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It's About the Metabolome of the Microbiome: It's Not About the CFU!

John P. Troup, Ph.D.

Fullscript Webinar Series

August 23, 2022

Prevalence of Digestive Health Issues

- Digestive Disorders (60 to 70 million individuals in US)
  - Irritable Bowel Syndrome (45.3 million individuals in US)
  - Ulcerative Colitis (619,000 individuals in US)
  - Crohn's Disease (359,000 individuals in US)
  - Category Specific Indication Use Revenues Estimated as $3B Nutrition and $12B Rx
- 1 in 4 Americans suffer from digestive discomfort that affects daily living
- Up to 70% of Americans experience some digestive issue or complications with 50% of these for 6 months or longer
- A large number of 'active health managers' represent consumer segments addressing a range of prevention to condition management
- Active health consumers routinely use nutritional solutions to manage a healthy gut. These represent the large majority of purchases across multiple categories.
- NBJ Reports have estimated that 40% of consumers would prefer to use a natural nutritional product to manage these conditions routinely and up to 60% as a preferred initial course of treatment

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Agenda

Digestive health is more than a probiotic!

The microbiome is about viability, diversity and synergy

The metabolome of the microbiome influences all underlying systems of health influence

Influencing the microbiome: Strains, Sustainability, Synergies and System

Focus on Effective Digestive Functional Improvement: Precision Probiotic support*

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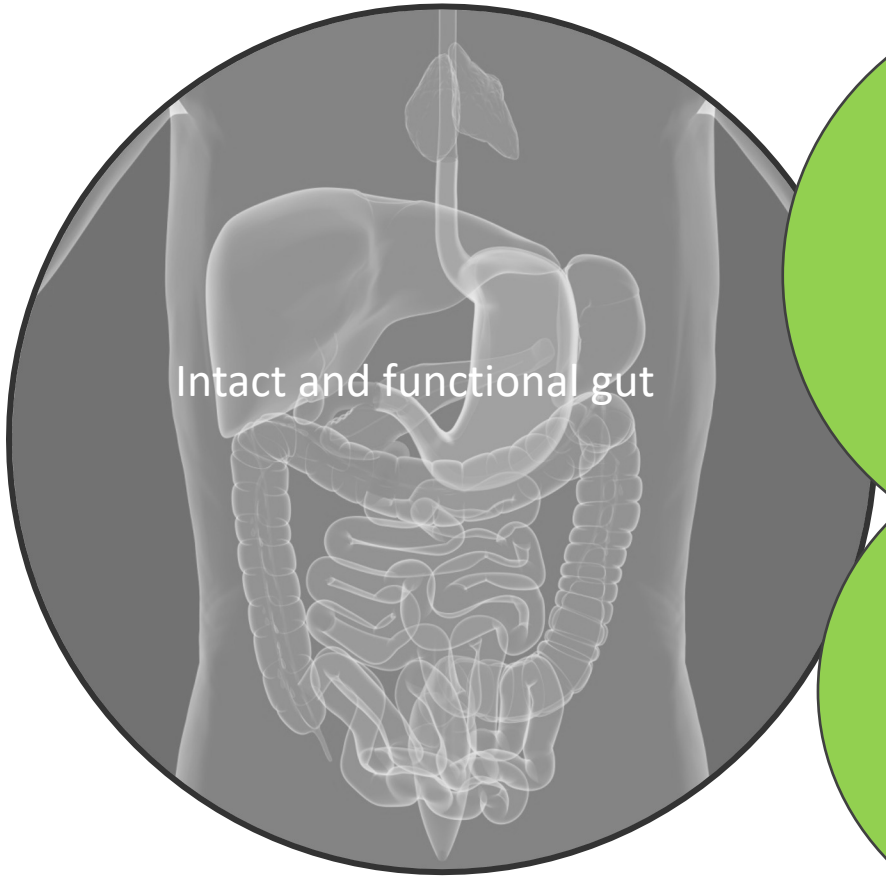
The gut and its key functions



Food digestion for absorption of macro- and micronutrients[1]

Immune functions, with 70% of the immune system in the gut[2]

Metabolomic Response Influences Underlying Systems Determining Gut Function and Progression to Digestive Disorders

1. Nix S, ed. *Williams' Basic Nutrition and Diet Therapy*. 2013;1-12.
2. Perdigon G, et al. *Curr Issues Intest Microbiol*. 2001;2:27-42.

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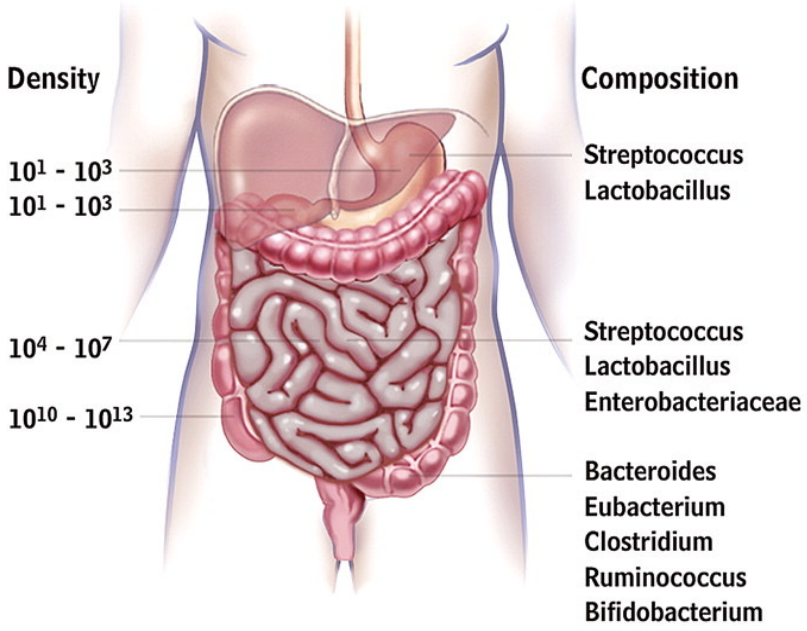
The Gut Microenvironment Shapes the Microbiome
More is Not a Selection Criteria!

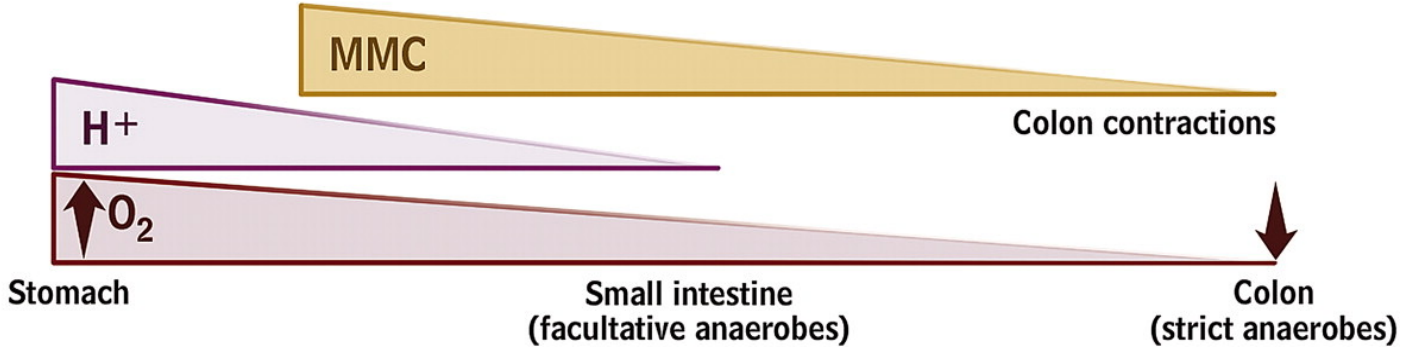


Intrinsic factors

- Gastric acid
- O_2
- Motility
- Mucus
- GI secretions
- Antimicrobial peptides
- Immunity (sIgA)

Extrinsic factors

- Diet, Pre and probiotics
- PPIs, H2 blockers
- Antibiotics
- Prokinetics
- Laxatives
- Opioids
- NSAIDs



Simrén M et al. Gut doi:10.1136/gutjnl-2012-302167

GUT hyperbiotics

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Its Not about the Activity Level (#CFU), rather
Its about the *Viability* of a Strain and its Impact on the Gut Environment

Knowing minimum clinical efficacy threshold and the impact of a probiotic strain is critical

Impact on the viability of the selected strain determines the metabolic and functional effect and benefit; Every probiotic strain needs a symbiotic environment and activator

All strains have a functional effect, but not all strains have the same functional effect

Multiple strains must be complimentary to be viable

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Four Critical Issues in Selecting a Probiotic That Delivers a Targeted Benefit*

Strain:	How does it work and what does it do
Synergy:	How to maximize the metabolomic potential
Sustainability/Viability:	What is its preferred energy source(prebiotic)
Systemic Impact (clinical effect):	What is the clinical benefit

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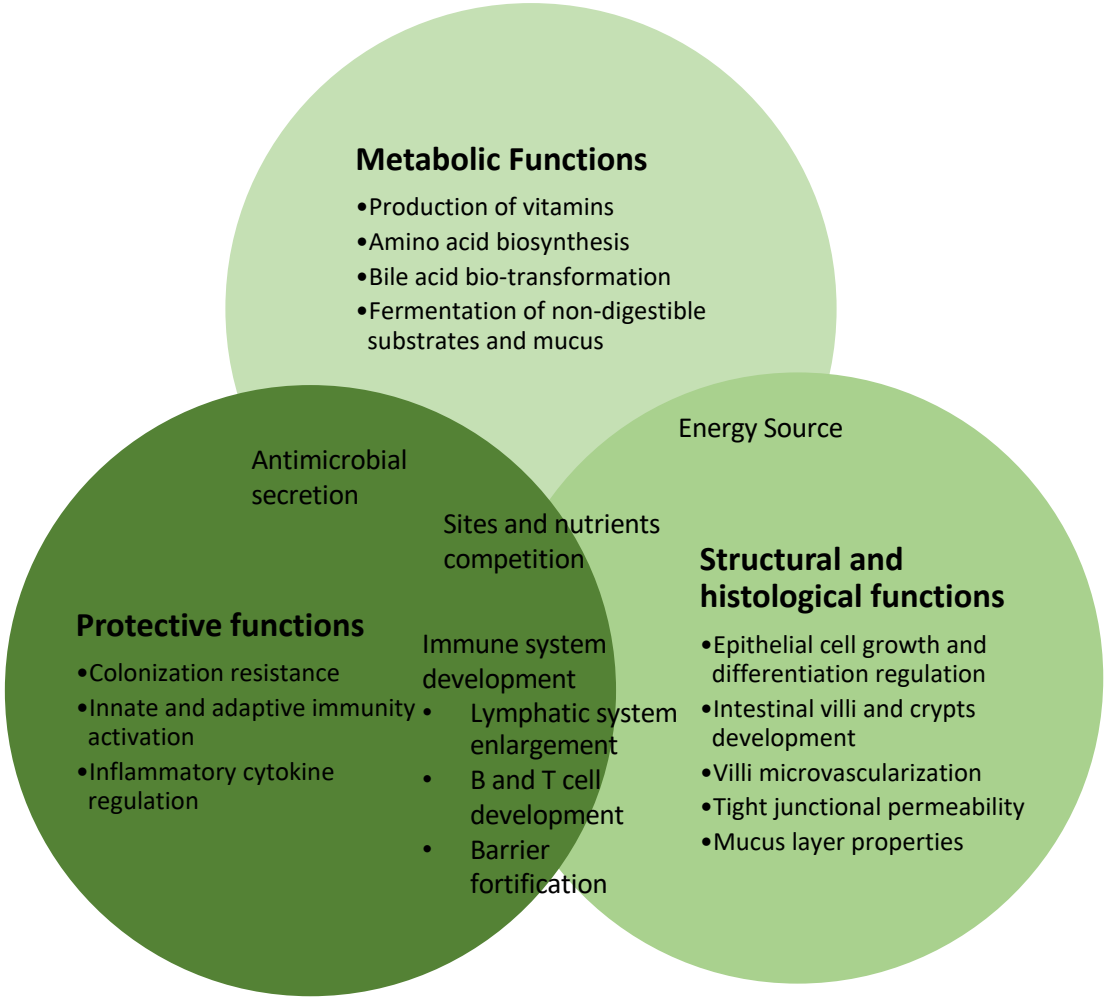
Functions of the gut microbiota



Adapted from: *Prakash, S. Biologics. 2011;5:71-86*

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Balancing the ‘Gut’ is Core to Success in Improved Patient Care

- Competition for dietary ingredients as growth substrates
- Reduction of inflammation*
- Production of growth substrates for other bacteria
- Improved barrier function*
- Metabolic Support & Bioavailability (Digestibility)*
- Stimulation of innate immune response*

O'Toole PW, Cooney JC. *Interdiscip Perspect Infect Dis.* 2008;2008:175285.

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A healthy gut has many benefits and systems of influence. Progression of Disorder May lead to Condition Specific Progression and Complications

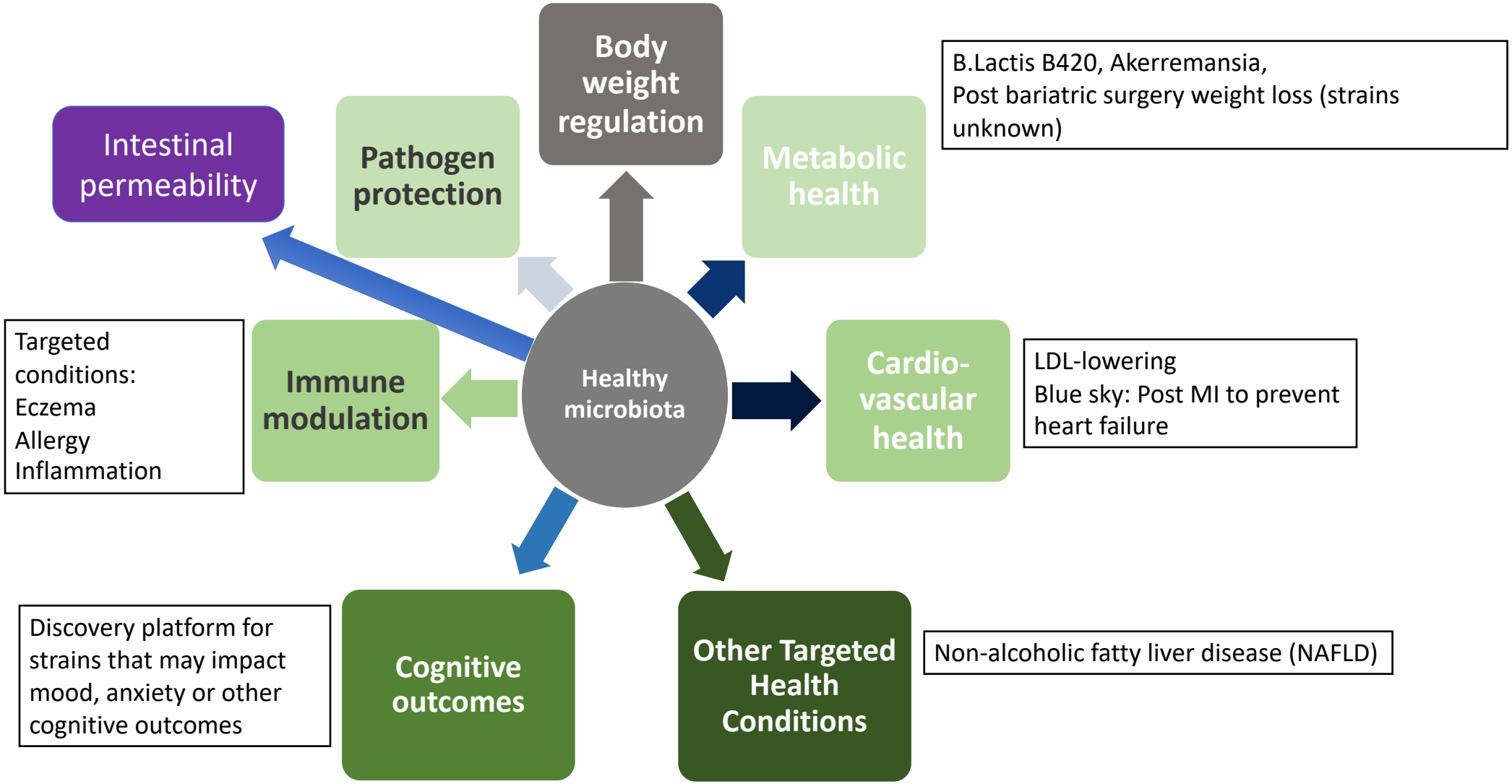

Figure modified from:

1. Guinane CM, Cotter PD. *Therap Adv Gastroenterol*. 2013;6:295-308.
2. Sekirov I, et al. *Physiol Rev*. 2010;90:859-904.

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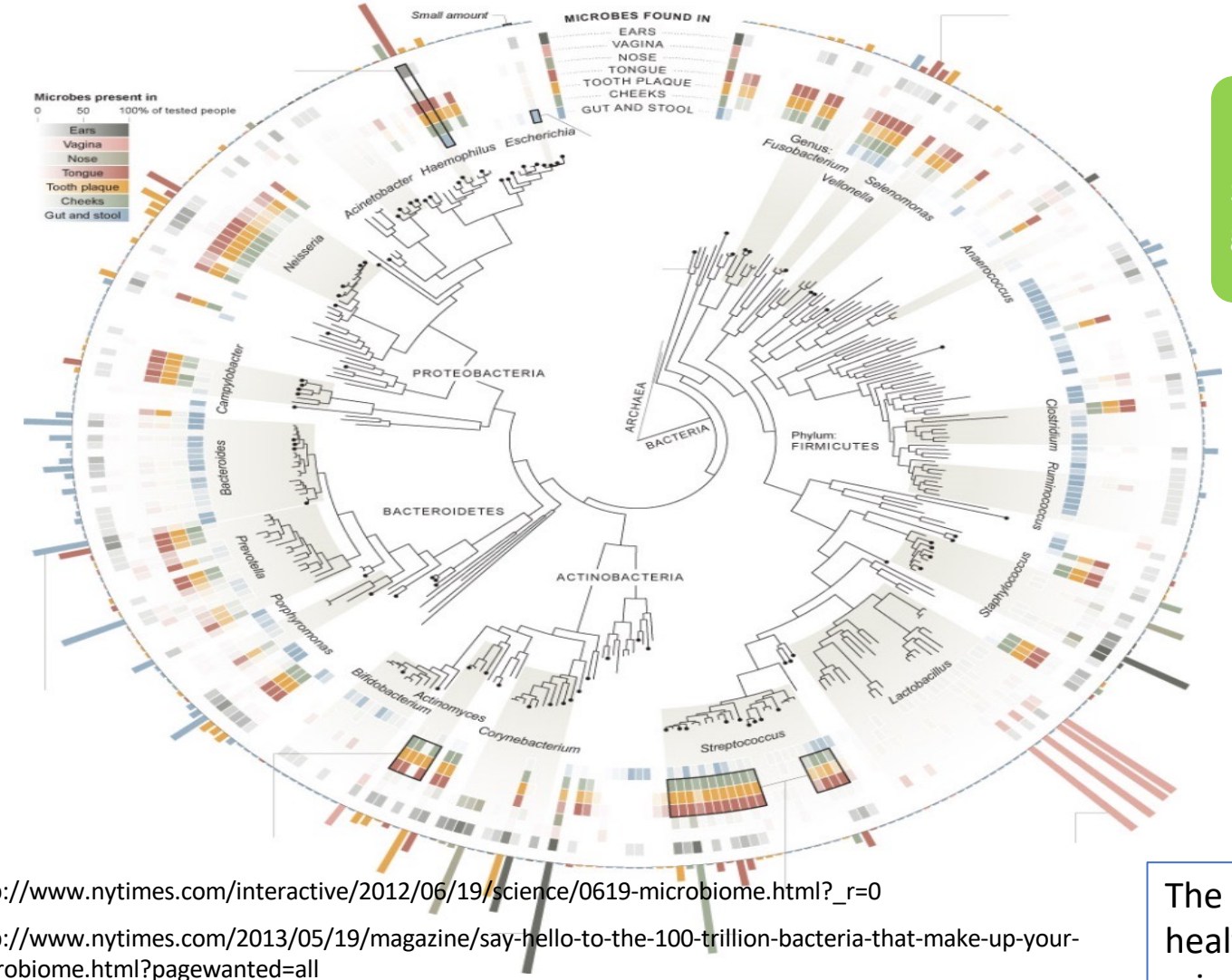
Microbiome Impacts the Metabolome



Microbes exist on all body surfaces: skin, oral cavity, vagina, gut.

The human microbiome is diverse (The gut contains on average 40,000 species alone).

Dysbiosis or microbial imbalance may play a role in immunological, metabolic and neurological diseases.

http://www.nytimes.com/interactive/2012/06/19/science/0619-microbiome.html?_r=0

http://www.nytimes.com/2013/05/19/magazine/say-hello-to-the-100-trillion-bacteria-that-make-up-your-microbiome.html?pagewanted=all

The Human Microbiome Project has led to the finding that health conditions are in part defined and influenced by specific microflora.

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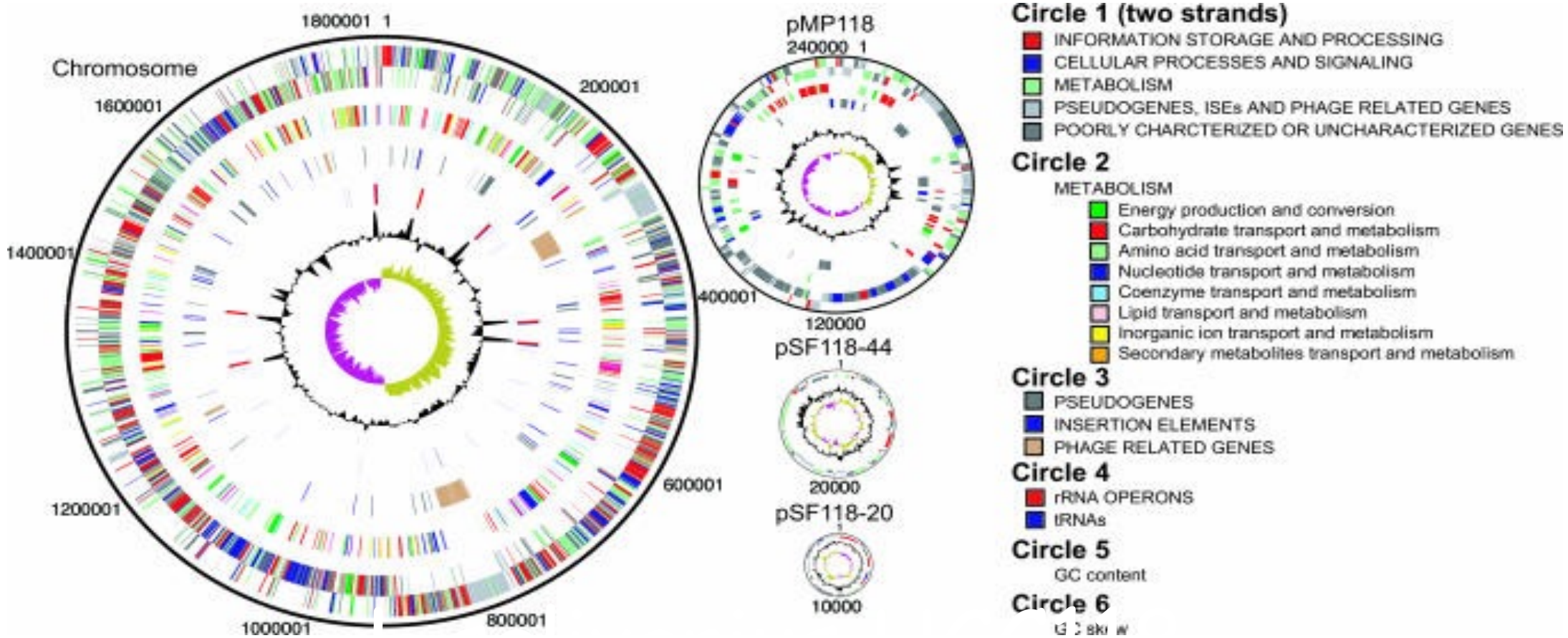
Genomics

Characterization and Prediction of Functions



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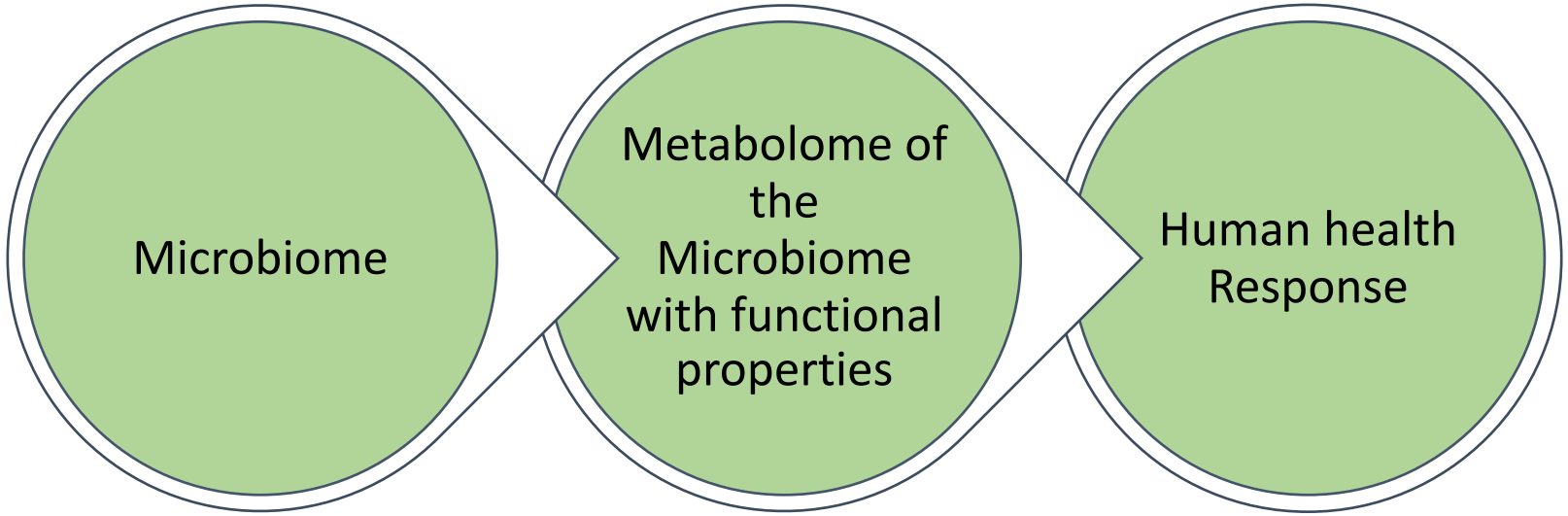
Its about the Metabolome of the Microbiome and Understanding how microbial metabolic processes affect human health in a systems matrix



Contemporary medical research initiatives promise to help us harness the potential of our resident microbes to achieve better health.

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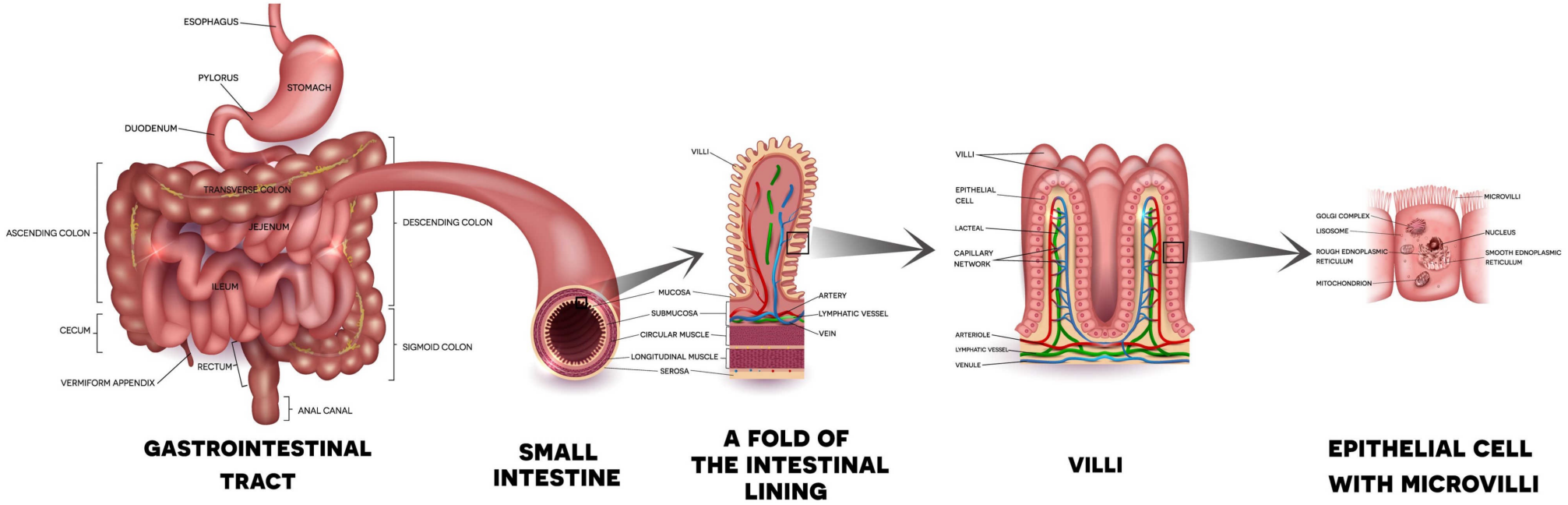
The Microbiome: Diversification is facilitated with probiotic strains that influence digestive and metabolic processes and improve nutrient bioavailability and minimize gut discomfort*

Selective Probiotics Can

- Support digestibility*
- Protect gut barriers and improve absorption*
- Support immune response*
- Improve long term gut function and regularity*



World J Gastroe
Published online 2017 Jul 14. Diarrhea after bariatric procedures: Diagnosis and therapy; Yves M Borbély, Alice Osterwalder, Dino Kröll, Philipp C Nett, and Roman A Inglin

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Core System Influences

How Does it Work?

Barrier Against Infection

- Compete with pathogens for nutrients
- Occupy the adhesion sites and inhibit harmful bacteria from colonizing
- Reinforce the barrier function of the intestinal lining
- Produce bacteriocin which inactivate Pathogens

Metabolic Effect

- Produce enzymes which break down carbohydrates and facilitate absorption of energy
- Produce lactase that improves lactose tolerance
- Ferment indigestible carbohydrates and lower blood cholesterol

Probiotics

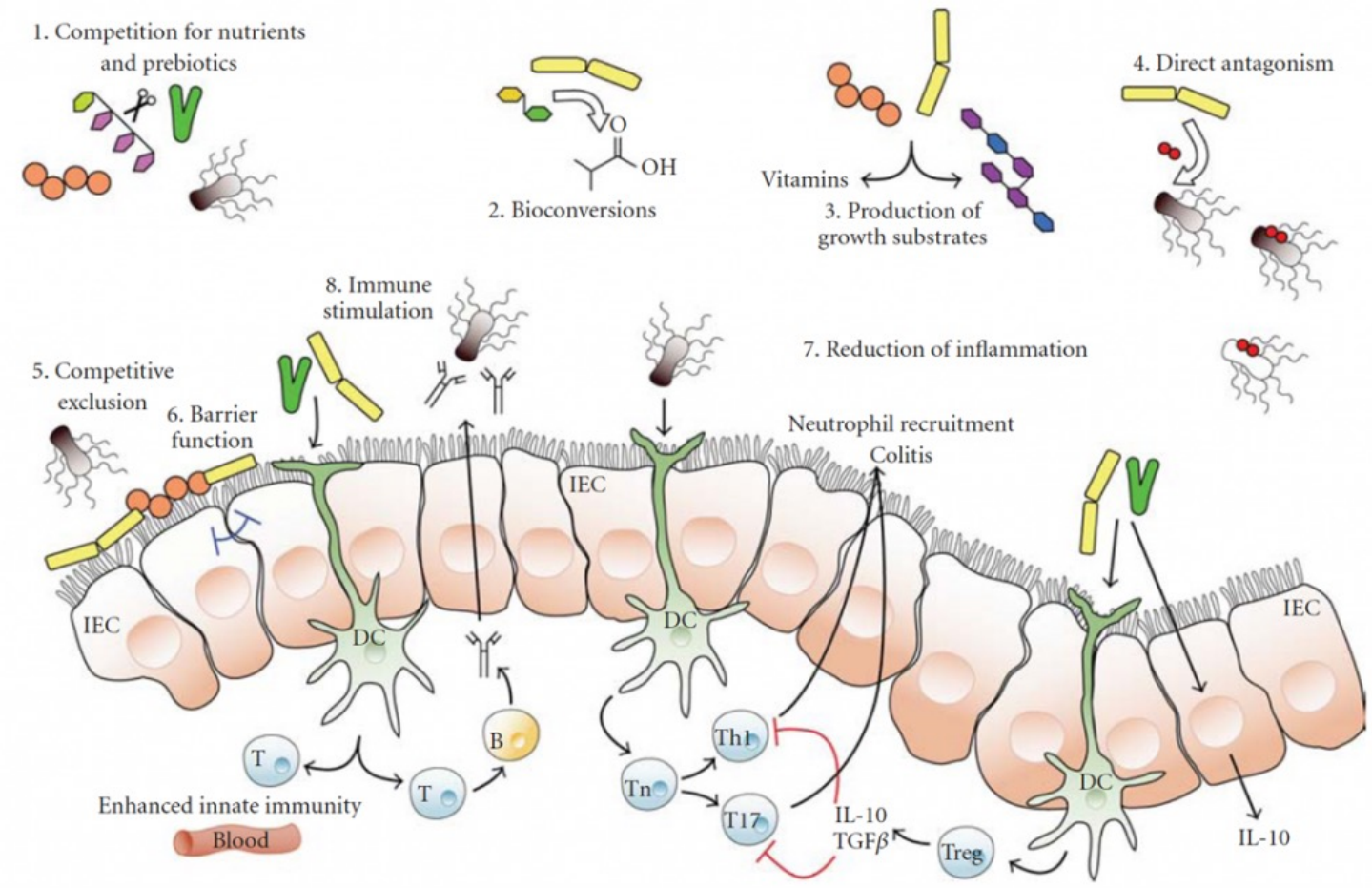
Nutritional Effect

- Produce acids which improve solubility of minerals and increase absorption
- Promote production of SCFA
- Synthesise B-vitamins, K-vitamin & folic acid

Immune Modulation

- Stimulate both non-specific and specific immune response by activating
- Immuno reactive cells and immune factors
- Downregulate inflammation

The Gut Has a core role in healthy functional capacity. This is influenced by The Microbiome, composition and function, and metabolic responses. The right Strains selected are the starting point!



World J Gastroenterol. 2017 Jul 14; 23(26): 4689–4700.
Published online 2017 Jul 14. Diarrhea after bariatric procedures: Diagnosis and therapy; Yves M Borbély, Alice Osterwalder, Dino Kröll, Philipp C Nett, and Roman A Inglin

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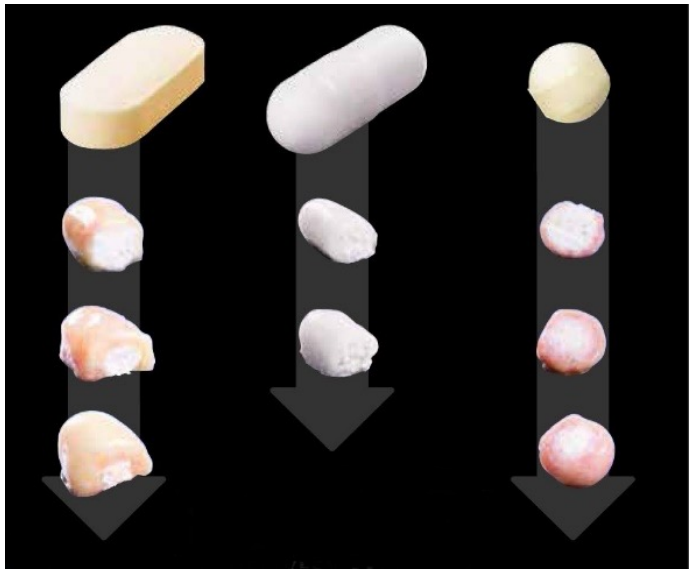
Sustainability Technology: BIO-*tract*®

BIO-*tract* ADVANTAGES*

15x More Survivability Than Veggie Capsules*

- Patented to Survive Stomach Acids*
- Time-Released Over 8–10 Hours*
- Uniquely Tailored Formulas For Kids and Adults
- Diverse, Targeted Probiotic Strains
- Quality Ingredients
- Zero Refrigeration Required



Targeted delivery of diverse strains & viable in both Small and large intestine

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	BROAD SPECTRUM DIGESTIVE PROBIOTIC		TARGETED FORMULAS BY DEMOGRAPHIC						TARGETED FORMULAS BY SPECIALIZED CONDITION					
	PRO-15	PRO-15 Advanced	PRO-Kids	PRO-Women	PRO-Moms	PRO-Men	PRO-Bifido	PRO-Pets	Immune	PRO-Kids ENT	Glucose Support	Better Body	Gut-Brain Balance	PRO-Dental
# CFU	5 Billion	15 Billion	3 Billion	5 Billion	5 Billion	5 Billion	3 Billion	3 Billion	4 Billion	3 Billion	5 Billion	5 Billion	6 Billion	3 Billion
# Strains	15 Strains	15 Strains	4 Strains	6 Strains	6 Strains	6 Strains	7 Strains	6 Strains	5 Strains	5 Strains	7 Strains	6 Strains	6 Strains	4 Strains
# Tablets	60 Pearls	30/60 Tablets	60 Micro-Pearls	30/60 Tablets	30 Tablets	30 Tablets	60 Tablets	60 Micro-Pearls	60 Tablets	45 Chewable Tablets	60 Tablets	60 Tablets	60 Tablets	45/90 tablets
Prebiotic	FOS (25 mg)	Actazin® Kiwifruit Pow-der (250 mg)	FOS (25 mg)	FOS (25 mg)	Actazin® Kiwifruit Pow- der (250 mg)	FOS (25 mg)			FOS (50 mg)			Orafti P95 (50 mg)	FOS (100 mg)	
Additional Ingredients				Cran-Gyn (250 mg)		Meriva® Curcumin Phytosome (250 mg)			Vit C (500 mg) Zinc (10 mg) EpiCor® (500 mg) Echinacea (100 mg)		Banaba Leaf Extract (3 mg), Vitamin D (1000 IU)	White Kidney Bean Extract (500 mg)	Suntheanine® (L-theanine) 100 mg	Chelated Zinc (2 mg)

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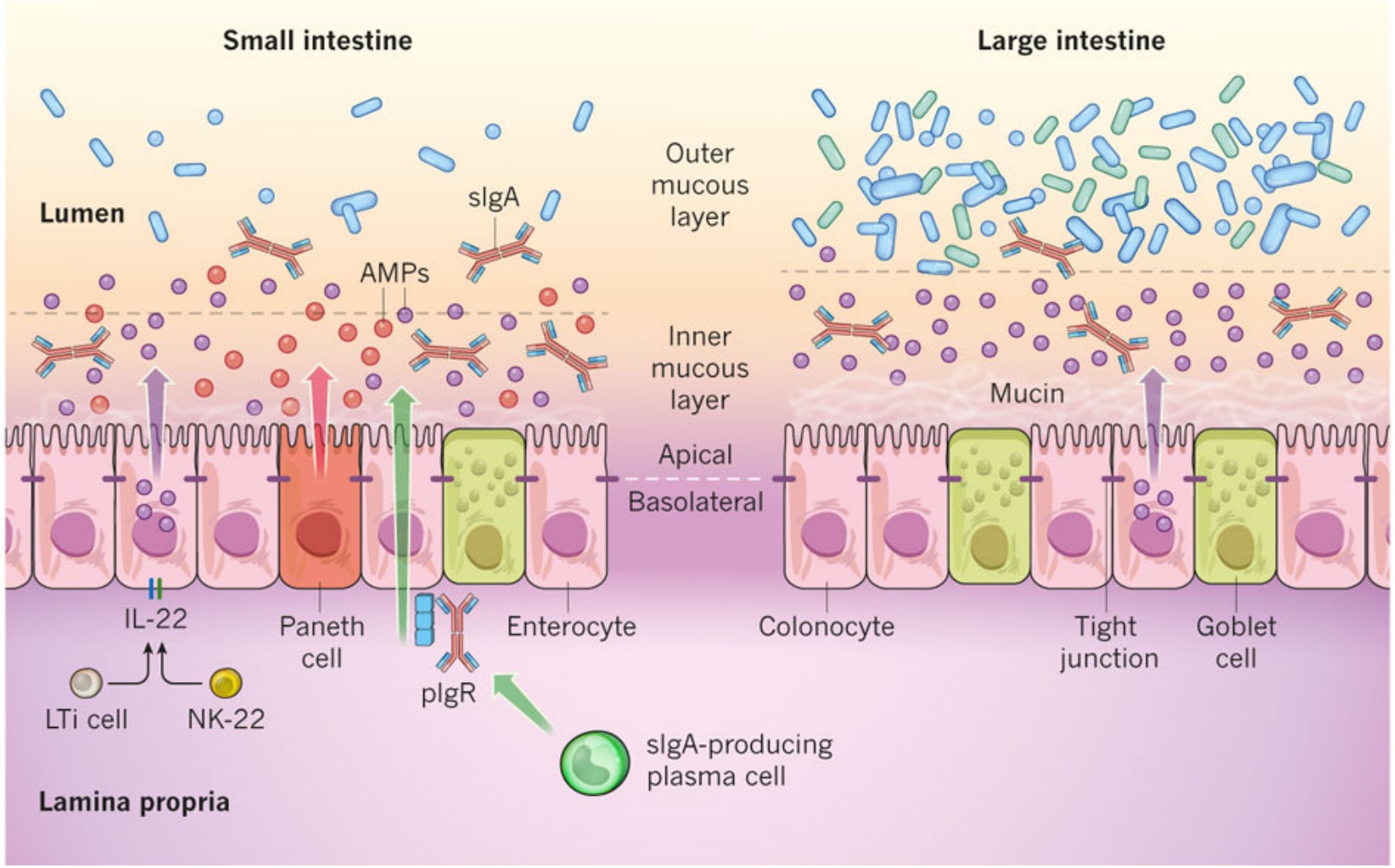
Epithelial Barrier Function: Synergistic Effect of the Microbiome



Compete with, and exclude, pathogens

Anti-bacterial effects:
- Produce bacteriocins
- Denature toxins

Enhance gut barrier function
Modulate motility and sensation

Enhance host immunity
- Immune modulation
- Cytokine modulation
- IgA production

Metabolic functions
- Produce valuable metabolites

Maynard_ 2012

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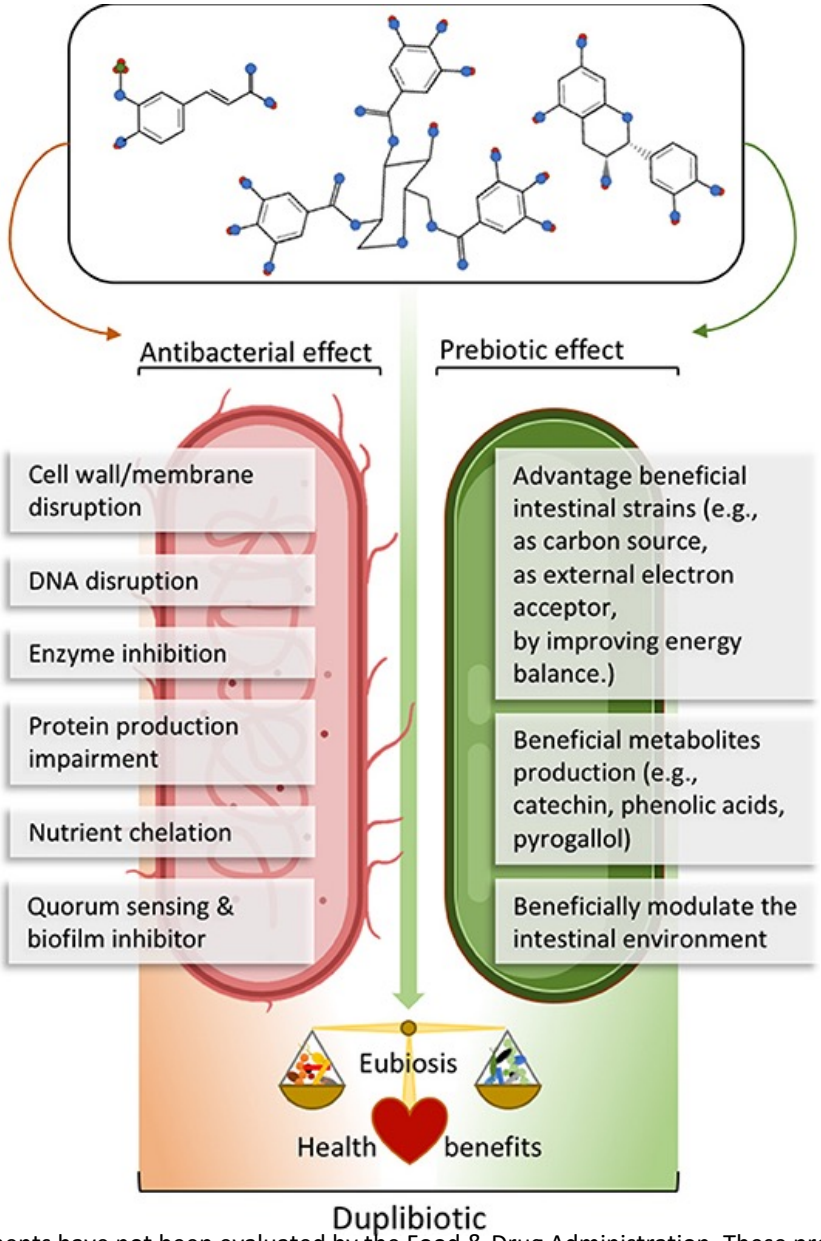
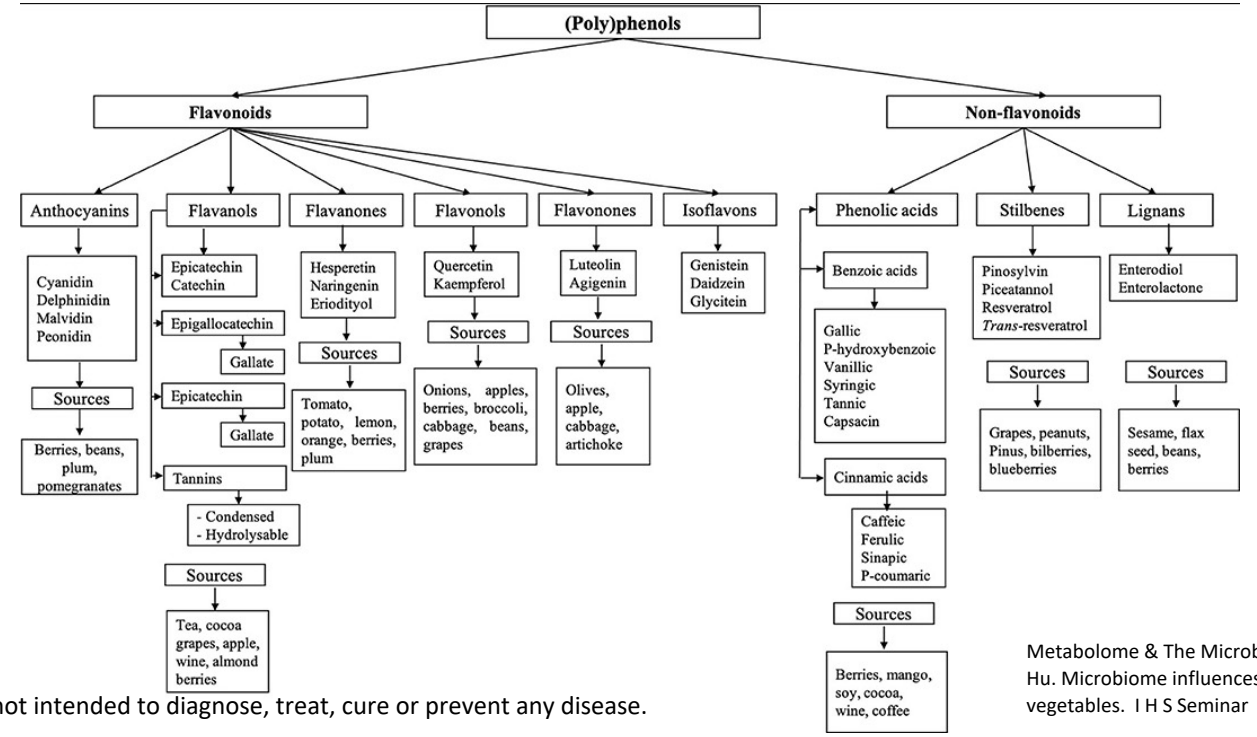


Synbiotics do more than support viability of probiotics.*

Phytonutrients provide a synbiotic impact on the metabolome and influences systems of the body*



Metabolome & The Microbiome. Frank Hu. Microbiome influences of fruits and vegetables. I H S Seminar 2018

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Increasing digestibility of food-stuffs results in synergistic effects with probiotics leading to improved gut function and digestive comfort.*

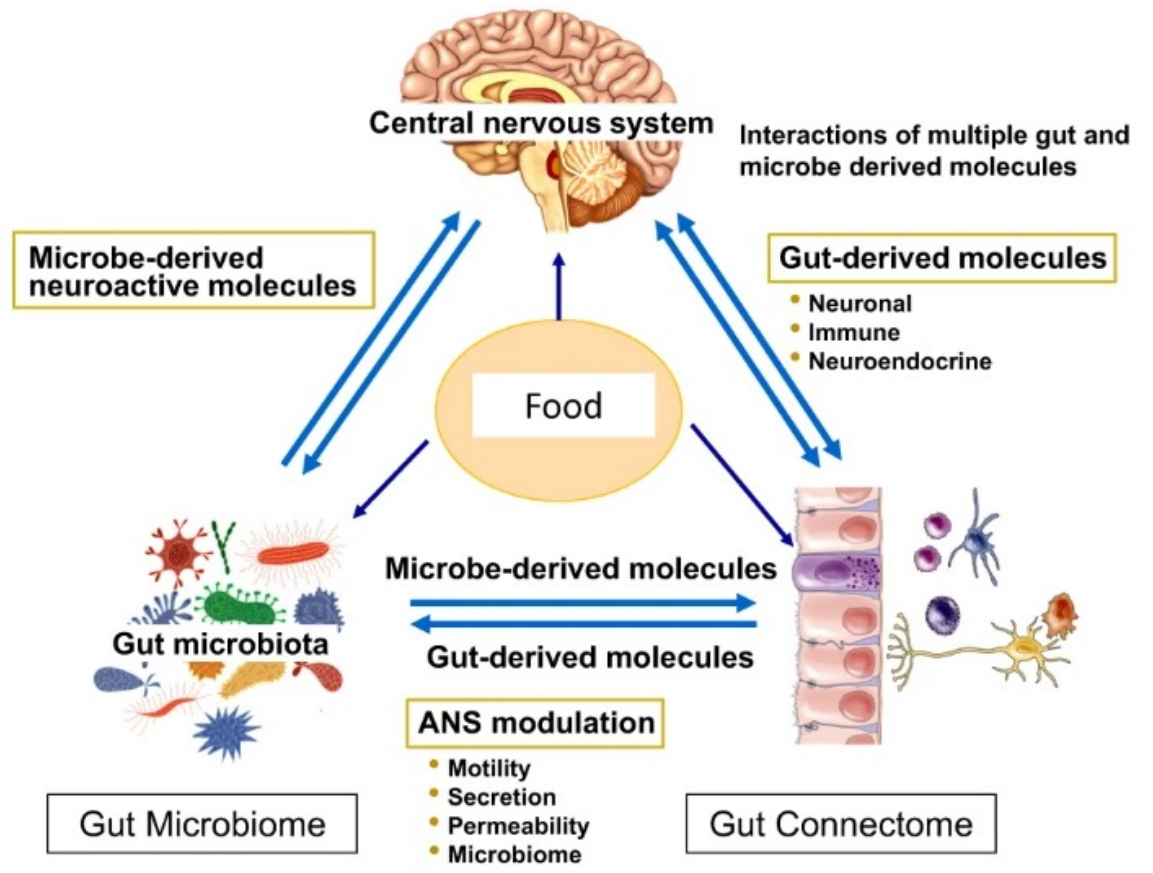
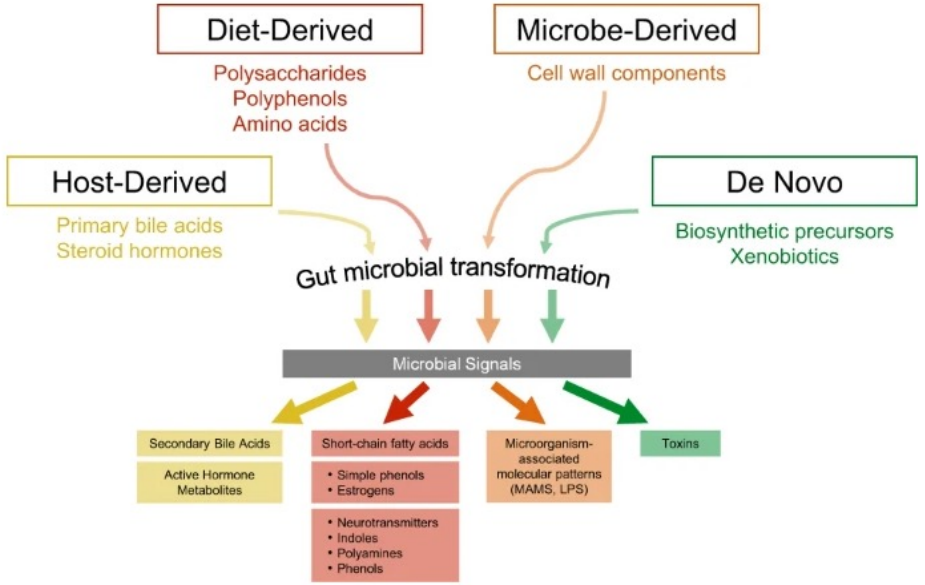


Fig. 3: Four sources for gut microbial signaling molecules.



Gut microbial signaling molecules are derived from at least 4 different sources: Diet-derived, microbe-derived, host-derived and newly synthesized molecules. Chemical transformation of these molecules results in a vast number of signaling molecules which can influence not only cells in the gut (immune, nerve, endocrine cells), but following dissemination throughout the body are able to modulate all organs, including the brain. Certain diet-derived microbial metabolites have neuroactive effects on the central and autonomic nervous system, while microbial cell wall components can activate the immune system by interacting with TLRs. Some microbial metabolites (in particular the SCFA butyrate) exert anti-inflammatory effects. Modified with permission from Needham et al., 2020.

Role of diet and its effects on the gut microbiome in the pathophysiology of mental disorders
•J. Horn, D. E. Mayer, S. Chen & E. A. Mayer
Translational Psychiatry **volume 12**, Article number: 164 (2022)

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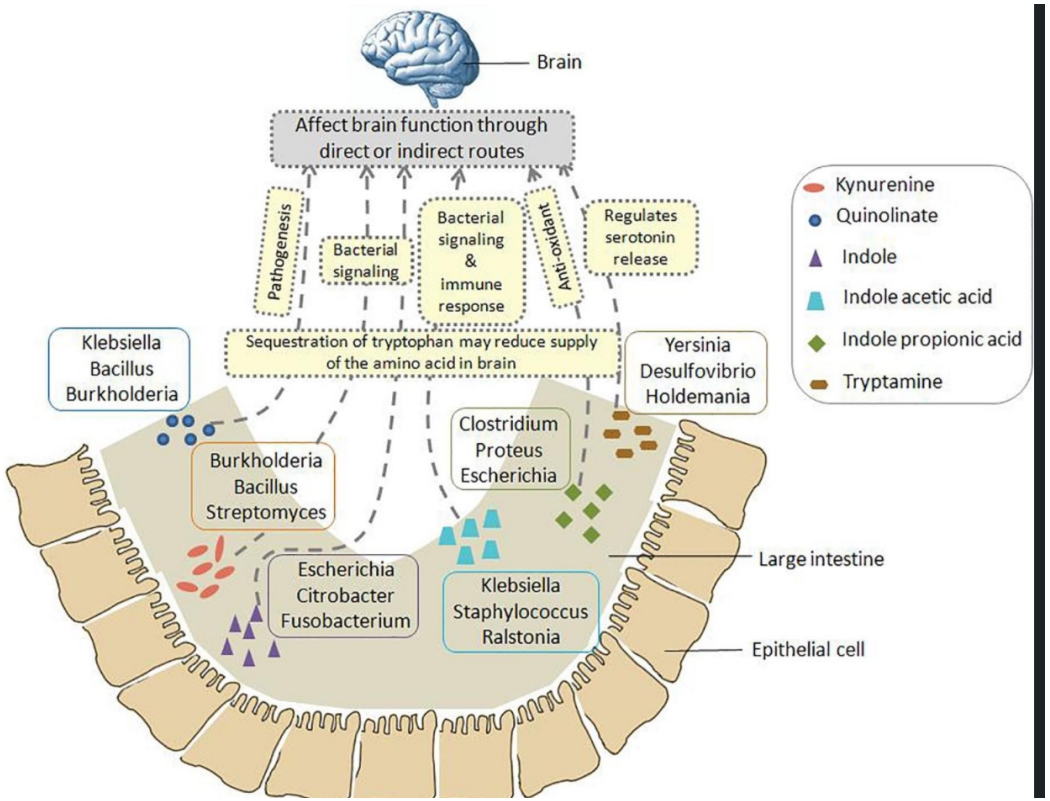
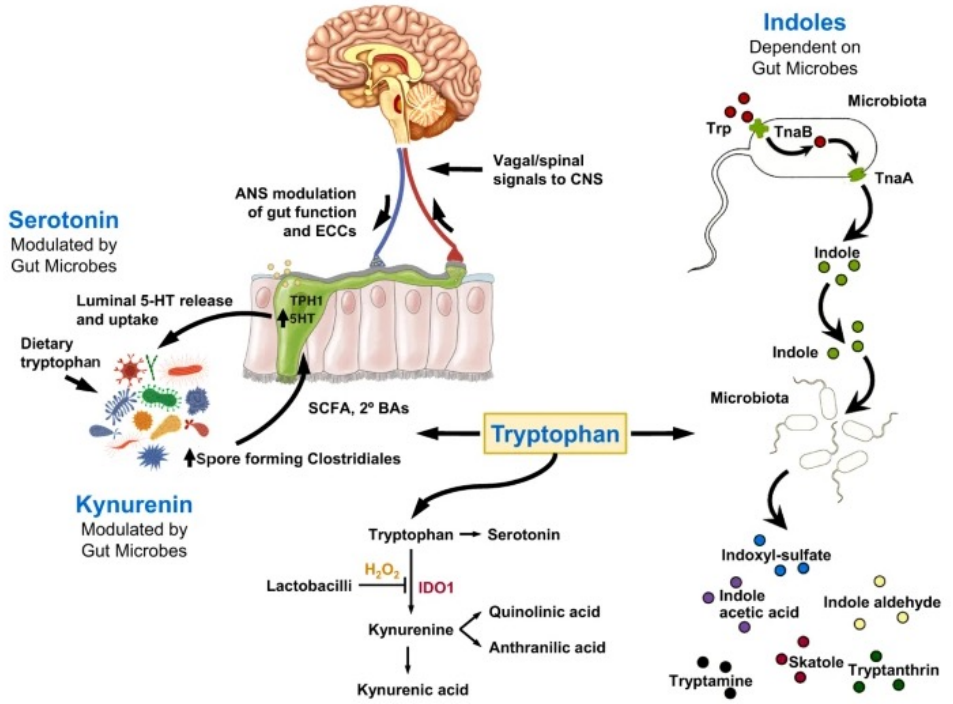


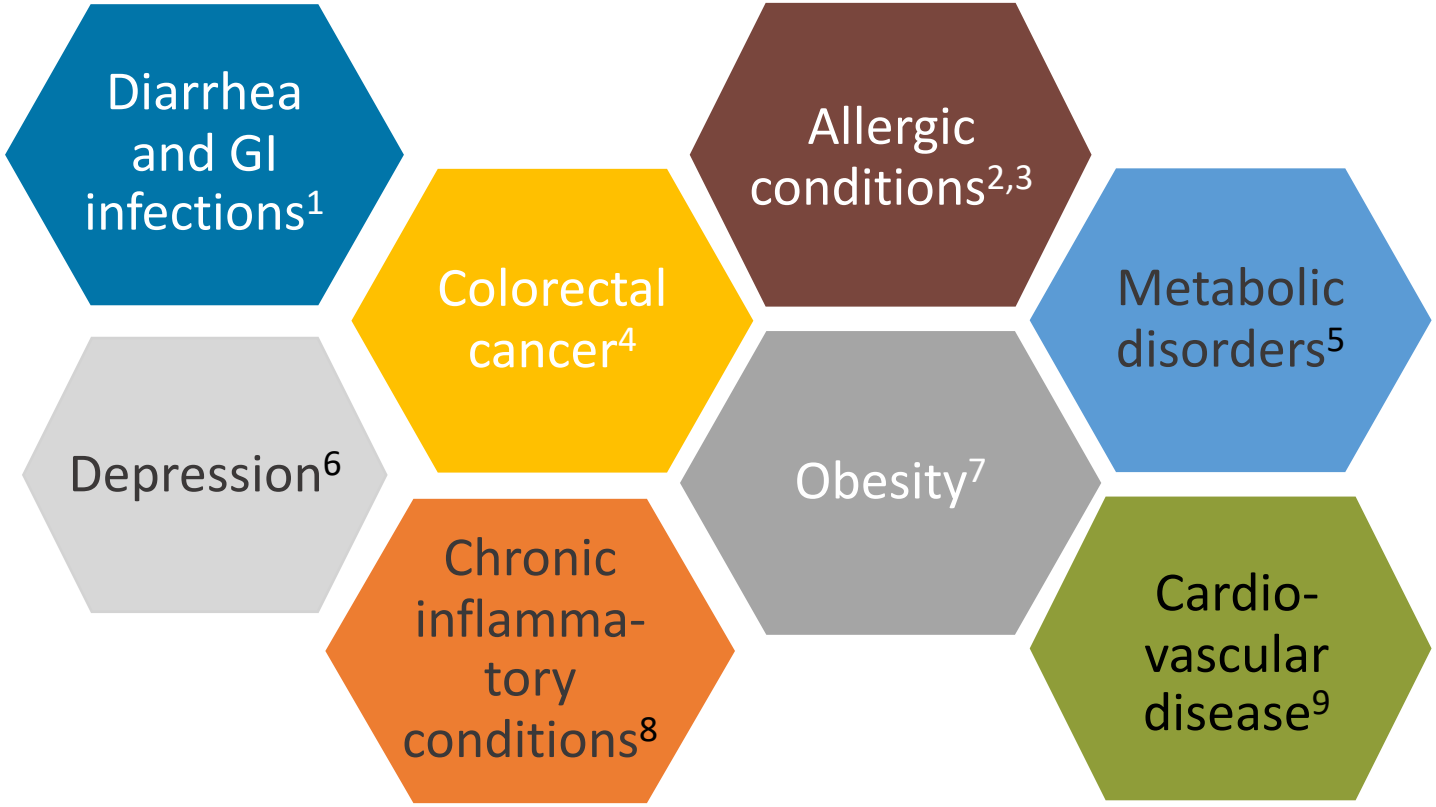
Fig. 2: Gut microbes generate neuroactive metabolites from tryptophan.



The essential amino acid Tryptophan is the precursor for a number of neuroactive signaling molecules including serotonin, kynurenine and indoles. Whereas microbes only play a *modulatory* role in the generation of serotonin and kynurenine, the synthesis of indoles is fully dependent on gut microbial metabolism. The relative abundance of the 3 metabolites is dependent on tryptophan intake, on the relative abundance of involved microbial taxa and on stress induced input from the autonomic nervous system. Modified with permission from Martin et al., 2018.

J Gastroenterol. 2017 Jul 14; 23(26): 4689–4700. Diarrhea after bariatric procedures: Diagnosis and therapy; Yves M Borbély, et al.

An Integrative & Functional Medicine Approach using Systems Biology to Identify Underlying Root Causes of Disease Suggest that Gut Health is Involved in a Number of Health Issues and Conditions



1. Sekirov I, et al. *Physiol Rev.* 2010;90:859-904. **2**. Berin MC. *Int Arch Allergy Immunol.* 2014;163(3):165-167. **3**. Stefka AT, et al. *Proc Natl Acad Sci U S A.2014;*111(36):13145-13150. **4**. Arthur JC, et al. *Science.* 2012;338(6103):120-123. **5**. Qin J, et al. *Nature.* 2010;464(7285):59-65. **6**. Vitetta L, et al. *Inflammopharmacology*. 2014. **7**. Clarke SF, et al. *Gut microbes*. 2012;3:186-202. **8**. Shanahan F. *Nutr Rev*. 2012;70 Suppl 1:S31-37. **9**. Mendelsohn AR, Larrick JW. *Rejuvenation Res*. 2013;16:241-244.

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The Continuum of Digestive Health

*Insights on Selection of Probiotics**

Healthy & Balanced → Irregularity → Dysbiosis → Functional Impairment → Digestive Disorders

Microflora + Nutrient Bioavailability = Microbiome Metabolome

Prebiotics + Enzymes + ProBiotics PostBiotics + Synbiotics + Precision ProBiotics

General & Preventive*	Digestive Function & Regulation*	Patient & Condition Specific Support*	Advanced Clinical Specific Support*
Genus, species specific; Diversity, Colonization and Activity Levels are key in selection	Specific Probiotics with Clinical Support; Full characterization. Target Mechanism and General Benefit. Minimum Scientific Efficacy Threshold	Strain specific with target mechanistic action; Full characterization. Clinically effective dose selection	

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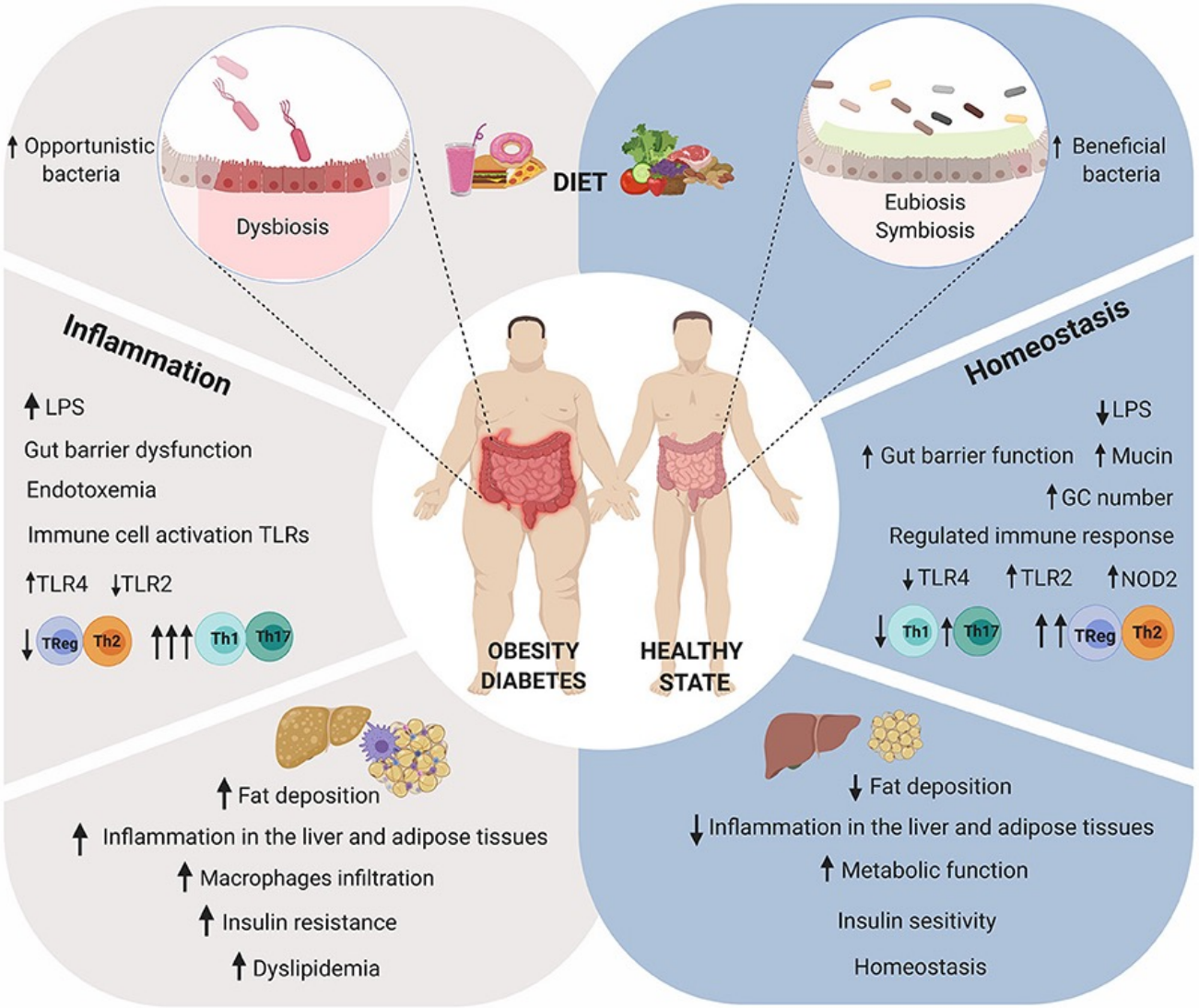

Dysbiosis will alter the metabolome and lead to a progression to digestive disorders and contribute to the development of chronic health issues

Level 1 Support: Stabilize and Balance Microflora & Microbiome*

Level 2 Support: Balance the Metabolome and Optimize the Microbiome*

Level 3 Support: Precision ProBiotics addressing advanced conditions in digestive disorders.*

Shanahan, F, et al. Continuum of Digestive Disorders and the Influence of the Microbiome on the Metabolome, ASPEN Seminar Series, 2018. Austin TX.

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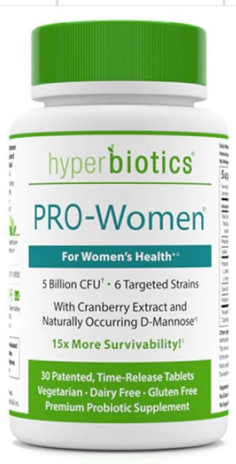
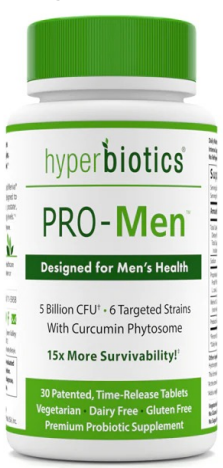
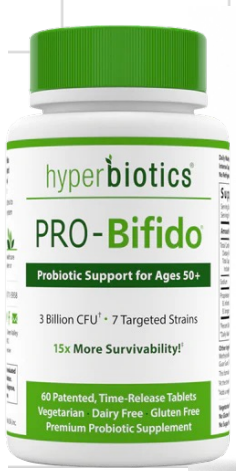
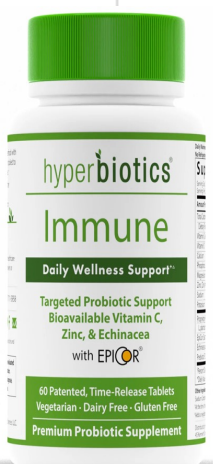
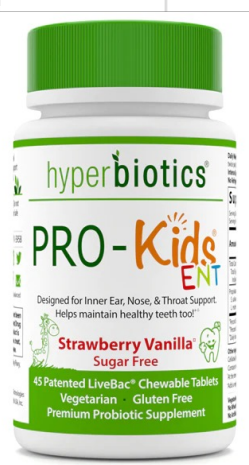
# Tablets	60 Pearls	30/60 Tablets	60 Micro-Pearls	30/60 Tablets	30 Tablets	30 Tablets	60 Tablets	60 Micro-Pearls	60 Tablets	45 Chewable Tablets	60 Tablets	60 Tablets	60 Tablets	45/90 tablets
L. plantarum	x	x	x	x	x		x	x	x		x	x		
L. plantarum 6595						x							x	
L. fermentum	x	x		x	x	x			x		x		x	
L. acidophilus	x	x	x	x	x	x	x	x	x		x		x	
B. infantis	x	x	x		x		x		x		x			
L. casei	x	x				x					x		x	
B. longum	x	x				x	x	x						
L. rhamnosus	x	x		x	x							x		
B. lactis	x	x	x				x	x			x	x	x	
L. reuteri	x	x		x	x	x		x	x	x	x			x
L. salivarius	x	x												x
L. paracasei	x	x								x		x		x
L. gasseri	x	x										x		
B. bifidum	x	x		x			x							
B. breve	x	x					x					x		
S. thermophilus	x	x												
L. sakei										x				x
L. brevis													x	
S. salivarius K12, M18														
Lactobacillus plantarum HEAL9														
Lactobacillus paracasei 8700:2														
Prebiotic														
Additional Ingredients														

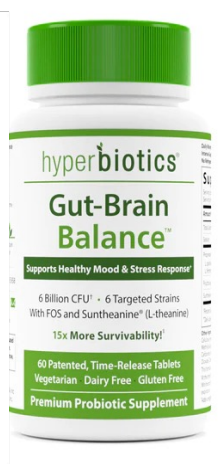


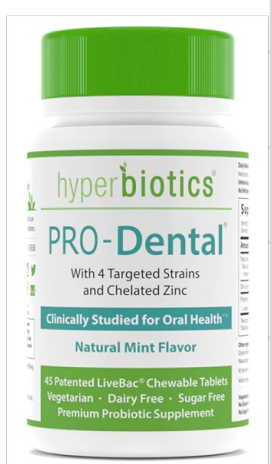












*These statements have not been evaluated by the Food & Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.

Hyperbiotic Product Portfolio – User Entry Points and Target Needs

hyperbiotics®
Your healthiest days are ahead.®

General & Preventive*	**General Health and Early Issues Care***	PRO-15 PRO-Kids PRO-Women PRO-Men PRO-Mom PRO-Bifido PRE-biotic powder
Digestive Function & Regulation*	**Acute digestive system concerns***	PRO-Dental PRO-15 Advanced Immune PRO-Kids ENT
Patient & Condition Specific Support*	**Chronic digestive disorders***	Immune Gut Brain Balance Blood Sugar Support Better Body
Advanced Clinical Specific Support*	**Complex & Advanced Care***	Immune Gut Brain Balance

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Key Summary Points & Insights

1. The Microbiome is the net combine effect of synergistic activity in the gut

2. Synergistic effect determined by diverse microflora sustainable and metabolically active*

3. Metabolic activators enhance the viability of the microflora*

4. All probiotic strains require nutrient energy sources to proliferate and metabolize

5. The resulting metabolome influence systemic metabolic processes, immune system response and CNS activation*

6. Probiotics products should be selected based on diversity, sustainability (viability), metabolic & synergistic co-factors and the resulting targeted clinical benefit*

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Thank You!