Human Microbiome

The microbes (such as bacteria, fungi and viruses) that live inside and on our body
Microbiome

IN NUMBERS

100 Trillion symbiotic microbes live in and on every person and make up the human microbiota.

95% of our microbiota is located in the GI tract.

150:1 The genes in your microbiome outnumber the genes in our genome by about 150 to one.

The human body has more microbes than there are stars in the milky way.

The surface area of the GI tract is the same size as 2 tennis courts.

You have 1.3X more microbes than human cells.

>10,000 Number of different microbial species that researchers have identified living in and on the human body.

2kg The gut microbiota can weigh up to 2Kg.

The gut microbiota can be viewed as the body's second genome.

90% of disease can be linked in some way back to the gut and health of the microbiome.

Viruses:Bacteria in the gut microbiota: 5:1

2.5 The number of times your body's microbes would circle the earth if positioned end to end.

Each individual has a unique gut microbiota, as personal as a fingerprint.
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Interfacing Food & Medicine

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HOW GUT BACTERIA AFFECTS THE BRAIN AND BODY

DEPRESSION
More than a third of depression sufferers have “leaky gut,” or permeability of the gut lining that allows bacteria to seep out into the bloodstream.

SCHIZOPHRENIA
Studies in mice have linked a lack of normal gut bacteria with changes in brain development, but the genetics of the disorder are complex and not fully understood.

OBESITY & DIABETES
A number of studies have linked instability in the gut microbiome to obesity and obesity-related health problems.

COLON CANCER
Sugar-loving microbes in the gut — along with the carbs that feed them — can fuel colon cancer. High carb-diets may even be contributing to the rise of colon cancer.

RHEUMATOID ARTHRITIS
Studies have found a link between low levels of certain good gut bacteria, high levels of unhealthy Prevotella copri bacteria, and autoimmune joint disease.

ANXIETY
Prebiotics can have anti-anxiety and antidepressant effects. Consuming beneficial bacteria can also positively change the way the brain responds to the environment.

AUTISM
Autism often co-occurs with gastrointestinal issues like leaky gut or irritable bowel syndrome.

PARKINSON’S DISEASE
People suffering from this disease have different gut bacteria than healthy people.

CROHN’S DISEASE
Abnormally high levels of certain bacteria strains may be present when Crohn’s Disease develops, possibly triggering an atypical immune response.

ULCERATIVE COLITIS
Imbalances in gut flora may be a main factor in both the onset and continuing symptoms of ulcerative colitis.

IRRITABLE BOWEL SYNDROME
There is a definitive link between IBS and an overgrowth of bacteria in the small intestines.
Gut bacteria associated with allo-HCT outcomes

Causes of Death after allo-HCT

- Organ Toxicity
- Infection
- GVHD
- Relapse

Schematized from CIBMTR Summary Slides
Gut bacteria associated with allo-HCT outcomes

Adapted from Taur 2016
Gut bacteria associated with allo-HCT outcomes

- **Clostridia**
  - Increased indoxyl sulfate; reduced mortality
  - Reduced indoxyl sulfate; increased mortality
  - More GVHD
  - Stein-Thoeringer 2019

- **Bacteroidetes**
  - Increased overall survival
  - Taur 2014

- **Proteobacteria**
  - Decreased GVHD
  - Jenq 2015
  - Increased overall survival
  - Taur 2012
  - Protection against Enterococcus domination
  - Ubeda 2013

- **Firmicutes**
  - Decreased relapse
  - Peled 2017
  - Increased indoxyl sulfate; and reduced mortality
  - Holler 2014

Adapted from Taur 2016
Microbiota as Predictor of Mortality in Allogeneic Hematopoietic Cell Transplantation


Duke

Anthony Sung
Nelson Chao

Hokkaido University

Daigo Hashimoto
Takanori Teshima

University Hospital Regensburg

Ernst Holler
Daniela Weber

Memorial Sloan Kettering Cancer Center

Jonathan Peled
Antonio Gomes
8,691 samples from 1,361 HCT recipients from 4 international transplantation centers

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>MSKCC</th>
<th>Regensburg</th>
<th>Duke</th>
<th>Hokkaido</th>
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</thead>
<tbody>
<tr>
<td><strong>N = 1361</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSKCC</td>
<td>1121 (82.4)</td>
<td>1121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regensburg</td>
<td>76 (5.6)</td>
<td></td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duke</td>
<td>98 (7.2)</td>
<td></td>
<td></td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Hokkaido</td>
<td>66 (4.8)</td>
<td></td>
<td></td>
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### Disease (%)

<table>
<thead>
<tr>
<th>Disease</th>
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</thead>
<tbody>
<tr>
<td>AML</td>
<td>496 (36.4)</td>
<td>390 (34.8)</td>
<td>41 (53.9)</td>
<td>33 (33.7)</td>
<td>32 (48.5)</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>242 (17.8)</td>
<td>208 (18.6)</td>
<td>8 (10.5)</td>
<td>19 (19.4)</td>
<td>7 (10.6)</td>
</tr>
<tr>
<td>NHL</td>
<td>207 (15.2)</td>
<td>182 (16.2)</td>
<td>12 (15.8)</td>
<td>8 (8.2)</td>
<td>5 (7.6)</td>
</tr>
<tr>
<td>ALL</td>
<td>129 (9.5)</td>
<td>100 (8.9)</td>
<td>6 (7.9)</td>
<td>8 (8.2)</td>
<td>15 (22.7)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>111 (8.2)</td>
<td>99 (8.8)</td>
<td>3 (3.9)</td>
<td>8 (8.2)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>other</td>
<td>77 (5.7)</td>
<td>61 (5.4)</td>
<td>0 (0.0)</td>
<td>13 (13.3)</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>CLL</td>
<td>33 (2.4)</td>
<td>30 (2.7)</td>
<td>3 (3.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>31 (2.3)</td>
<td>27 (2.4)</td>
<td>0 (0.0)</td>
<td>4 (4.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CML</td>
<td>29 (2.1)</td>
<td>24 (2.1)</td>
<td>1 (1.3)</td>
<td>3 (3.1)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>AA</td>
<td>5 (0.4)</td>
<td>0 (0.0)</td>
<td>2 (2.6)</td>
<td>2 (2.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>1 (0.1)</td>
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<td>0 (0.0)</td>
<td>1 (1.5)</td>
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### Graft Source (%)

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<tbody>
<tr>
<td>BM unmodified</td>
<td>112 (8.2)</td>
<td>85 (7.6)</td>
<td>11 (14.5)</td>
<td>10 (10.3)</td>
<td>6 (9.1)</td>
</tr>
<tr>
<td>cord</td>
<td>217 (16.0)</td>
<td>187 (16.7)</td>
<td>0 (0.0)</td>
<td>16 (16.5)</td>
<td>14 (21.2)</td>
</tr>
<tr>
<td><strong>PBSC T-cell Depleted</strong></td>
<td>450 (33.1)</td>
<td>450 (40.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>PBSC unmodified</td>
<td>581 (42.7)</td>
<td>399 (35.6)</td>
<td>65 (85.5)</td>
<td>71 (73.2)</td>
<td>46 (69.7)</td>
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### Conditioning Intensity (%)

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<tr>
<td>Ablative</td>
<td>763 (56.1)</td>
<td>615 (54.9)</td>
<td>10 (13.2)</td>
<td>91 (92.9)</td>
<td>47 (71.2)</td>
</tr>
<tr>
<td>Reduced Intensity</td>
<td>472 (34.7)</td>
<td>387 (34.5)</td>
<td>66 (86.8)</td>
<td>0 (0.0)</td>
<td>19 (28.8)</td>
</tr>
<tr>
<td>Nonmyeloablative</td>
<td>126 (9.3)</td>
<td>119 (10.6)</td>
<td>0 (0.0)</td>
<td>7 (7.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>sex = M (%)</strong></td>
<td>828 (60.8)</td>
<td>682 (60.8)</td>
<td>46 (60.5)</td>
<td>63 (64.3)</td>
<td>37 (56.1)</td>
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</table>
No apparent clustering of baseline samples by geography. Diversity declines with similar kinetics across centers.

Institutions
- MSK
- Regensburg
- Duke
- Hokkaido

Baseline samples (d-30 to d-6)

Simpson reciprocal

New England Journal of Medicine 382 (2020) 822-34

Patients
- Duke: 93
- Hokkaido: 66
- MSK: 97
- Regensburg: 10

Samples
- Duke: 31
- Hokkaido: 217
- MSK: 79
- Regensburg: 167
Low Intestinal Diversity at neutrophil engraftment is associated with decreased overall survival

Discovery Cohort (MSK)

Validation Cohort (Duke+Regensburg+Hokkaido)

Peled, NEJM 2020

stratified by above- and below-median Simpson Reciprocal Index in each cohort
single sample per patient, collected day 14 +/- 7
Factors that affect the intestinal microbiota composition

- Antibiotics
- Conditioning regimen
- Diet
- Other drugs
Therapeutic approaches targeting microbiota

**Antibiotics**
- Gut decontamination
- Rifaximin
- Commensal-sparing regimens
- Timing of initiation or discontinuation of prophylactic and empiric-fever treatments

**Postbiotics**
- Short-chain fatty acids (e.g. butyrate)
- Indole derivatives
- Avoidance of foods that compromise mucus barrier

**Prebiotics**
- Non-digestible carbohydrates
- Avoidance or encouragement of certain foods

**Probiotics**
- Faecal transplant
- Engineered microbes
- Rationally selected strains

*Peled et al. Nature Microbiology 2016*
Probiotic Therapy - History

• **Egypt 1500 BC**: Ebers papyrus, 50 medications containing feces

• **Italy 17th century**: Feces for GI disease in veterinary medicine

• **China 4th century**: Fecal suspension for food poisoning and diarrhea (*yellow soup*)

• **USA 1958**: Fecal matter transplant for *Clostridium difficile*
Elie Metchnikoff (1845-1916)

- Discovered phagocytes
- Established cell mediated immunity
- Nobel prize (1908) with Paul Ehrlich for “his work on Immunity”
- *The Prolongation of Life: Optimistic Studies*: life-lengthening properties of lactic acid bacteria *Lactobacillus*
- Drank sour milk every day
Probiotic Therapy

- $30 billion annual sales; mostly as food supplements (*Lactobacillus, Bifidobacterium*)
- Food supplements: regulated by FDA for proper branding and adulteration; no health claims
- Drugs: usual FDA rules for safety and efficacy
A gut microbe called Akkermansia muciniphila may help patients respond to certain cancer immunotherapy drugs. M. Derrien et al., *International Journal of Systematic and Evolutionary Microbiology*, 10.1099/ijs.0.02873-0, 2014

Your gut bacteria could determine how you respond to cutting-edge cancer drugs

By Jocelyn Kaiser | Nov. 2, 2017, 2:00 PM
Are probiotics making immunotherapy less effective?

Taking over-the-counter probiotic supplements correlated with a 70 percent lower chance of responding to checkpoint inhibitor immunotherapy.
Conclusions

• Changes in intestinal flora are associated with OS, lethal GVHD, bacteremia/sepsis, engraftment and relapse in allo-HCT patients

• Antibiotics/drugs, diet and conditioning regimens can affect flora changes
Funding

NIH:

- **NIA:** P01 AG052359-04
- **NHLBI:** R01 HL123340-06
  - R01 HL125571-05
  - R01 HL147584-02
- **NCI:** P01 CA023766-40  
  - P30 CA008748-54
  - R01 CA228308-03
  - R01 CA228358-03
- **NIAID:** U01 AI124275-05

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