolomic analysis of spent medium shows distinct ratio of organic and shortchain fatty acids produced from synbiotic regimen

Greenhalgh et al. (2019) Cell Reports 27:1621-1632. Patent: EP18206858.5

#### Synbiotic molecular cocktail is key



- Individual cell exposure to formate, acetate and lactate (10 mM) increases
  cell self-renewal capacity in cell line and primary tumor cells
- Synbiotic molecular cocktail attenuates cancer cell self-renewal capacity

**Mechanism!** 

Greenhalgh et al. (2019) Cell Reports 27:1621-1632.

Patent: EP18206858.5





Millions of different molecules **50-90 % unknown** 

## Conclusion

- Wet- and dry-lab methodologies for systematic integrated multi-omics of microbial communities
- Microbiome and disease (type 1 diabetes): disruption of ecosystem services
- Functional gene expression may differ in the absence of differences in community structure
- Earliest "functional" colonisation impacts host physiology and interactions
- Form (community structure) follows function

#### Function first (taxa second)

Heintz-Buschart & Wilmes (2018) Trends in Microbiology 26:563-574.

 HuMiX offers exciting prospects for identifying key mechanisms underlying host-microbiome interactions in health and disease



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# Thank you very much for your attention!

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