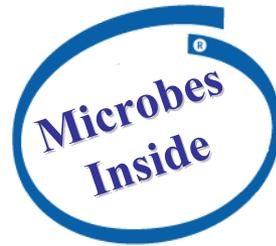


Health Care By Your Microbes Inside



The Soehngen Institute of
Anaerobic Microbiology

willem.devos@wur.nl



Netherlands Organisation for Scientific Research



SUOMEN AKATEMIA
FINLANDS AKADEMI • ACADEMY OF FINLAND

Professor & Chair of Microbiology Wageningen University
Professor of Molecular Microbiology Helsinki University
Finland Academy Professor – Finnish Academy of Sciences



European Research Council
Scientific Council



Microbial Metagenomics: Faster, Better & Cheaper



Few Thousand Species in the Human Gut – > 1000 Species Cultured

High Throughput Technologies → > 10 M Gut Genes !

Microbes Dominate Our Body

Karyome

~ 10^{13} human cells
single genome
3 Gbase sequence
~ 30 k proteins



Mitochondriome

~ 10^{14} mitochondria
single genome
17 Kbase sequence
13 proteins

Intestinal Microbiome

~ 10^{14} microbial cells ~ $10^3 - 10^4$ species
reference genome of ~ 10 M genes or proteins (~ 10 Gbase)
0.5 – 1 M Genes per Subject

J Qin et al MetaHit Consortium - Nature 464 (2010) 59-65

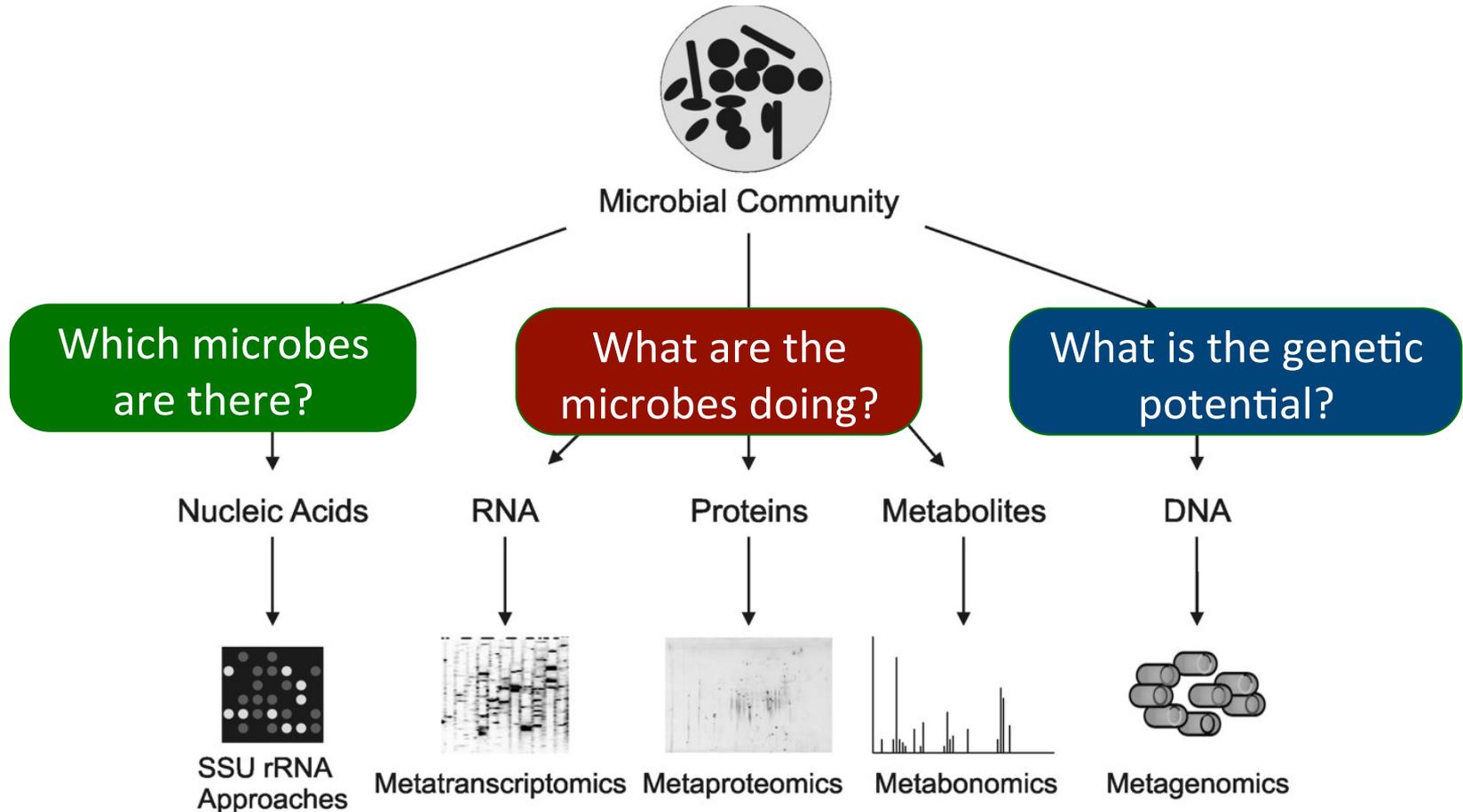
M Amurugam et al MetaHit Consortium – Nature 473 (2011) 174-180

E Le Chatelier et al MetaHit Consortium – Nature 500 (2013) 541-546

S Sunagawa et al – Nature Meth 10 (2013) 1196-99

WM De Vos & M Nieuwdorp – Nature 498 (2013) 48-49

...How to Learn More from the Gut....



Holistic & High Throughput Avenues - Cohorts & Controlled Interventions - Systems Approaches

Our Microbiome: A Hot Topic

Nature Biotechnology April 2013

A snapshot of the microbiome field

A survey of leading scientists from academia and industry highlights notable papers that have garnered momentum in microbiome research.

Translating the human microbiome

James Brown, Willem M de Vos, Peter S DiStefano, Joël Doré, Curtis Huttenhower, Rob Knight, Trevor D Lawley, Jeroen Raes & Peter Turnbaugh

Nine experts discuss the challenges in translating current research on the human microbiome into strategies for disease prediction, diagnosis and therapy.

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Ranked
1st



Qin, J. et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65 (2010).



"The first gene catalog of the human microbiome, demonstrating that the [gut microbiome] metagenome contains 150-fold more genes than our own genome." **Frederik Bäckhed**, University of Gothenburg, Sweden.



Anumugam, M et al. Enterotypes of the human gut microbiome. *Nature* **473**, 174–180 (2011).



"Stirred up discussions but indicates high-level clustering that will be useful to provide further segmentation." **Willem de Vos**, Wageningen University, The Netherlands.

Ranked
2nd



Turnbaugh, P.J. et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **444**, 1027–1031 (2006).



"Demonstrated in rodents that an obese phenotype could be transferred or reversed by fecal transplant of the microbiota." **Peter DiStefano**, Second Genomes, San Bruno, California, USA.



"The authors showed that the microbiome could actively shape disease susceptibility. All the ingredients of microbiome research (germ-free mice, next-generation sequencing and fecal transplantation) are included in this paper. The study has trail-blazed this field of research and provided a template for investigation of the impact of the microbiome on diseases and health such as cancer, diabetes, behavior and colitis." **Christian Jobin**, University of North Carolina at Chapel Hill, USA.

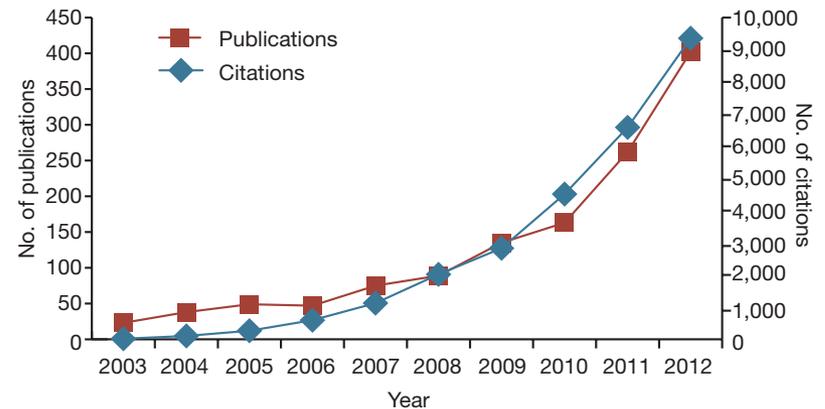
Susan Jones, Senior Editor, *Nature Biotechnology*

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VOLUME 31 NUMBER 4 APRIL 2013 NATURE BIOTECHNOLOGY

Publications over time

Since 2003, microbiome research publications have undergone explosive growth.



Source: Thomson Reuters Web of Science, accessed 6/3/2013, using title search terms (human microbiota, human microbiome, human microbial, human microbes or gut ecology) for the period 2003–2013. Citations are to source items indexed within Web of Science. All article types are included.

Rapid Development Due To EU & NIH Funding

... We Are All Different ...



Dozen Subjects – Discovered Dozen Years Ago

Zoetendal et al (1998) AEM

Growing Up In A Microbial World

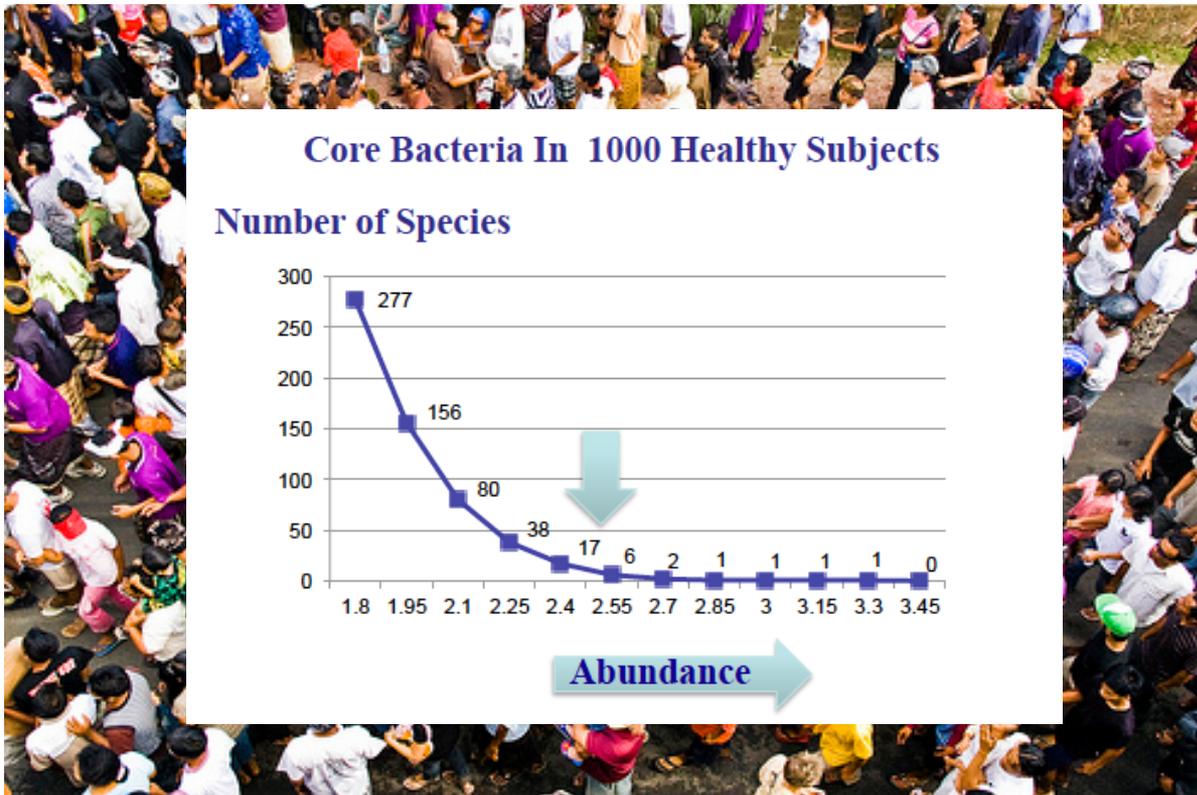


Happy Birthday: Born Virtually Sterile

Early Life Colonization Is A Programmed Fecal Transplantation

Millions of Baby - Mother Transfers – Mom Knows Best !

... We Are All Different ...

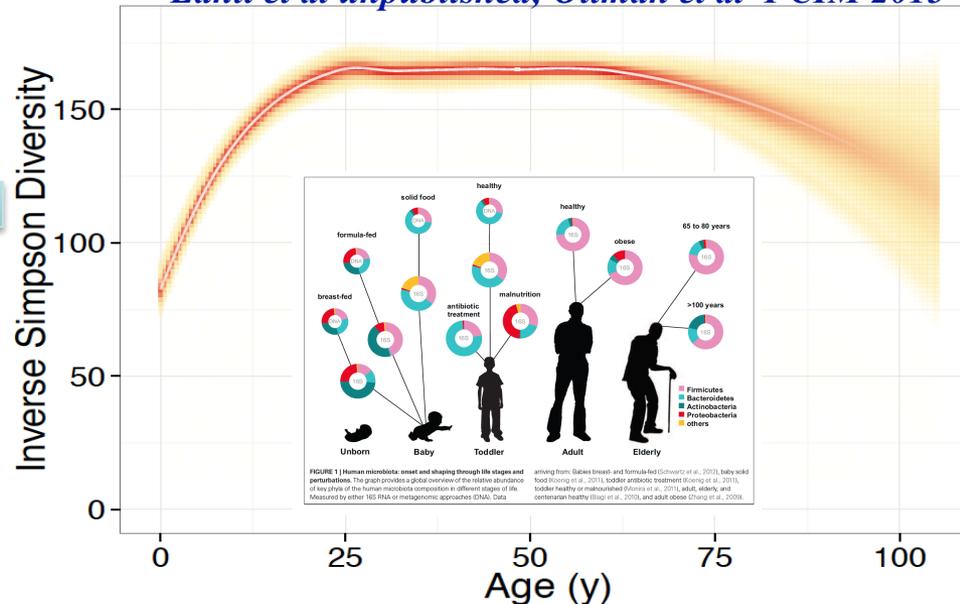


...But A Bit The Same...

Development Provides Opportunities

Diversity Development in 3000 Subjects

Lahti et al unpublished; Ottman et al FCIM 2013



**Colic Babies
2-4 weeks**

Crying



**Reduced Diversity
Microbiota
Signatures**

**De Weerth et al
Pediatrics 2013**

**Centenarians
>100 yers**

Inflaming



**Reduced Diversity
Microbiota
Signatures**

**Biagi et al
PLoS One 2010**

Striking Similarities in Signatures:

Butyrate Producers Reduced & Pathobionts Up

Signaling & Immune Impact - Very Early Biomarkers !

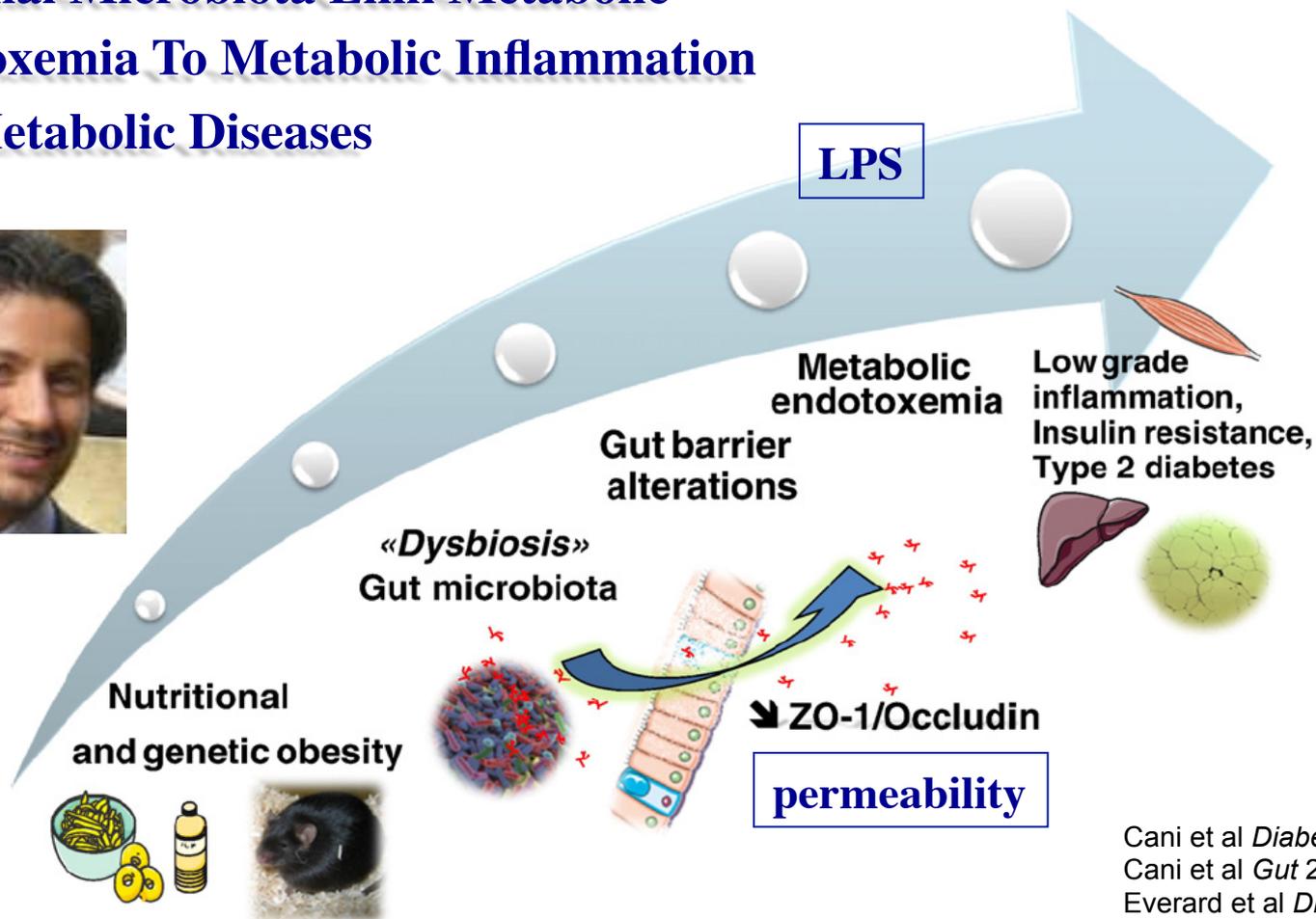
Impact of Our Intestinal Microbiome



Role of the intestinal microbiome in health and disease: from correlation to causation

Intestinal Microbiota in T2D & Obesity

Intestinal Microbiota Link Metabolic Endotoxemia To Metabolic Inflammation And Metabolic Diseases



Cani et al *Diabetes* 2007
Cani et al *Gut* 2009
Everard et al *Diabetes* 2011

T2D Prediction MGWAS Better Than GWAS

GENOMICS

Nature May 2013

A gut prediction

Characteristic profiles of gut microorganisms in people with type 2 diabetes could aid diagnostics and therapies, but differing signatures between ethnicities and genders highlight the need for further studies.

WILLEM M. DE VOS & MAX NIEUWDORP

	Karlsson <i>et al.</i> ⁴	Qi <i>et al.</i> ⁸
Population	145 European females.	345 Chinese males and females.
Cohorts	Normal, impaired glucose metabolism and T2D.	Normal and T2D.
Confounding factors	Only postmenopausal females. Some participants on medication.	More males than females. Cohorts not age-matched. Some participants on medication (not reported but probable).
Main findings	Butyrate-producing <i>Roseburia</i> species and <i>Faecalibacterium prauznitzii</i> lower in T2D cohort. <i>Lactobacillus gasseri</i> and <i>Streptococcus mutans</i> higher in T2D cohort. Genes involved in oxidative stress response higher in T2D cohort. Genes involved in riboflavin metabolism lower in T2D cohort. Genes involved in assembly of bacterial flagella lower in T2D cohort.	Butyrate-producing <i>Roseburia intestinalis</i> and <i>F. prauznitzii</i> lower in T2D cohort. Proteobacteria higher in T2D cohort. Genes involved in cofactors and vitamins lower in T2D cohort. Genes involved in assembly of bacterial flagella lower in T2D cohort.

T2D, type 2 diabetes

More Butyrate Producers In Controls

More Proteobacteria In T2D - LPS

Model for A Healthy Gut Metabolic Network

Nature August 2013

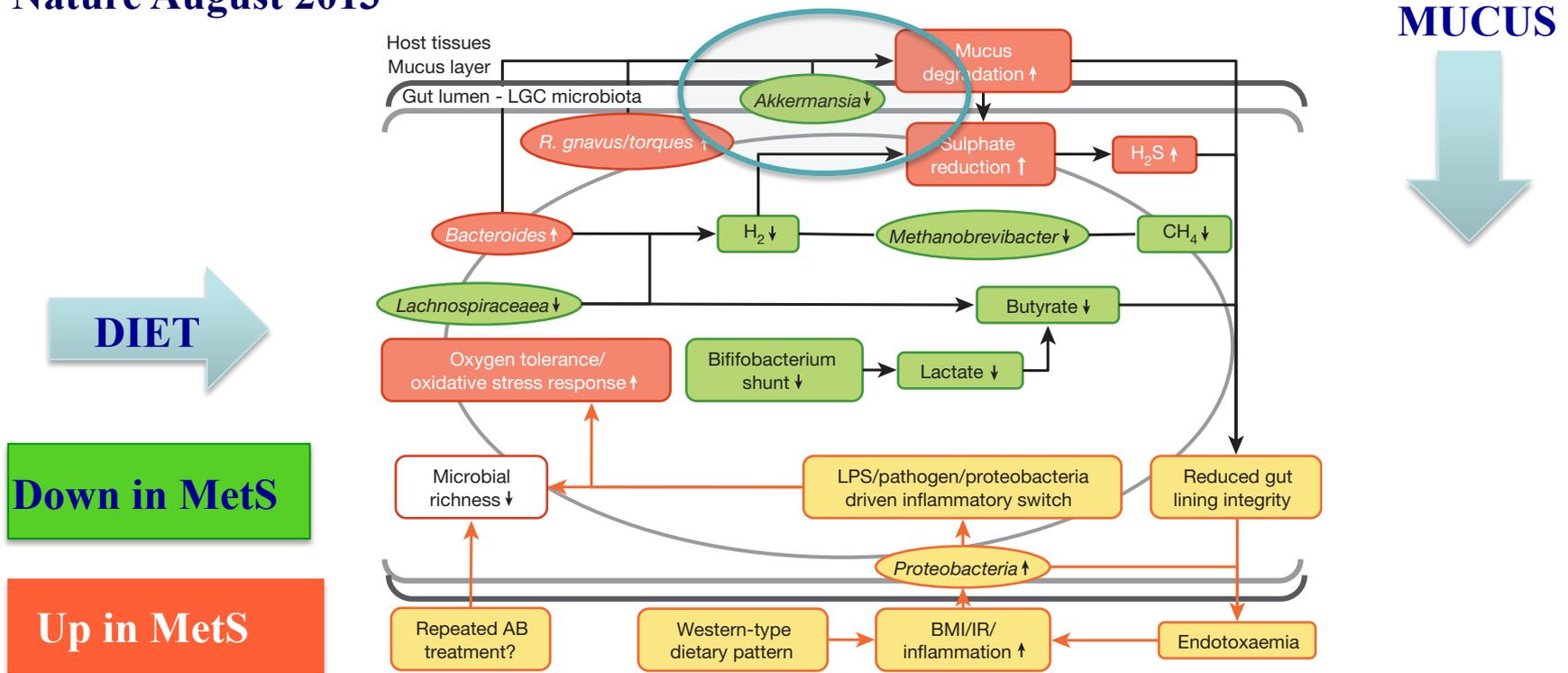


Figure 3 | Functional and phylogenetic shifts in the LGC microbiome. Top, observed increase (red) or decrease (green) of functions and phylogenetic groups. Bottom, potential drivers (yellow) of inflammation related to decreased richness. Left, antibiotic-mediated perturbation of the richness; Right, proteobacterial lipopolysaccharide-mediated perturbation of the richness. AB, antibiotic; IR, insulin resistance.

MetS = metabolic syndrome like: insulin resistant, low grade inflammation & obese

Akkermansia in the Intestinal Tract

Dedicated Mucus Utilizer – Abundant in Mucosal Layer

Low in Obesity, UC & IBD Mucosa

3 Mb Genome – Propionate Producer - Specific Signaling to the Host

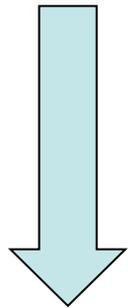
Akkermansia (Ak.ker.man'si.a. N.L. fem. n. *Akkermansia* derived from Antoon Akkermans, a Dutch microbiologist recognized for his contribution to microbial ecology).



*Derrien et al 2004; Derrien et al 2010;
Derrien et al 2011; Rajilic-Stojanvic et al IBD 2013*

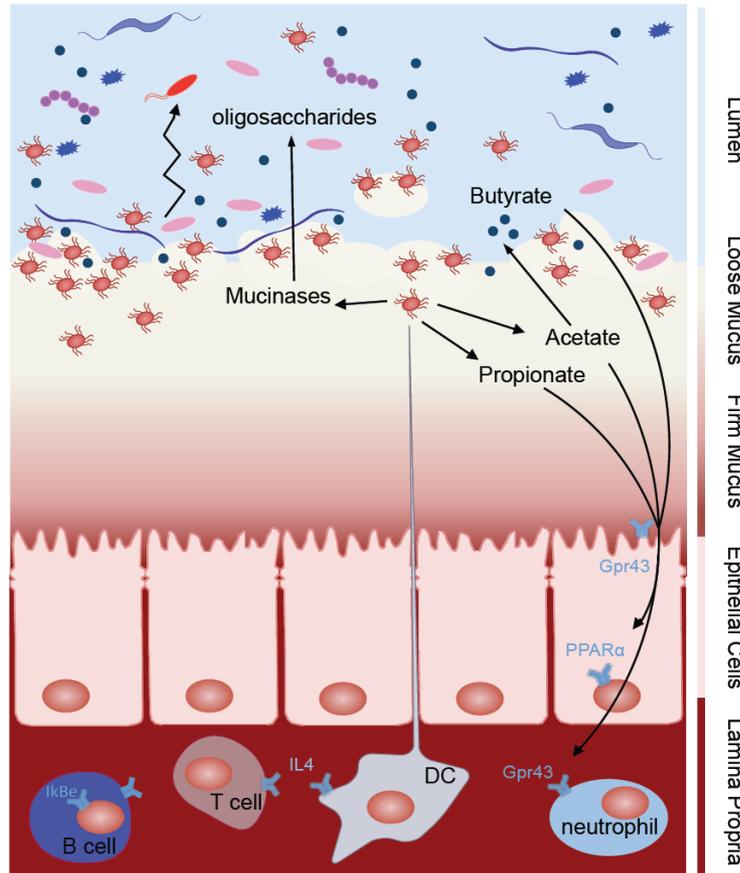
Akkermansia: Gate Keeper of Our Mucus

Cell & Surface Components

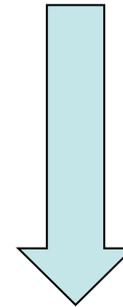


Signalling to TLRs

Immune & Metabolic Impact



Propionate & Butyrate



Signalling to GPRs

Immune & Metabolic Impact

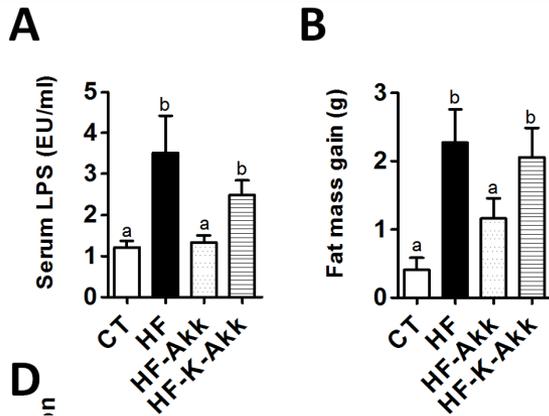
Belzer & De Vos ISME J 2012

Competitive Exclusion & Signaling – Reduced Inflammation
Improved Barrier Function - Potential for Therapeutic Approaches

Akkermansia muciniphila > 100,000 Google Hits

PNAS 2013

Live but not Killed (K) *Akkermansia*
Reduces
High Fat (HF) Induced Inflammation
– LPS & Fat Reduction



Nature News 2013



Obese mice lost weight after being fed the microbe *Akkermansia muciniphila*, which appears to have a symbiotic relationship with the inner lining of the intestine.

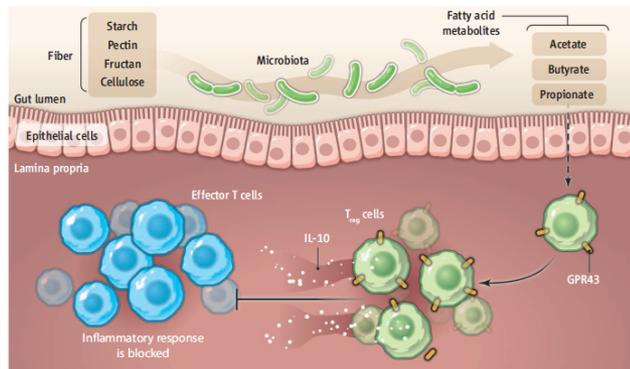
...Select Your Preferred Picture...

Treg Immune Signaling by *A.muciniphila*

IMMUNOLOGY

Feed Your T_{regs} More Fiber

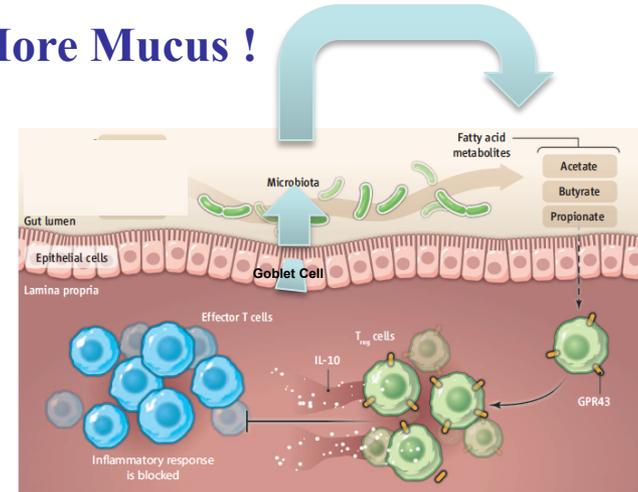
Julia Bollrath and Fiona Powrie



Bacterial metabolites fight intestinal inflammation. Commensal bacteria metabolize fiber and generate short-chain fatty acids. These fatty acids are ligands for GPR43 expressed by T_{reg} cells and stimulate their expansion and immune-suppressive properties such as the production of IL-10, thereby controlling proinflammatory responses in the gut.

Gate Keeper Function

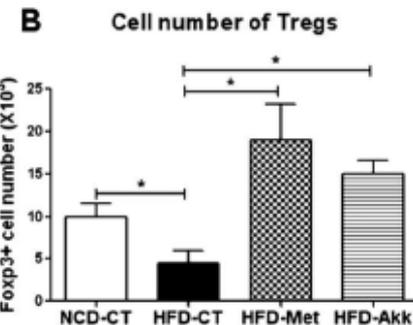
Or Make More Mucus !



Bacterial metabolites fight intestinal inflammation. Commensal bacteria metabolize fiber and generate short-chain fatty acids. These fatty acids are ligands for GPR43 expressed by T_{reg} cells and stimulate their expansion and immune-suppressive properties such as the production of IL-10, thereby controlling proinflammatory responses in the gut.

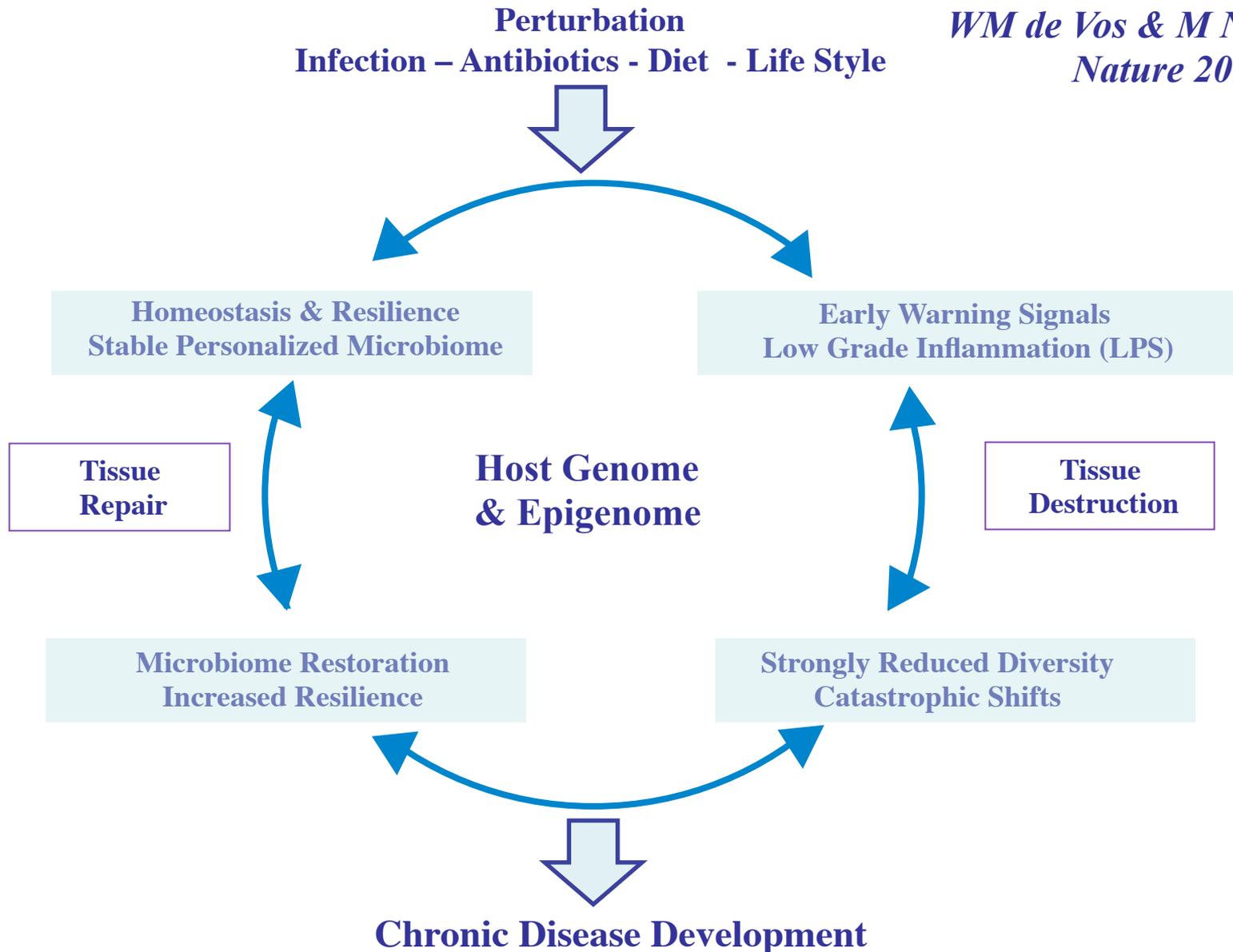
...Confirmed by Shin et al Gut 2014

($p < 0.0001$). Oral administration of *Akkermansia muciniphila* to HFD-fed mice without metformin significantly enhanced glucose tolerance and attenuated adipose tissue inflammation by inducing Foxp3 regulatory T cells (Tregs) in the VAT.



Model for the Impact of Human Microbiome

*WM de Vos & M Nieuwdorp
Nature 2013*



Potential for Radical Innovation

**Microbial
Diagnostics**



**Microbial
Therapies**

New Concepts - New Technologies - New Paradigms

Early Days ... Large Promise Food & Pharma...

Microbes Inside



We Feed Them & They Feed Us

They Talk To Us

...We Just Need To Understand Them Better...