The microbiome as a source of next-generation probiotics and therapeutic microbes

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Emergence of the probiotic concept

Postulated that supplementation of diet with lactic acid bacteria, an early probiotic intervention, has health benefits including promoting longevity.

"The dependence of the intestinal microbes on food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes"

E. Metchnikoff, E. Optimistic studies New York: Putman’s Sons, 1908, 161-183.
Giving rise to a whole industry and a broad range of products

The active bacteria are mostly lactic acid bacteria and Bifidobacteria

WHO definition of probiotics: "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host".
Science provides increasing rational and opportunities for probiotic concepts ...

... surfing the wave of the human « microbiome » revolution
**Human microbiome:** totality of microbes (microbiota) and their genomes in and on the human body

Complex microbial communities
Large diversity across body sites
The human gut microbiome – key findings
High complexity and (interpersonal) diversity

Relative abundance of species

Numbers

In the population
- 1100 species
- 3.3 mln → > 10 mln genes

In each individual
- around 160 species
- appr 540 k genes - with any person we share appr. 290 k genes

Nielsen et al. Nature Biotechnol. doi:10.1038/nbt.2939
The stage is set, the world knows: No longer « the best microbe is a dead microbe »

Scientists

Global opinion makers

Business

http://www.economist.com/
August 16, 2012

http://www3.weforum.org/

Commensals as next generation probiotics, mentioned by all as important lever
Large public and private investments!!
The intestine - interfacing with a complex microbial ecosystem

Surface of approximately 300m²

60 to 70% of our immune cells

100 million neurons

100.000 billion bacteria
Extremely high diversity
1-2 Kg. 50% of the fecal weight

Advances in sequencing and bioinformatics technologies fueled scientific progress

As many microbial cells as human cells
More than 100x more genes than human genes
Its implication in obesity and metabolic disease put the microbiome on the front page

Bacterial species abundance differentiates IBD patients and healthy individuals

Microbial alterations
- Decreased richness
- Altered taxonomic profiles
- Altered metabolic output

Richness of human gut microbiome correlates with metabolic markers

Dietary intervention impact on gut microbial gene richness

Development of mechanistic models
Testable hypothesis
Diet is key!
Gut microbiota and cardiovascular diseases
Crucial role of TMA - a single food compound from GM metabolism

Blood serum metabolomics
Identifies TMAO linked to CVD

Wang et al, Nature 2011

TMAO is both a diagnostic and prognostic marker
High person-to-person variation of TMA production
Levels depend on differences in microbiota metabolism
"Fecal transplants" for *C. difficile* have been boosting the enthusiasm

Gut microbiota transfer via Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection

Microbiota “Diversity” in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

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Can it be generalized or is this a «specific» ecological disease?

Safety, regulatory acceptance of Fecal transplants is questionable!
Increasing consumer (and patient) awareness that will influence dietary habits and consumer behaviour

New services and products emerging
Personalized Nutrition by Prediction of Glycemic Responses

Highlights

- High interpersonal variability in post-meal glucose observed in an 800-person cohort
- Using personal and microbiome features enables accurate glucose response prediction
- Prediction is accurate and superior to common practice in an independent cohort
- Short-term personalized dietary interventions successfully lower post-meal glucose

Zeevi et al., 2015, Cell 163, 1079-1094
Microbiome in health and disease
Science provides a daunting array of potential targets

Microbiota abnormalities (dysbiosis)?

******many areas in health and disease.....
....from associations to causal relationships...
...can we modulate microbial interventions
Rather than being invaded by enemies we may have lost some friends

Three major challenges

• Which microbe for which health endpoint

• What will regulatory look like across pharma, infant and food

• How to produce and formulate these sensitive microbes

Supplementing “missing microbes” to prevent and treat disease?
From scientific opportunity to application

CHR. HANSEN ACCELERATES EFFORTS WITHIN HUMAN MICROBIOME

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09-04-2015

Establishes a new research and development consortium and secures access and commercialization rights to an important resource of strains

Chr. Hansen has taken an important step in its strategic venture into new generations of probiotic products and therapeutic microbes. Through the creation of a new research and development consortium and the securing of strain access and commercialization rights, the company will strengthen its capabilities and gain access to renowned bio-banks of human gut bacteria.

university of groningen

Rowett Institute of Nutrition and Health
University of Aberdeen


Development of large well-documented strain libraries of gut commensals

PRESS RELEASE

January 14, 2016

Chr. Hansen enters first collaboration on production of a next generation probiotic from the Human Microbiome

Bacteria that live in and on our bodies outnumber the number of human cells by 10 to 1. There is an increased awareness that these bacteria, called the microbiome, play a crucial role in human health and diseases. Numerous studies have highlighted the therapeutic potential of specific bacteria in preventing and treating metabolic, gastrointestinal and other diseases. Today, Chr. Hansen and Caelus Health announce their collaboration on the development of *Eubacterium hallii* as a next generation probiotic for prevention and treatment of metabolic disease.

From candidate strain to clinical development for preventing/treating metabolic disease
Simply adding microbes may not be enough
They are not there because conditions were unfavorable
A triple entry to increase efficacy?

Drugs, food, ingredients impacting pH, inflammation, bile salts, redox

Favour physico-chemical conditions

Supplementing missing microbes

Adding substrate

(Epi)genetics, lifestyle, ...

Targeted therapeutics

Healthy state

Diseased state

Next gen probiotics
Therapeutic microbes

(Personalized) food
Prebiotics

Future (personalized) foods designed to optimise microbiome-host symbiotic relations