Il mondo complesso dei microbiomi e la loro importanza per la nutrizione e la salute dell'uomo

Vincenzo Di Marzo

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Istituto di Chimica Biomolecolare, CNR, Pozzuoli (NA)

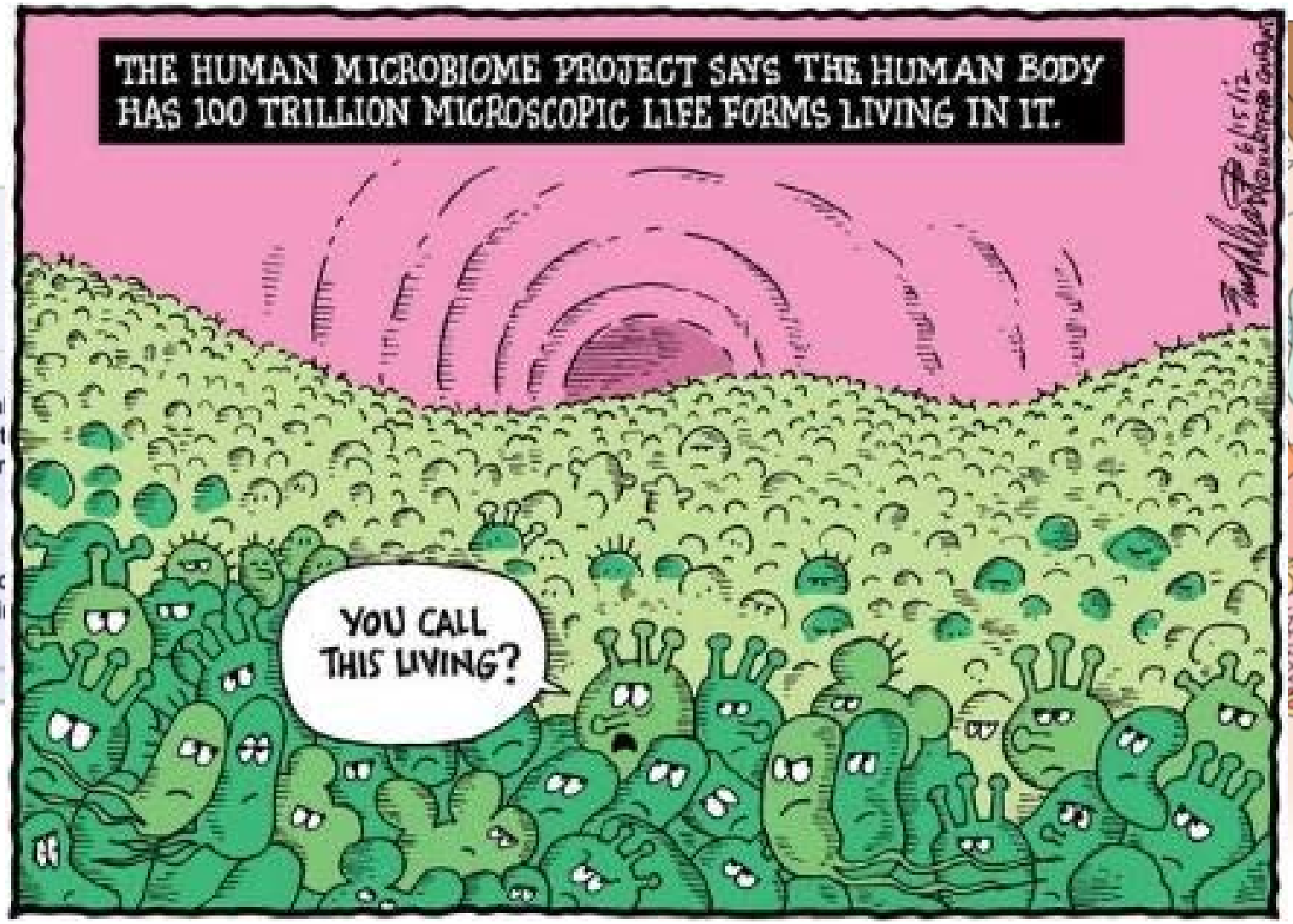
www.umilaval.cnr.it **https://cerc-mend.chaire.ulaval.ca/en/home/**

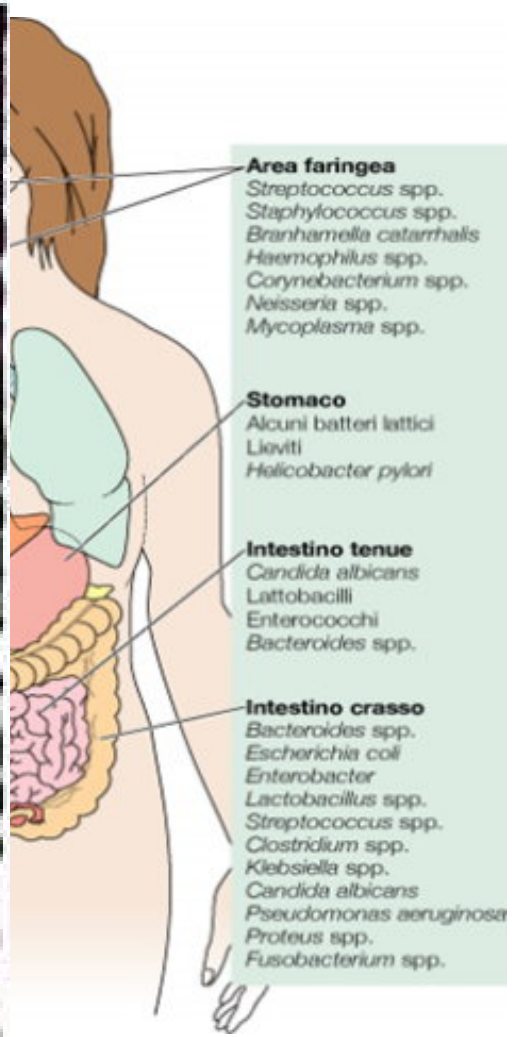
Fino al 90% delle cellule che portiamo con noi è costituito da « microbi »: il microbiota

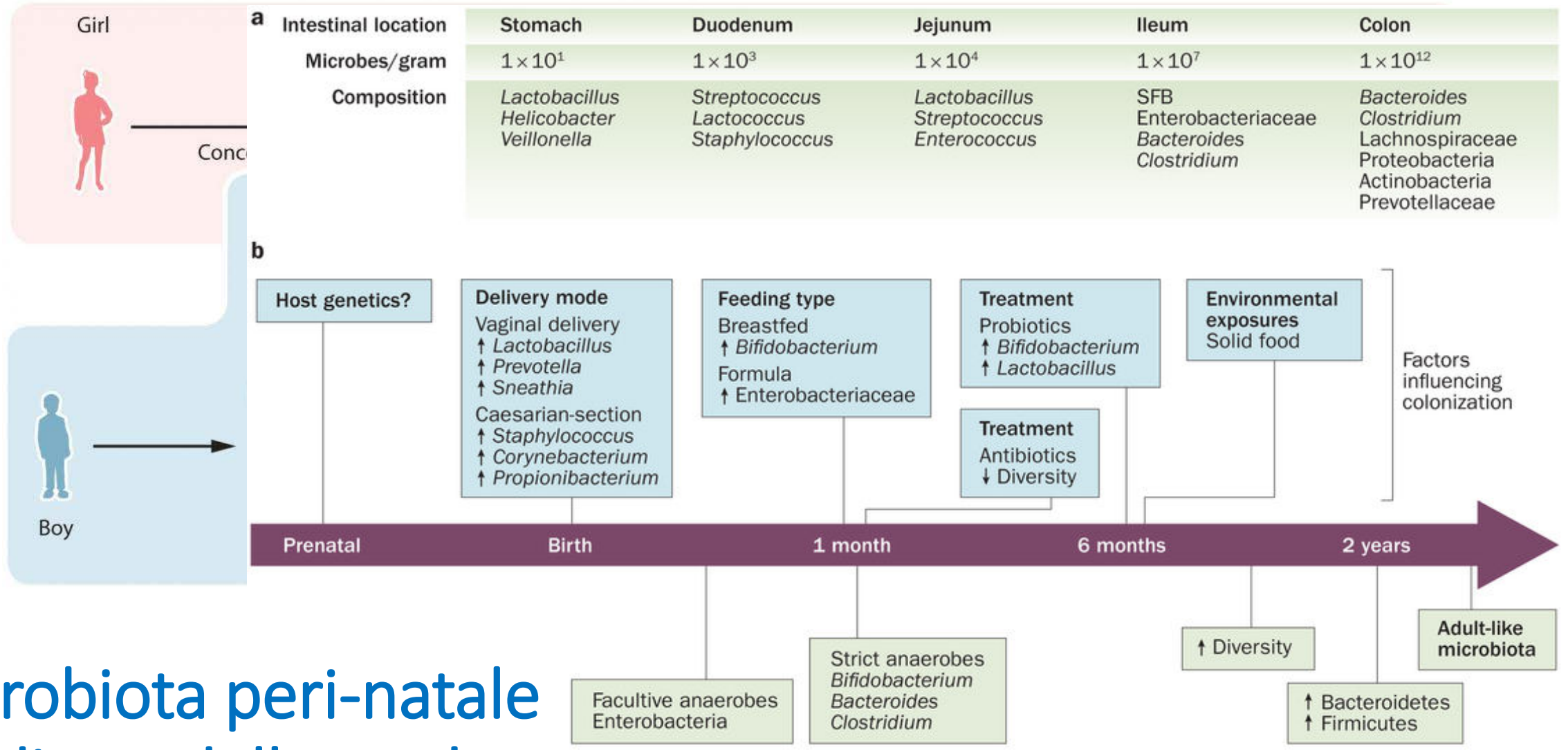
We are composed of several species:

As adults our microbial census exceeds the tot number of our own hur cells

The largest collection c microbes resides withi intestine

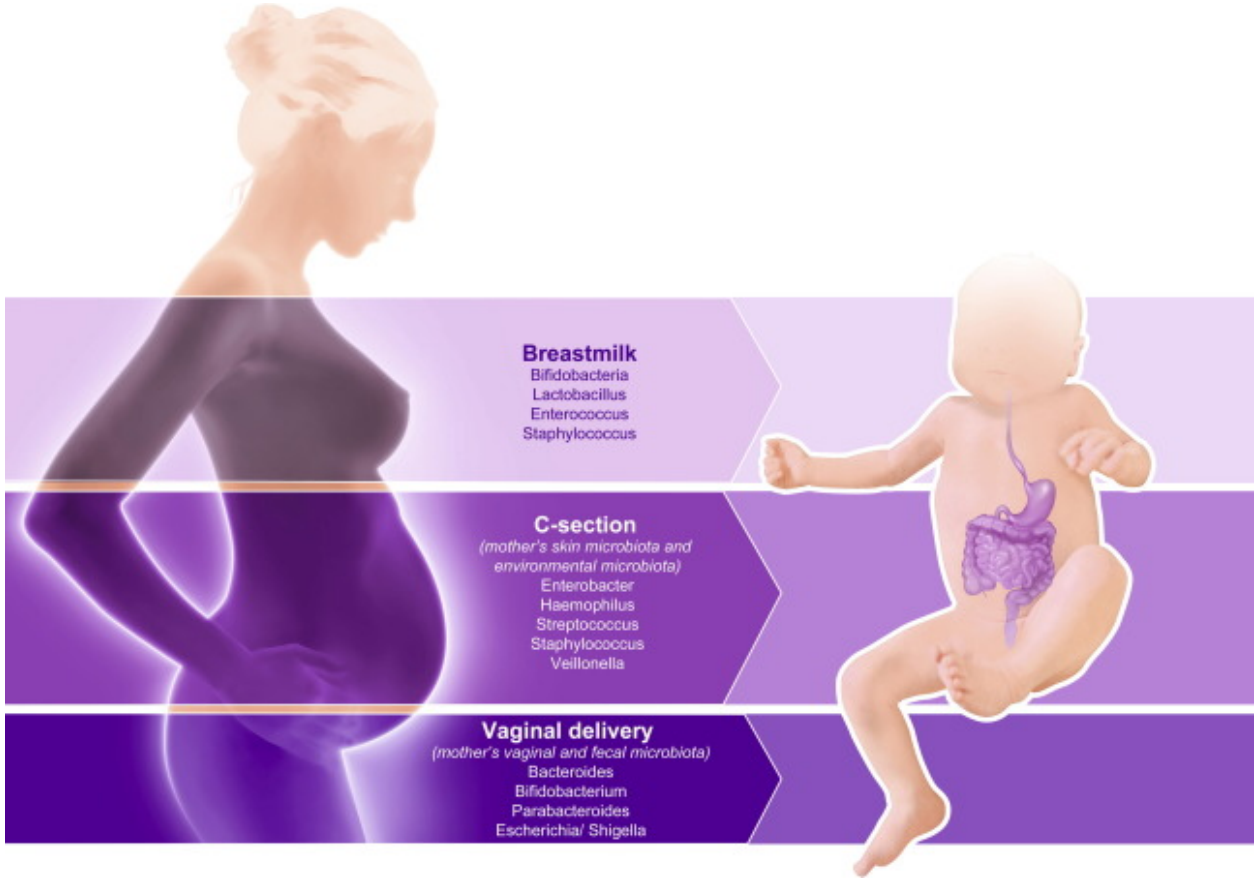


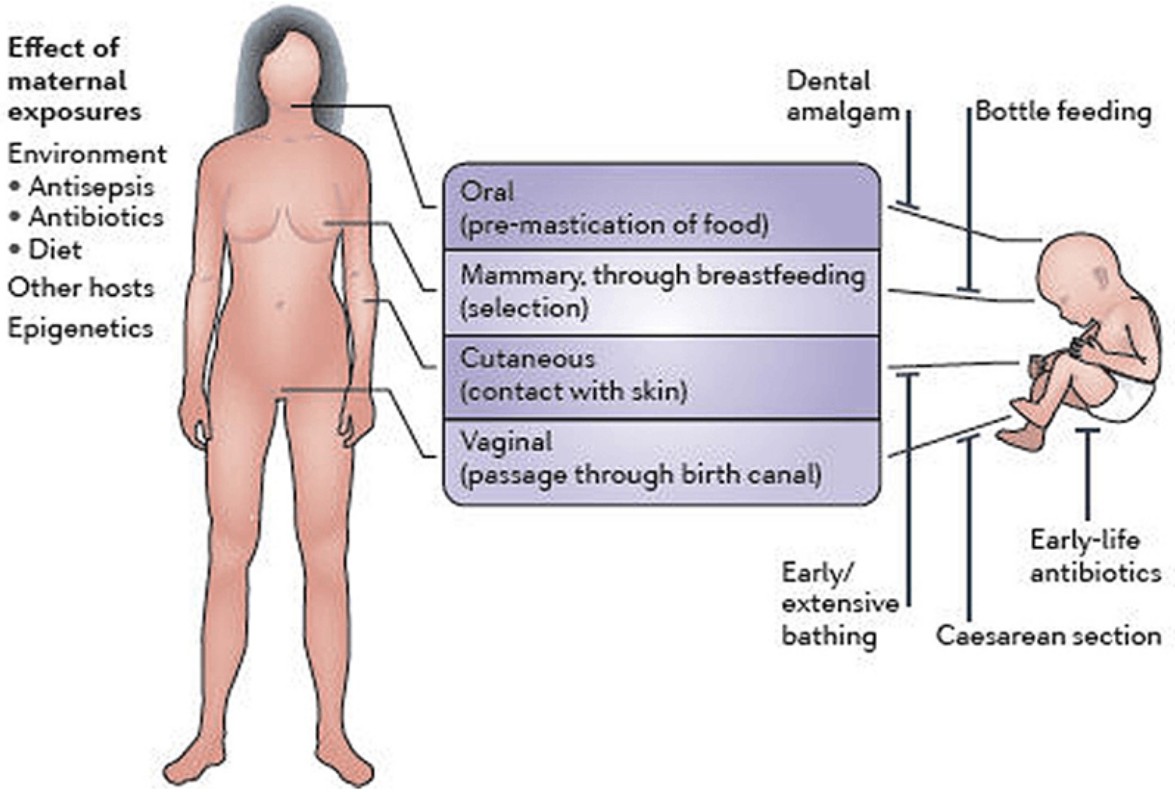




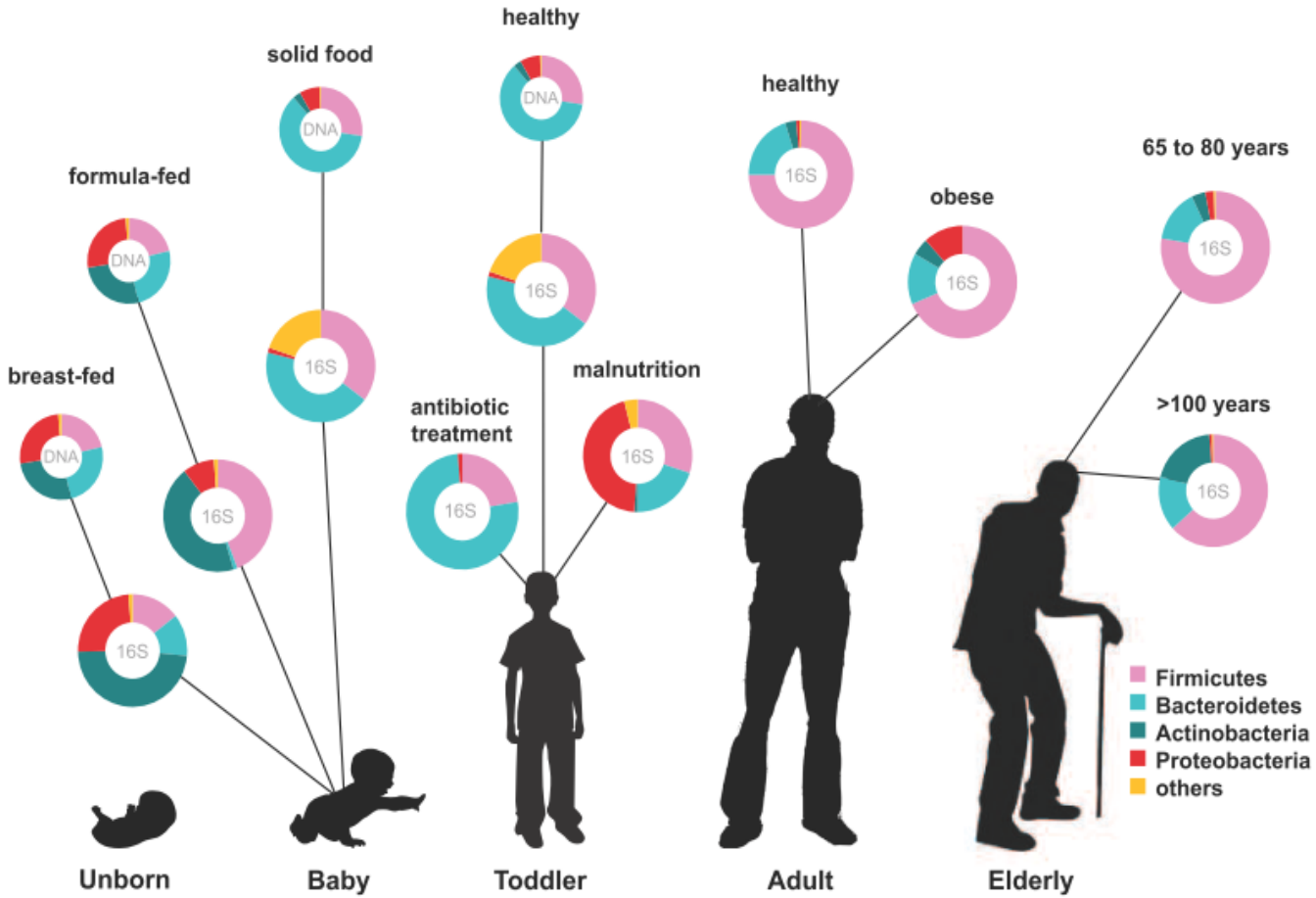
Il microbiota peri-natale è ereditato dalla madre per poi cambiare con l'età

Molti fattori esterni interferiscono con la trasmissione del microbiota da madre in figlio

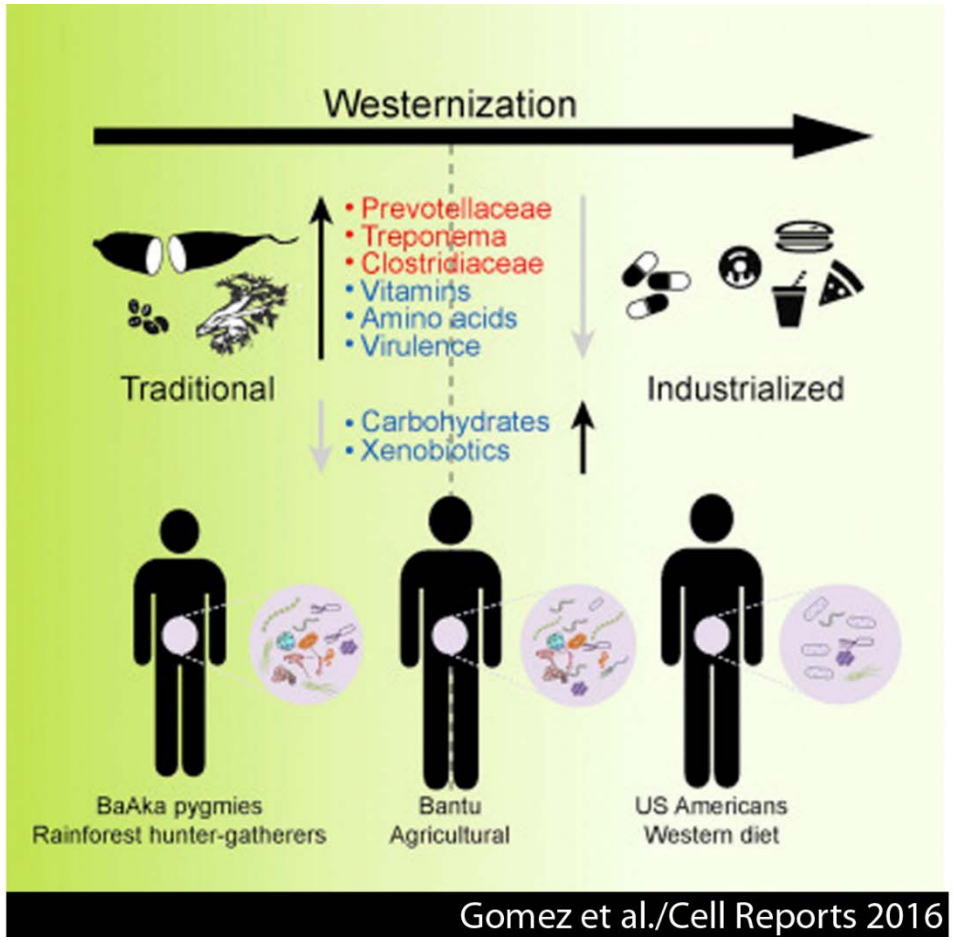




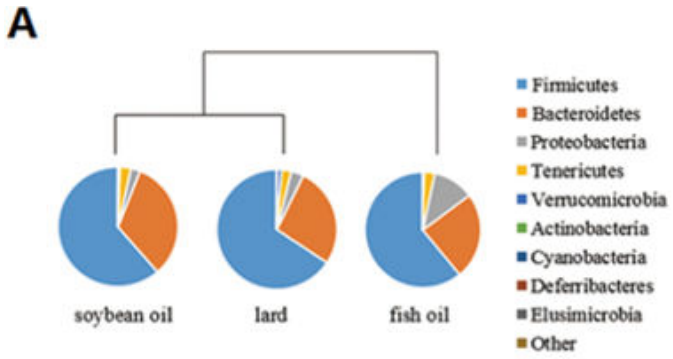
Il microbiota intestinale è profondamente alterato da fattori sia fisiologici che ambientali

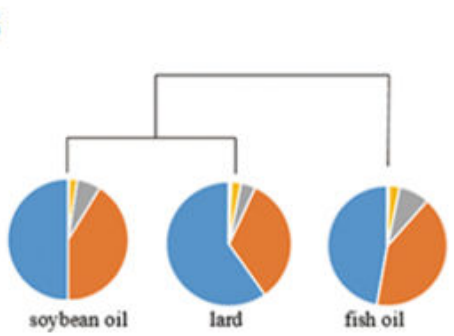


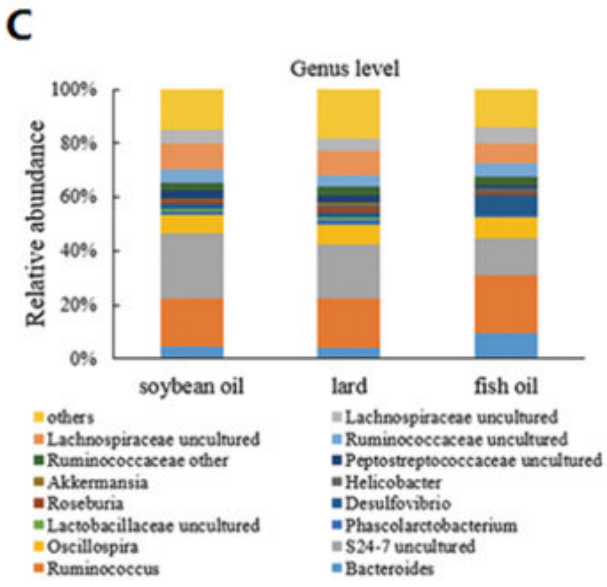
Source: Ottman, 2012

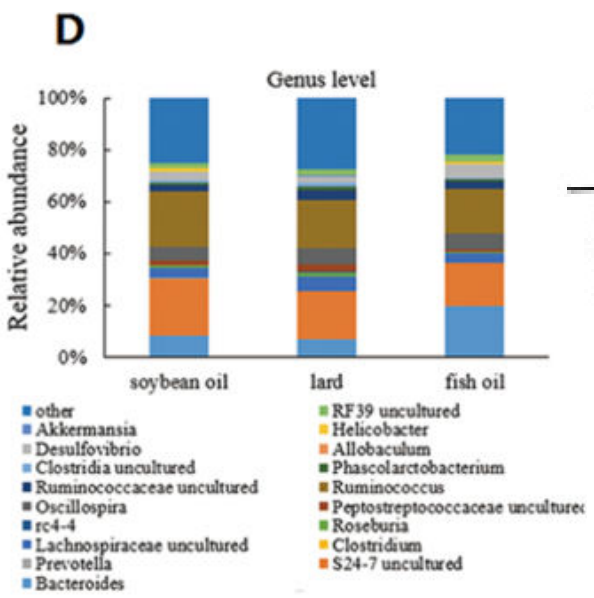


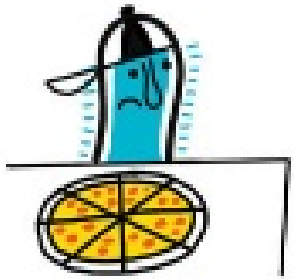
Il microbiota intestinale è alterato dal tipo di dieta

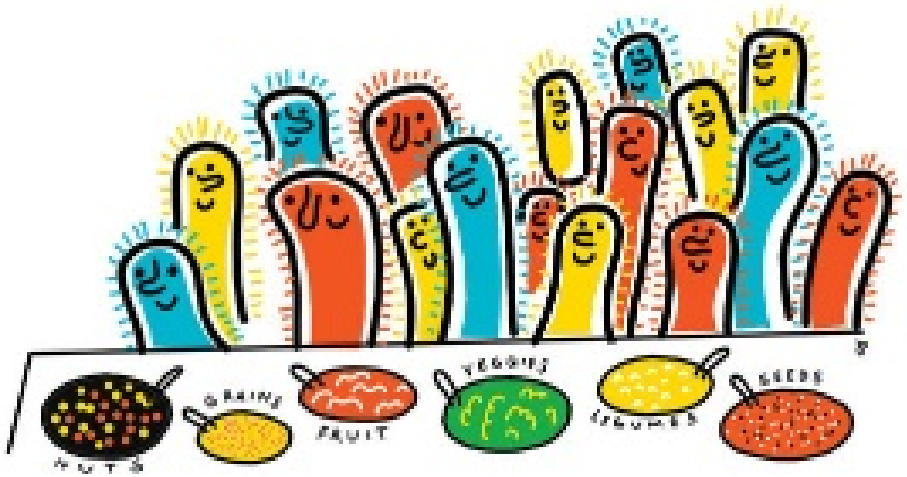




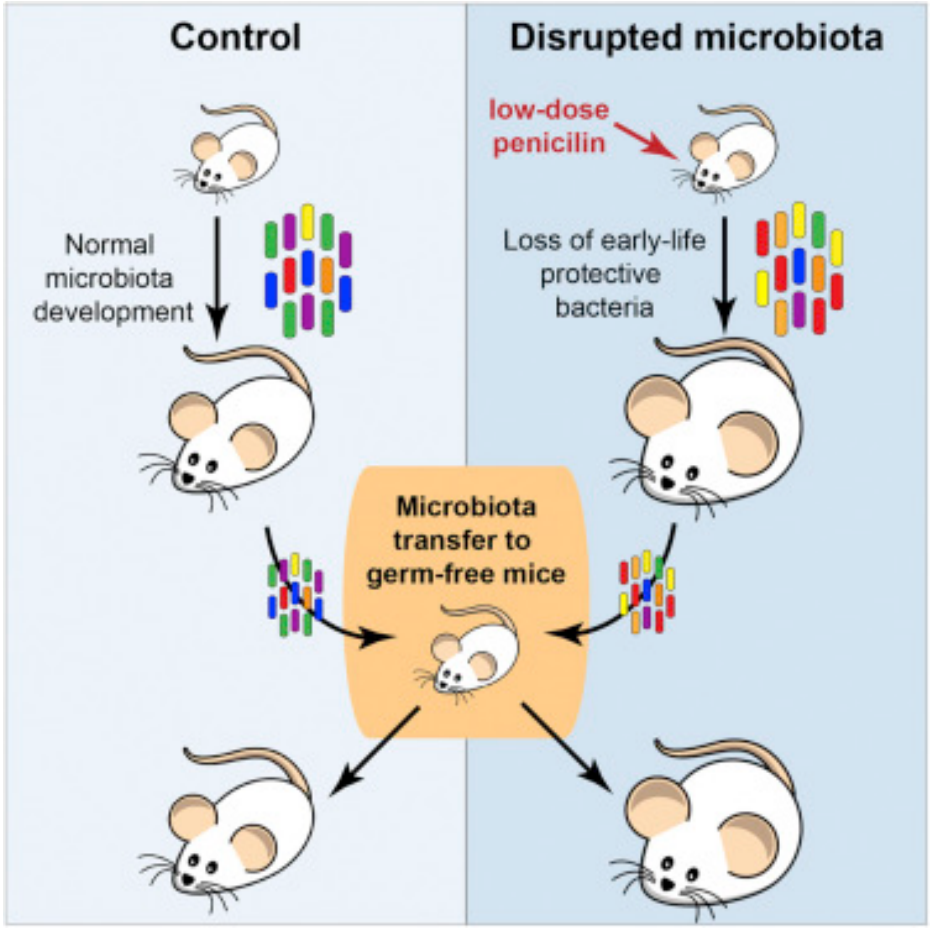


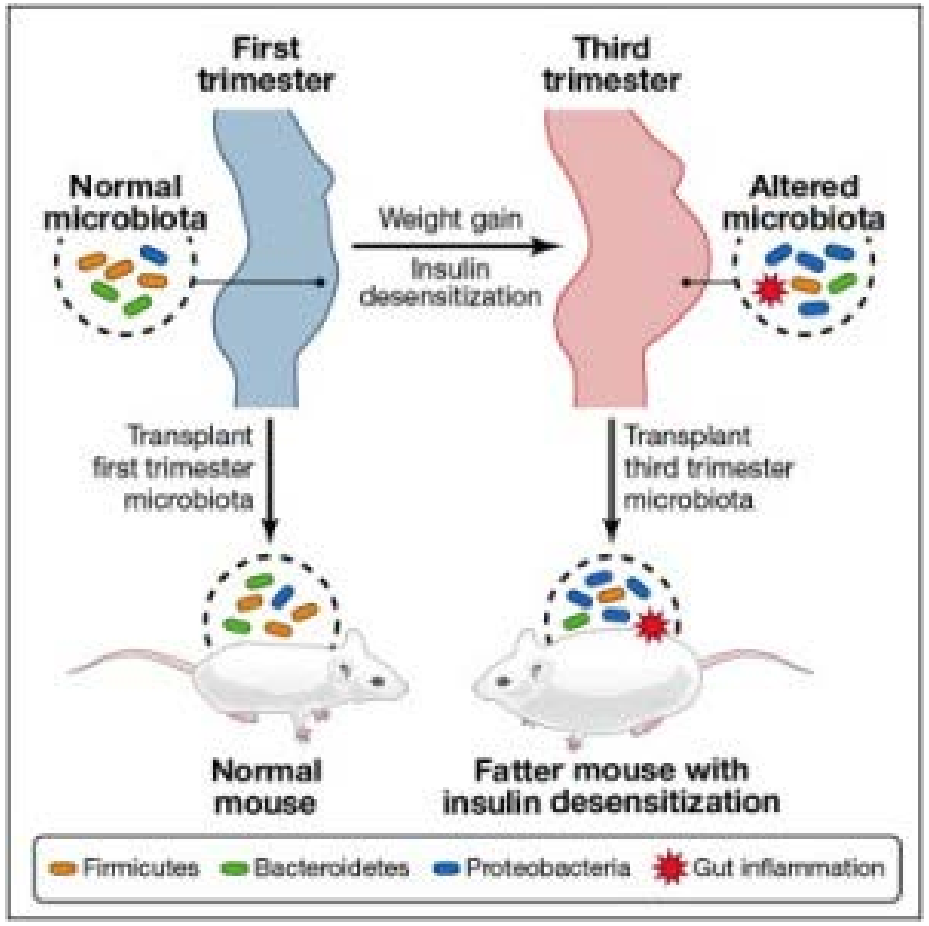






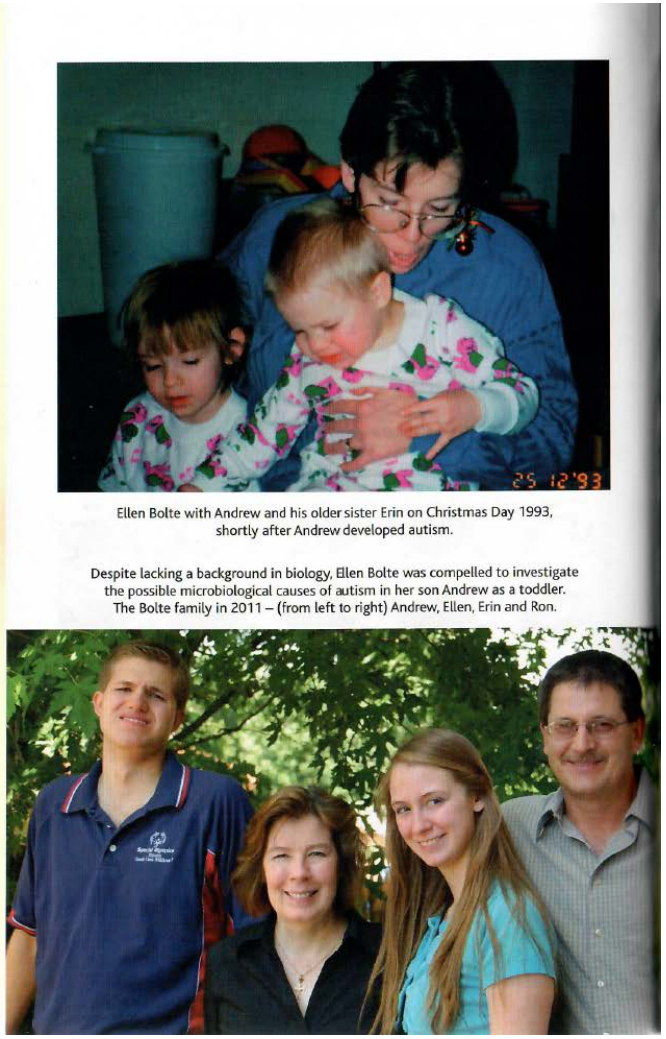
Oltre l'ereditarietà genetica: trasmissibilità delle funzioni controllate dal microbiota





E' possibile trasmettere anche i comportamenti attraverso il microbiota, e anche tra specie diverse?

Se siamo quello che mangiamo è anche a causa del microbiota? Effetti sul comportamento in malattie neuropsichiatriche e neurologiche



Ellen Bolte with Andrew and his older sister Erin on Christmas Day 1993, shortly after Andrew developed autism.

Despite lacking a background in biology, Ellen Bolte was compelled to investigate the possible microbiological causes of autism in her son Andrew as a toddler. The Bolte family in 2011 – (from left to right) Andrew, Ellen, Erin and Ron.

Clinical Commentary

Biological Psychiatry

More Than a Gut Feeling: The Implications of the Gut Microbiota in Psychiatry

Pochu Ho and David A. Ross

http://dx.doi.org/10.1016/j.biopsych.2016.12.018
ISSN: 0006-3223

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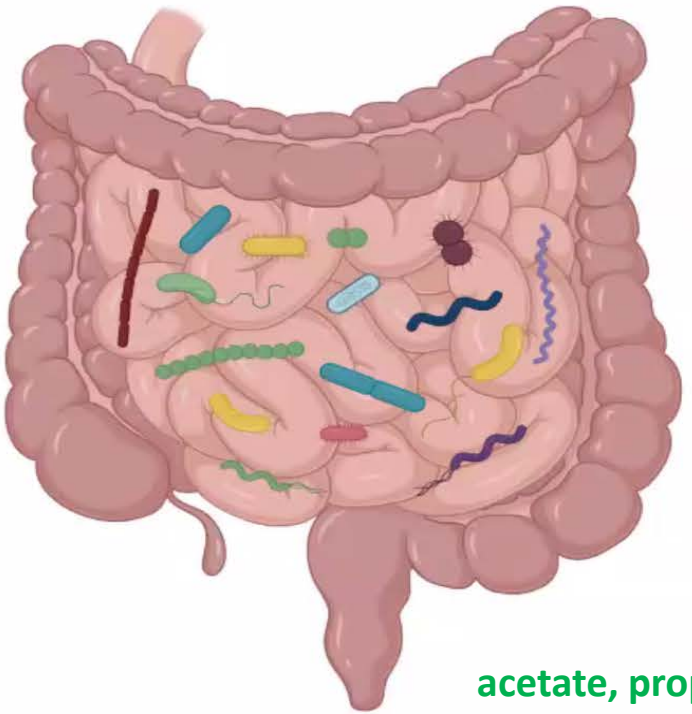
Biological Psychiatry March 1, 2017; 81:e35–e37 www.sobp.org/journal

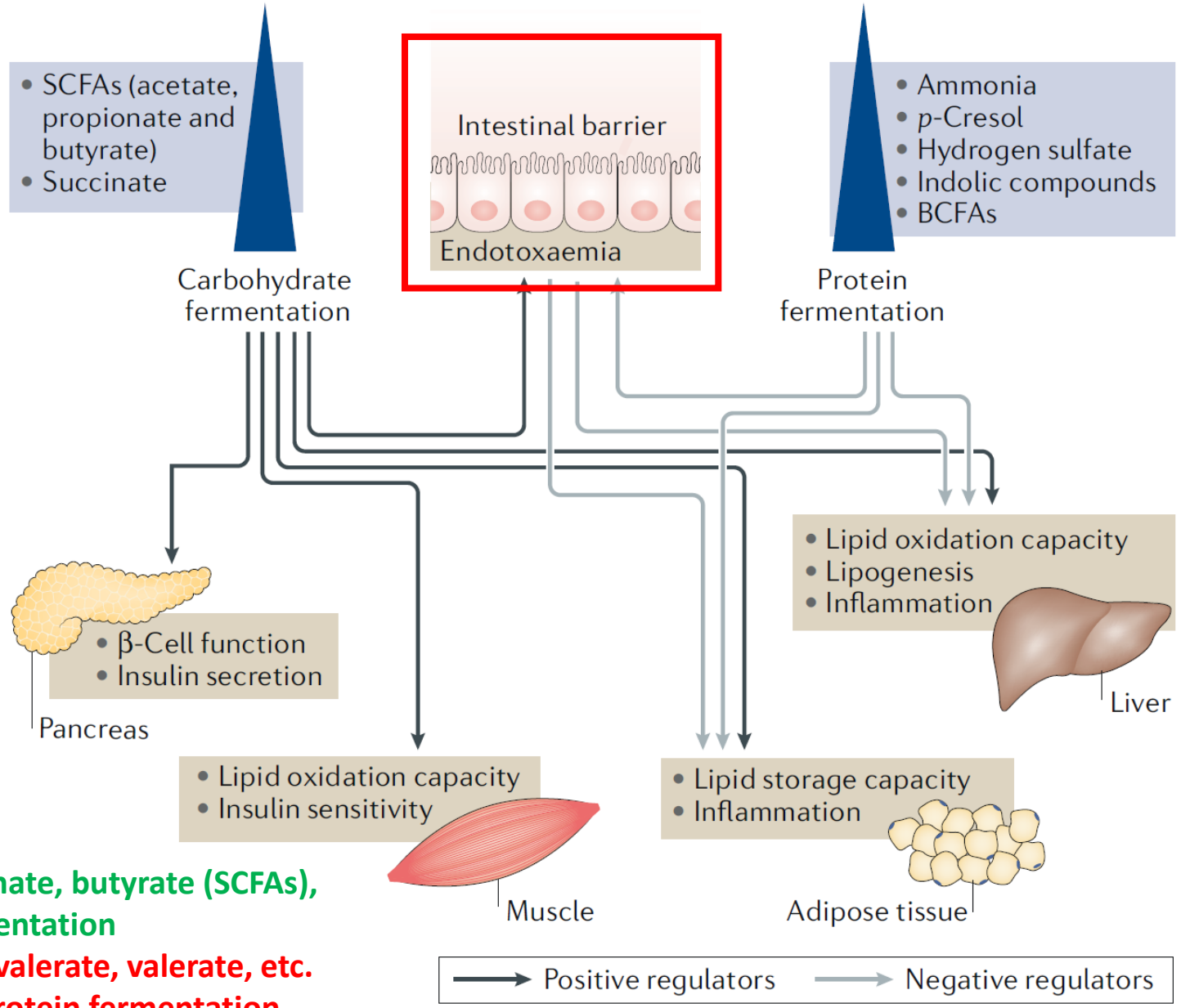
Autism spectrum disorders
Attention Deficit/ Hyperactivity Disorder
Schizophrenia and obsessive/compulsive disorders

Anxiety
Depression

Alzheimer's
Parkinson's

The microbiome impacts distant organs





acetate, propionate, butyrate (SCFAs), from fiber fermentation

isobutyrate, isovalerate, valerate, etc. (BCFAs), from protein fermentation

Canfora et al, Nat Rev Endocrinol 2019

Joint International Research Unit on Chemical and Biomolecular Research on the Microbiome and Its Impact on Metabolic Health and Nutrition (MicroMeNu) www.umilaval.cnr.it

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Parties, Objectives, Mission and Initial Topics

1. Constituent Parties

The JIRU is initially founded by the Parties which are a signatory to this Agreement, specifically the following entities:

- The Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval (IUCPQ – UL);
- The Institut sur la nutrition et les aliments fonctionnels (INAF), which is part of Université Laval;
- The Institute of Biomolecular Chemistry which is part of the CNR;
- The Faculté de médecine from Université Laval
- The Faculté des sciences de l'agriculture et de l'alimentation from Université Laval
- Any other entity in connection with the proposed theme and which the Parties approve in writing.

2. Objective

2.1 The objective of the JIRU is to be a world reference in the field of biomolecular chemistry, the microbiome, nutrition and cardiometabolic health through the specialized training it offers, its joint inter-university development model and its capacity to transfer the knowledge and technologies resulting from its work.

2.2 The mission of the JIRU is to encourage networking, expansion and an international presence for the joint research and educational activities of its members.

2.3 The specific objectives of the JIRU shall be developed by the Steering Committee of the JIRU during the year following the signature of this Agreement. These objectives shall be attained through research, innovation, education and transfer projects (hereafter the "**Projects**") performed under the purview of the JIRU.

APPENDIX 1

Main scientific development streams of the JIRU

- Characterization of transcriptomic, metabolomic and lipidomic profiles of the oral and gut microbiome of healthy individuals as compared to those of individuals with high cardiometabolic risk.
- Identification and chemical characterization of "post-biotics", i.e. abundant microbiome-derived bioactive metabolites that, by virtue of their chemical structures and biological activity, may be used to reduce cardiometabolic risk through nutritional approaches.
- Medium scale culturing (bioreactors) of bacterial species found to be differently associated with healthy individuals vs. those with high cardiometabolic risk in order to produce high amounts of "post-biotics".
- Incorporation of prebiotics/nutrients into bacterial culture systems in order to assess changes on, and maximize the production of, the above mentioned "post-biotics".
- Medium scale chemical synthesis of "post-biotics" to ensure sufficient quantities for their biological testing in vitro and in vivo.
- In silico analyses of identified "post-biotics" that, by virtue of their chemical structures, suggest potential interactions with metabolically relevant targets.
- *In vitro* screening of identified "post-biotics" in metabolically relevant assays to assess activity on processes such as hepatosteatosis, insulin secretion and action, mitochondrial activity, and brown and white adipose tissue functions.
- Establishment of zebrafish models for the study of cardio-metabolic risk and screening therein of "post-biotics" for risk improvement through nutritional approaches.
- Formulation of "post-biotics" by using nanotechnologies suitable for nutritional approaches, in order to increase their stability and bioavailability, and ensure their delivery to target, in animal models and in human subjects.

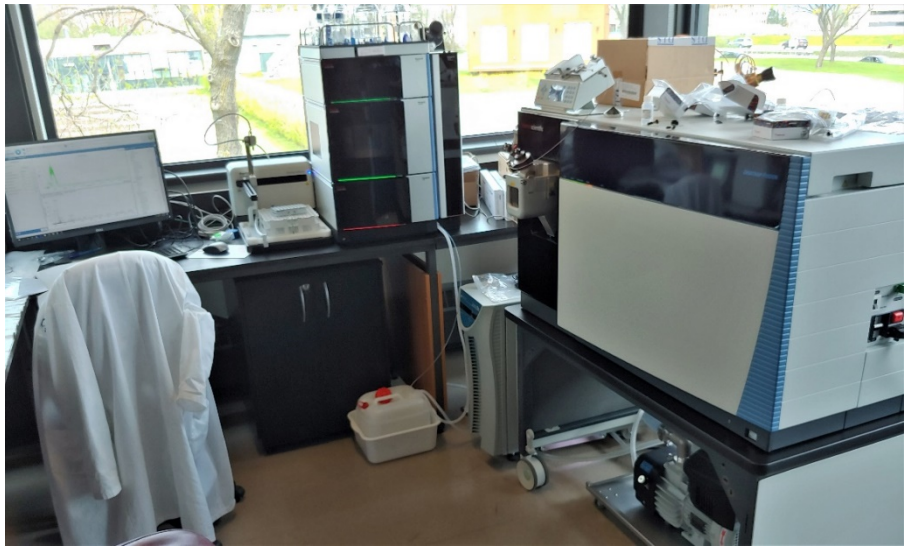
The UMI fosters collaborative research between Ulaval, the CNR and Italy

The UMI has funded the following bilateral projects between Université Laval and CNR for the years 2018-2022:

1) Arctic Biofilms: Sentinels of Environmental Change and Microbial Reservoirs of Novel Biomolecules;
2) A platform for understanding and exploiting polyphenols microbial metabolites based on a combined experimental-chemoinformatic approach;
3) Targeting the gut microbiota with new extracts enriched with omega-3 PUFAs and polyphenols from nordic biosources to alleviate cardiometabolic diseases;
4) Defining the endocannabinoidome and the microbiota in asthma and its severity;
5) Nordic berries as sources of polyphenols and indigenous lactic acid bacteria for the development of unique synbiotic and postbiotic products;
6) Investigation into the effects of vitamin D on antipsychotic drug metabolic side effects: focus on the gut microbiome;
7) Novel biomarkers for early diagnosis of Parkinson Diseases;
8) Pinealocyte-derived melatonin modulates metabolic health through photoperiod-mediated effects on the gut microbiome and endocannabinoidome.

Complex systems (omes) require complex technology: Lipidomics, Metabolomics and Proteomics

LC-MS/MS



Lipidomics

INSTITUT UNIVERSITAIRE DE CARDIOLOGIE ET DE PNEUMOLOGIE DE QUÉBEC

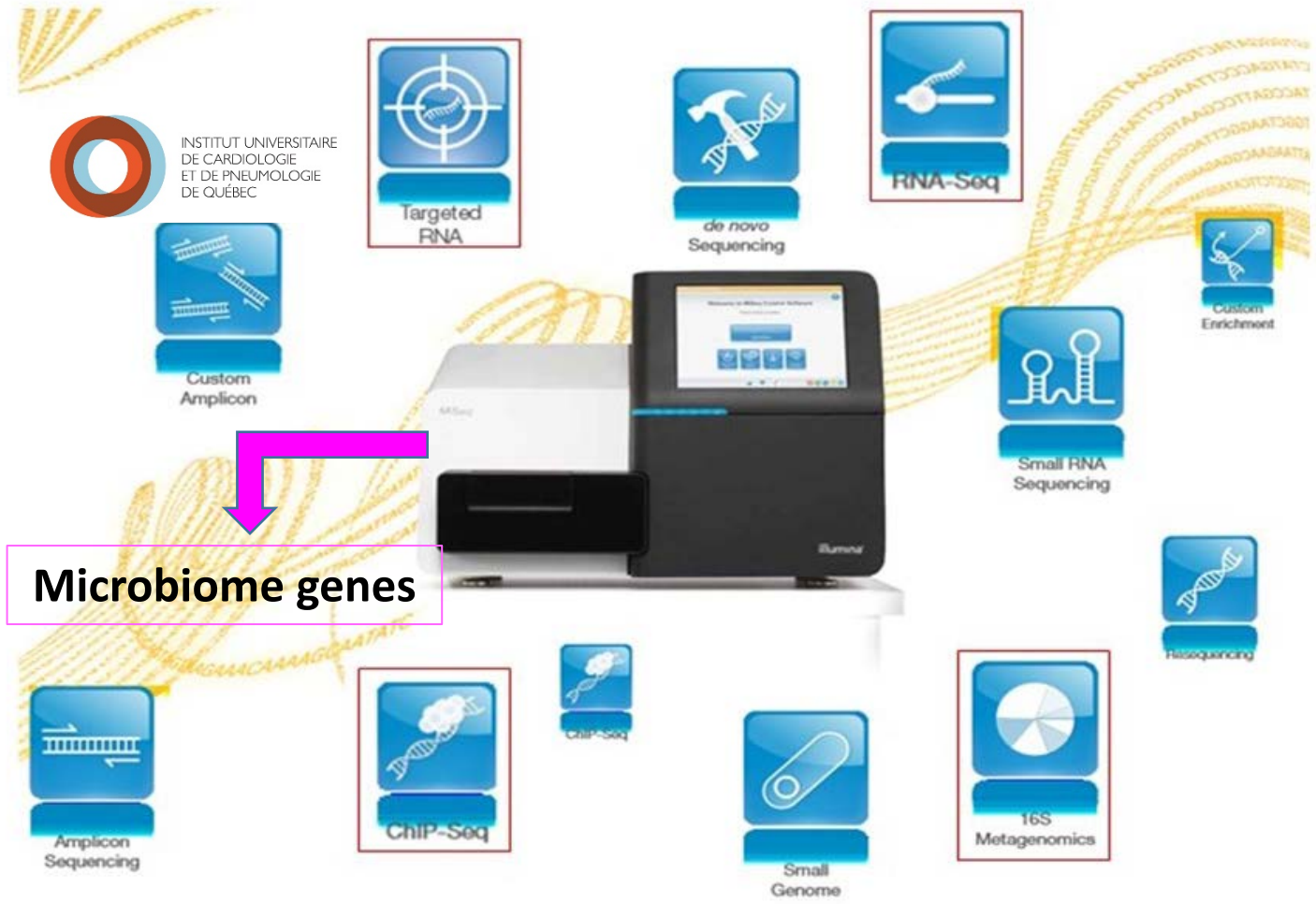
Microbiome metabolomics and proteomics

INAF INSTITUT SUR LA NUTRITION ET LES ALIMENTS FONCTIONNELS

Proteome and metabolome imaging on tissue or cultures

INSTITUT UNIVERSITAIRE DE CARDIOLOGIE ET DE PNEUMOLOGIE DE QUÉBEC

Next generation sequencing for ribosomal 16S DNA metagenomics, and qPCR array transcriptomics



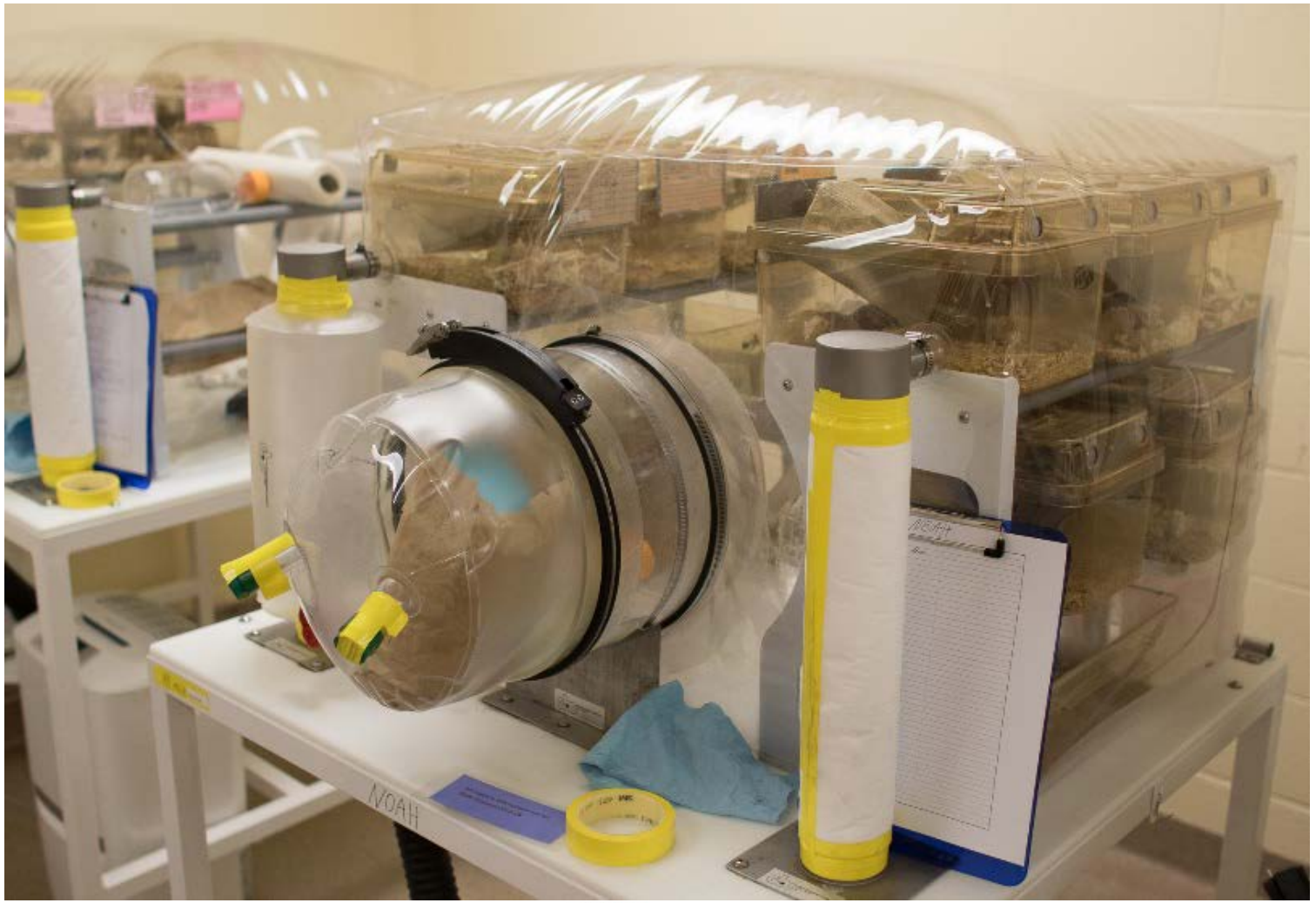
Gènes	Cerveau	Foie	Iléon	Tissu adipeux
Cacna1b	23		28	
Cacna1h	24		24	29
Cnr1	21		25	26
Cnr2	28	28	27	27
Gpr18			28	29
Gpr55	27		26	30
Gpr110		27		
Gpr119	29		28	28
Ppara	25	23	22	24
Pparg	29		27	22
Ptgfr	29		28	28
Trpa1			27	
Trpm8				
Trpv1				26
Trpv2	24		25	26
Trpv4	26		27	25

Gènes	Cerveau	Foie	Iléon	Tissu adipeux
Abhd12	20	24	21	23
Abhd16a	21	24	22	23
Abhd4	22	25	22	23
Abhd6	22	25	21	24
Agk	25		27	27
Akr1b3	23	27	23	23
Alox12	27	29	27	28
Alox15			27	27
Ces1gd	27	22	23	20
Ces2h	28		29	
Comt	22	20	21	21
Dagla	23	30	25	26
Daglb	23	25	23	24
Dgke	22	29	25	25
Enpp2	20	24	24	21
Faah	22	23	20	26
Fam213b	22	27	21	23
Gde1	20	23	21	22
Gdpd1	23		20	27
Glyatl3				
Hrasls5				29
Inpp5d	25	29	25	25
Mgll (Magl)	21	23	23	20
Mogat1	28		28	23
Naaa	23	28	23	23
Napepld	24	30	25	24
PAM	21	25	21	22
Pla1a	27	24	27	23
Pla2g10			25	
Pla2g4e	27			
Pla2g5	26		25	28
Plcb1	22	27	25	24
Ppt1	22	25	22	23
Ptges	26		25	23
Ptgs2	27		27	29
Ptpn22	27	30	24	26

Facilities for microorganism-mediated bio-transformation, « culturomics » experiments and germ-free (axenic) mice

Simulator of the Human Intestinal Microbiome Ecosystem (SHIME)

INAF INSTITUT SUR LA NUTRITION ET LES ALIMENTS FONCTIONNELS



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Quando il microbiota puo' curare … in modo « sgradevole »

OpenBiome staff member Mary Njenga processing donated faecal samples to send to *C. diff* patients in hospitals and clinics across the United States for faecal microbiota transplantation.

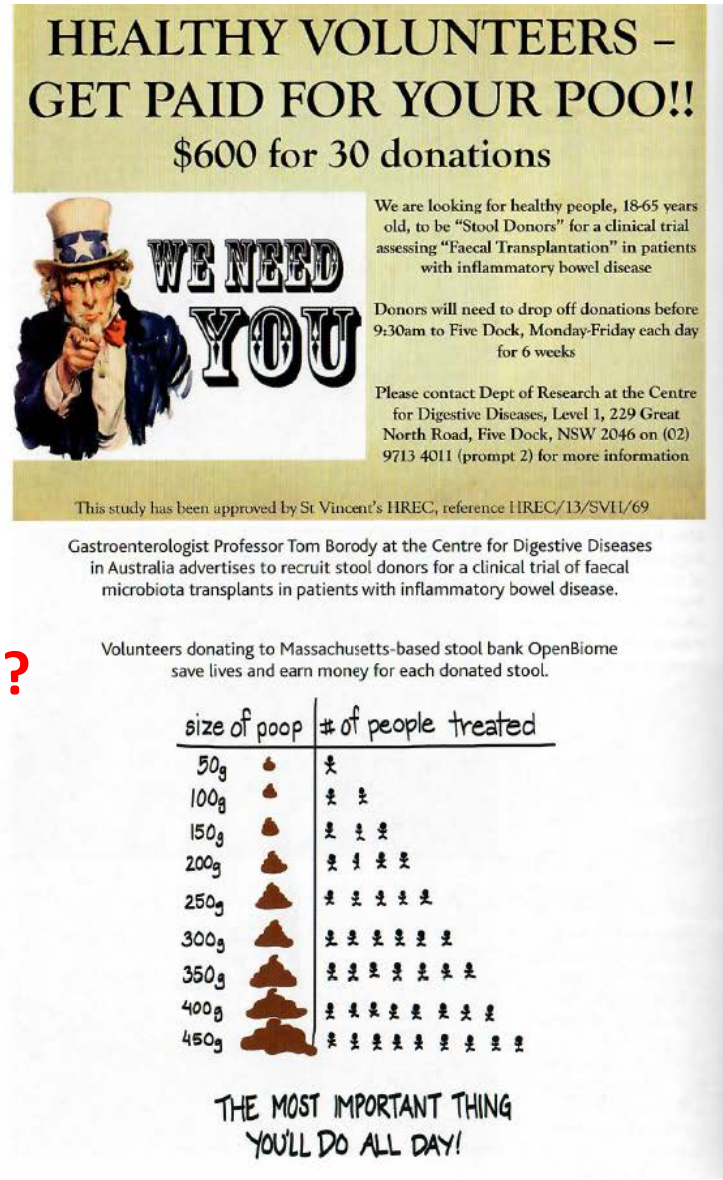
Volunteers wishing to donate stool to OpenBiome are screened for microbiota-related health problems, including obesity, allergies, autoimmune diseases and mental health problems. Only a small proportion of volunteers are eligible to have their stool processed as a faecal microbiota preparation.

***Clostridioides (Clostridium) difficile* infections**

Inflammatory bowel disorders ?

Obesity and type 2 diabetes ?

Others?



Gastroenterologist Professor Tom Borody at the Centre for Digestive Diseases in Australia advertises to recruit stool donors for a clinical trial of faecal microbiota transplants in patients with inflammatory bowel disease.

Volunteers donating to Massachusetts-based stool bank OpenBiome save lives and earn money for each donated stool.

Le « scorciatoie » piu’ gradevoli: probiotici, prebiotici, polifenoli e post-biotici

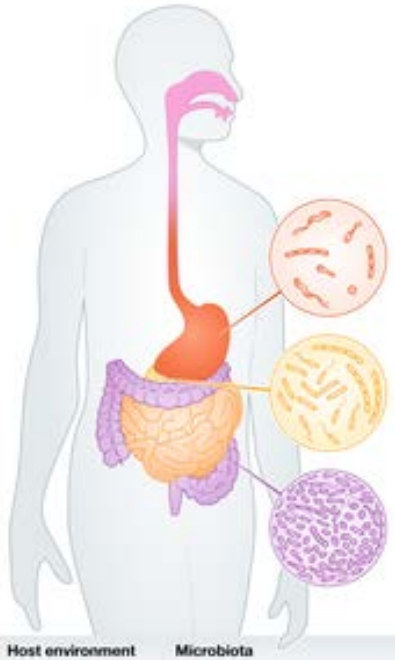
Probiotici = microorganismi vivi che, somministrati in quantità adeguate, apportano un beneficio alla salute dell'ospite. Andrebbero definiti tali solo quelli che, oltre a non essere patogeni, raggiungono l’intestino senza essere in gran parte eliminati nello stomaco. Essi possono essere aggiunti a particolari alimenti

Prebiotici = sostanze presenti nel cibo non assorbite dall'organismo ed utilizzate perché favoriscono la crescita e l'attività di specie batteriche importanti per la salute dell'organismo ospite. Nella grande maggioranza sono carboidrati, in particolare oligosaccaridi (frutto-oligosaccaridi quali l'inulina). Le «fibre alimentari» possono considerarsi dei prebiotici

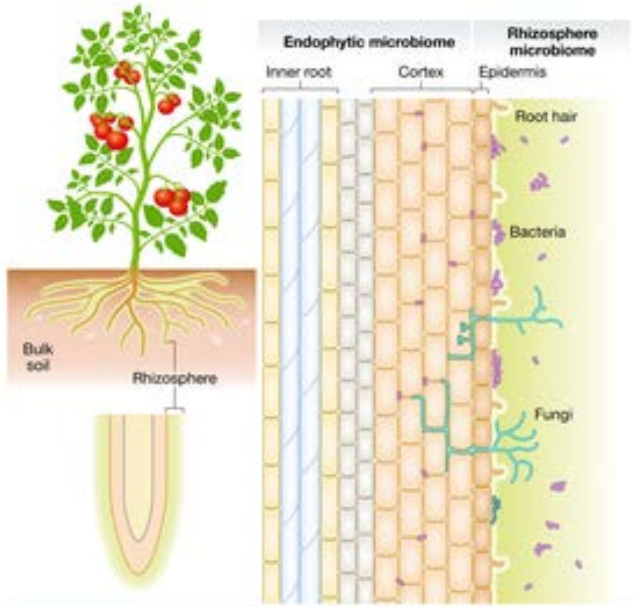
Polifenoli = molecole naturali con proprietà antiossidanti. Sono utili a ridurre i radicali liberi o agiscono come «substrati» del microbiota per la produzione di principi attivi?

Post-biotici = molecole bioattive prodotte dal microbiota con potenziali proprietà terapeutiche

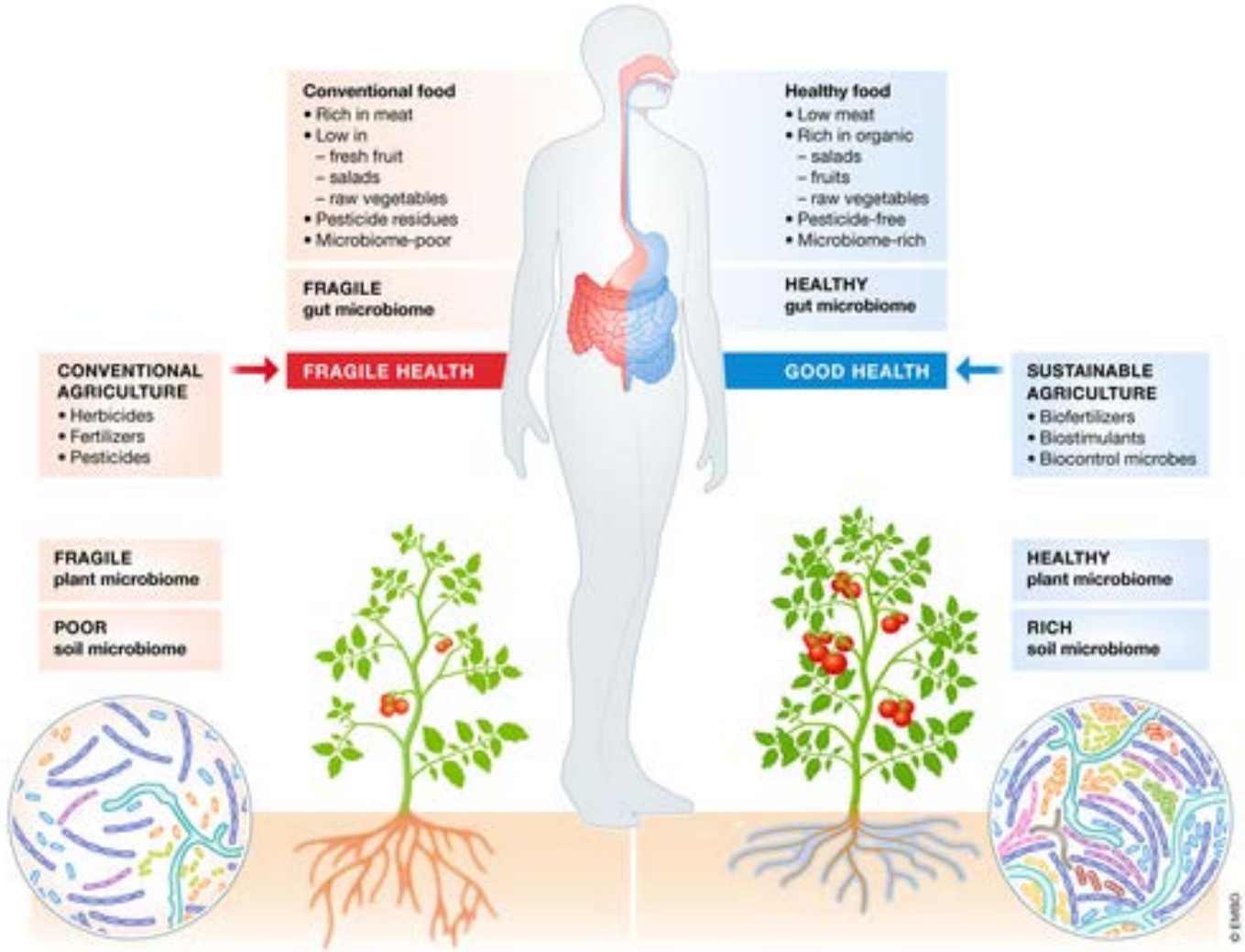
Dal microbioma del suolo al microbioma umano



Host environment	Microbiota
Stomach	
• Acidic pH • Oxygenated	• Sparse bacterial load (10^1/g) • Low–moderate diversity • Predominating microbes – Firmicutes – Actinobacteria
Duodenum	
• Neutral pH • Low O_2 • Bile • Mucus • Mono- and disaccharides	• Increased bacterial load (10^3/g) • Low diversity • Predominating microbes – Firmicutes – Proteobacteria
Colon	
• Neutral pH • Low O_2 • Mucus • Host-indigestable polysaccharides	• High bacterial load (10^{12}/g) • High diversity • Predominating microbes – Firmicutes – Bacteroidetes



Host environment	Microbiota
Soil	
• Variable pH 3.5–10 • Oxygenated • Low nutrients	• High diversity (4×10^3–5×10^4 different bacterial species) • High numbers (10^8–10^{10} bacteria/g soil) • High competition with other microbiota and organisms (arthropods, nematodes, earth worms, ...)
Rhizosphere	
• Neutral pH • Oxygenated • Mucilage and root exudates (sugars, amino acids, organic acids, ...)	• Medium diversity • High numbers (10^8–10^{10} bacteria/g rhizosphere soil) • Low competition with other soil microbiota and organisms
Endosphere	
• Acidic pH • Low O_2 • High nutrient access	• Low diversity • Low numbers (10^4–10^8 bacteria/g plant) • No competition with soil microbiota and other soil organisms



Hirt, EMBO Reports, 2020

Le domande ancora irrisolte sul microbiota

Fino a che punto il microbioma è, assieme alla modulazione epigenetica, uno degli artefici degli effetti a lungo termine dell'ambiente sulle nostre funzioni vitali?

Se il buono o il cattivo funzionamento delle nostre funzioni vitali è trasmissibile, fino a che punto cio' è dovuto a « passaggi » di microbiota da un individuo all'altro?

Siamo quello che mangiaNO? La dieta puo' davvero influenzare il nostro comportamento attraverso il microbiota?

Il consumo eccessivo, attivo e passivo, di antibiotici ha davvero contribuito all'esplosione delle malattie del 20º secolo (malattie autoimmuni, allergie, autismo, obesità, malattie psichiatriche, ecc.), e fino a che punto è coinvolto il microbiota?

Quali sono gli effettori molecolari (proteine, piccole molecole, RNA, ecc.) delle azioni del microbiota, fino a che punto essi sono derivati dalla sua interazione con l'ospite, e come possiamo utilizzarli per sviluppare nuovi farmaci?

Correlazione non implica causalità: il microbiota puo' davvero spiegare ….. tutto?

Ringraziamenti

Istituto di Chimica Biomolecolare

Endocannabinoid Research Group

Consiglio Nazionale delle Ricerche

Canada Excellence Research Chairs

Chaires d'excellence en recherche du Canada

Sentinelle Nord

INAF Institut sur la nutrition et les aliments fonctionnels

Ministère de l'Économie et de l'Innovation Québec

Institut universitaire de cardiologie et de pneumologie de Québec

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Chaire d'excellence en recherche du Canada sur l'axe microbiome-endocannabinoïdome dans la santé métabolique