Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

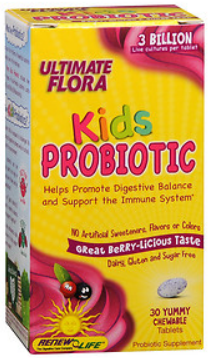
DHEST
Department of
Health Sciences and Technology

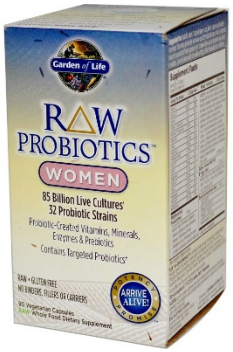
Probiotics: On the path of the Holy Grail or an oversold concept ?

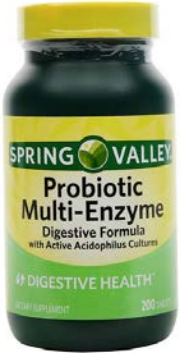
Prof. Dr Ing. Christophe Lacroix

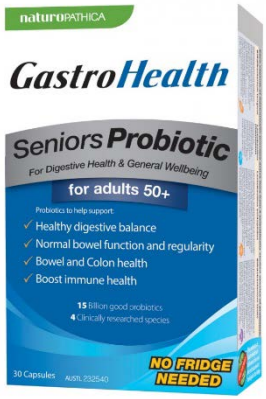
Laboratory of Food Biotechnology
Institute of Food Science, Nutrition and Health
ETH-Zurich, Zurich, Switzerland

Example of probiotics products

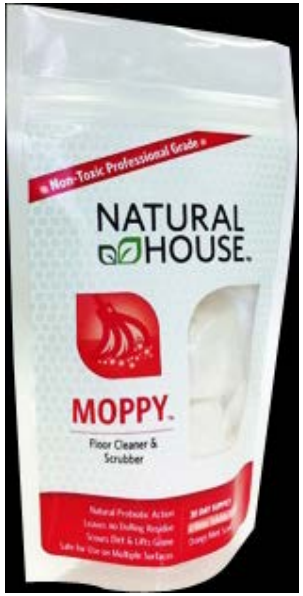






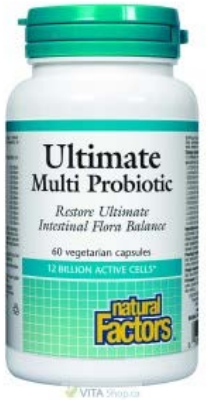


Misleading and false?



The product even continue to work until the next time you clean due to the beneficial organisms.

Daily use of Jourdan's probiotic aftershave lotion will leave your face feeling comfortable and moisturized



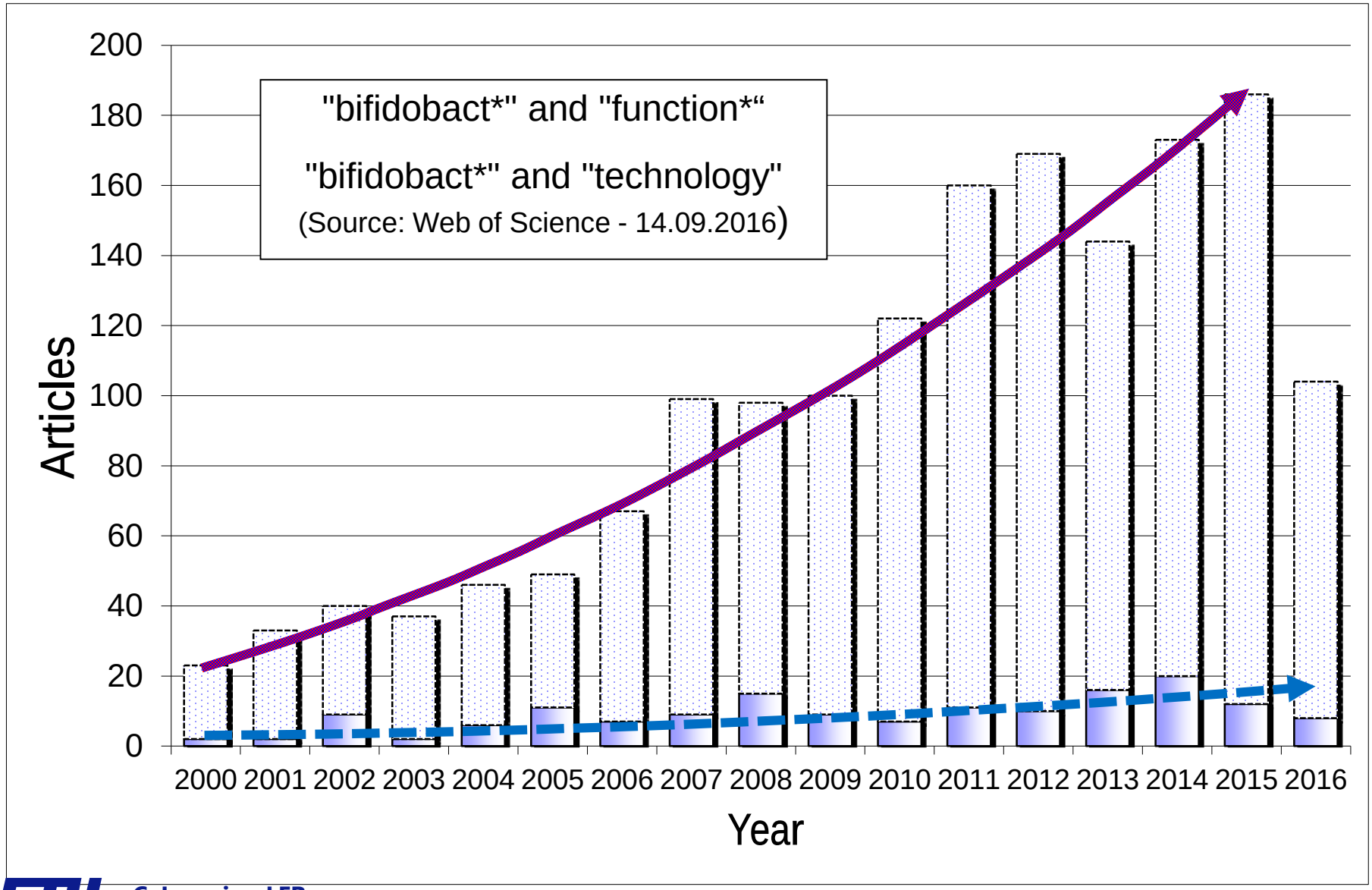
12 strain blend for the ultimate health of the full length of the small and large intestine.

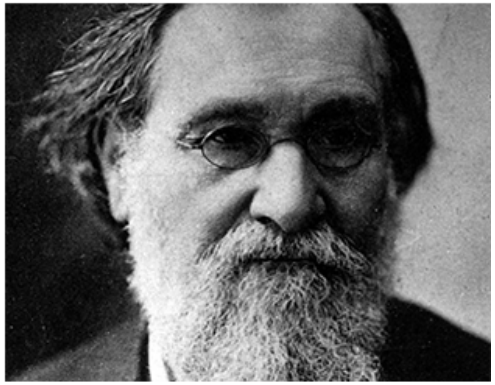
Purotex, Allergy UK approved probiotics, keeps the mattress naturally hygienic and dust/mite free.

Pro-/Pre-biotics are Making an Impact in Research and in the Global Marketplace !

- A vast body of science of 7000+ publications.
- Hundreds of probiotic foods and dietary supplements
- High global market for prebiotic cereals, probiotic drinks, yoghurts, pills represent a **€22bn+ (2012)**.
- Market estimates have that global market expanding about 30% to be worth **€35bn in 2017**
- Regulators, scientists and marketers do not always see eye-to-eye.
- EU Regulation Nutrition & Health Claims (NHCR) 1924/2006: banned all pre- and probiotic claims & even the use of the terms ‘prebiotic’ and ‘probiotic’- heavily challenged the industry.

Scientific papers «bifido*» and «function*»

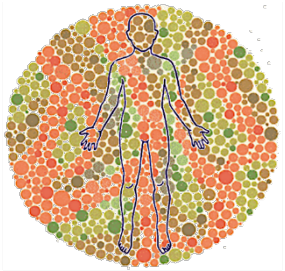




ELIE METCHNIKOFF
CREDIT: Mondadori Portfolio / Getty Images

Outline

- The Probiotic concept
- The GI Microbiota ‘’organ’’, where most of the action takes place!
- Probiotic bacteria, selection and challenges?
- Outlook for the probiotic-microbiota-human health



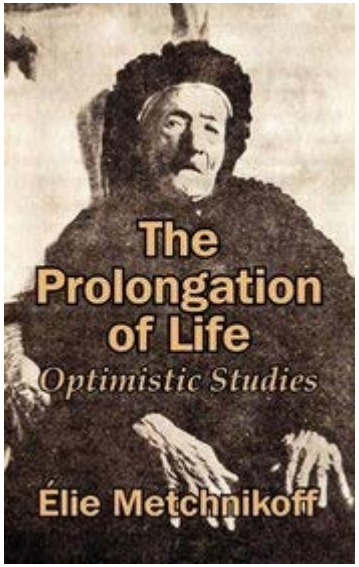
The Origin of the Probiotic Concept

Ilie Metchnikov (1845-1916)

An Ukrainian Biologist

1908 Nobel Price Medecine:

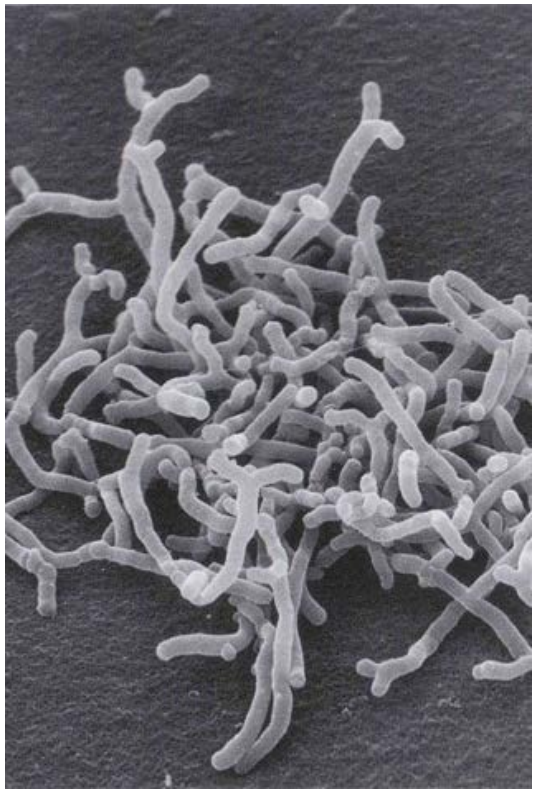
discovered phagocytes and other immune system components



Observation on longevity of Bulgarian paysants:

« The ingestion of high amounts of lactic acid bacteria in fermented milks increase life expectancy by protecting the organism against several diseases … »

Probiotic definition pro - bios = for life



Bifidobacterium longum

- Microorganisms that enhance health
- Lactic acid bacteria could inhibit the growth of detrimental bacteria through acidification (Metchnikoff).

Definition der FAO/WHO 2001:

Living microorganisms, which, when administered in adequate amounts, confer a health benefit on the host

- Include strains of:
  - *Bifidobacterium* sp.
  - *Lactobacillus* sp.
  - *Saccharomyces* sp.
  - *Enterococcus* sp.

First probiotic are “lactic acid bacteria”

- Historical focus on lactobacilli and bifidobacteria

  Metchnikoff (1907): Lactobacilli linked to longevity

  Tissier (1905): Bifidobacteria present in high number in infants

- No significant pathogens among LAB

- Other currently used probiotics:

  Escherichia coli (Nissle 1917)

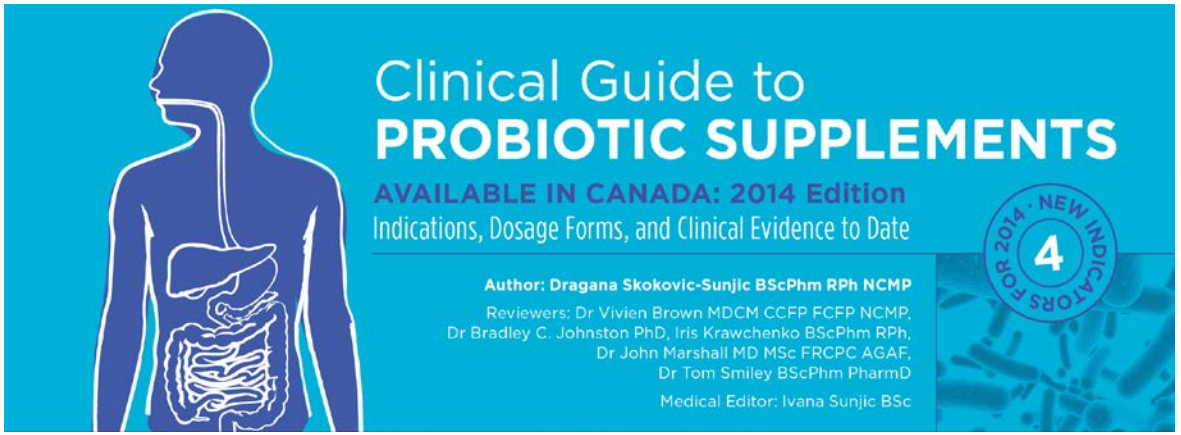
  Enterococci: *E. faecium* SF68

  Yeasts: *Saccharomyces boulardii*

Common Questions on the Benefits of Probiotics

- What can beneficial microorganisms really accomplish?
- Can these products benefit human (or animal) health?
- When it comes to probiotics, what is real and what is fiction?
- What is the best product for ….?
- What scientific research to support the rational development of probiotic functional foods with approved health claims?

http://www.mdpassport.com/ResourceCentres/nutrition/pdfs/Canadian%20Probiotic%20Chart%202014.pdf

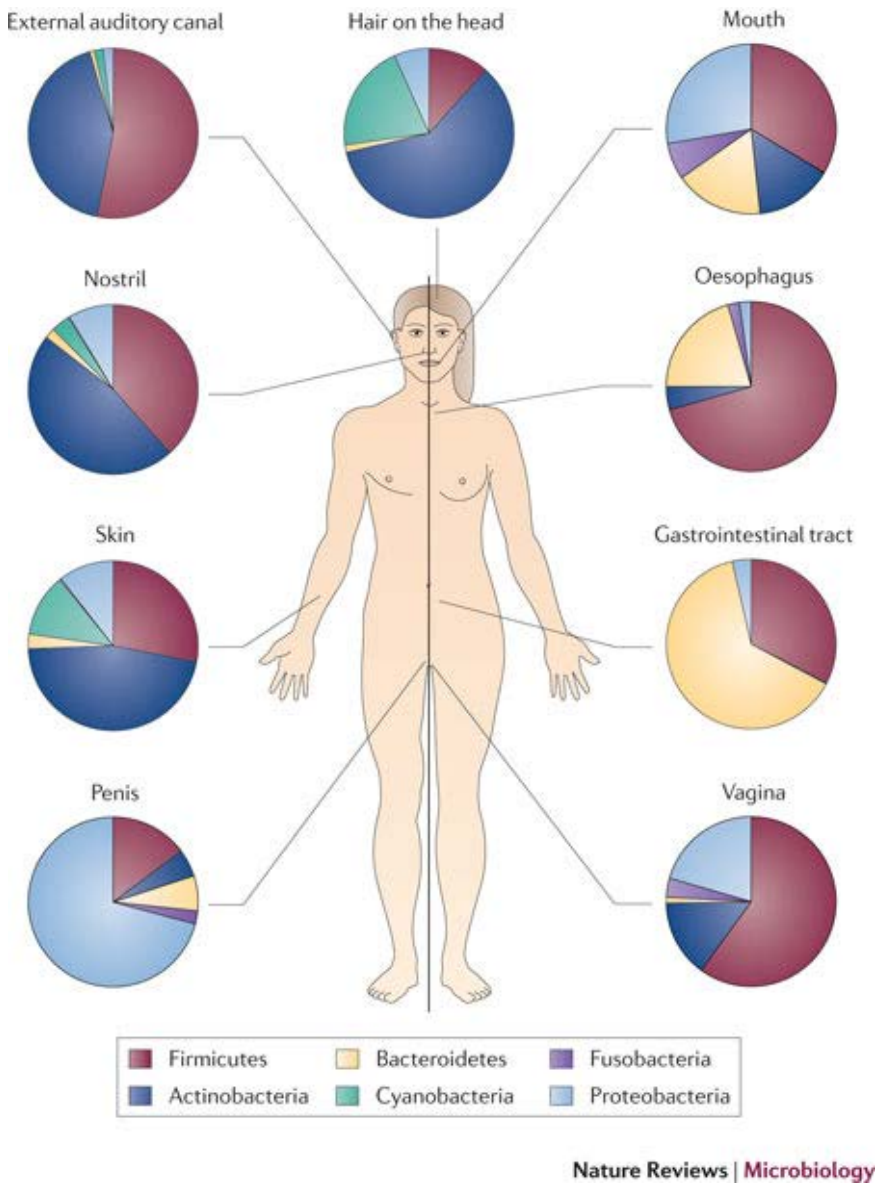


Our Microbiota

- The human body offers several niches for microbial life
- Colonizing bacteria have coevolved into a mutualistic relationship with their host

Microbiota:

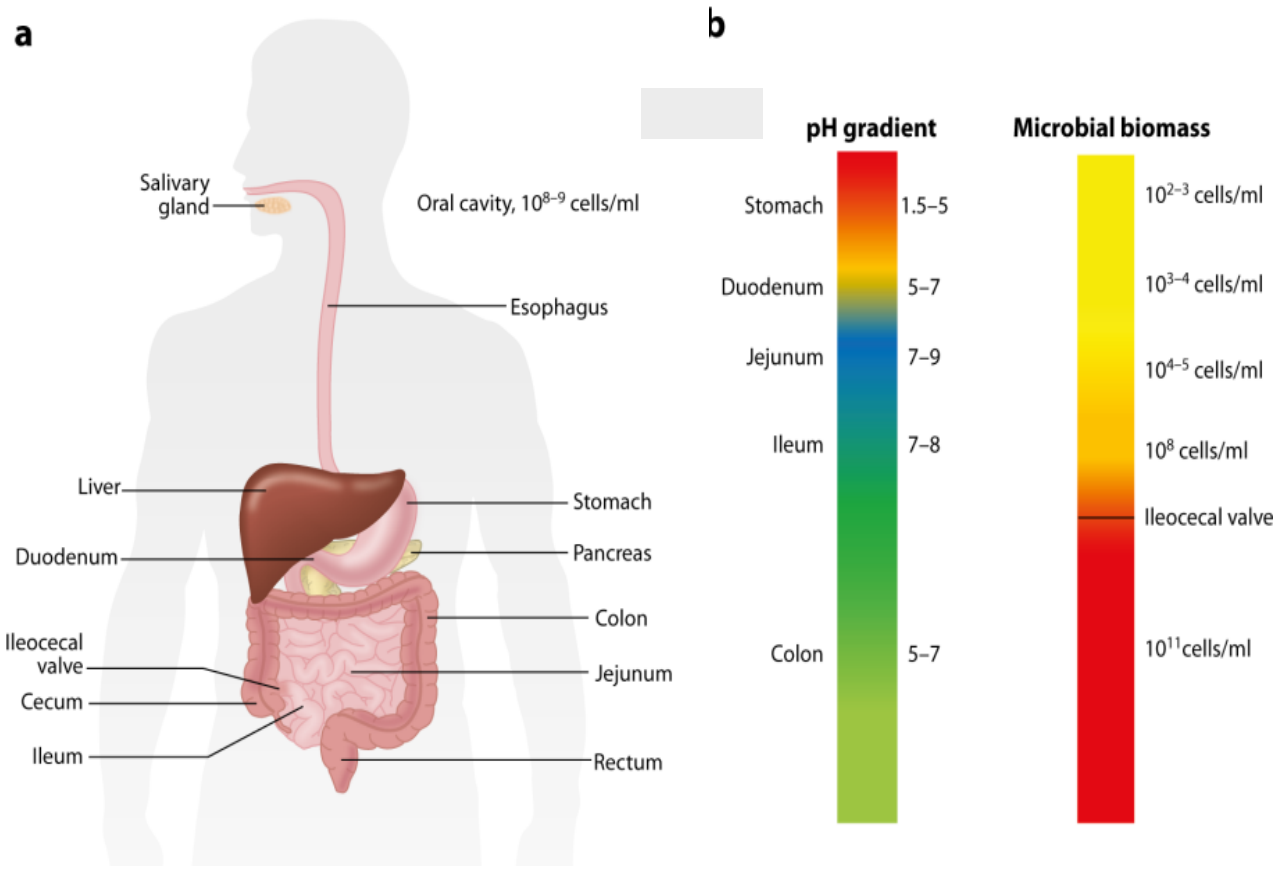
Microbial life forms within a given habitat or host



Spor et al. Nat. Rev. Microbiology, 2011

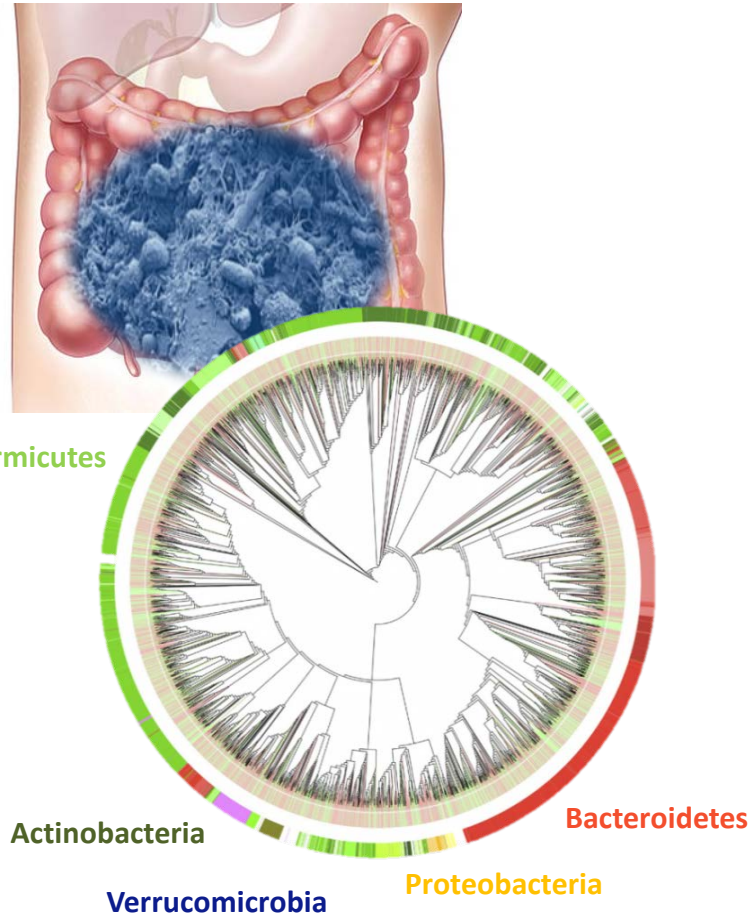
The human GI tract as a niche for bacterial life

- The human GIT offers a multitude of niches for bacterial life
- Each niche is colonized by different bacterial species adapted to the specific environment
- The most densely colonized niche is the large intestine with up to 10^{11} cells/ml



Adapted from: Walter, J and Ley R E, Ann. Rev. Microbiol. 2011

Gut microbiota - forgotten organ - second genome



Quin et al. 2010 Nature 464:59
Saulnier et al 2011 Gastroenterol 141:1782
Dorrestein et al 2014 Immun 40:824

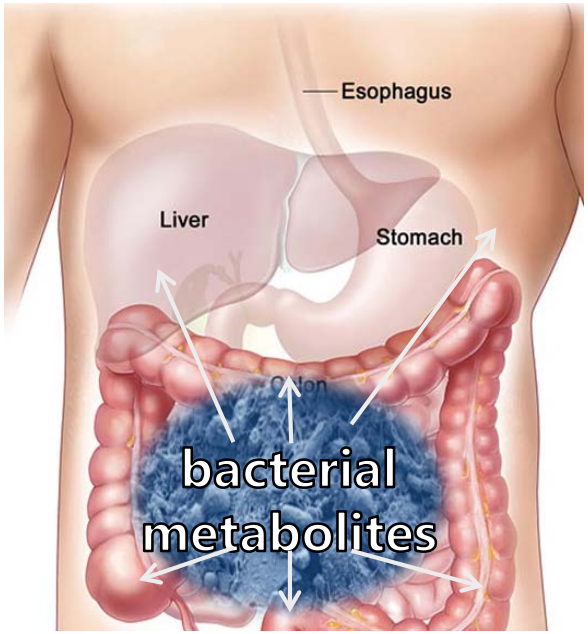
- Human intestine contains ca. **1 kg bacteria**

→ **Very high density** (10^{14} bacteria) ~ own cells

→ **Metagenome** (over 3 M genes) ~100x own genome, encoding ca. 20'000 proteins

- **Highly diverse ecosystem** → mostly strict anaerobic species of which many are not yet identified or yet cultivated
- Each individual harbours at least 160 abundant bacterial species, with **high individuality**
- Normal consortium **adapted, resilient and functionally stable**

Gut microbiota – Impact host physiology & health



- → **Acetate:** energy source, precursor
- → **Propionate:** gluconeogenesis cholesterol synthesis, anti-inflam.
- → **Butyrate:** energy for colonocytes, cellular proliferation, anti-inflam.

- Development of **digestive system physiology**
- **Immune system** training & regulation
- **Colonization resistance** to pathogens
- **Digestive capacity**: Anaerobic metabolism degrades indigestible compounds:
  - **SCFA** → **++** host health, extra energy
  - **H_2S, ammonia, phenols** → **--** host health
  - degradation of **xenobiotics**
- **Interactive host-microbiota metabolome**, signaling, & immune-inflammatory axes (> 500'000 compounds) physiology connect the gut, liver, muscle, and brain.

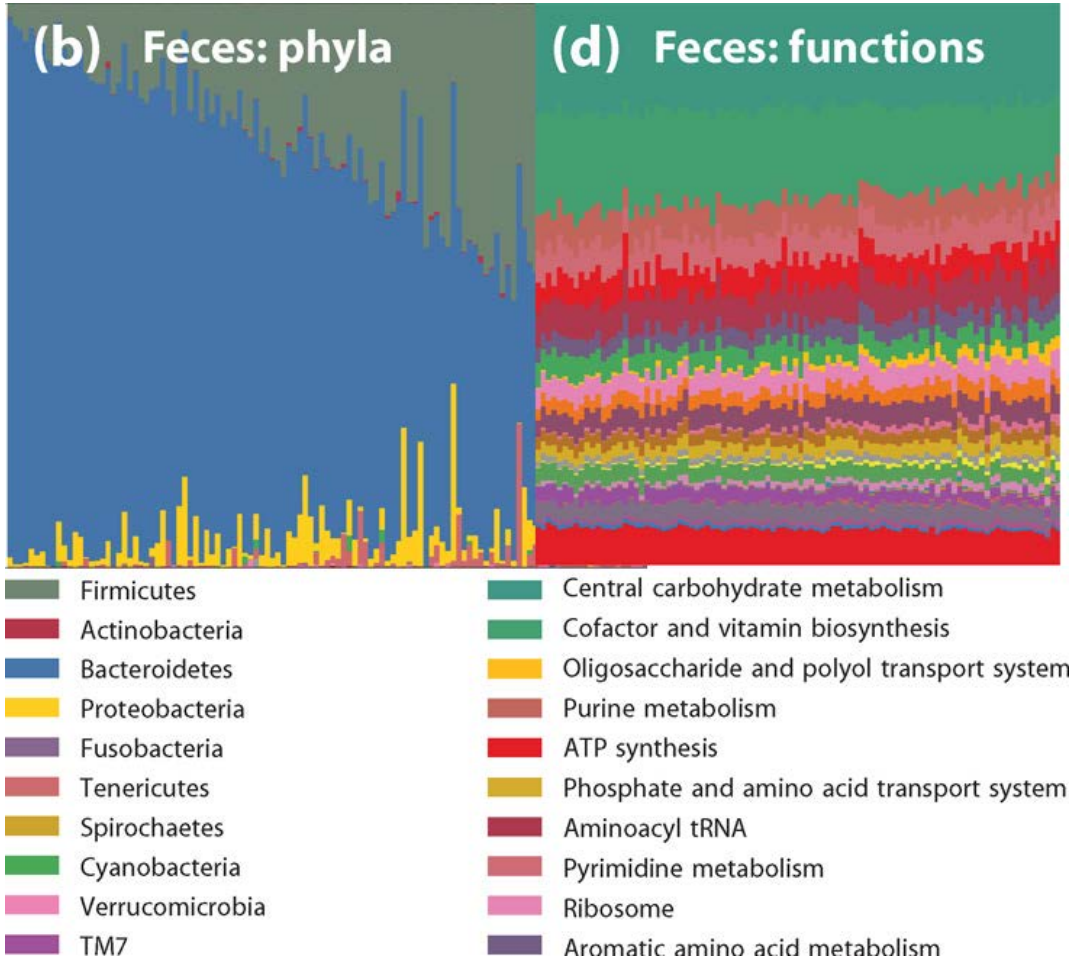
Structure of the intestinal microbiota

Great **phylogenetic diversity**

- Individuality of microbiota composition
- Impacted by age, diet, disease

Little functional variation

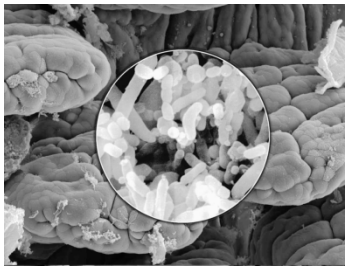
- Common functional requirements
- Niche specific functions
- Resilience of the microbiota

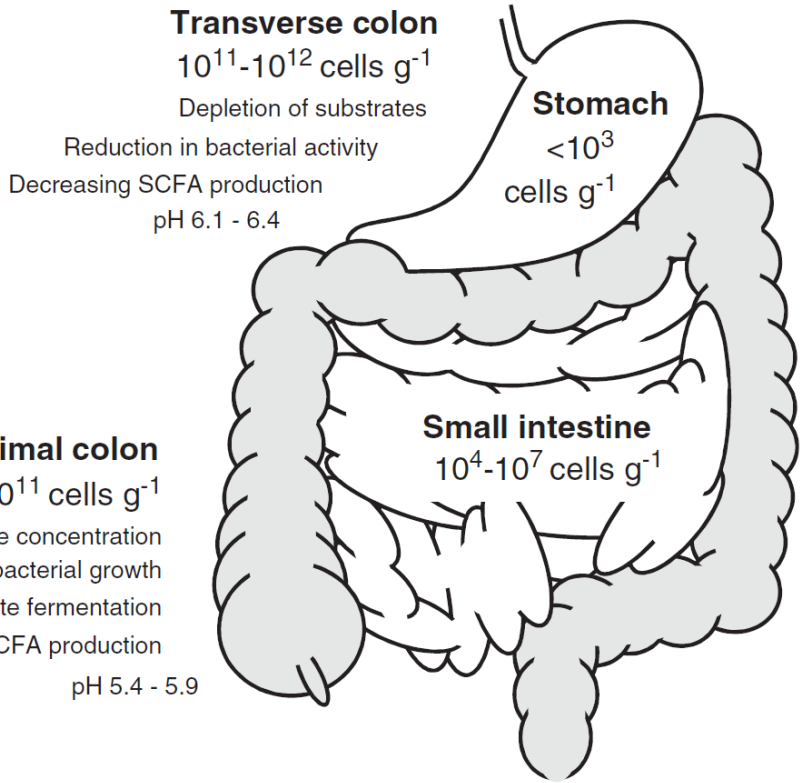


Lozupone, C. et. al., Nature, 2012

Fermentative Activity in the Human Colon

To salvage energy from non-digested dietary residues (carbohydrates) and endogenous secretions (e.g. enzymes and mucus) through fermentation

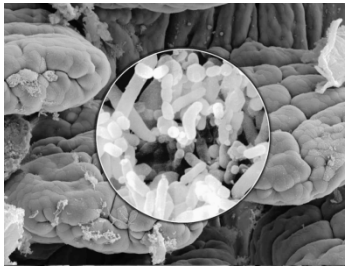


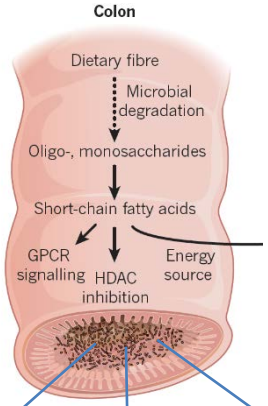


Payne et al 2012 Trends Biotechnol 30:17

Fermentative Activity in the Human Colon

To salvage energy from non-digested dietary residues (carbohydrates) and endogenous secretions (e.g. enzymes and mucus) through fermentation





Crossfeeding:

metabolites from fibrolytic and glycolytic bacteria are continuously used by other groups of microbes

Acetate **Propionate**

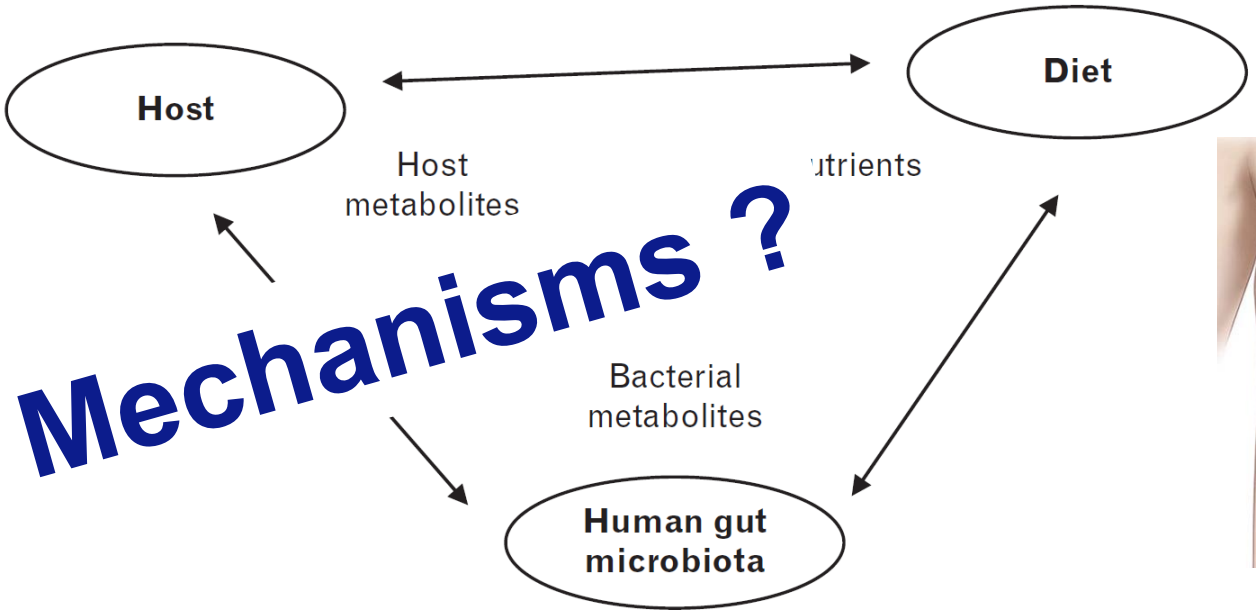
gluconeogenesis and lipogenesis

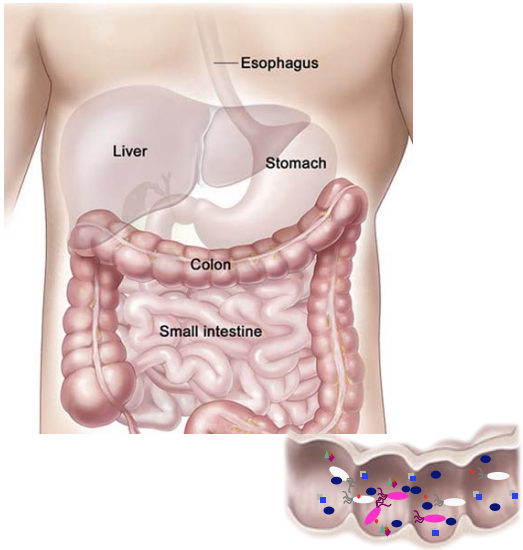
Butyrate

energy for colonic signaling

Beneficial effect on gut health

Ecological interactions in the human colon





- Microbial perturbations & dysbiosis reported for many diseases and disorders
- A plastic metagenome

Chassard & Lacroix 2014 Curr Opin Clin Nutr Metab Care 16:453

The Importance of the Gut Microbiota

The impact of microbes has been underestimated
Potential to improve human health through gut biota

- Affected by diet, ageing, exogenous microbes
- Correlated with > 20 chronic diseases, inflammatory disorders, obesity, metabolic syndrome, diabetes,…etc.
- Involve with the programming of host metabolism!

How to influence the gut microbiota?

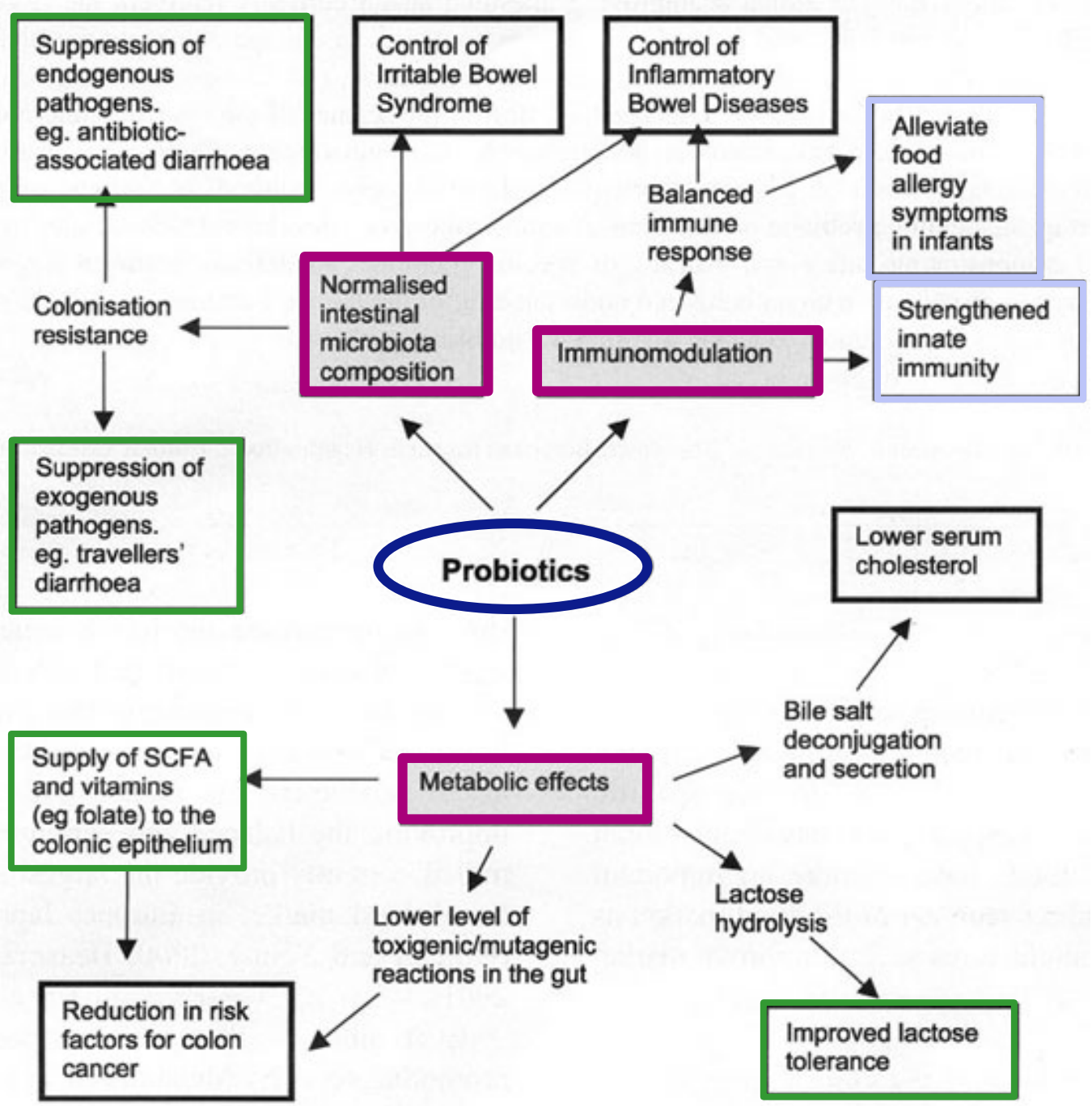
- Ingest **food** which influences microbial composition (maybe prebiotics)
- **Drugs**, e.g. infection and antibiotics
- Ingest **bacteria** (probiotics)

Need for strong scientific evidence!

Proposed Health Benefits from Probiotics

Strain specific properties!

Mechanisms??



Saarela et al., 2002 Int J Food Microbiol 78:99-117

Rauch & Lynch 2012 Cur Op Biotechnol 23:192

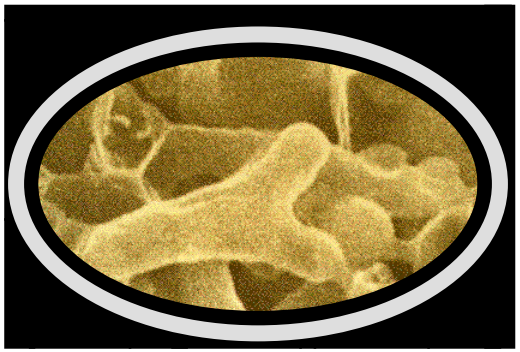
Four pilar selection for probiotic microbes

Safety

- Human origin
- Strain typing
- Virulence factors
- Antibiotic resistance
- Genetic stability
- Growth impact

Functionality

- (Human origin)
- Survival in the GIT
- Adhesion to epithelial cells
- Immuno-stimulatory with appropriate cytokines
- Inhibit GI pathogens
- Desirable metabolic activities
- Anti-mutagenic and anti-carcinogenic properties

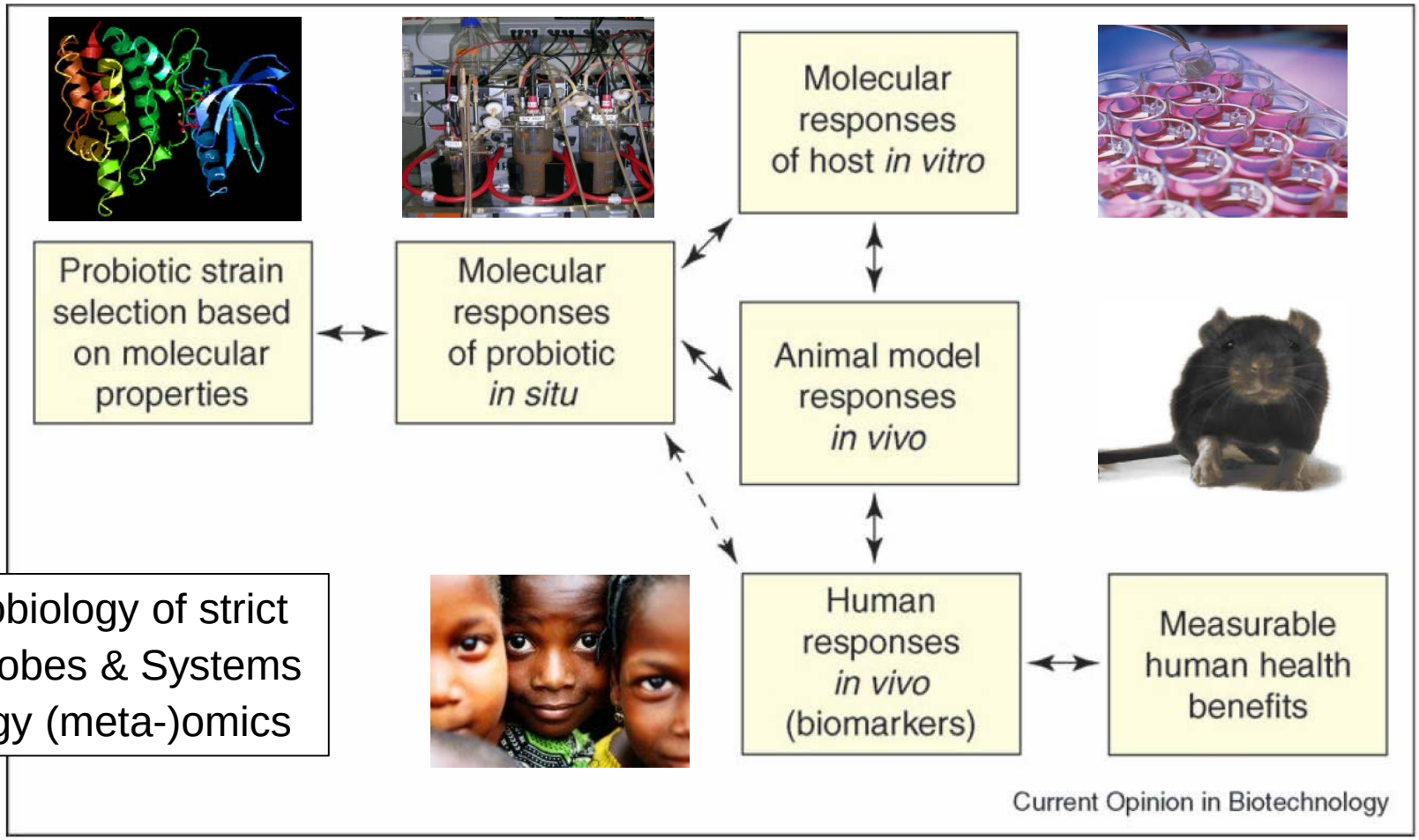


- Easy and cheap cultivation
- High viability in process
- Stability in products
- Robust physiology
- No off-flavours

Technology

Efficacy and effectiveness *in vivo* (animal and human)

Probiotic Mechanism & Validation

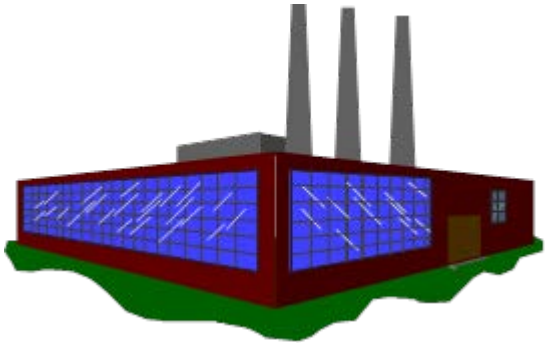


Microbiology of strict anaerobes & Systems biology (meta-)omics

Marco et al 2006 Curr Opinion Biotechnol 17:1 *Payne et al 2012 Trends Biotechnol 30:17*

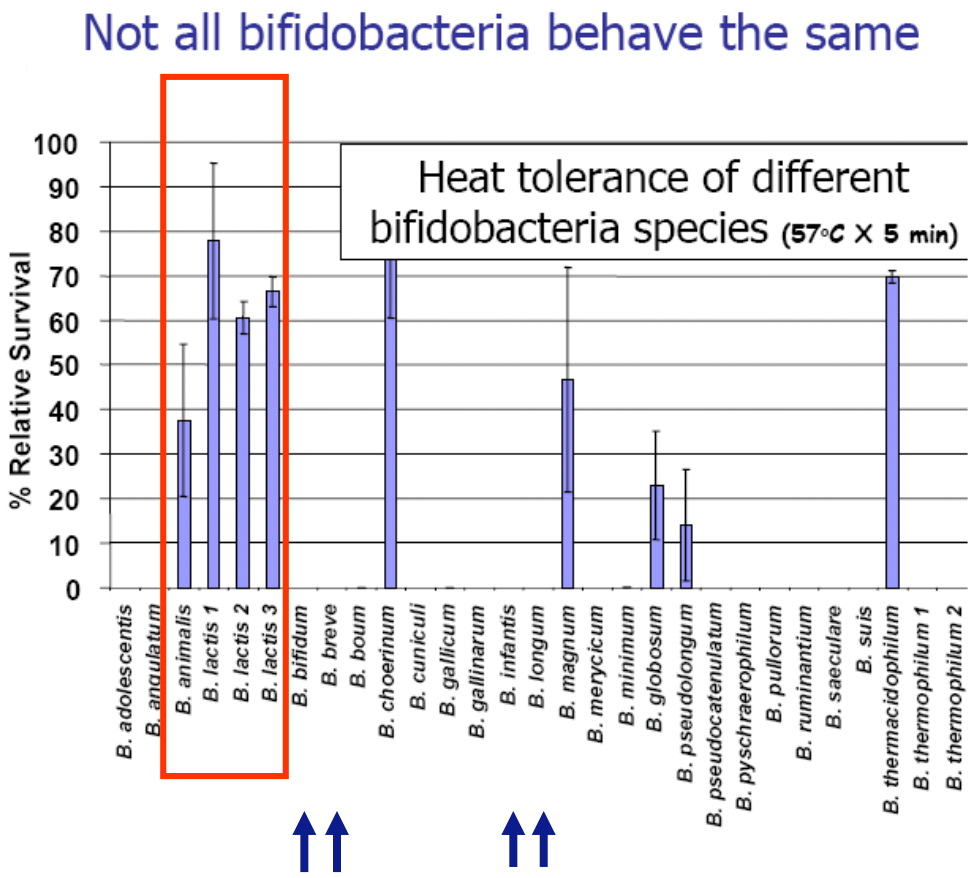
Technology, a Major Bottleneck of Probiotics

- To date selection of probiotics has been largely limited by their **technological suitability: growth, stability - high viability in products.**
- Strains with exceptional functional health properties are often not considered for application.
- Currently used strains only represent a **tiny proportion of the potential in the GIT.**
- As a result the **only a limited number of strains are “viable options”** as commercial probiotics.



Selection of stress tolerant probiotics

e.g. heat, oxygen, product application



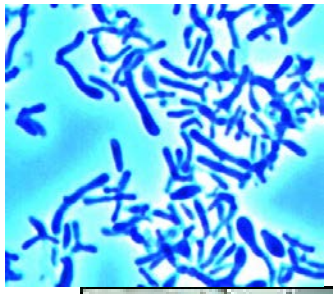
Simpson et al. 2005 JAM 99:493

The spore solution:

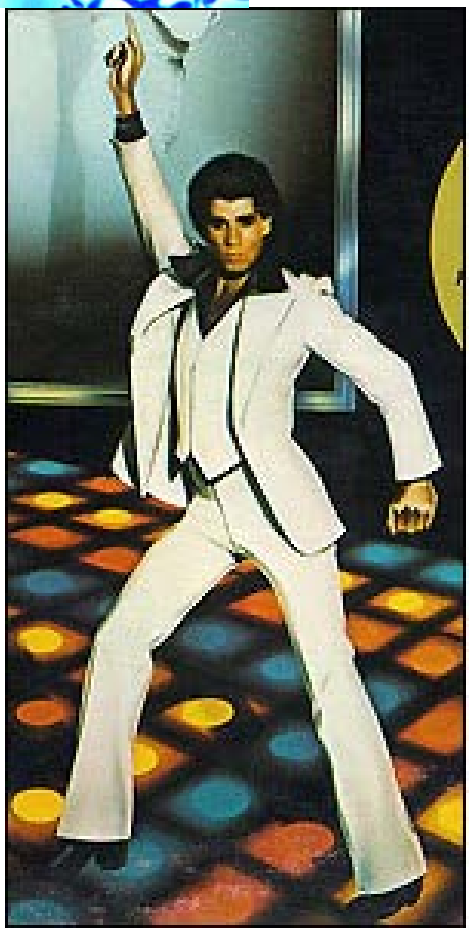
Bacillus coagulans

Bakery, chocolate, candies, coffee, tea, …

Staying Alive !



- ✓ **Critical for product effectiveness**: general accepted limit of 10^6 - 10^7 viable cells/ml or g during shelf-life



Current challenges for probiotic technology:

- **Existing probiotic strains**

  Increased robustness leading to greater product efficacy and diversification, e.g. by physiology programming

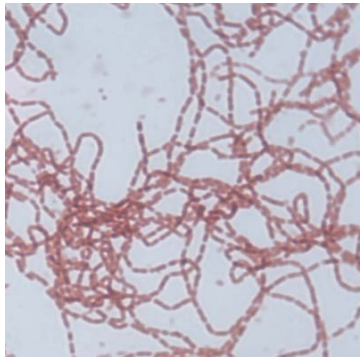
- **New probiotic strains**

  Get technologically unsuitable strains with high functionality in products

- **Set up accurate methods to measure viability**
- **Develop valid biomarkers of activity**

Claims for microbial strains are (currently) only possible in the pathway of pharmaceuticals

Functional microbial strain



Food pathway
(probiotics)

Drug pathway
(pharmabiotics)

efsa
European Food Safety Authority

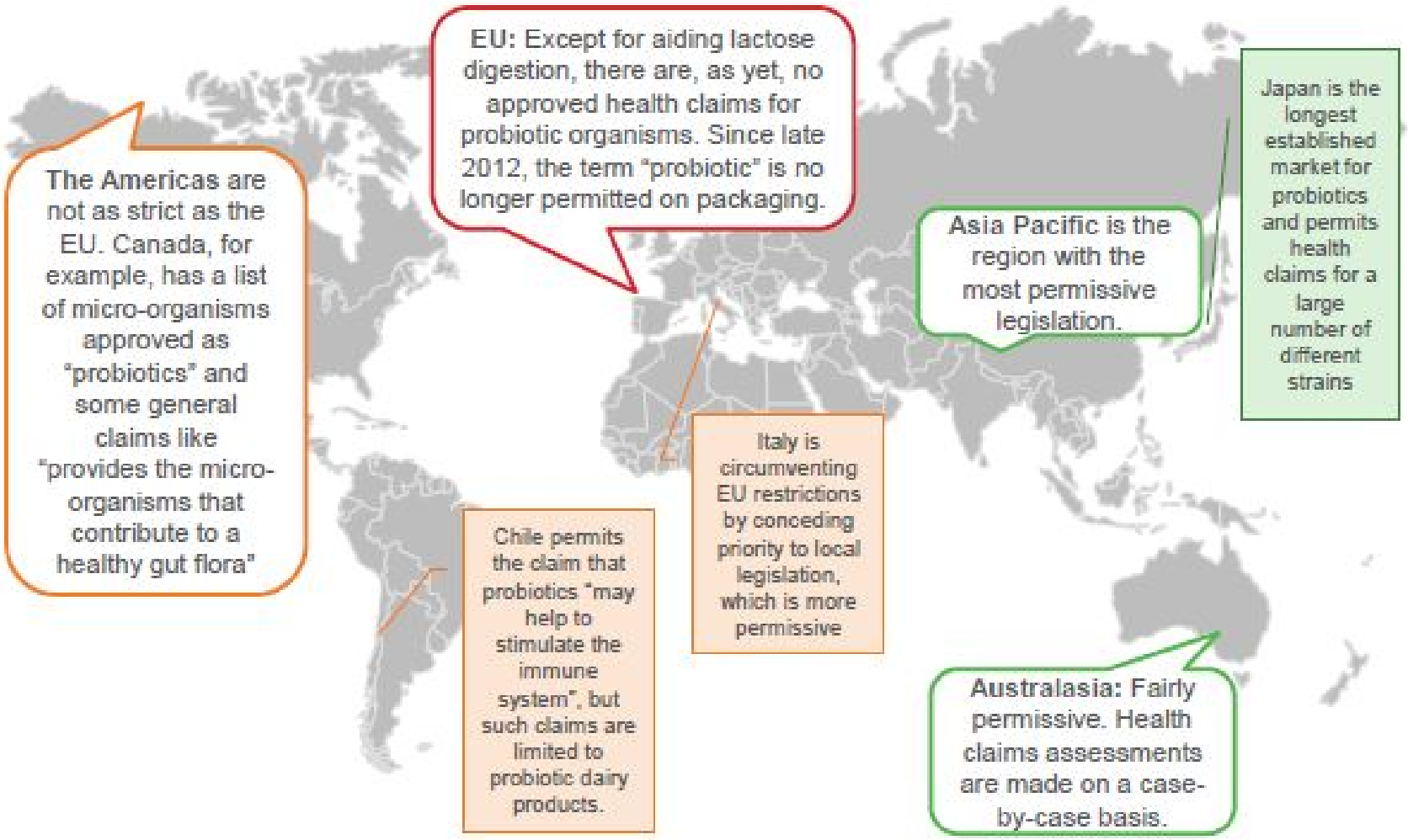
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Limited to QPS species
- Health claims at most (none so far)

- No QPS limitation
- Disease claims (need to prove)
- Developing field, regulation required

ETH

Regulatory environment varies greatly across the globe



How is Health Claim Scientific Data Assessed?

EU Regulation Nutrition & Health Claims (NHCR) 1924/2006

efsa
European Food Safety Authority

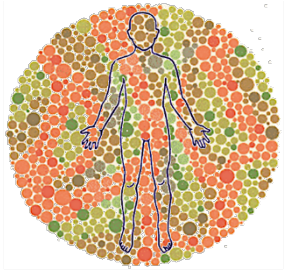
PASSCLAIM: *Process for the Assessment of Scientific Support for Health Claims on Foods:*

1. The bioactive substance (constituents) must be clearly **characterized**.
2. The claimed health benefits must represent a **benefit for human health**.
3. A **cause-effect relationship** must be proven.
4. Need support from Well Designed, RCT Clinical Studies in a **normal, healthy population**

Bioactive Substance / Food

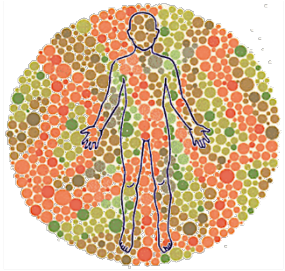
Health Benefit

Outlook: Probiotics for Food



- **Mechanisms and causality** of gut microbiome-dysbiosis-disease
- **Biodiversity of gut microbiota** is key to health: e.g. barrier effect to pathogens, IBD, NEC, diabetes, etc.
- The **concept of single strain probiotics** may be oversimplistic.
- **Probiotic functionality** is key but very difficult to scientifically prove in healthy populations.
- **Mechanisms and validation** of probiotic efficacy in double-blind placebo-control randomized trials: data in high demand!

Microbial Therapy in Medecine



- **A fully open field with huge potential!**
- New paradigm for how we treat disease: e.g. antibiotics for infections
- **Systemic targets** are multiple : infections (CDI), obesity-metabolic syndrome, inflammatory / allergic diseases, depression.
- Anaerobic culture and technology is key for the generation of **second generation probiotics** :
  - ***Akkermansia muciniphila***, dominant commensal of the mucus layer, control obesity & associated metabolic diseases?
  - ***Faecalibacterium prautznii***, butyrate-producer, treatment of IBD.
- **Third generation probiotics as new medical therapeutics** likely to rely on trophic interactions for network reconstruction.


Thank you for your attention!