Anton van Leeuwenhoek (1683) noticed a white layer between his teeth.

“I found, to my great surprise,” he wrote, “that it contained many small animalcules, the motions of which were very pleasing to behold.”
T. Escherich (1886)

First pioneer in Intestinal Microbiology of Early Life

Mechnikov (Nobel prize 1908)

“When people have learnt how to cultivate a suitable flora in the intestines of children as soon as they are weaned from the breast, the normal life may extend to twice my 70 years”
Full gene repertoire of the adult gut microbiota

- 5 phyla
- > 20 genera
- > 1000 species (60 core species)
- > 3.3 million microbial genes
- Billions of bases (576 Gb)
The Gut, central organ in human physiology

Surface of $300\text{m}^2$

$60\text{ - }70\%$ of immune cells

100 million neurons

100 trillion bacteria "Gut Microbiota"
Gut Microbiota, essential role in human physiology

**Metabolic Role**
- Improves digestion
- Produces SCFA and vitamins
- Supplies micronutrients
- Metabolizes bile acids
- Degrades fibers/mucus
- Trophic effects

**Protective Role**
- Colonization resistance
- Immune homeostasis
- Improves barrier effect
- Detoxification
Gut Microbiota, essential role in human health

Figure 1. Diseases influenced by gut microbial metabolism. The variety of systemic diseases that are directly influenced by gut microbial metabolism and its influence on other mammalian pathways, such as the innate immune system, are shown. Specifically highlighted are the metabolic pathways involved in drug metabolism and obesity that are directly influenced by the gut microbial content. Ags, antigens; C. bolteae; DCC, dendritic cells; SCFA, short-chain fatty acid; TLR, Toll-like receptor.
Demonstrated in rodents that an obese phenotype could be transferred or reversed by transplant of the microbiota

From a protected environment...
... to a challenging extra-uterine world...

...Breast feeding is important for optimal development of infants
The early intestinal microbiota

- **Prepartal**: Sterile?
- **Birth**: Mode of delivery
- **4 days**: Inoculation with maternal/environmental microbiota
- **20 days**: Genetics
- **4-6 months**: Dietary influence

- **Dietary influence**:
  - Human milk
  - Formula
  - Weaning transition to adult
Inoculation in early life: microbiota transplant?

First contact
PREGNANCY

Second contact
AT BIRTH

Third contact
BREASFEEDING

Microbial Source

Microbiota transfer from mother to baby

Transmission of Intestinal *Bifidobacterium longum* subsp. *longum* Strains from Mother to Infant, Determined by Multilocus Sequencing Typing and Amplified Fragment Length Polymorphism

Hiroshi Makino, Akira Kushiro, Eiji Ishikawa, Delphine Muylaert, Hiroyuki Kubota, Takafumi Sakai, Kenji Oishi, Rocio Martin, Kaouther Ben Amor, Raish Oozeer, Jan Knol, and Ryuichiro Tanaka

Yakult Honsha European Research Center for Microbiology, ESV, Technologiepark 4, 9052 Ghent-Zwijnaarde, Belgium; Yakult Central Institute for Microbiological Research, 1796 Yaho, Kunitachi, Tokyo 186-8650, Japan; and Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands
### Bifidobacterium longum transfer from mother to baby

**Makino H et al.** Appl. Environ. Microbiol. 2011;77:6788-6793

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**Bifidobacteria transfer from mother to baby**

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### (B) *B. bifidum*

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### Mother-to-Infant Transmission of Intestinal Bifidobacterial Strains Has an Impact on the Early Development of Vaginally Delivered Infant's Microbiota

Hiroshi Makino¹,², Akira Kushiro¹, Eiji Ishikawa¹, Hiroyuki Kubota¹,², Agata Gawad², Takafumi Sakai¹, Kenji Oishi¹,², Rocio Martin³, Kaouther Ben-Amor⁴, Jan Kno³,⁵, Ryuichiro Tanaka¹
Microbiota transfer from mother to baby

Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns

Maria G. Dominguez-Bello\(^{a,1,2}\), Elizabeth K. Costello\(^{b,1,3}\), Monica Contreras\(^c\), Magda Magris\(^d\), Gilda Hidalgo\(^d\), Noah Fierer\(^e,\)\(^f\), and Rob Knight\(^b,9\)

\(^a\)Department of Biology, University of Puerto Rico, San Juan, Puerto Rico 00911; \(^b\)Department of Chemistry and Biochemistry, \(^c\)Department of Ecology and Evolutionary Biology, and \(^d\)Cooperative Institute for Research in Environmental Sciences, University of Colorado, Boulder, CO 80305; \(^e\)Center of Biophysics and Biochemistry, Venezuelan Institute for Scientific Research, Caracas 1020A, Venezuela; \(^f\)Amazonic Center for Research and Control of Tropical Diseases, Puerto Ayacucho 7191, Amazonas, Venezuela; and \(^g\)The Howard Hughes Medical Institute, University of Colorado, Boulder, CO 80305

Edited by Jeffrey I. Gordon, Washington University School of Medicine, St. Louis, MO, and approved May 24, 2010 (received for review March 2, 2010)
Babies delivered by Caesarean section at higher risk of asthma and allergies

C. Roduit et al., 2009, Thorax, 64(2):107-13

Asthma at 8 years of age in children born by caesarean section

Marra et al., 2006, Chest, 129(3):610-8

Does Antibiotic Exposure During Infancy Lead to Development of Asthma?*

Cesarean delivery showed link with gut microbiota, atopic dermatitis


Does early life exposure to antibiotics increase the risk of eczema? A systematic review.

Tsakok T¹, McKeever TM, Yeo L, Flohr C.
Surviving in symbiosis

GUT MICROBIOTA

Married to our gut microbiota

For richer for poorer, in sickness and in health. Our relationship with our microbiota—the vast array of microorganisms that live on or inside the human body—lasts a lifetime.

...are we more microbe than man?
Intestinal microbiology of early life: establishing a symbiosis

Pediatric Allergy and Immunology
Volume 25, Issue 5, pages 428-438, 5 JUN 2014
Microbiota disturbances in allergic eczema

Allergic

Healthy

C. difficile
S. aureus
E. coli
Enterobacteriaceae

Bifidobacterium
Lactobacillus
Bacteroides
Enterococcus
Increasing prevalence of allergic diseases

Hygiene hypothesis
Hygiene hypothesis revisited

Candela et.al. (2012)
Intestinal Microbiota of Infants With Colic: Development and Specific Signatures

**WHAT’S KNOWN ON THIS SUBJECT:** Colic affects many infants, with incidence rates of up to 25%. The pathogenesis is not well understood. Initial studies based on traditional culturing approaches and in infants >6 weeks of age point at abnormalities in intestinal microbiota.

**WHAT THIS STUDY ADDS:** Infants with colic showed lower microbiota diversity and stability than did control infants in the first weeks of life. Colic/control differences in the abundance of certain bacteria were also found at age 2 weeks. These microbial signatures possibly explain the excessive crying.
Human milk directs microbiota development

Breast-fed babies develop a microbiota often dominated by Bifidobacteria.

Formula-fed babies develop a more “adult-like” microbiota.

Harmsen, H. et al, 2000 JPGN
Human milk contains microbial substrates

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Concepts to modulate gut microbiota

Prebiotic

is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health*

Probiotic

is live microbial food ingredient that beneficially effects health**

Synbiotic

Specific Prebiotic Mixture:
Mimicking Size, Linkage, partly Building Blocks and Prebiotic function of HMOS

90% scGOS:
low molecular weight (short chain)

Galacto-OligoSaccharides
(enzymatic from lactose)

$\text{[Gal(\beta1-1,4 3/4/6)Gal(\beta1-4)Glc]}$

Lactose

10% IcFOS:
high molecular weight (long chain)

Fructo-OligoSaccharides
(fraction from chicory)

$\text{[Frc(\beta2-n\geq8 1)Frc(\beta2-1)Glc]}$

Sucrose
Early nutrition prebiotics impact microbiota composition and activity

**Bacteria**

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<td>0.8 g/100ml (n=27)</td>
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Group difference according to Mann-Whitney U-test: * p<0.05 vs. 0.0, # vs. 0.4

**SCFA**

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<td>% (means ± SD)</td>
<td>% (means ± SD)</td>
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<td>% (means ± SD)</td>
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</tbody>
</table>
Spectrum of clinically relevant pathogens: *Acinetobacter*, *Klebsiella*, *Bacillus subtilis*, *Streptococcus group B*, *Enterobacter*, *Clostridium difficile*, *Proteus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Staphylococcus epididermidis*

GOS/IcFOS prebiotics: Reduction of Pathogens

- Control (n=13)
- OS formula (n=12)

P=0.0387 according to Mann-Whitney U-test

Breast feeding yields in general a lower faecal pH => FOS/GOS also lowers faecal pH

**Effect of GOS/IcFOS on Fecal pH**

**6 weeks**

Breast feeding yields in general a lower faecal pH => FOS/GOS also lowers faecal pH

Knol et al. 2005. JPGN (40): 36-42
Prebiotics can reduce atopic dermatitis symptoms

Incidence of atopic dermatitis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23.1%</td>
</tr>
<tr>
<td>scGOS/IcFOS</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

p<0.03

Moro et al. 2006, Arch. Dis. Child
Prebiotics can reduce incidence of diarrhea

**Reduction of incidence of acute diarrhea**

**Reduction of antibiotics courses used**

**scGOS/IcFOS reduces incidence of acute diarrhea and antibiotic courses in infants**

Bruzese et al., 2009, Clinical Nutrition 28: 156-161
Concepts to modulate gut microbiota

**Prebiotic**

*is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health* *

**Probiotic**

*is live microbial food ingredient that beneficially effects health**

**Synbiotic**


SYNBIOTIC MORE EFFECTIVE IN PREVENTING CMA THAN GOS/FOS OR B. BREVE M-16V ALONE

FIGURE 1  Acute allergic skin response of whey-sensitized mice fed a control, B. breve, GOS/FOS, or synbiotic diet. The acute ear swelling response was measured 1 h after i.d. challenge with whey. Values are means ± SEM, n = 6. Means without a common letter differ, P < 0.05.
**B. BREVE M-16V REDUCED AIRWAY HYPER-REACTIVITY IN OVA ALLERGIC MICE**

**Oral Treatment with Probiotics Reduces Allergic Symptoms in Ovalbumin-Sensitized Mice: A Bacterial Strain Comparative Study**

S. Houge
A.J.M. Vriesema
S.C. Wijering
L.M.J. Knippels
G. Folkerts
F.P. Nijkamp
J. Knol
J. Garsse

*Danone Research – Centre for Specialised Nutrition, Wageningen, †Department of Pharmacology and Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, and ‡Numico Research, Wageningen, The Netherlands*
To investigate the nutritional efficacy and acceptance/tolerance characteristics of an extensively hydrolysed whey protein formula with added **synbiotics** in infants
Double-blind, placebo-controlled, multi-centre study

- 90 infants SCORAD > 15
- Age < 7 months

Feeding regime

- formula feeding for 12 weeks

Formulas

- Extensively hydrolyzed formula (n=44)
- Extensively hydrolyzed formula plus 0.8 g/100 ml scGOS/lcFOS and *Bifidobacterium breve* M-16V (n=46)

Outcome parameters

- Primary outcome: incidence of atopic dermatitis (SCORAD)
- Secondary outcome: intestinal microbiota composition
Clinical Efficacy; Microbiota

The graph shows the percentage of Bifidobacteria in the synbiotic and control groups over different weeks. The y-axis represents Bifidobacteria (%) ranging from 0 to 60, while the x-axis shows the time points: week 0, week 1, and week 12. Bars for the synbiotic group are shown in orange, and the control group in blue. Statistical significance is indicated with asterisks: * for week 1 and *** for week 12.
Clinical Efficacy; improved SCORAD children high IgE
Clinical Efficacy; 1 year follow up, asthma like symptoms

NOISY BREATHING

NOISY BREATHING

FREQUENT WHEEZING

FREQUENT WHEEZING

*p = 0.001*

*p = 0.04*

*P<0.05; Mantel Haenszel Test with rank scores for ordinal data*
Some key questions

- When and how do we acquire our essential microbes?
- What drives the composition / functionality of the microbiota?
- What could be appropriate microbiota markers for disease outcomes?
- If we understand the microbial ecosystem better can we adapt our nutrition to improve the symbiosis?
Epigenetics

How the first nine months shape the rest of your life

The new science of fetal origins
BY ANNIE MURPHY PAUL

The Facebook Movie: The secret history of social networking

Environment Special: The oceans—why 70% of our planet is in danger

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.

Histones
Histone tails
Me
Me
Chromosome
Developmental Microbiology

Optimal Growth
- Metabolism, Epigenetics, Digestion, Absorption, Brain Development, Immune Maturation

Healthy Adults

Balanced Microbiota

Initial Colonisation

-9 months

Birth

Optimal Growth

Developing Microbiota

Altered growth
- Allergy, Adipose tissue development, Infections, Discomfort

Disease
- Obesity, Coronary Heart Disease, Asthma, Diabetes, IBS
Acknowledgements

Danone Nutricia Research

Rocio Martin
Kaouther Ben Amor
Raish Oozeer
Thomas Ludwig
Rob Slump
Harm Wopereis
Tiemen van Eijndthoven
Petra Scholtens

Wageningen University

Clara Belzer
Willem de Vos
Hauke Smidt

Infants, parents, and pediatricians!!
We are not alone...