Biotics: Pre-, Pro, Syn- and Antibiotics

Biotics refers to Bacteria

*Staphylococcus aureus*
Nomenclature & Definitions

Microorganism: Largely unicellular organisms that need optical magnification to be seen

Procaryotic: Organisms like bacteria which lack a membrane-defined nucleus. DNA “free” in the cytosol

Eucaryotic: Protozoans and all multicellular life forms that possess a nucleus surrounded by a membrane that contains genomic DNA in the form of “interrupted genes”, i.e. introns and exons.

Plasmids, Mitochondria, Chloroplasts etc: Self-replicating “organelles” in cells that contain their own DNA which is separate from nuclear DNA

Biotics: A term that is functionally equivalent to “bacteria”
   Probiotics: Viable microorganisms, given in sufficient amounts (10^8 -10^10 daily) that reach the intestine in active form and exert a positive health effect.
   Prebiotics: A food source especially for the existing microbiome and for probiotics
   Synbiotics: A therapeutic mixture of pre- and probiotics
   Antibiotics: Substances especially made by bacteria and fungi, that kills or arrest the growth of other bacteria
   Microbiome: The ecological community of bacteria that lives on and within us
Life on Earth Belongs to Three Supergroups

Bacteria (Eubacteria & Archea) are Procaryotic Organism

Eubacteria and the Archea account for >98% of all species and 85% of the world biomass

60% of the planet is marine and therefore harbors the majority of the world’s bacteria and biomass

A column of ocean in the Marianas contains $10^{30}$ microbes with a biomass equal to 240 billion African elephants

Eucaryotes (Eucarya) were late comers and comprise a small fraction of the world biomass
Eucaryotes and Vertebrates Arrived Late in the Development of Life on Earth

For ~4 billion years autotrophs that were able to derive energy from $\text{H}_2$, $\text{S}$ and $\text{CO}_2$, were the dominant life forms.

Full oxygenation, aerobic Eubacteria 2.4 Ga; 4:40 AM

Photosynthesis 3.2 Ga; 2:29 AM

Archea 3.8 Ga; 0:20 AM

Anaerobic Eubacteria 3.6 Ga; 1:12 AM

Life on Earth in Billions of Years

Hominoids 11:58 PM

Land vertebrates 11:25 PM

Mammals 11:50 PM

Land plants 0.45 Ga; 10:35 PM

Fishes 0.52 Ga; 10:30 PM

Multicellularity 1.7 Ga; 6:55 PM

Unicellular eucaryotes 1.8 Ga; 6:36 PM
Life on Earth Built a Pyramid Four Billion Years before the Egyptians

- Vertebrates
- Terrestrial Plants & Animals
- Mutualism
- Rise of Symbiosis
- Archeobacteria (Archea) (Autotrophs)
- Multicellular (Eucaryotic) Aquatic
- Anaerobic

- Marine
Humans are a mobile ecosystem of bacteria, viral DNA and eukaryotic cells that share a common chemistry

Human and other life forms are linked by their use of nucleic acids, e.g. DNA
- DNA directs all the systems that control/regulate life on earth
- Replication of DNA allows for traits to be passed from one generation to the next

All life forms build structures and mediate their metabolism through the use of proteins
- Proteins provide the building blocks for structural features of life
- The regulatory elements that control the actions of DNA are proteins
- The enzymes that control metabolism, e.g. enzymes, are proteins

Humans and bacteria share > 90% of their genes
- The mechanisms for DNA (gene) replication found in bacteria is retained in higher life forms
- Phage and viral DNA is incorporated into the genome of bacteria and higher life forms
- Bacterial and eukaryotic cells carry self-replicating organelles for certain functions

Niel deGrosse Tyson (astrophysicist): “More bacteria live and work in your colon than the sum of all humans ever born”
The Gut Microbiome Evolved from Commensals to Mutualists

Humans harbors $10^{14}$ bacteria of ~1000 species in their gut, i.e. the Gastro-Intestinal Tract (GIT) microbiome. [Punn intended: “Git up and Go”]

That means 2 bacteria for each human cell

The human microbiome weighs 3 lbs or about the same as the brain

60% of your feces is your microbiome [The “Go” in git up and Go]

Commensals utilize nutrients and do no harm

Pathobionts are harmful to the host, cause disease and tissue damage.

Most members of the GIT microbiome are mutualists that thrive in a nutrient-rich environment and provide critical metabolites for the host.

The human host provides:
- Shelter from dessication and a stable temperature and pH
- A continuous supply of food for all members of the microbiome
- Attachment sites that are critical for the survival of some microbiome members
What does the Gastrointestinal (GIT) Microbiome do for the host?

**Nutrient value of GIT mutualists**
- The GIT microbiome generates vitamins B and K
- Certain bacteria convert complex polysaccharides into short-chain fatty acids (SCFA) that are required to maintain the integrity of the gut epithelium
- Ruminant mammals, cockroaches, termites and many others, are almost entirely dependent on the GIT microbiome for their nutrition

**Protective value of GIT mutualists**
- “Competitive exclusion” or “colonization resistance” prevents pathobionts from dominating the gut ecosystem
- Mutualists secrete anti-microbial (antibiotics) like bacitracin that kills or inhibits the growth of pathobionts
- Surface colonization and “quorum sensing” provides inter-bacterial communication that adjusts and maintains a barrier that discourages pathogens
- The microbiome keeps the GIT in a state of “controlled inflammation”, i.e. the host immune system is in a state of readiness
### Bacterial Diversity

#### Stem Procaryote

- **Archaebacteria** ([Archaea](#))
- **Eubacteria** [“Bacteria”](#)

#### Gram Positive
- **Aerobic**
- **Faculative Anaerobes**

#### Gram Negative
- **Aerobic**
- **Anaerobic**
- **Faculative Anaerobes**

#### Shape
- **Rods**
- **Cocci**
- **Spiral**

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<thead>
<tr>
<th>Common Example</th>
<th>Genus</th>
<th>Disease</th>
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<td>Gram positive cocci</td>
<td><em>Staphylococcus</em></td>
<td>Wound and urinary infection</td>
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<td></td>
<td><em>Streptococcus</em></td>
<td>Bacterial pneumonia</td>
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<tr>
<td>Gram positive rod</td>
<td><em>Mycobacterium</em></td>
<td>Tuberculosis</td>
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<td></td>
<td><em>Clostridium</em></td>
<td>Tetanus, Botulism, Colitis</td>
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<td>Intracellular Gram positive rod</td>
<td><em>Listeria</em></td>
<td>Meningitis</td>
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<td>Gram negative aerobic rod</td>
<td><em>Bordetella</em></td>
<td>Whooping cough</td>
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<td>Gram negative facultative rod</td>
<td><em>Salmonella</em></td>
<td>Typhus, food poisoning</td>
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<td><em>E. coli</em></td>
<td>Diarrhea</td>
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<td>Gram negative spiral</td>
<td><em>Borrelia</em></td>
<td>Lymes disease</td>
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<td><em>Treponema</em></td>
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<td><em>Helicobacter</em></td>
<td>Gastric ulcers</td>
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The History of Probiotics: From “Yaks to Yogurt”

4000 BC  Abraham owed his longevity to sour milk (Genesis 18:8)

76 BC  Plinius recommended fermented milk for gastritis

1907  Metchinikoff (“father of cellular immunology”) suggested fermented milk (Lactobacillus) could ameliorate the “negative effects” of gut flora

1921  Lactobacillus acidophilus can restores the positive effect of “healthy gut flora”

1953  Kollath first coined the word “probiotics” as “being necessary for life”

1965  Lilly & Stillwell: Probiotics made antibiotics that encouraged growth of other bacteria

1992  Currently accepted definition of probiotics by Havenaar et al (refer to slide #2)

1995  First definition of prebiotics (Gibson and Roberfroid)
Growth of the Probiotics Industry

A 10 billion dollar industry in 2000 has grown to 48 million in 2017
Japan has been the leader with > 300 firms
The probiotic soft drink (Bikkle) launched in 1993 achieved 11 billion in sales in 2015
Highest future growth is expected in China, India and Japan
Europe has been the world’s largest market and 250 million kg of yogurt were produced in 1997
After 2000 the rate of publications increased faster than the experiments that supported them!

“Vertrauen ist gut aber Kontroll ist besser”
Probiotics: 21st Century Wonder Drug Re-discovered?

Probiotics claim to resolve/reduce > 20 human maladies from diarrhea to cancer and multiple sclerosis (MS).

Diarrhea

Helicobacteria pylorus

Increase in Anti-allergic Cytokines

Decrease in frequency of “common cold”
Prebiotics Provide the Nutrients for Probiotics and the Resident GIT Microbiome

Prebiotic strategy

Control or modify the GIT microbiome by starving “bad” bacteria and nourishing “good” bacteria
[“Good” versus “Bad” bacteria will be discussed in Session 2]
Giving a nutrient favored by probiotics will expand their populations and increase their residency in the GIT
Giving both probiotics and prebiotics is called a “Synbiotic”

What is a prebiotic?

An undigestable carbohydrate, i.e. dietary fiber, like inulin found in e.g. gava fruit, chicory and Jerusalem artichoke
Nutrients fermented by “good” bacteria such as Bifidobacteria and Lactobacillus. Some call them “bifidogenic”
A health food store product or something promoted on the internet, which is of undefined composition

Prebiotics have differential effects

Each human volunteer responded differently
Not all strains of Bifidobacteria and Lactobacillus respond [not shown]
Inulin also feeds Faecalbacteria prausnitizii that is associated with colorectal cancer
Infants are generally the most consistent responders [not shown]
Proposed Mechanisms for the Action of Prebiotics

Short chain fatty acids (SCFA) produced by fermentation of e.g. inulin, have defined effects
- Increase the height of villi and depth of the crypts creating a more absorptive mucosa
  [Note: The gut anatomy will be described in Session 2]
- Strengthen tight junctions and thus prevent intestinal leakage, i.e. improve barrier function
- Increase secretion of mucous and the thickness of the mucosal barrier

Prebiotics shift the composition of the microbiome to favor lactic acid bacteria (Lactobacillus) which lowers the pH and thus favors Firmicutes that produce butyrate and other SCFA

Comments by European Food Safety Authority say:
Since < 2% of the GIT microbiome can be cultured and studied, “all bets are off” regarding their actual role.
Inulin and other prebiotics may act independently from the GIT microbiome
Prebiotics are best targeted to infants in which the importance of Bifidobacteria has been more firmly studied.

[ Session 3: Dr. Ziegler]