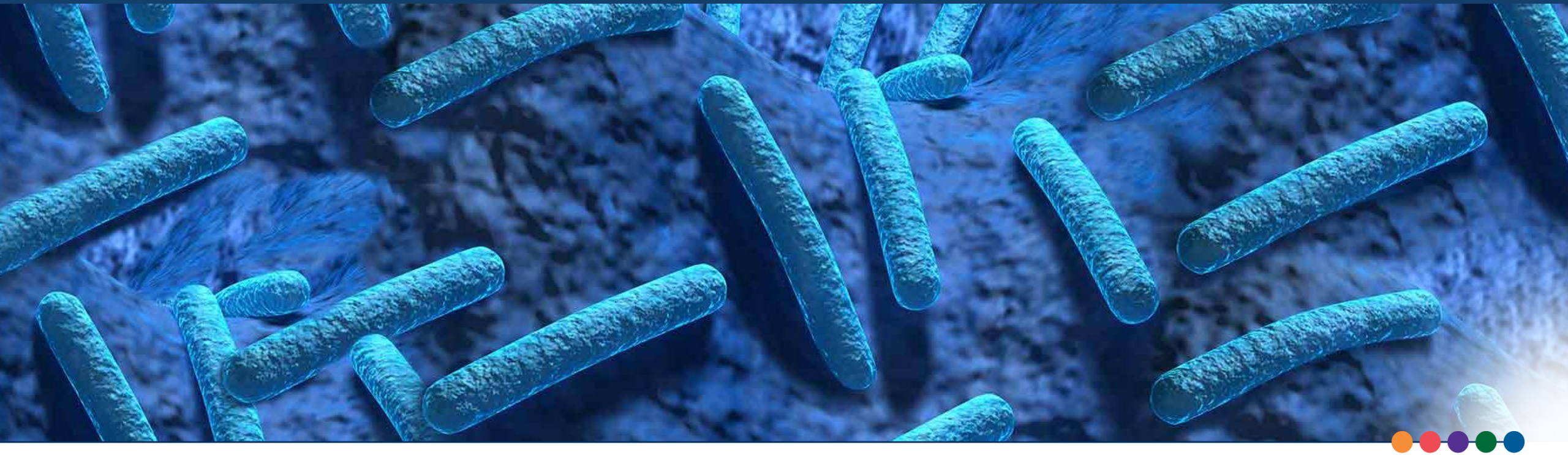

Modulating the Gut Microbiome: The Role of Probiotics & Prebiotics

Presented by:
Stephen Olmstead, MD

Michael Chapman, ND

Medical Education Specialist - Asheville

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Stephen Olmstead, MD

Chief Science Officer
ProThera Inc.

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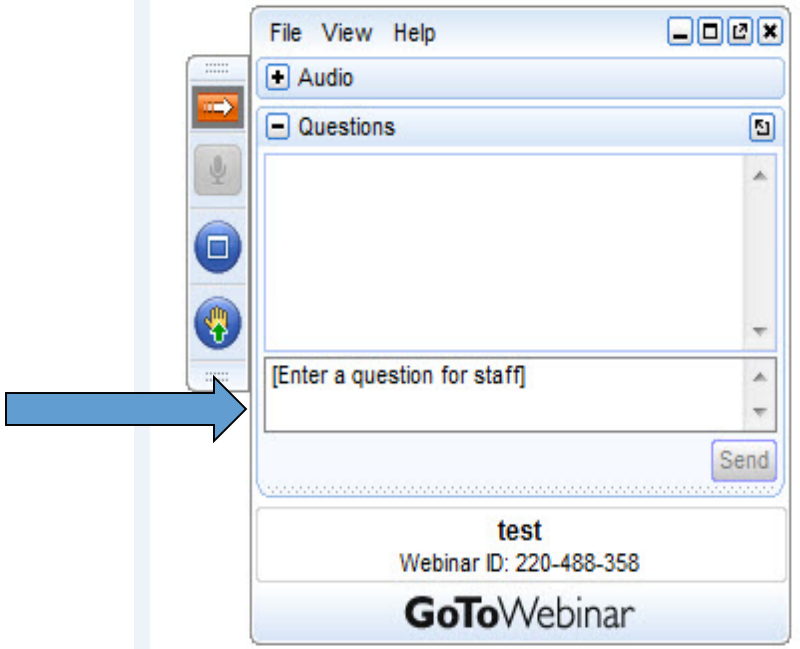
Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



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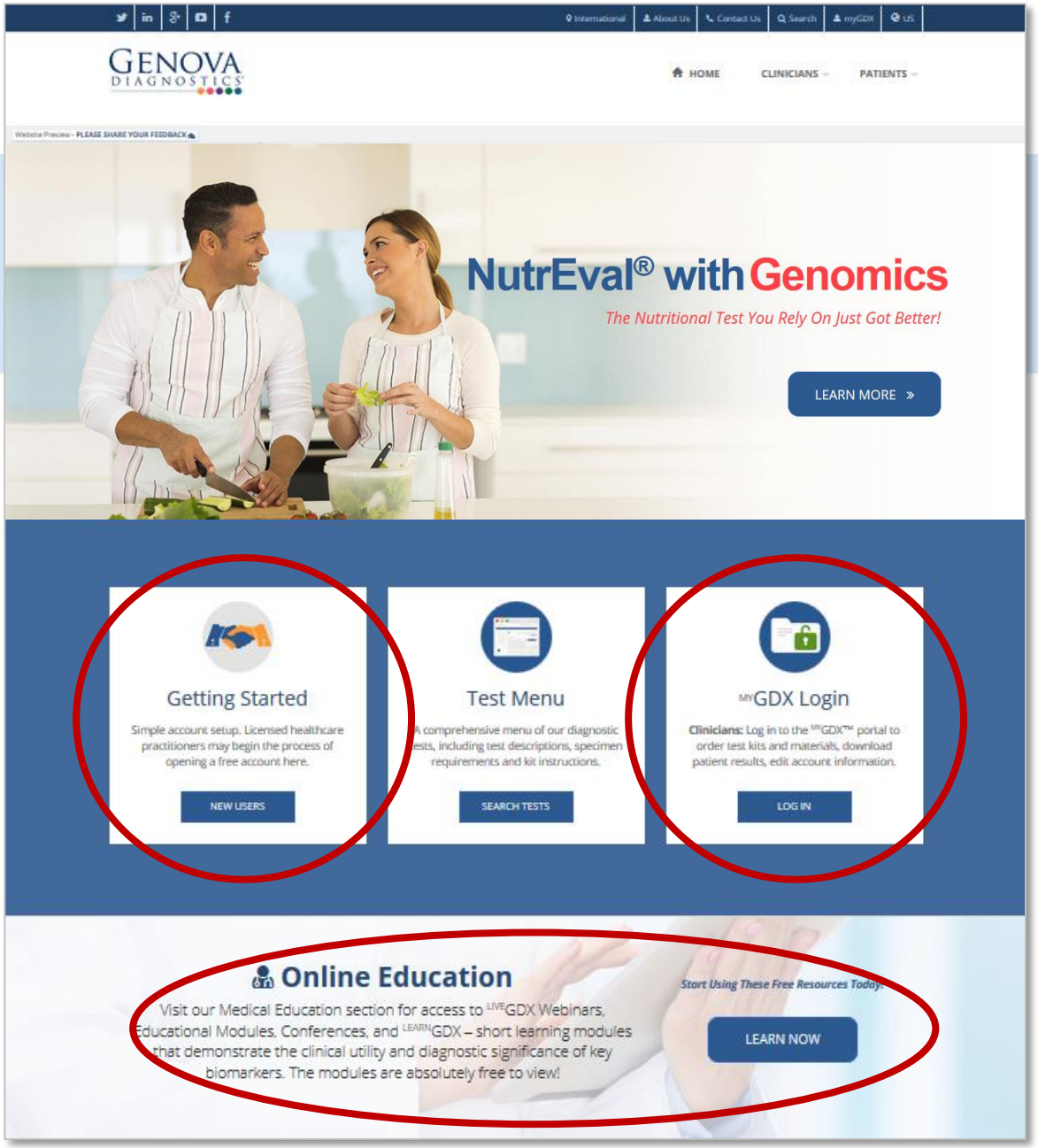

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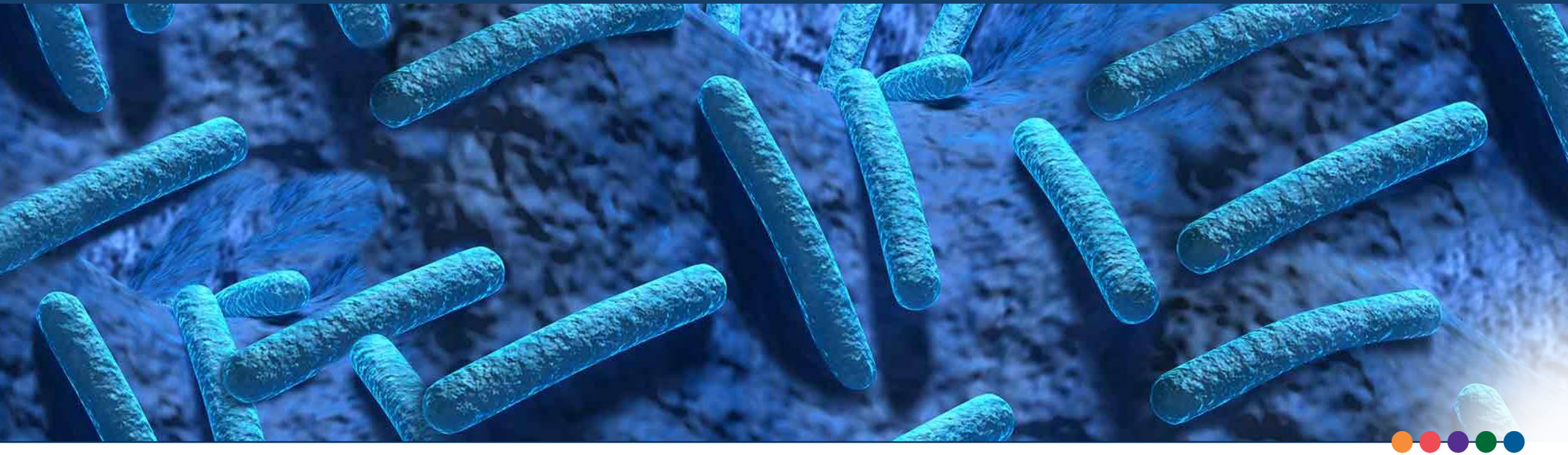

Modulating the Gut Microbiome: The Role of Probiotics & Prebiotics

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Chief Science Officer ProThera Inc

The Human Intestinal Microbiota

Human Colon
false color barium enema

- **100 trillion microorganisms**
- **10 x number human cells**
- **>150 x number human genes**
- **>1800 genera by rRNA**
- **15,000-36,000 species by rRNA**
- **>500 cultured species**
- **Dominated by 2 divisions**
  - **Firmicutes (64%)**
  - **Bacteroidetes (23%)**
- **99% anaerobic**

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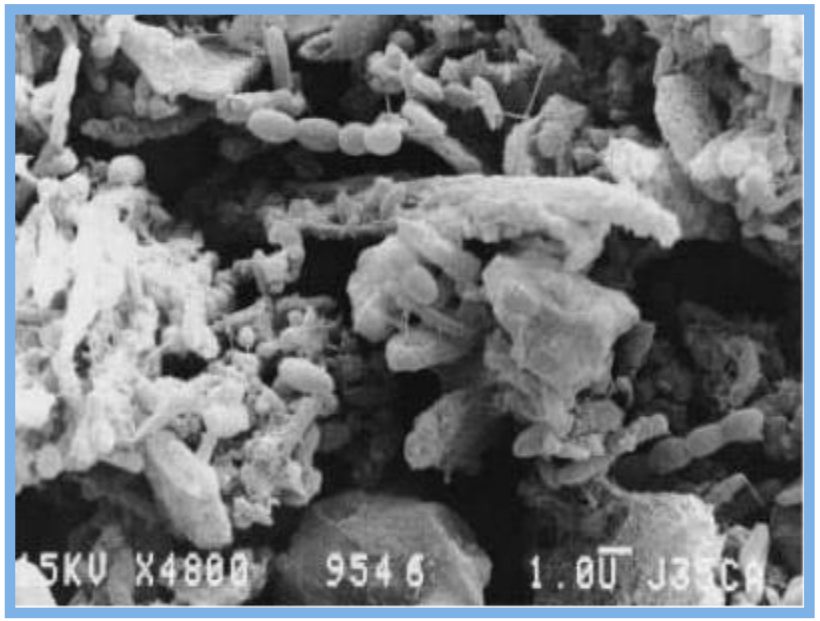
Qin et al. *Nature* 2010;464:59-65

The Intestinal Microbiota Organ



Colonic mucosa
scanning electron microscopy

- **Unique & vital organ**
- **Weighs 1.5 Kg**
- **Metabolic activity rivals liver**
- **Immune & GI maturation**
- **Normal CNS development**
- **Colonization resistance**
- **Immune system modulation**
- **Metabolic modulation**

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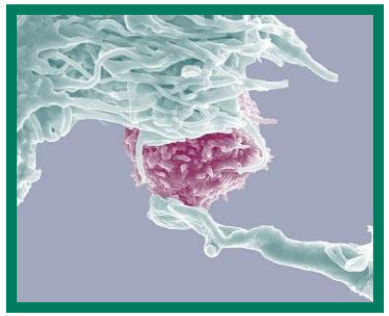
Transfer of Maternal Microbiota

Maternal microbiota secreted in breast milk



Maternal microbiota transferred to lymphocytes

Dendritic cells sample maternal microbiota

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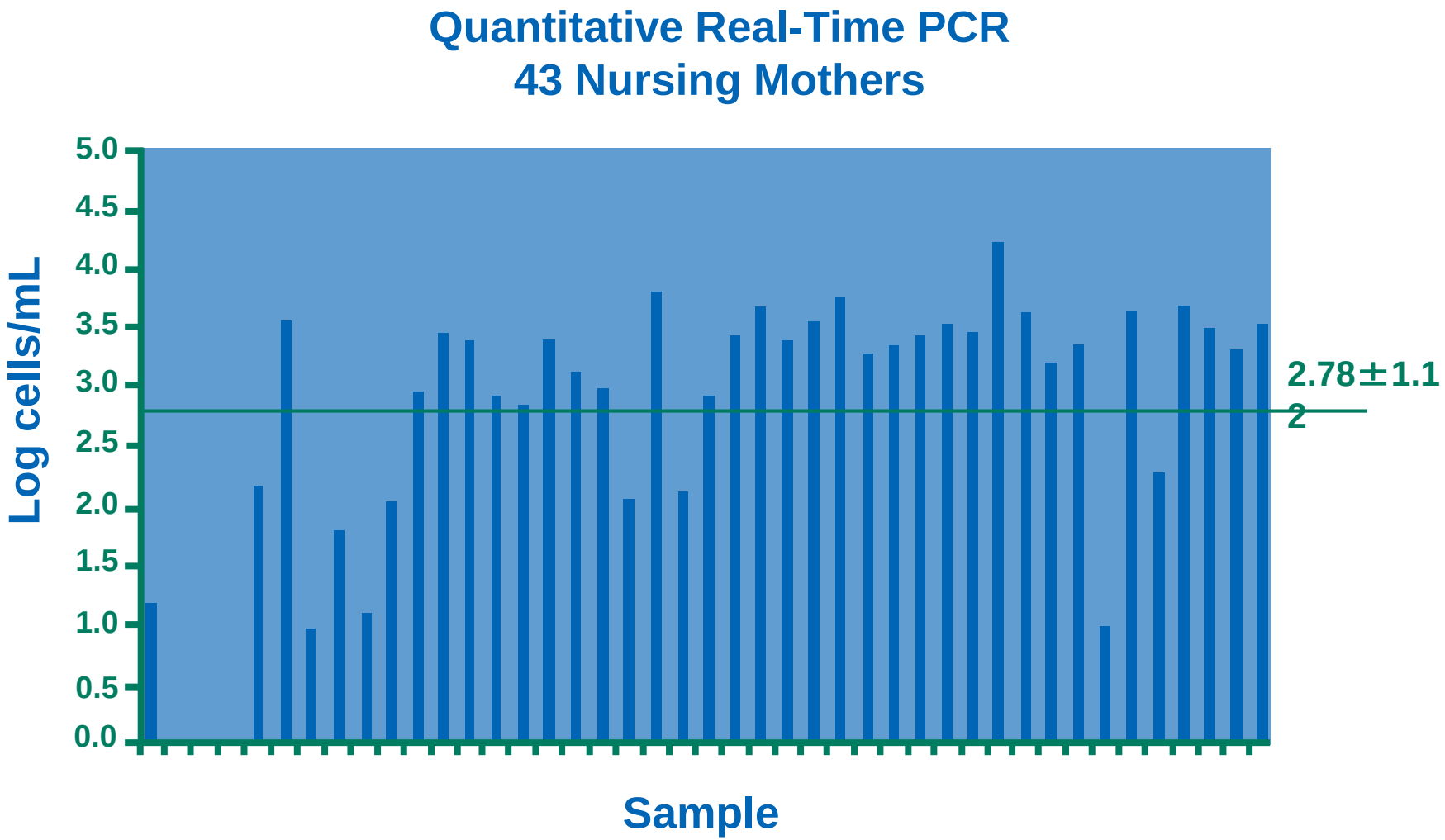
Rescigno et al. *Nat Immunol* 2001;2:361-7

Breast Milk *Bifidobacterium* Content



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Gueimonde et al. 2007

Prenatal Microbial Exposure

Bacteria Isolated from Amniotic Fluid & Meconium

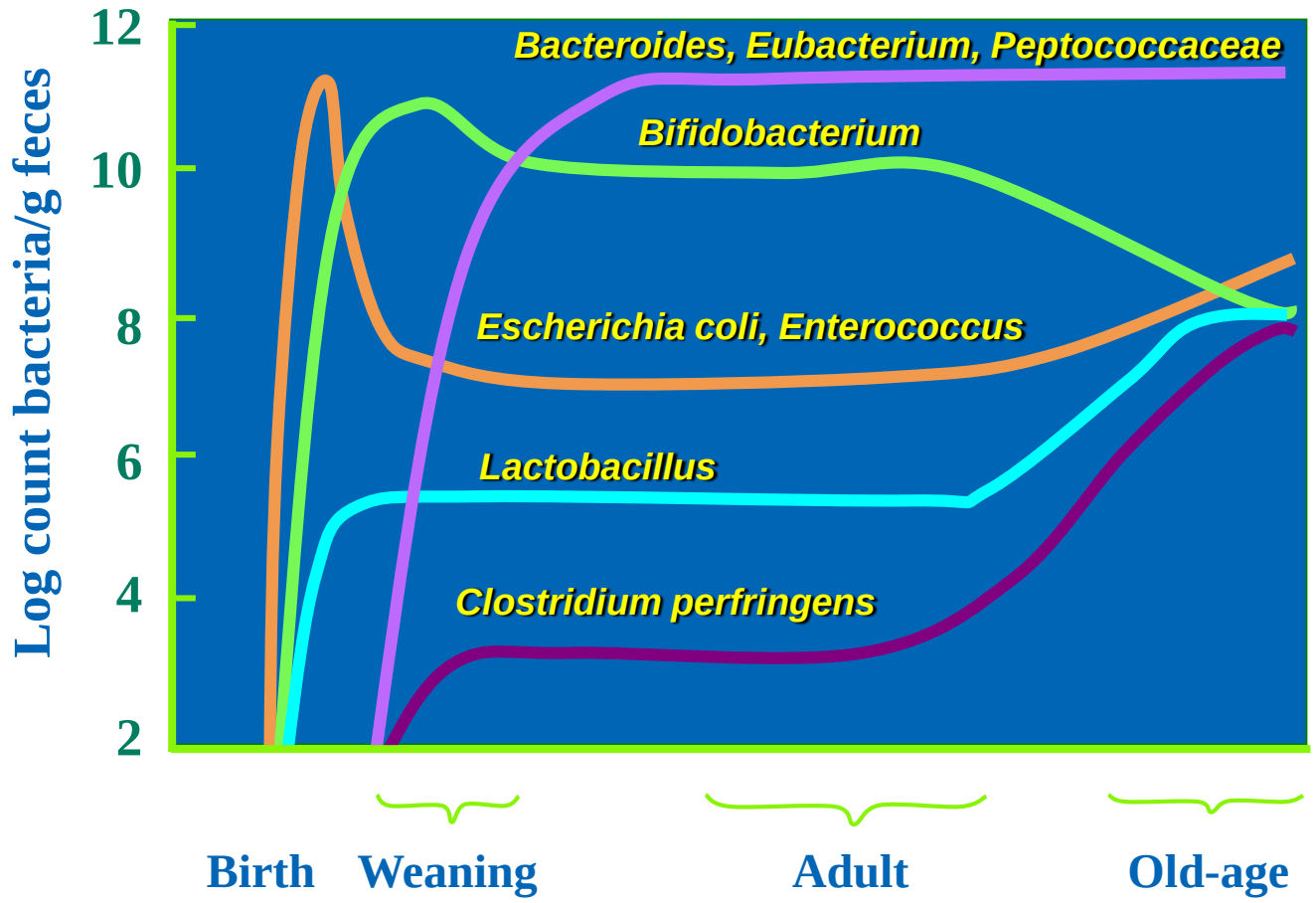
Fetal ultrasound

- *Enterococcus*
- *Staphylococcus*
- *Streptococcus*
- *Leuconostoc*
- *Bifidobacterium*
- *Rothia*
- *Enterobacter*
- *Klebsiella*
- *Parabacteroides*
- *Bacteroides*

GENOVA DIAGNOSTICS

Jiménez et al. *Res Microbiol* 2008;159:187-93

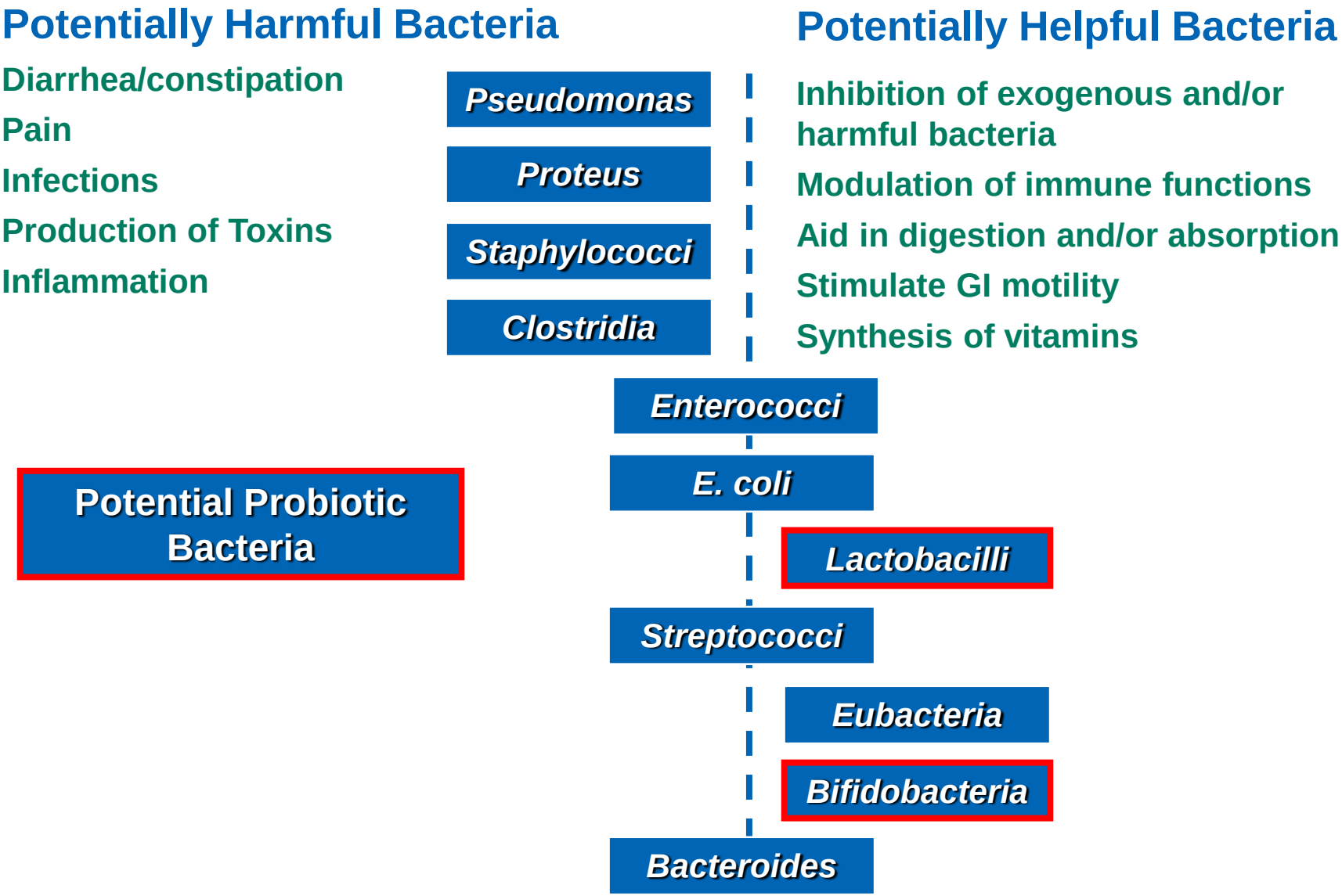
Changes in Microbiota with Age



GENOVA DIAGNOSTICS

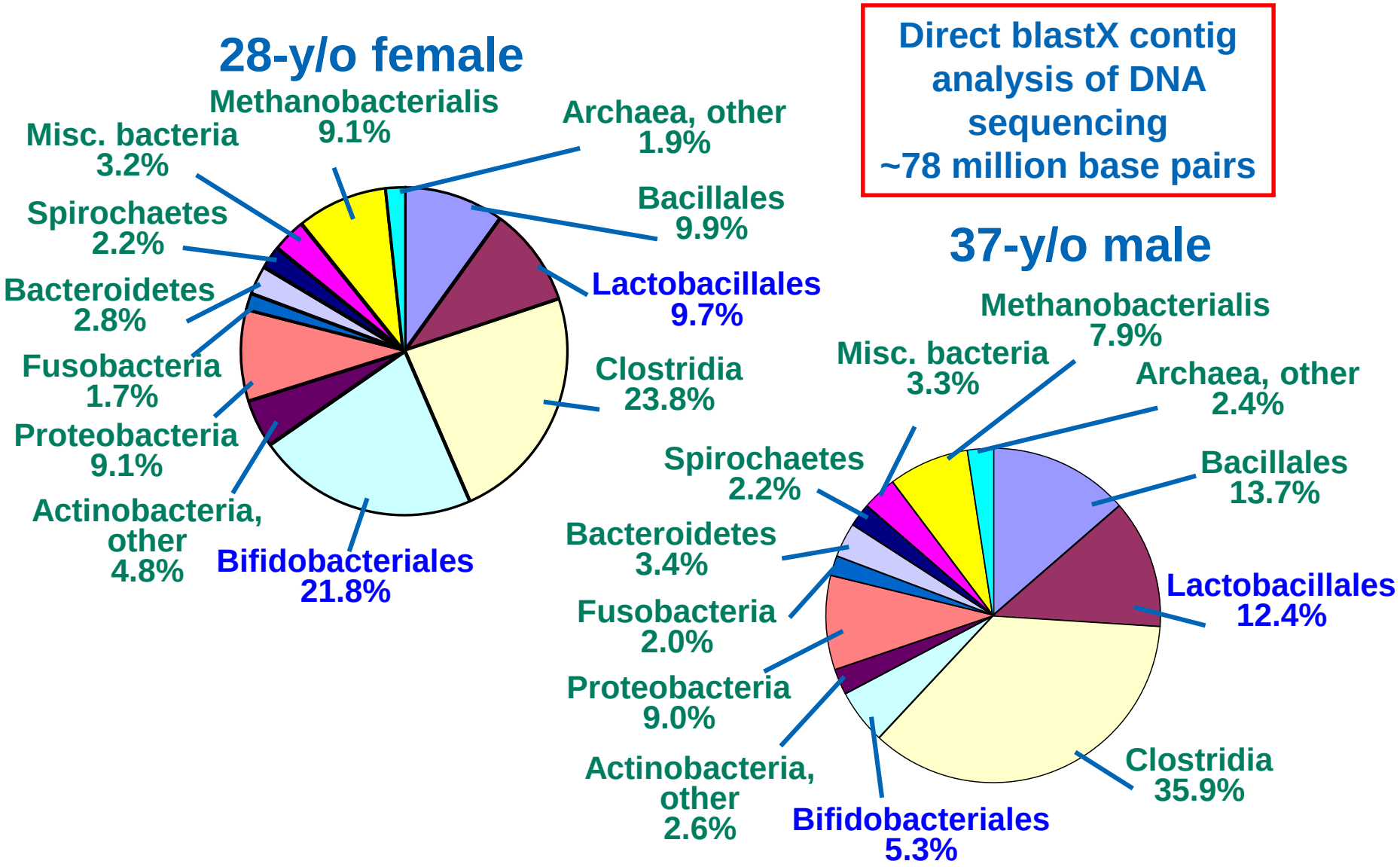
Mitsuoka *Nutr Rev* 1992;50:438-46

GI Microbiota – A Balanced Microecosystem



Gibson GR. *J Nutrition* 1995;125:1401-12

Metagenomic Analysis of the Human Distal Gut Microbiome



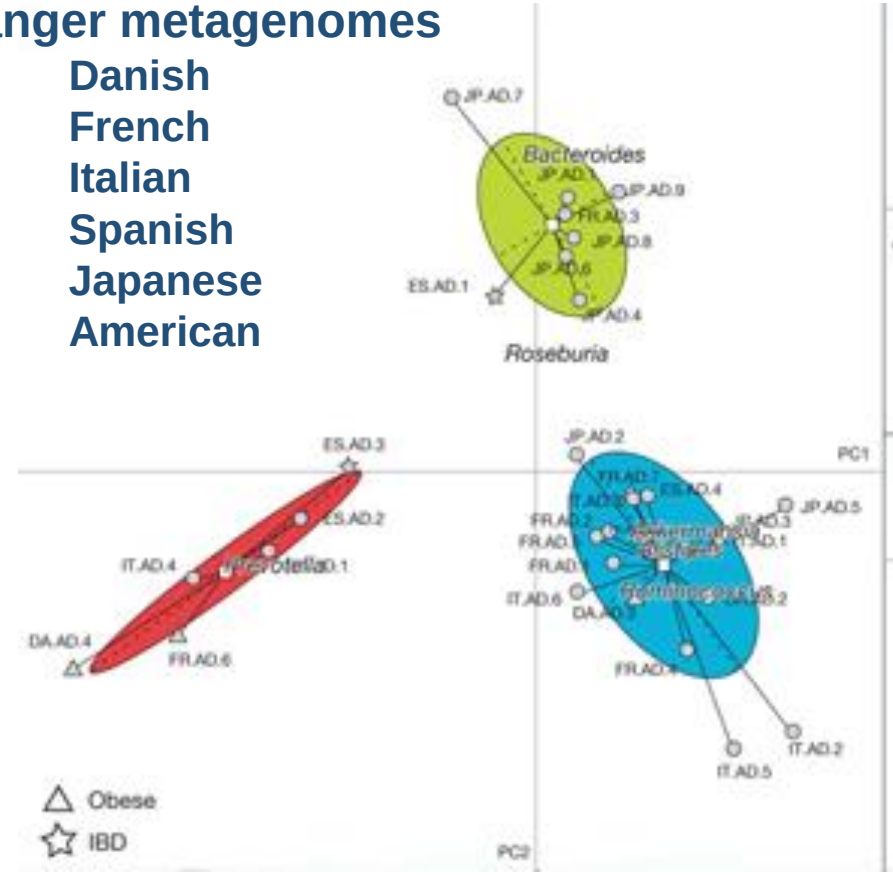
GENOVA DIAGNOSTICS

Gill et al. *Science* 2006;312:1355-9

Gut Microbiota Enterotypes

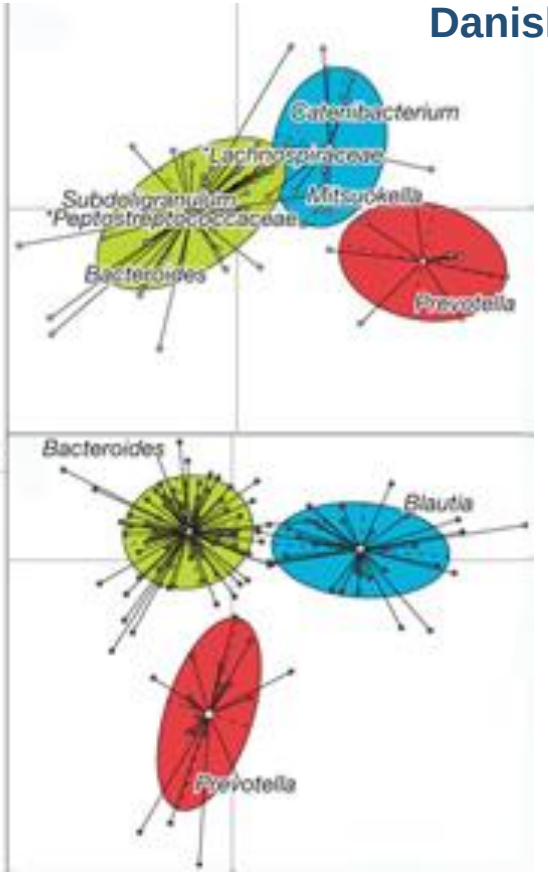
33 Sanger metagenomes

- Danish
- French
- Italian
- Spanish
- Japanese
- American



85 Sanger metagenomes

Danish



154 pyrosequenced 16S sequences

American females

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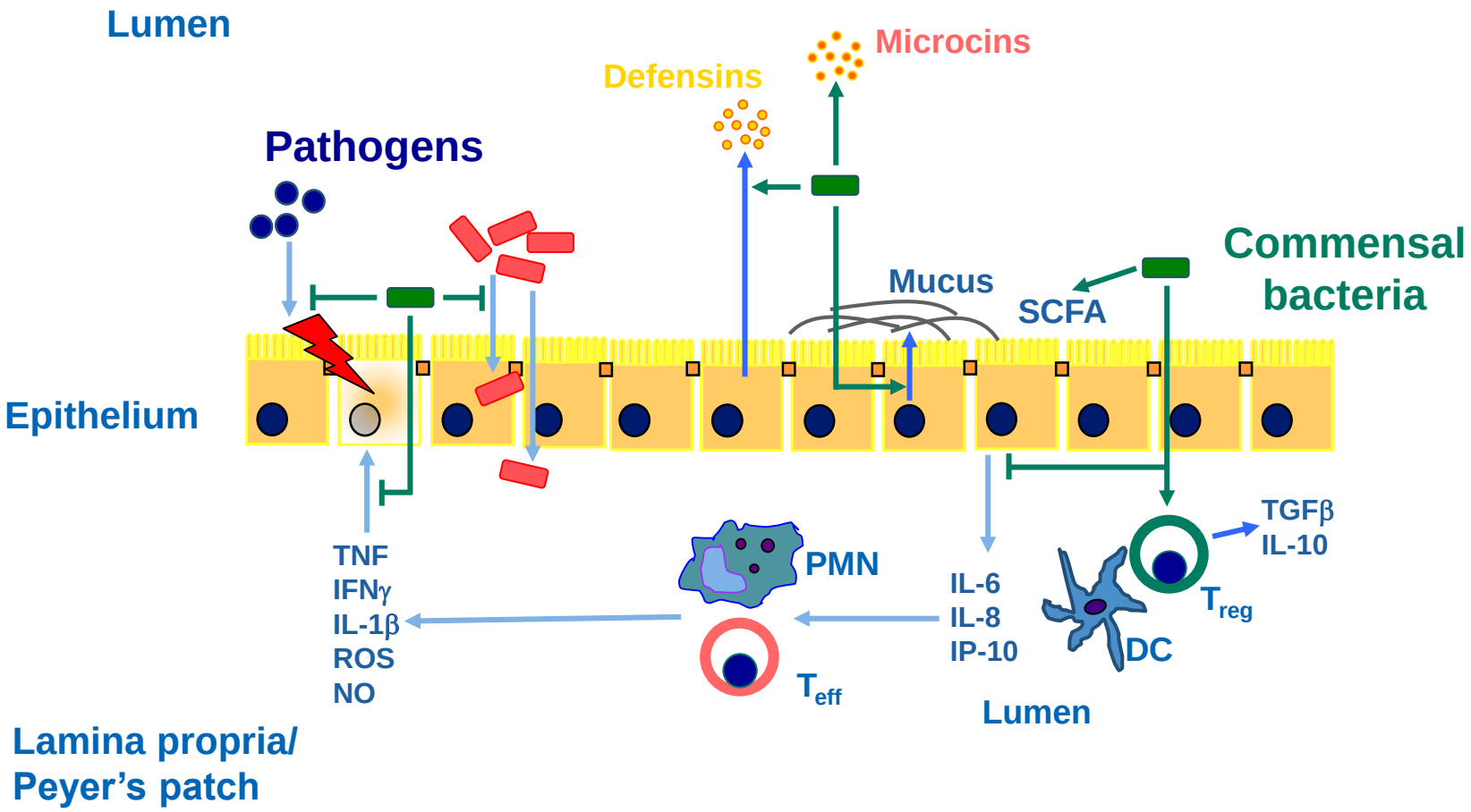
Arumugam et al. *Nature* 2011;473:174-80

Microbiota Maintains Intestinal Integrity



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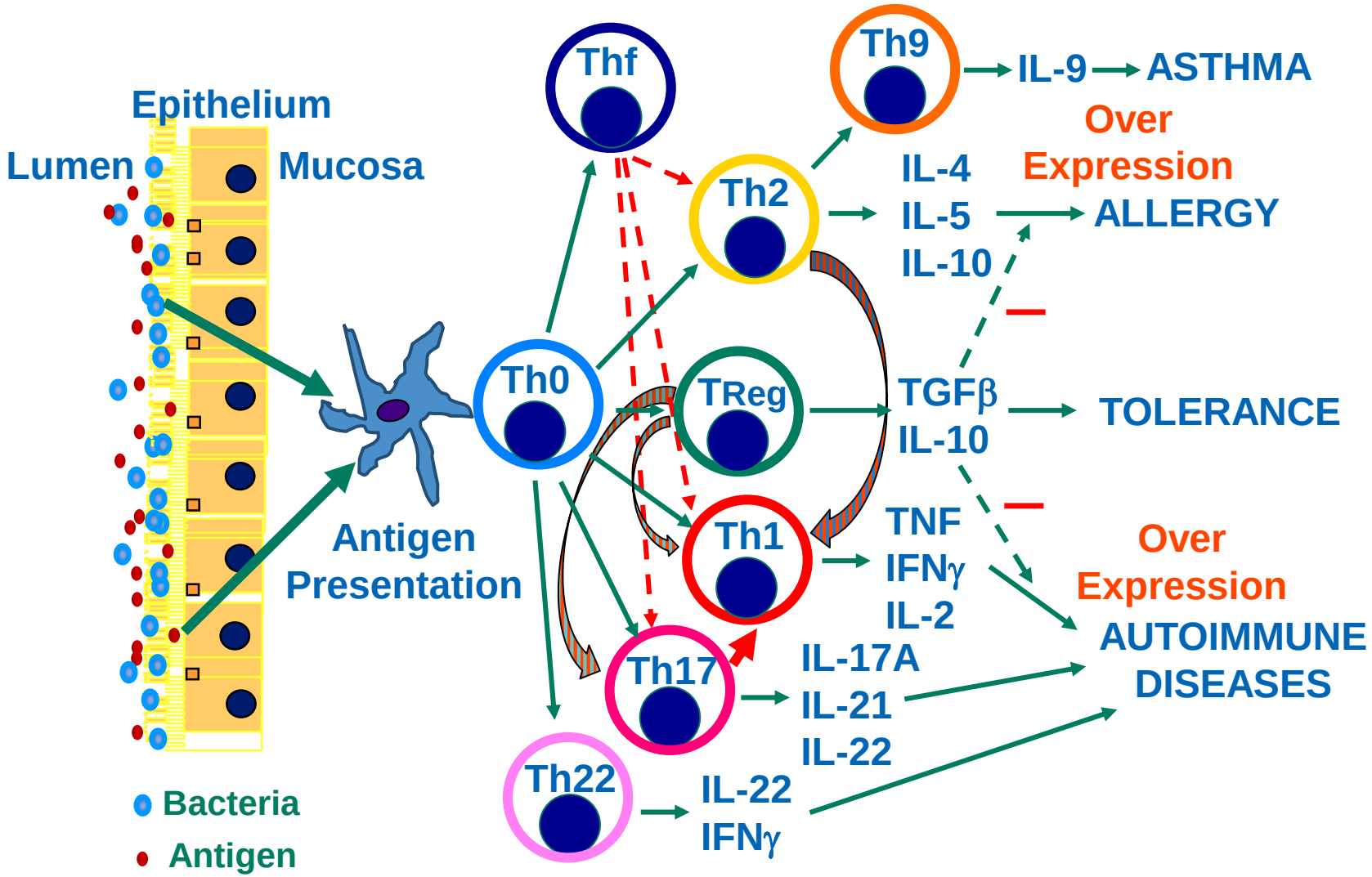
Gut Associated Lymphatic Tissue
T Cell Activation & Differentiation



GENOVA DIAGNOSTICS

O'Shea & Paul. *Science* 2010;327:1098-1102

Modulating the Gut Microbiome

- **Diet**
- **Probiotics**
- **Prebiotics**
- Antibiotics
- Fecal transplantation

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Definitions

Probiotics

1965 Lilly & Stillwell - microbe produced growth promoting factors

1989 Fuller - live microbial feed supplements, which benefit the host by improving intestinal microbial balance

2001 “viable microbial food supplements which beneficially influence the health of humans.”
International Life Sciences Institute Europe, consensus document

Definitions

Prebiotics

Gibson & Roberfroid - non-digestible substances that stimulate the growth and/or metabolic activity of selected GI microbes leading to health benefits

Synbiotics

Gibson & Roberfroid - a food or supplement that combines pro- & prebiotics

GENOVA DIAGNOSTICS

Gibson & Roberfroid J Nutr 1995;125:1401-12

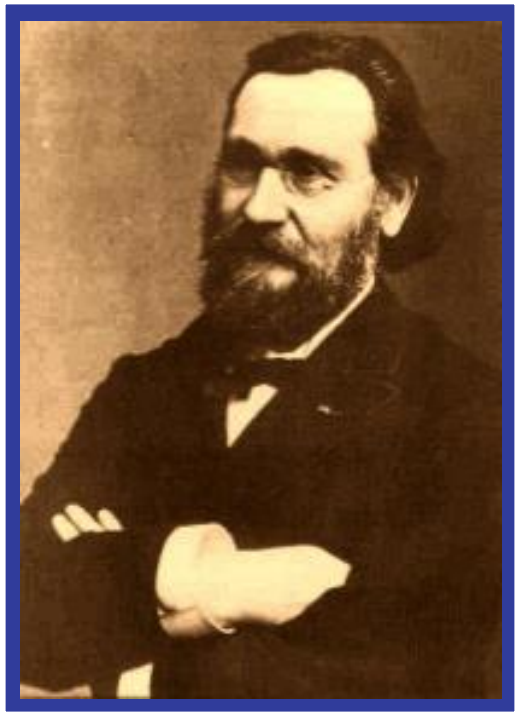
Probiotics - A Brief History

Cacik

Turkish yogurt dish

- Essential probiotics
- Probiotics on fruit & vegetables
- 10,000 BCE fermented beverages
- 3,000 BCE yogurt
- Hippocrates (460-370 BCE)
  Sour milk for GI disorders
- Pliny the Elder (23-79 CE)
  Health benefits of sour milk
- Francis I (1476-1531)
  Cured of dysentery by yogurt

The Godfather of Probiotics



Eli Metchnikoff
Nobel laureate 1908
1848-1916

"The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and replace the harmful microbes with useful microbes."

The Prolongation of Life 1907

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Types of Probiotics

- **Lactic acid bacteria**
  - *Lactobacillus* species
  - *Bifidobacterium* species
  - *Streptococcus thermophilus*
  - *Enterococcus faecium*
  - *Lactococcus* species
  - *Leuconostoc* species
  - *Pediococcus* species
- **Non-lactic acid bacteria**
  - *Bacillus* species
  - *Proprionibacterium* species
  - *E. coli* Nissle 1917
- **Non-pathogenic yeast**
  - *Saccharomyces boulardii*

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Lactobacillus Characteristics

- Gram-positive, non-sporulating rods or coccobacilli
- Homofermentative (primarily lactic acid)
- Heterofermentative

  (lactic acid, CO_2, ethanol & acetic acid)
- Digest & metabolize proteins & carbohydrates
- Synthesize B vitamins & vitamin K
- Catabolize bile salts
- Enhance innate & acquired immunity
- Inhibit pro-inflammatory mediators
- Antimicrobial activities against array of pathogens:
  - *Pseudomonas*, *E. coli*, *Staph. aureus*, *Salmonella*,
  - *Shigella*, *C. difficile*, *Candida & Helicobacter pylori*

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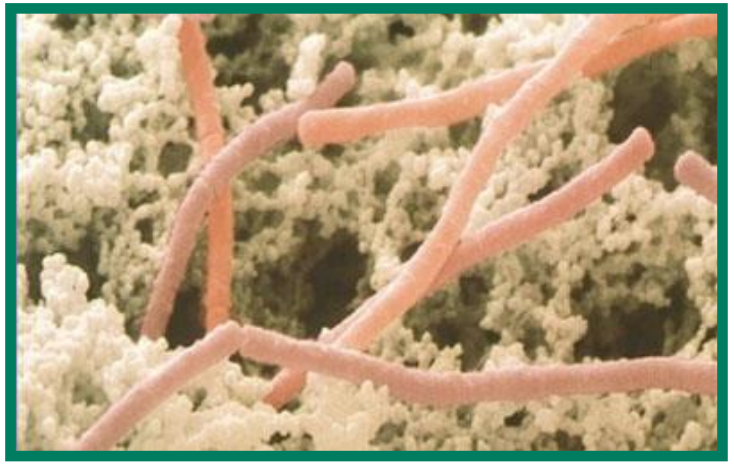
Lactobacillus Probiotics

- ***L. acidophilus***
- ***L. brevis***
- ***L. bulgaricus***
- ***L. casei***
- ***L. crispatus***
- ***L. fermentum***
- ***L. gasseri***
- ***L. helveticus***
- ***L. jensenii***
- ***L. johnsonii***
- ***L. paracasei***
- ***L. plantarum***
- ***L. reuteri***
- ***L. rhamnosus***
- ***L. salivarius***



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Lactobacillus acidophilus

- Prototypic probiotic
- Many strains reclassified
- Transient GI species
- Obligate homofermentative; DL-lactate isomers
- Resistant to acid, bile, pepsin & pancreatin
- >20 known peptidases; breaks down casein & gluten
- Ferments lactose, other sugars & polysaccharides
- Antagonizes array of pathogens
- Reduces GI concentrations of carcinogenic enzymes

Lactobacillus rhamnosus

- Most studied probiotic
- Relatively fragile
- Transient GI species
- Facultative heterofermentative; L(+)-lactate isomer
- Excellent colonic mucosal adherence
- More peptidases than any other *Lactobacillus*
- Enhances innate & acquired immunity
- Inhibits proinflammatory cytokines
- Antagonizes rotavirus & *C. difficile*
- Suppresses enterohemorrhagic *E. coli* internalization

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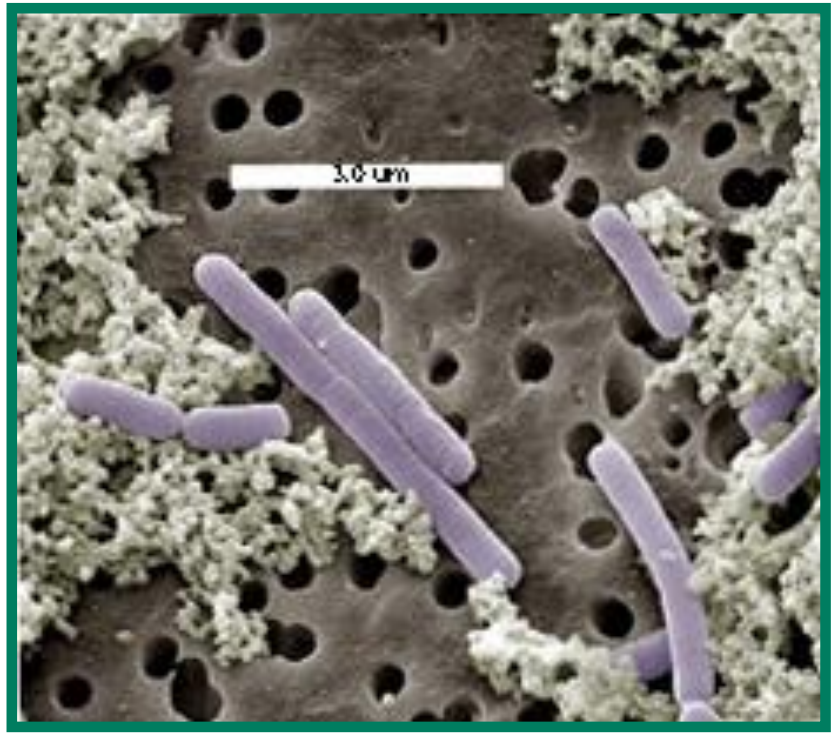
Lactobacillus casei



- Hardy, adaptive probiotic
- Closely related to *L. rhamnosus*
- Transient species
- Proline-specific peptidases
- Facultative heterofermentative; L(+)-lactate isomer
- Critical for dendritic cell differentiation
- Augments number intestinal IgA-producing cells
- Decreases proinflammatory cytokines secretion
- Inhibits EHEC intestinal cell adherence & invasion

GENOVA DIAGNOSTICS

Lactobacillus plantarum

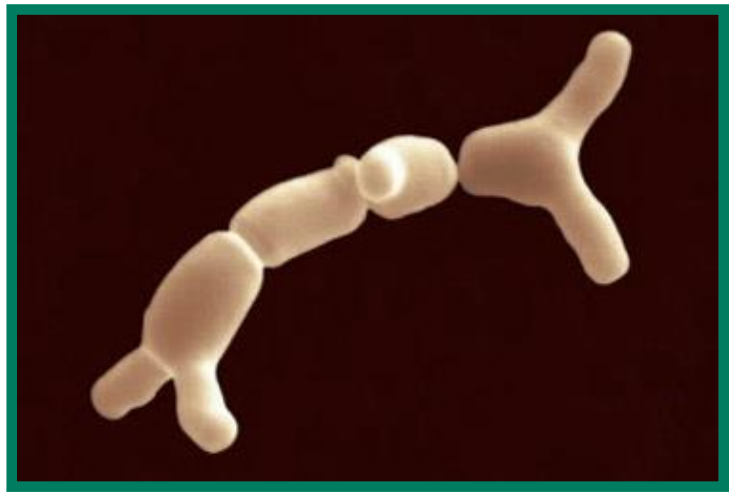
- Ubiquitous on plants
- Lacking in modern diets
- Transient GI species
- Facultative heterofermentative; DL-lactate isomers
- Highly resistant to acid & bile
- Facilitates induction IL-10, central regulatory cytokine
- Decreases production of inflammatory mediators
- Supports intestinal barrier function
- Reduces translocation of gut flora
- Antagonizes *C. difficile*

Bifidobacterium Characteristics

- Gram-positive, non-sporulating rods or Y-shaped
- Strictly anaerobic & fastidious
- Unique metabolic hexose pathway – “Bifidus shunt”
- All metabolize lactose
- Ferment non-digestible oligosaccharides
- Synthesize B vitamins & vitamin K
- Enhance innate & acquired immunity
- Inhibit proinflammatory mediators
- Inhibit pathogens via organic acids & H_2O_2

Bifidobacterium Probiotics

- *B. adolescentis*
- *B. animalis*
- *B. bifidum*
- *B. breve*
- *B. infantis*
- *B. lactis*
- *B. longum*
- *B. thermophilum*



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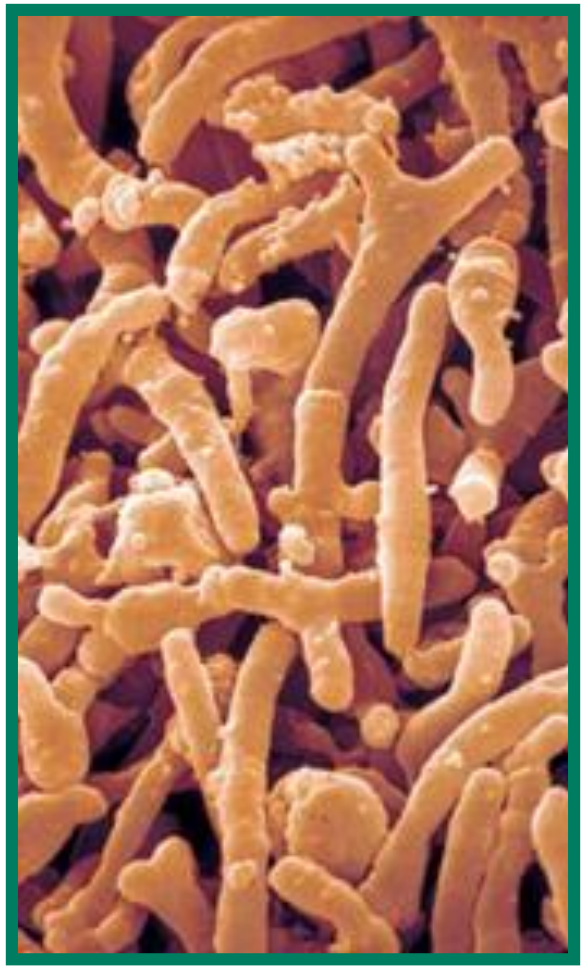
Bifidobacterium longum

- Often dominant GI bifidobacteria
- Ferments array of oligosaccharides
- Resistant to bile salts
- Inhibits enterotoxigenic *E. coli* receptor binding & translocation
- Inhibits *Clostridium* proliferation
- Enhances GI sIgA response to dietary antigens
- Modulates cytokine response to respiratory antigens



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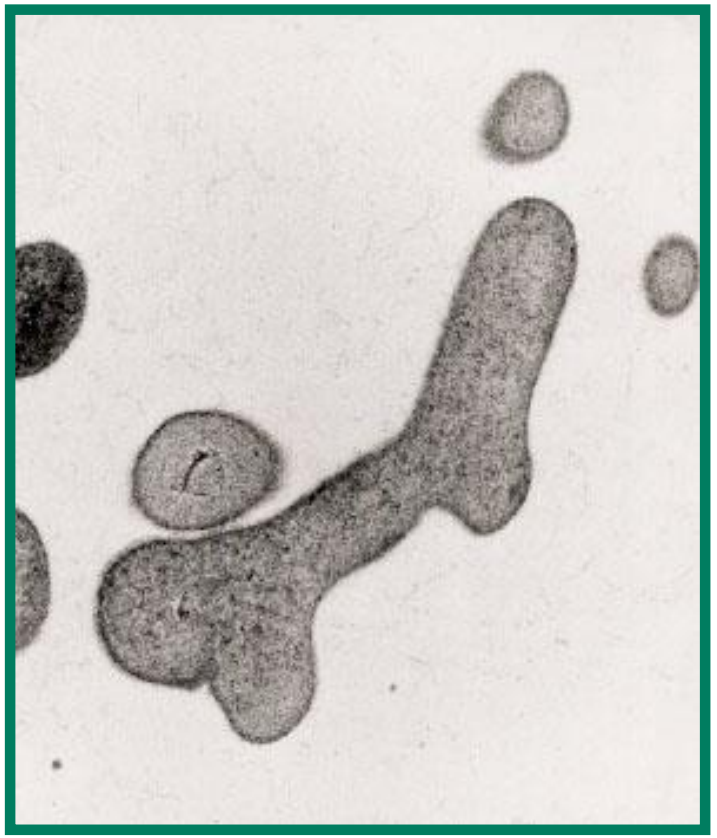
Bifidobacterium bifidum



- Present in large numbers
- Reduced in allergic infants
- Populations decline with age
- Suppresses total & antigen-specific IgE production
- Enhances IgM & IgG responses to select antigens
- Activates B cell IgA secretion
- Enhances IgA response to *C. difficile* toxin A
- With *L. acidophilus*, supports normal flora during antibiotic Rx; reduces (+) *C. difficile* toxin A testing

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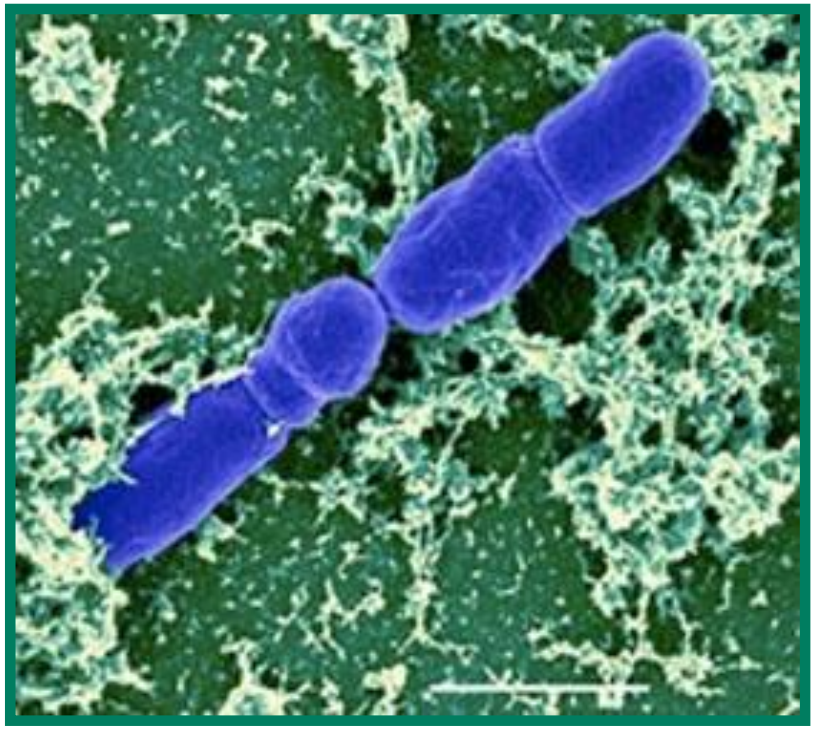
Bifidobacterium infantis

- Frequent in infants
- Rare in adults
- Suppresses populations of *Bacteroides vulgarus*
- Reduces proinflammatory cytokine production
- Improves cytokine ratios in IBS
- With *L. acidophilus*, reduces risk of necrotizing enterocolitis in very low birth weight infants
- Promotes normal microbiota in children with diarrhea



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Bifidobacterium breve

- Reduces *Bacteroides fragilis & C. perfringens* populations
- Improves weight gain in very low birth weight infants
- Stimulates Peyer's patch B cell proliferation
- Resistant to acid, bile, pepsin & pancreatin
- Enhances B cell antibody production
- Eliminates *Camphylobacter jejuni*
- Antagonizes rotavirus & decreases rotavirus shedding

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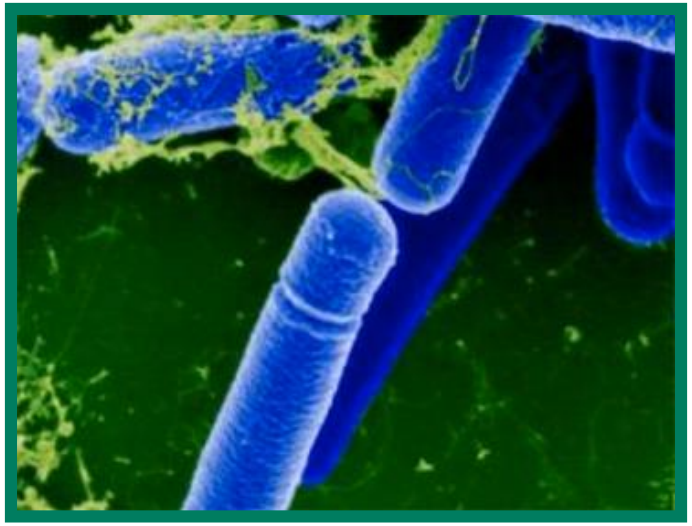
Bacillus Characteristics

- Gram-positive, sporulating rods
- Facultative anaerobes
- Fermentation end products include lactate, acetate, ethanol, acetoin, 2,3-butandiol
- Transient commensals
- Used in traditional fermented fish, manioc, soy foods
- Enhance innate & acquired immunity
- Inhibit pathogens via bacteriocins & lipopeptides
- Promote colonocyte health via heat shock proteins

Bacillus Probiotics

- *B. cereus*
- *B. clausii*
- *B. coagulans*
- *B. laterosporus*
- *B. subtilis*
- *B. licheniformis*
- *B. pumilus*



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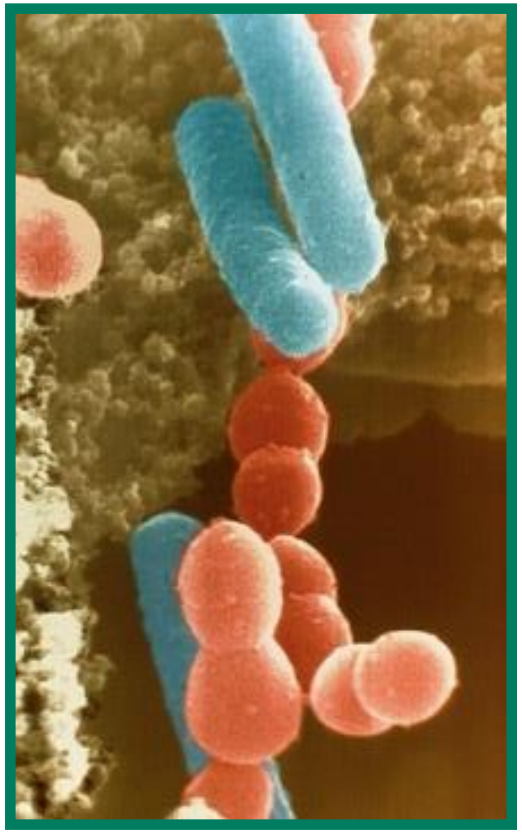
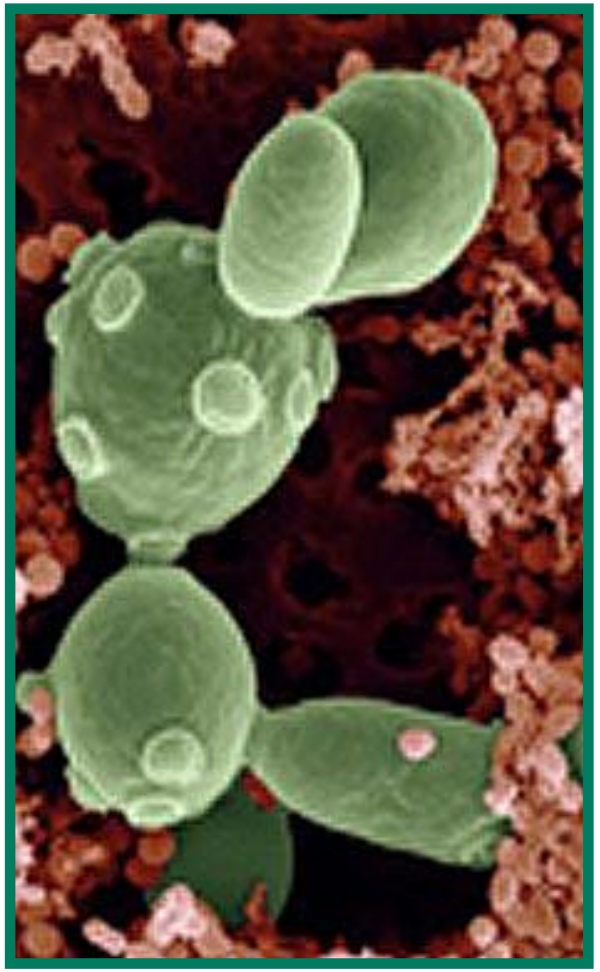
Streptococcus thermophilus



- Yogurt & cheese starter
- Highly adapted to lactose
- Transient GI species
- Protocooperation with *L. bulgaricus*
- Formate, acetoin, acetylaldehyde, diacetyl & acetate
- Inhibits pathogen proliferation
- Reduces DNA damage & premalignant lesions
- Clinical uses from rotavirus to ulcerative colitis
- Protection from pathogenic *Streptococcus* spp.

Saccharomyces boulardii

- Transient, non-pathogenic yeast
- Heat & pH resistant
- Active ingredient in Asian medicinal teas
- Increases brush border enzyme activities
- Secretes leucine aminopeptidase;
  supports against dietary protein allergies
- Increases gut short-chain fatty acid concentrations
- Increases intestinal sIgA; crypt cell Ig receptors
- Protease that inhibits *C. difficile* toxins A & B
- Antagonizes *Candida albicans* in the gut
- Effective against *Entamoeba hystolytica* & *Giardia*



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Probiotics - Documented Uses

- Antibiotic-associated diarrhea
- *C. difficile*-associated diarrhea
- Community acquired diarrhea
- Traveler's diarrhea
- Inflammatory bowel disease
- Irritable bowel disease
- Vaginal dysbiosis
- Urinary tract infections
- Allergies, atopic dermatitis, eczema
- Lactose intolerance
- Hyperlipidemia

Antibiotic-associated Diarrhea

- Disrupted GI microbiota
- Associated with ↓ short-chain fatty acids (SCFA)
- Occurs in 5-39% of adults; 11-50% of children
- Up to 50% of cases due to *Clostridium difficile*
- High relapse rate with *Clostridium difficile*
- Onset up to 2 mos. post antibiotics

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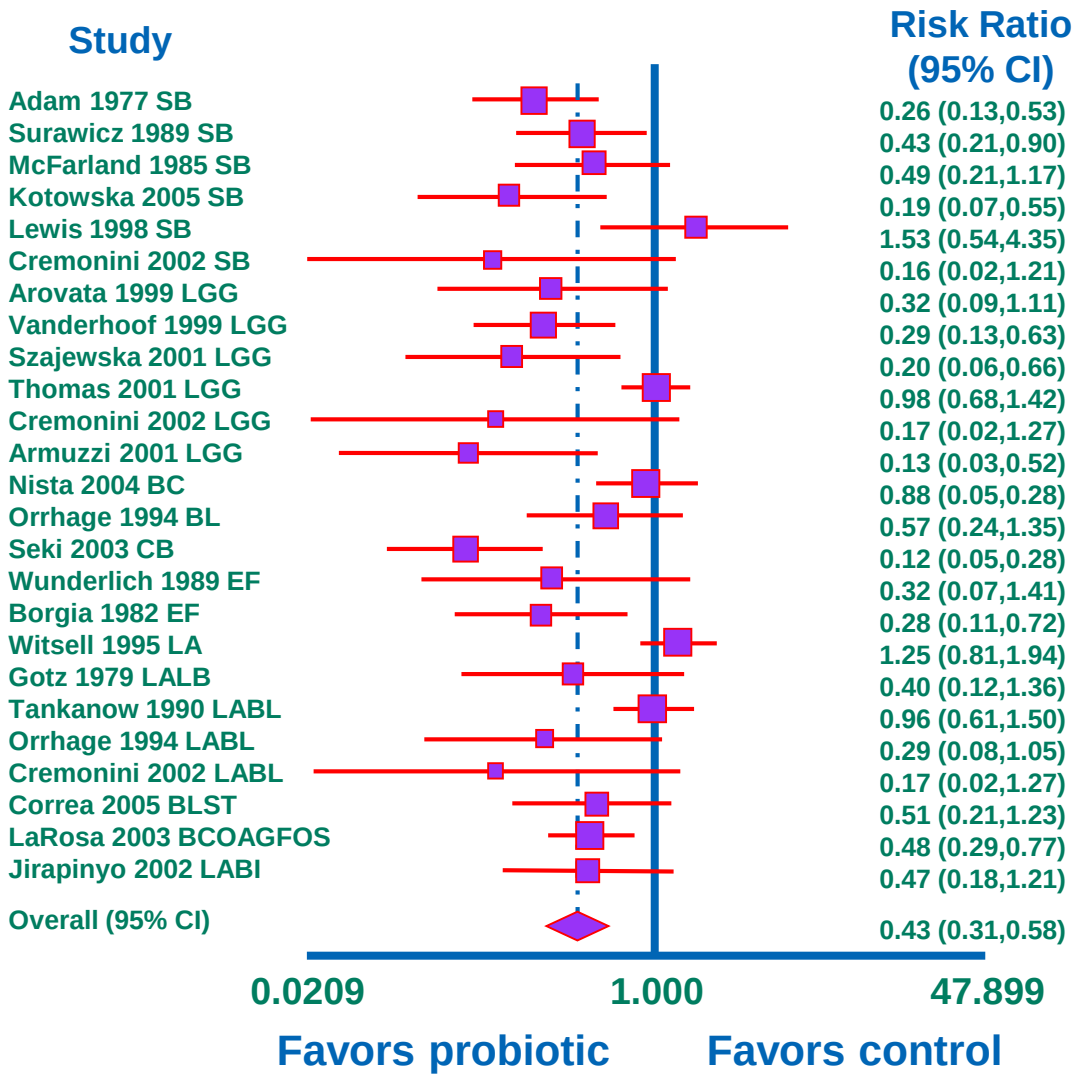
Meta-analysis: Probiotics & Antibiotic-associated Diarrhea



Of 25 RCT:

Overall RR= 0.43
(95% CI 0.31- 0.58)

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McFarland *Am J Gastro* 2006;101:812-22

Probiotics, Prebiotics & Antibiotics

- Use *Saccharomyces boulardii* 10 billion CFU/d
- Use *Lactobacillus rhamnosus* 5 billion CFU/d
- Use multistrain formulation with *Bifidobacterium*
- Consider prebiotics to increase SCFA-producing populations - *Eubacterium*, *Roseburia*
- Use during antibiotic Rx
- Take 1 hr before or 2 hrs post antibiotic dose
- 30 day total duration

Inflammatory Bowel Disease (IBD)

- Crohn's disease
- Ulcerative colitis
- Pouchitis
- Abnormal response to certain commensal bacteria
- High numbers of *Bacteroides*, *Enterobacteriaceae*, & *Peptostreptococcus*
- Low numbers of *Bifidobacterium*

Colitis

Normal colon

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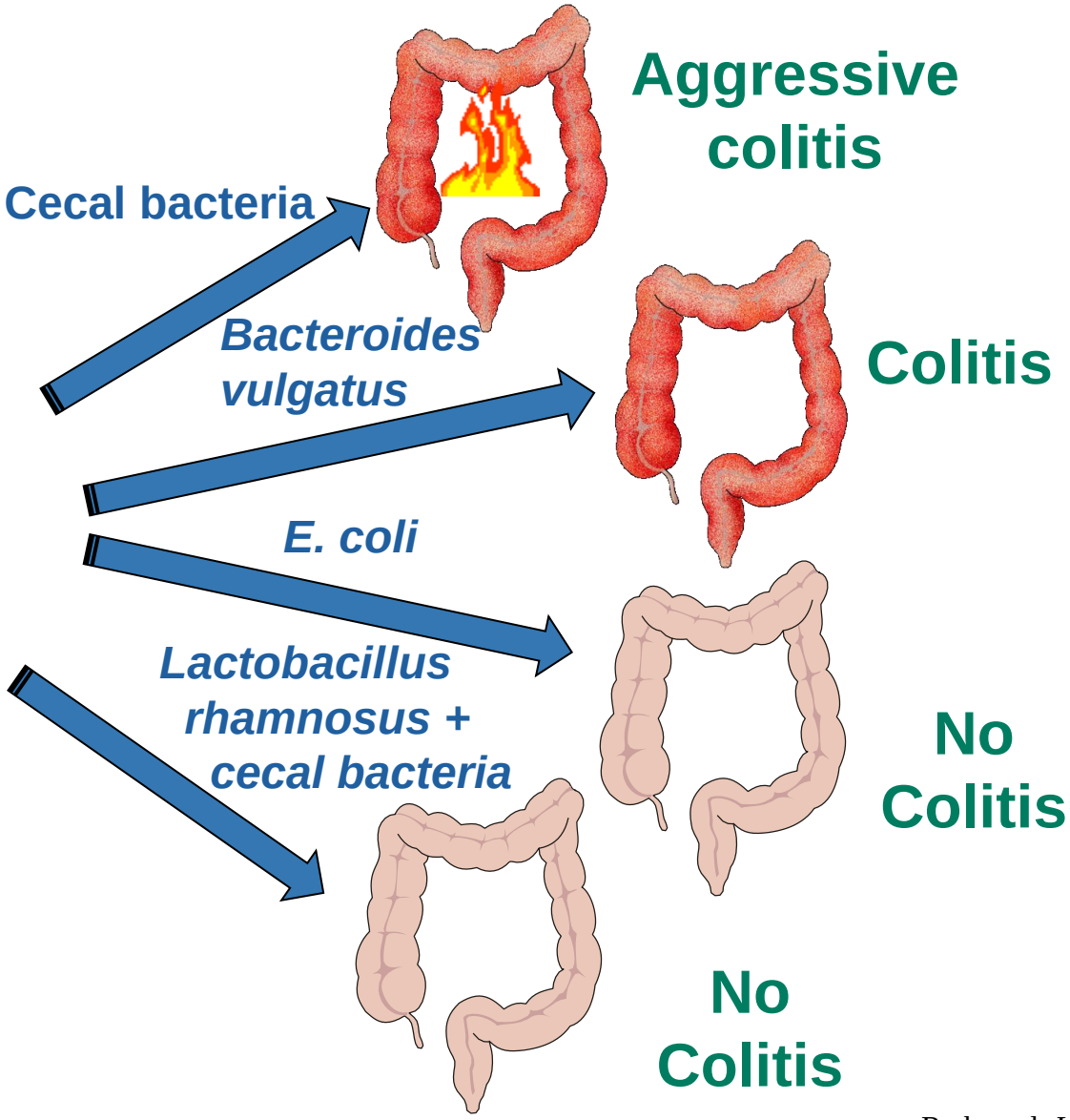
IBD Animal Model

HLA B_{27} Transgenic Rat

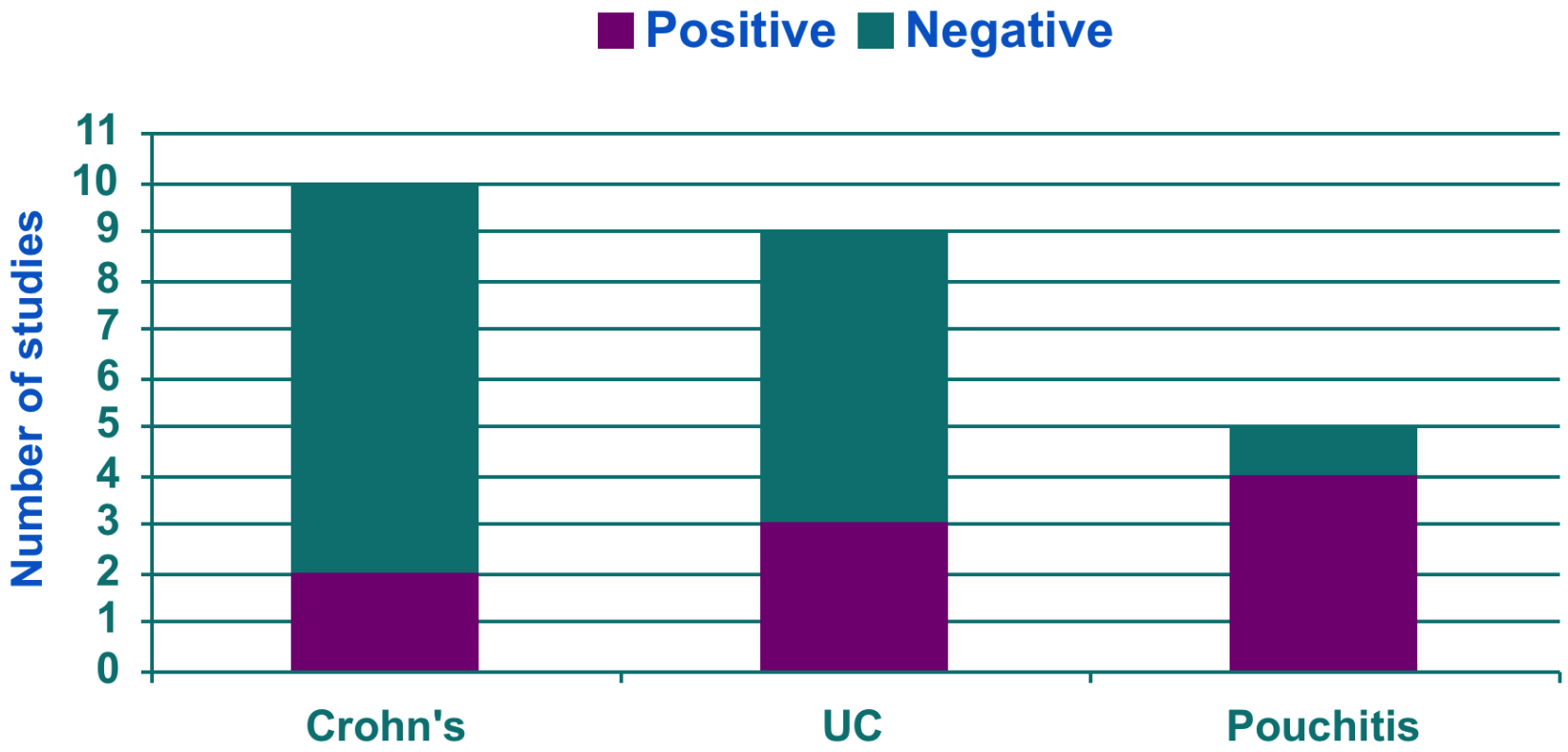
Germ-free, no colitis



GENOVA DIAGNOSTICS

Rath et al. *Infect Immun* 1999;67:2969-74

Summary of 25 RCTs of Probiotics for IBD



GENOVA DIAGNOSTICS

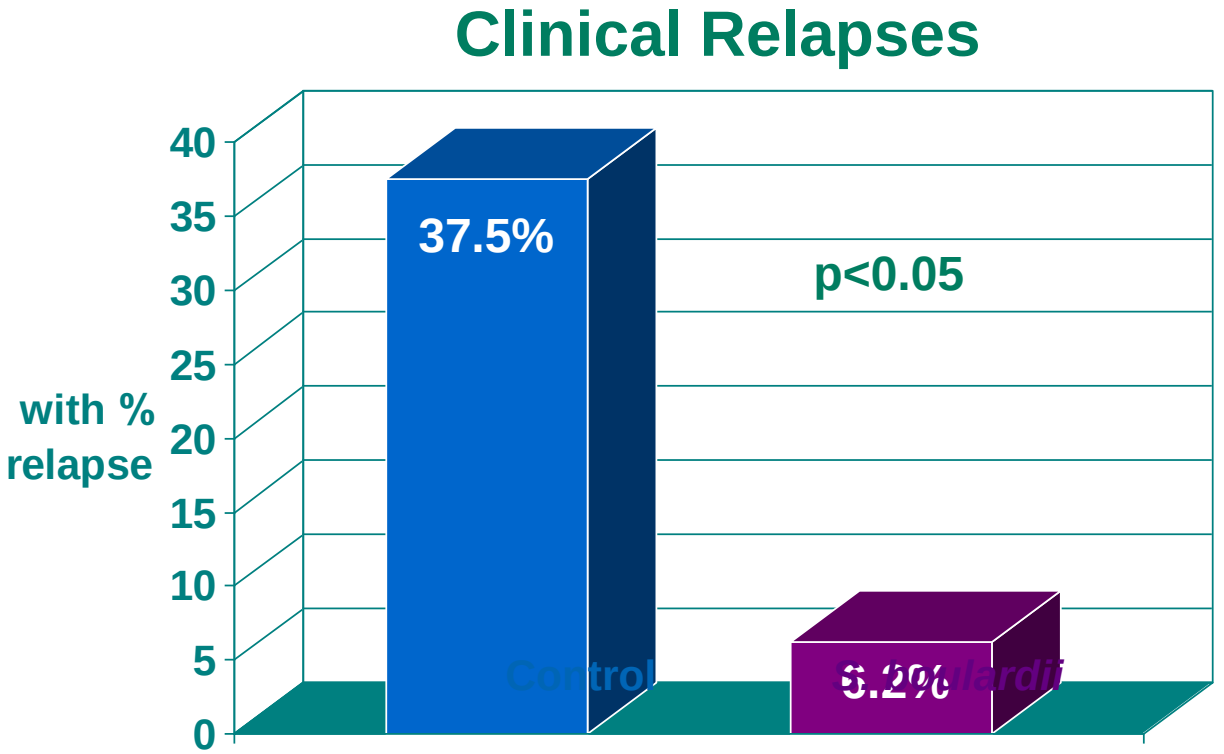
Hedin et al. *Proc Nutr Soc* 2007;66:307-15

Treatment of Crohn's Disease by *S. boulardii*

32 patients with CD in remission

Mesalamine (3 g/d) vs. mesalamine (2 g/d) & *S. boulardii* (2 x 10^{10}/d)

6 mos. Rx



GENOVA DIAGNOSTICS

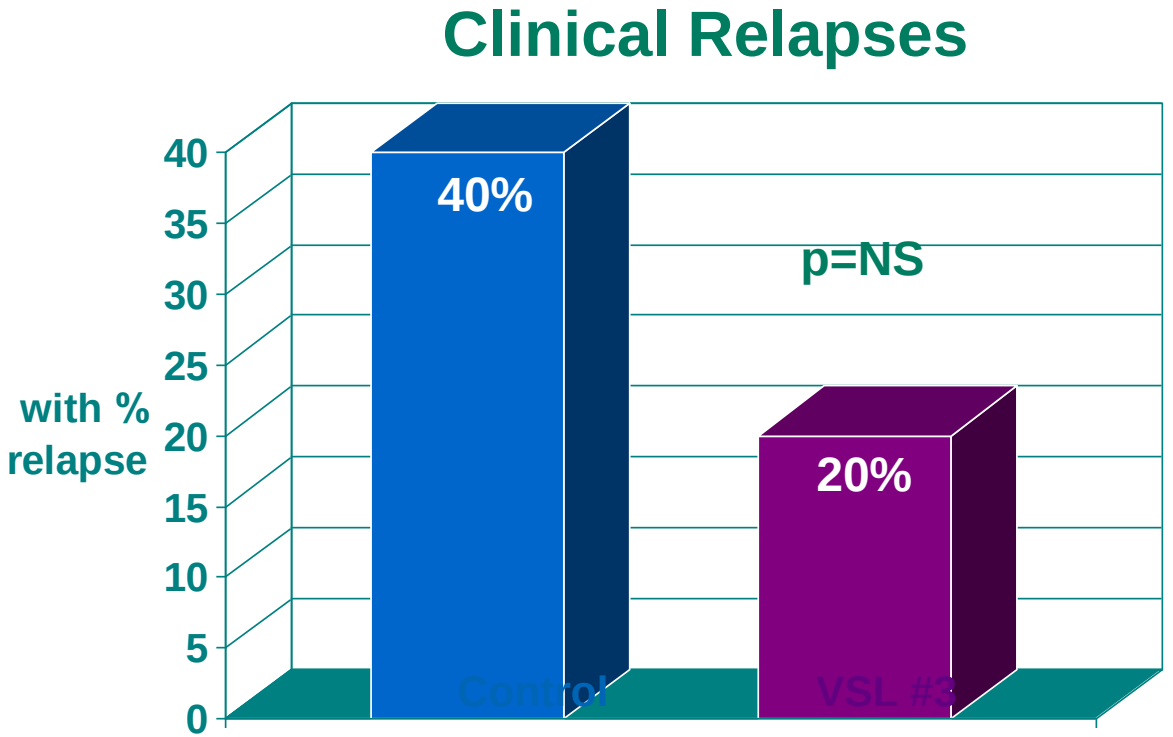
Guslandi et al. *Dig Dis Sci* 2000;45:1462-4

Prevention of Post Operative Crohn's Disease by VSL #3

40 patients with CD in remission

Mesalamine (4 g/d) vs. VSL #3 (3 x 10^{11}/d) after rifaximin

9 mos. Rx



GENOVA DIAGNOSTICS

Compieri et al. *Gastroenterol* 2000;118:A781

Treatment of Pouchitis by VSL #3

Gionchetti 2000

- 40 adults (2 x 10^{12} CFU/d)

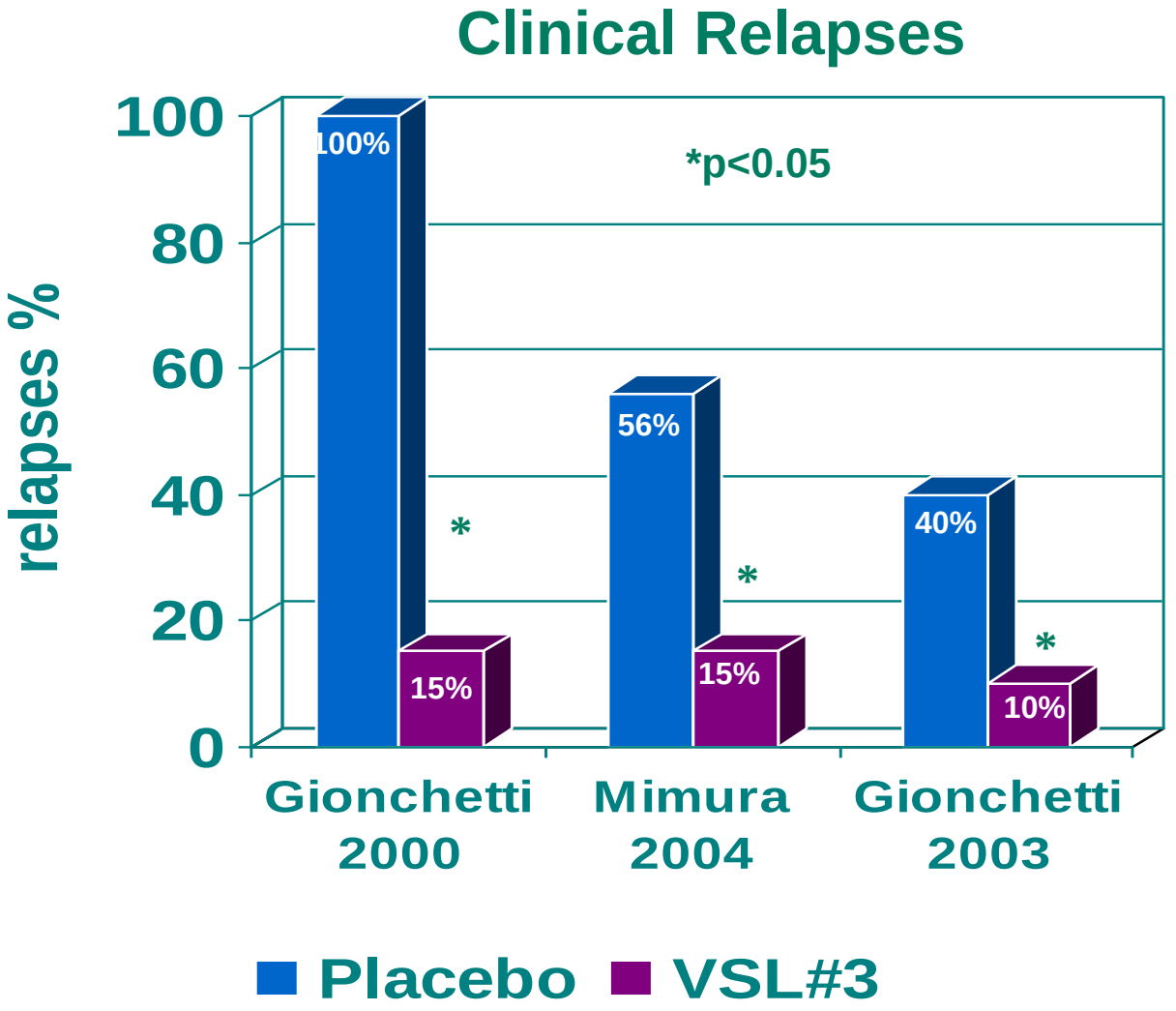
Mimura 2004

- 36 adults (3 x 10^{12} CFU/d)

Gionchetti 2003

- 40 adults (9 x 10^{11} CFU/d)

Followed for relapses
(9-12 months)



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Prebiotic Trials in IBD

Design	Substrate	Dose	Methods	Results	References
DBRCT	Inulin	24 g/d	Ileal pouch-anal anastomosis. Pts. (20) with pouchitis randomized for 6 wks & assessed clinically, endoscopically & histologically	Inulin lowered pH, increased butyrate, reduced *B. fragilis*, decreased inflammation, & effectively treated pouchitis	Welters et al. *Dis Colon Rect* 2002;45:621-7
Open Label	Inulin/FOS	15 g/d	Pts. (10) with active Crohn's disease assessed clinically and by laboratory findings.	Significant clinical improvement. Increased *Bifidobacterium*. Increased DC TLR4 expression.	Lindsey et al. *Gut* 2006;55:348-55
DBRCT	Inulin/FOS + *B. longum* $2x10^{11}$/d	6 g/d	Pts. (18) with active ulcerative colitis randomized for 1 mo. & assessed clinically, sigmoidoscopically & histologically	Significant clinical improvement. Improved sigmoidoscopy scores. Decreased tissue infllammation. Increased healing.	Furrie et al. *Gut* 2005;54:242-9

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Probiotics, Prebiotics & IBD

- Crohn's Disease
  - –Use Saccharomyces boulardii 10 B CFU/d
  - –3 mos on/1 mo off indefinitely
  - –Inulin-based prebiotics 6-15 g/d
  - –Multispecies probiotics (200-400 B CFU/d)
- Ulcerative colitis
  - –Use Saccharomyces boulardii 10 B CFU/d
  - –Multispecies probiotics (400-800 B CFU/d)
  - –Inulin-based prebiotics 6-15 g/d
- Pouchitis
  - –Multispecies probiotics (200-400 B CFU/d)
  - –Inulin-based prebiotics 6-15 g/d

Irritable Bowel Syndrome (IBS)

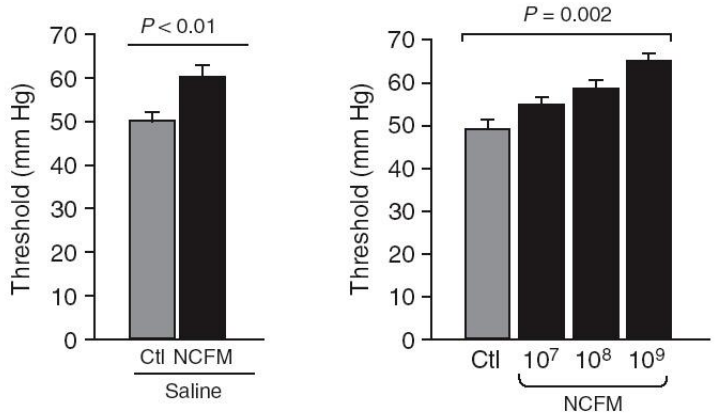
- Common (10-20% adults) benign disorder(s)
- Abdominal pain, bloating, diarrhea/constipation
- Intestinal transit disturbances
- Heightened visceral sensitivity
- Altered GI microbiota
  - –Decreased *Lactobacillus, Collinsella*
  - –Increased *Clostridium, Ruminococcus, Veilonella*

Lactobacillus acidophilus & Gut Pain

NATURE MEDICINE VOLUME 13 | NUMBER 1 | JANUARY 2007

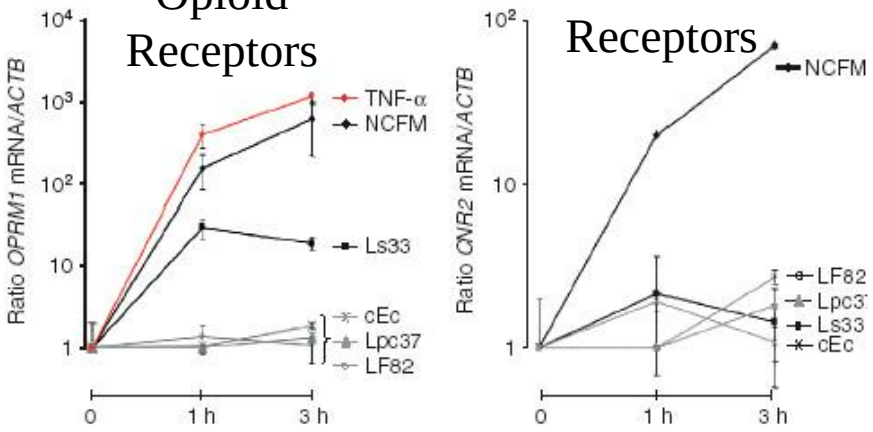
Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors

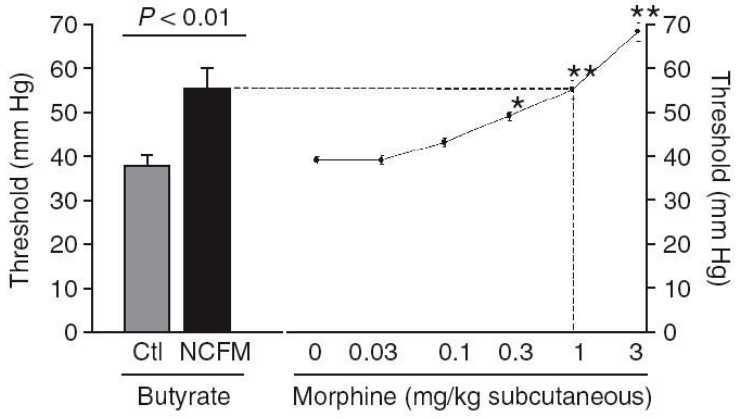
Christel Rousseaux[1–3], Xavier Thuru[1–3,10], Agathe Gelot[4–6,10], Nicolas Barnich[7], Christel Neut[1–3], Laurent Dubuquoy[1–3], Caroline Dubuquoy[1–3], Emilie Merour[1–3], Karen Geboes[8], Mathias Chamaillard[1–3], Arthur Ouwehand[9], Greg Leyer[9], Didier Carcano[9], Jean-Frédéric Colombel[1–3], Denis Ardid[4–6] & Pierre Desreumaux[1–3]



Opioid Receptors

Cannabinoid Receptors





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Meta-analysis of Probiotics & IBS

- 19 RCTs; 1650 Pts
- Probiotics significantly better than placebo
- RR =0.71 (95% CI 0.57-0.88)
- NNT = 4 (95% CI 3-12.5)
- Efficacious organisms/formulas
  - *Bifidobacterium infantis*
  - *Lactobacillus plantarum*
  - High-dose, multispecies formula
- Difficult population to study

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Moayyedi et al. Gut 2010;59:325-32

Probiotics & IBS

- High-dose (200-400 B CFU/d) multispecies probiotic
- Consider inulin-based prebiotic 10-15 g/d
- If there is a response, indefinite therapy
- Assess for food allergies/sensitivities
- Rule out gluten sensitivity
- Consider digestive enzymes

Allergies, Asthma & Dermatitis

- Pandemic effecting >20% of world's population
- Incidence of asthma ↑ by 50% from 1980 to 2000
- Related to post industrial lifestyle (Old Friends)
- Altered GI microbiota is implicated

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Probiotics Inducing Immunotolerance

- *L. casei*
- *L. bulgaricus*
- *L. paracasei*
- *L. rhamnosus*
- *B. bifidum*
- *B. breve*
- *S. thermophilus*

T cell & dendritic cell

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Probiotics & Atopic Dermatitis/Eczema

- 10 RCT
- 90% show significant reduction in incidence/severity
- Effective at prevention when given to pregnant women
- Effective given to breast-feeding women
- Effective given to infants in formula
- Protection up to 4 (RR=0.57) & 7 yrs (RR=0.64)
- Probiotics shown to be effective
  - *L. rhamnosus, L. acidophilus, B. lactis, L. reuteri*
  - Combination formulae effective

Probiotics & Allergic Rhinitis

- Probiotics reduce Sx & improve QOL measures
- Probiotics shown to be effective
  - *L. bulgaricus, L. paracasei, S. thermophiles*
  - Combination formulae effective

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Prebiotics & Allergies

- GOS & oligofructans increase regulatory T cells
- Prebiotics upregulate sIgA
- GOS/oligofructans ↓ atopic dermatitis in infants
- GOS/oligofructans ↓ allergies to cow's milk
- GOS/oligofructans ↓ allergies, eczema & wheezing up to 18 mos post Rx
- beta-Glucans (1→3; 1→6) reduce allergic rhinitis
- beta-Glucans (1→3; 1→6) reduce IgE levels

Prebiotics, Probiotics & Allergies

- Consider pre- & probiotics for pregnant women
  - Multispecies, broad spectrum 50-100 B CFU/d
- Consider low D(-)-lactate probiotics for infants
  - Multispecies Infant Formula 10-20 B CFU/d; doses up to 110 B CFU/Kg safe
- Consider GOS/beta-glucan for bottle-fed infants
  - Use 225-550 mg/d until weaned
- Multispecies, broad spectrum for children & adults
  - 50-100 B CFU/d indefinitely if response
- GOS/beta-glucans for children & adults
  - 5-10 g/d indefinitely if response

Probiotic Formulation Selection

- Monostrain probiotics
- Multistrain probiotics
- Multispecies probiotics
- Protocooperation & synergism
- ? antagonisms among species - no evidence
- Efficacy of multispecies formulation for ADD, IBS, URI, UC & pouchitis

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Chapman et al. *Eur J Nutr* 2011;50:1-17

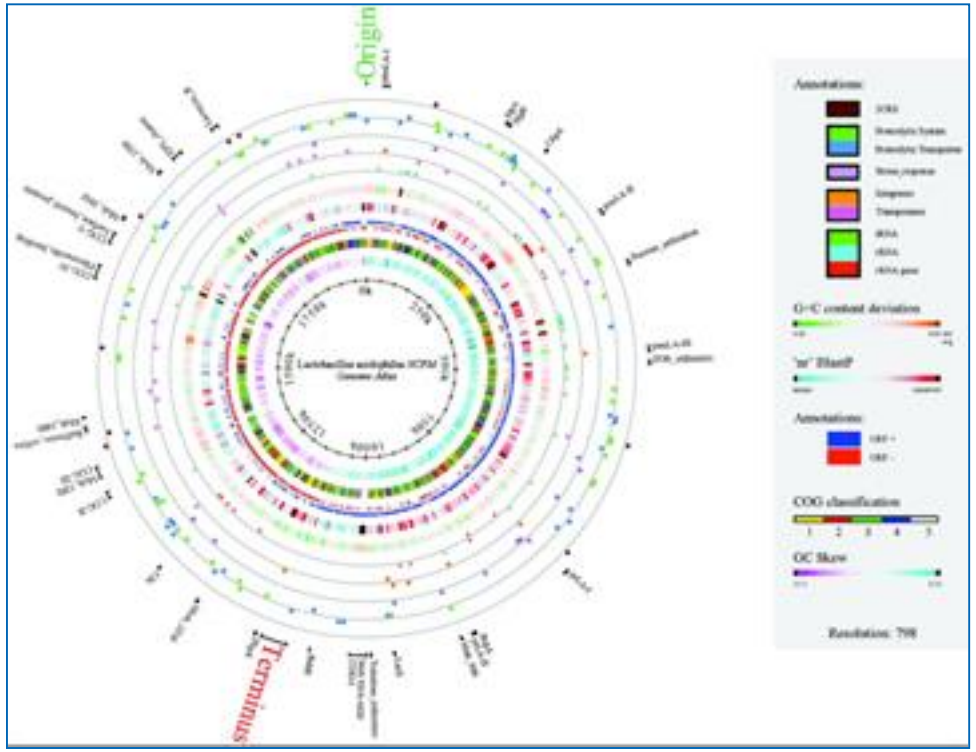
Are Probiotic Benefits Strain-specific?

- Strain-specific benefits a marketing claim
- Uncritically echoed by academics & regulators
- Validity requires head-to-head studies - Rare
- *L. rhamnosus* GG has unique pili
- Pili not linked to clinical benefit
- Multiple strains & species have benefit in studies
- Toxicity definitely strain-specific

Lactobacillus acidophilus Gene Sequencing

No significant differences between patented *L. acidophilus* NCFM & *L. acidophilus* La-14

- –Genome 99.98% identical
- –Single 416-bp deletion in ABC transporter
- –16 single-base pair indels
- –95 SNPs



L. acidophilus NCFM Genome

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Stahl. *Genome Announc* 2013;1:e00376-13

Probiotic Dosing

- Start low – 10-25 billion CFU/d
- Go slowly – increase dose weekly or as tolerated
- Minimizes gas, abdominal discomfort, diarrhea

Probiotic Dosing

With or without food?

Stomach pH: fasting: 0.8 – 1.5

with food: 5 – 7

Transit time: 30 min – 1 hr

Take with food.

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Probiotic Safety

- Daily doses >1 trillion CFU safe in adults;

  110 billion CFU/Kg in infants
- *Lactobacillus* bacteremia rare; usually endogenous
- *Bifidobacteremia* only in bowel perforation or PID
- *S. boulardii* fungemia in Pts w/ CV catheters
- Probiotics safe in immunosuppressed patients
- Probiotics safe in hospitalized & surgical patients

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Snydman. *Clin Infect Dis* 2008;46 Suppl 2:S104-11

Conclusions: Modulating the Gut Microbiome
The Role of Prebiotics & Probiotics

- Use of multispecies probiotics supported for a variety of GI conditions
- Use of S. boulardii supported for AAD, CDAD, IBD, & traveler's diarrhea
- Use of multispecies probiotics supported for prevention & treatment of allergic disorders
- Prebiotics show benefit for IBD and allergies
- Clinical trials to document formulation efficacy
- Outcomes studies - aging, cancer prevention

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Moderator:
Michael Chapman, ND

Presenter:
Stephen Olmstead, MD

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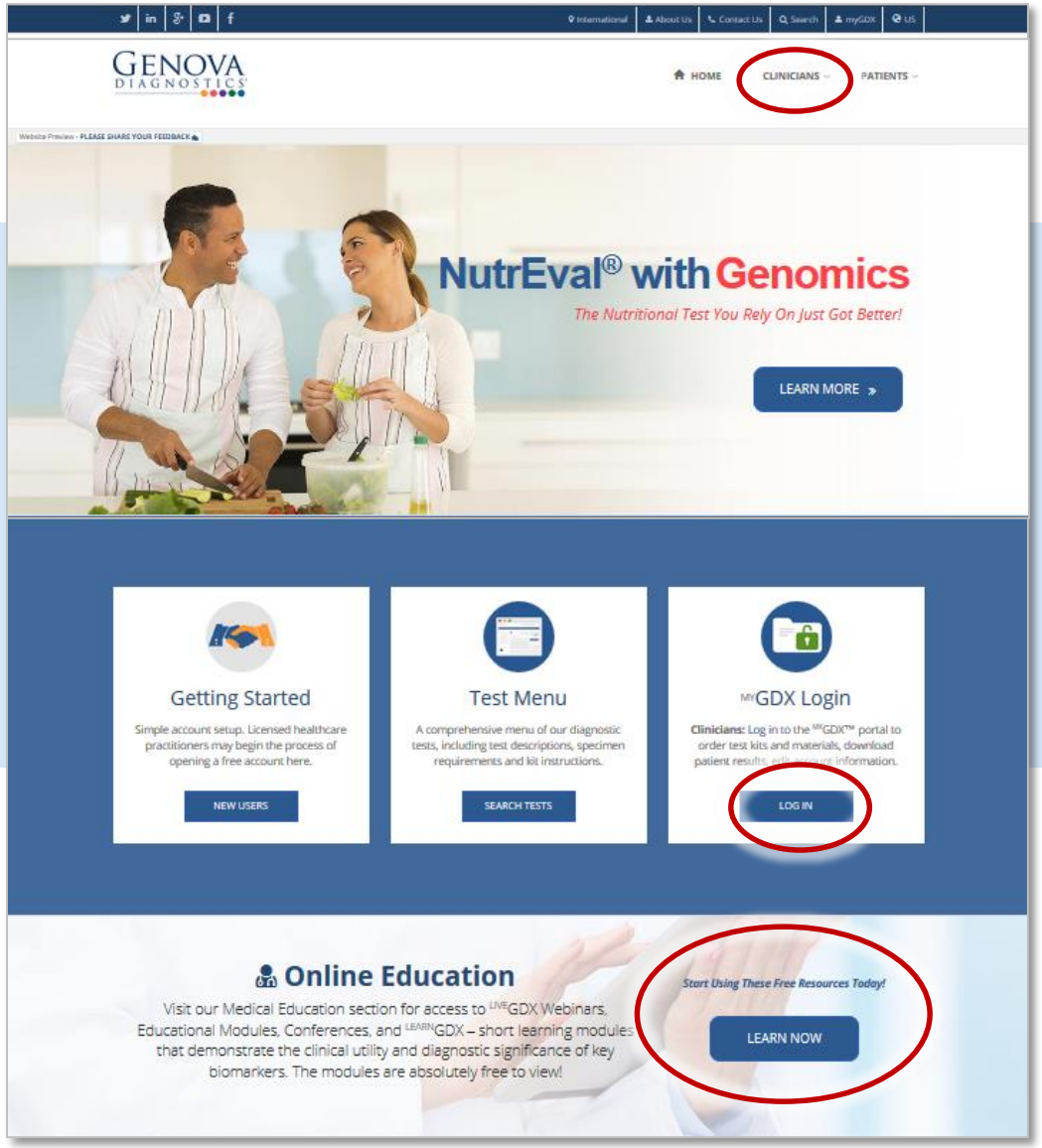

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Additional Questions?

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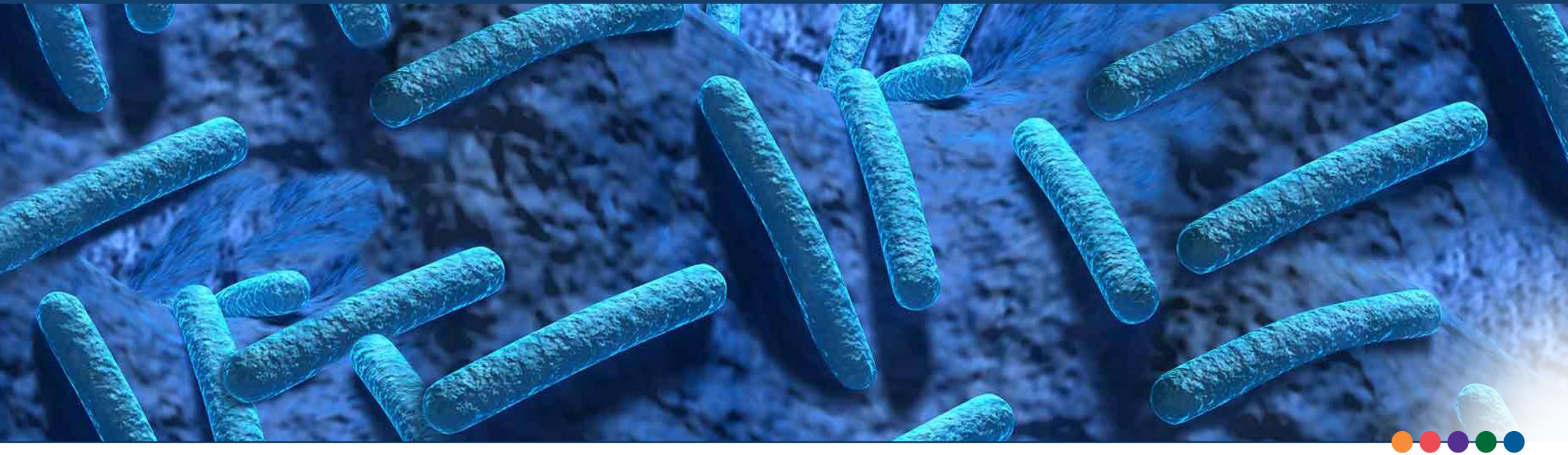

Modulating the Gut Microbiome: The Role of Probiotics & Prebiotics

Presented by:
Stephen Olmstead, MD