“our second genome”

“microbiome”

“holobiont”

“human ecosystem”

“metagenome”

“microbial organ”

“good germs”

Lita M Proctor, NHGRI/NIH

September 25, 2019
What are microbes?

- often used to mean bacteria
- broader meaning: microscopic lifeforms
- many kinds (bacteria, archaea, viruses, bacteriophage, fungi, protozoa)
- in nature, key principles: don’t live alone, interact as communities
Society’s war against infectious disease
(bubonic plague, smallpox, scarlet fever, yellow fever, tuberculosis, malaria, diptheria, dysentery, leprosy, typhoid fever...)}
The majority (>99%) of microbes (bacteria, viruses, fungi) do not cause disease; many are beneficial. Microbes on Earth: ~1400 human pathogenic microbes vs. ~1 trillion microbial species on Earth.
43% human cells vs 39 trillion microbes

~20,000 human genes vs 2-20 million microbial genes

doi: 10.1371/journal.pbio.1002533
What do these microbial genes code for?

Many kinds of vitamins, anti-microbials, anti-inflammatory agents, neurotransmitters, signaling molecules, host energy sources, etc, etc.

But also, thousands of new-to-medicine microbial proteins…
Beneficial role(s) of non-bacterial members of microbiome

Bacteriophage

Eukaryotic viruses

Fungi

10-100X more phage than bacteria in gut microbiome

Phage embedded in gut mucous may provide a form of immunity for host

Non-pathogenic viruses being discovered

Flaviviruses may play role in improved survival from infections

Dozens of commensal fungi in microbiome

Some fungi may provide anti-inflammatory role
Gut-microbiome-brain axis & human health and disease

Gut microbiota modulate CNS:
- vagus nerve activation
- hormonal system
- immunological system

Brain-gut-microbiota linkages:
- stress factors
- gut permeability changes
- neurotransmitter release

ex. serotonin synthesis by gut cells depends on gut bacteria

doi:10.1016/j.cell.2015.02.047

Neurological/mental conditions: *epilepsy, autism spectrum disorders, Alzheimer’s, psychiatric disorders, Parkinson’s, schizophrenia, Multiple Sclerosis, etc*
Microbiota are acquired anew each generation.

1) Infants obtain inoculum from mother or environment.
2) Microbial succession over ~1-2 yrs of life.
3) Microbiome becomes “adult-like” in ~2-3 yrs of life.
Human milk oligosaccharides (HMOs)*:
1) microbial food for the developing microbiome
2) protects against invading pathogens

100s of different kinds of HMOs

HMOs as molecular decoys

[Breastmilk (per 100 mls): Proteins = 2.5 g, Fats = 5 g and *HMOs = 0.5 g]
Does microbiome developmental period start at birth or before, during gestation?
The human body matures into an ecosystem of microbial habitats.

Human Microbiome Project Consortium (2012a)
But the microbiome is mutable and naturally changes over our lifetimes.

Factors that may affect gut microbiota composition and diversity:
- Gestational health/diabetes
- Maternal dietary habits
- Pregnancy weight gain
- Antibiotics/drugs
- Probiotic/prebiotic
- Bacteria in amniotic cavity and placenta
- Lifestyle/Hygiene

Stages of life:
- Gestation
- Parturition
- Infancy
- Puberty
- Adulthood
- Old-age

Factors affecting microbiota:
- Dietary factors
- Geographic and environmental influences
- Hygiene
- Proximity with siblings, friends, pets etc.
- Probiotics, fermented foods
- Childhood illnesses/fever
- Drugs/antibiotics
- Malnutrition
- Food allergies

Diets and health conditions:
- Diet
- Lifestyle habits
- Old-age illnesses
- Type of disease
- Medication/drugs/antibiotics
- Probiotic/prebiotic
- Physical activities
- Traveling/relocation
- Sleep/depression
- Pregnancy
- Menopause
2000

- Human genome sequence announced
- Four (4) US Genome Centers
- Sequencing technologies improving
- Cost/genome begins dropping

2006/2007

- NIH Common Fund established
- Sequence the ‘other genome’
- HMP: $215M, 10-yr program
- Create research toolbox
Ten-year (FY2007-2016) Human Microbiome Project
$215M to build research ‘toolbox’ and network

HMP program goals

1) Develop research resources:
e.g. reference datasets, clinical & analytical methods, statistical & computational tools and pipelines

2) Rapidly release resources:
e.g. public repositories & community databases, HMP Data Analysis Coordination Center (DACC), GitHub & meetings/webinars
**HMP one**

- Characterize microbiomes
- Correlate with phenotypes

**Benchmark Healthy Cohort Study**

- Host genome
- Community composition
- Predicted pathways

“Who’s there?”

**Demonstration Projects (12)**

**HMP two**

- Transcriptomic profiles
- Metabolomic profiles
- Cytokine profiles
- Proteomic profiles
- Community composition
- Predicted pathways
- Epigenomic profiles
- Antibody profiles

**HMP DACC**

- Collection of papers (3 flagship and ~20 companion)

Published in *Nature* in 2019
HMP research toolbox

www.hmpdacc.org

HMP one
~10 Tb data (sequence)

HMP two
~30 Tb data (multi omic)
Microbiota and host *interact* to regulate human health.

✓ digests the ‘indigestables’
   (ex. plant material, host cells, mucous)
✓ ‘educates’ the immune system
✓ produces energy substrates
   (ex. SCFAs such as acetate)
✓ metabolizes drugs
✓ produces beneficial compounds
   (ex. vitamins, antimicrobials)
✓ communicates with the brain
✓ regulates organ development/function
Is the appearance of chronic disease related to changes in the microbiome?

Increase in immune disorders over last ~ 75 yrs

Bach (2002)
Blaser and Falkow (2009)

Postulated systematic loss of microbiota inocula each generation.

Is the appearance of chronic disease related to changes in the microbiome?

Contemporary practices:
- Excessive hygiene
- Caesarean birth
- Antibiotic overuse
- Processed foods/additives
- Formula feeding
- Hg amalgams
- Other factors?

![Graph showing changes in microbiome representation over time](image)
Microbiome diversity appears to be decreasing across populations and across generations.
HMP catalysed human microbiome research at NIH*

Microbiome(s) and disease(s)

NIH funds studies in 100+ classes of disease

**Neurological/mental:** epilepsy, Alzheimer’s, psychiatric disorders

**GI tract:** irritable bowel disease (IBD), ulcerative colitis, Crohn’s disease, GERD, necrotizing enterocolitis (NEC)

**Heart:** cardiovascular diseases

**Cancers:** Hodgkins’ lymphoma, liver, gastric esophageal, colorectal, cervical, breast

**Lungs:** asthma, cystic fibrosis

**Skin:** eczema, psoriasis, acne, rheumatoid arthritis

**Vagina/Uterus:** bacterial vaginosis, preterm birth

**Liver:** non-alcoholic liver disease (NAFLD), alcoholic steatosis

**Systemic:** Obesity, Type 1 and type 2 diabetes, lupus, multiple sclerosis, autism, etc.
Recent advances in human microbiome research
(postulated mechanisms of disease initiation/exacerbation)

✓ Environmentally-derived microbes (ex. dental caries)

✓ Commensal microbes becoming pathogenic (ex. IBD)

✓ Gut translocation of microbes or microbial products (ex. lupus)

Each mechanism will inform specific interventions.
Recent advances in human microbiome research

(microbiome-based biomarkers for disease risk)

✓ Gut bacteria/bacterial metabolites and obesity

✓ Bacterial epigenetic effects on colorectal cancer

✓ Bacterial metabolites and cardiovascular disease
Recent advances in human microbiome research
(microbiome-based interventions and products)

Microbiome-based therapeutic interventions

- Fecal microbiota transplantation
- Microbiome-derived microbial consortia
- Live biotherapeutic products
- Therapeutic bacteriophage
- Microbial augmentation of treatment

Mining the microbiome for new pharmaceuticals (microbiome-based interventions and products)

- Anti-microbials
- Anti-inflammatory
- Prebiotics
- Enzymatic cofactors
- Neurotransmitter active compds
Gaps/challenges in human microbiome research

model system(s)?

cause or effect?

microbiome = organ system?

interventions for health?

role of host genetics?
Microbiome Centers (not all focused on human)

36+ Microbiome Centers around the country

Microbiome Centers Consortium (MCC) under development:
1st workshop: UC Irvine, June 25-26, 2019
(white paper upcoming in Nature Microbiology)

2nd workshop: Univ Chicago, May 16-17, 2020

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Growth of microbiome research and centers has just begun.
How can HRA engage?
Proposed HRA Cross-Cutting Initiatives

1. Create National Microbiome Cohort Registry

   I. Create National Microbiome Cohort Registry

1. Create a cohort registry for ongoing and upcoming cohort studies which could incorporate a microbiome component.

2. Establish a stool/tissue biobank from cohort studies which already include a microbiome component.
Proposed HRA Cross-Cutting Initiatives

II. Spearhead Standardization Efforts for Microbiome Datasets

• microbiome standards (mixed DNA, proteins stds)
• technology comparisons
• cross-lab blinded ‘round robins’
• ‘Maniatis-style’ manual of microbiome methods

Goal: curation of gold-standard publically-accessible clinical research datasets

‘Rosetta Stone’ for the microbiome
Proposed HRA Cross-Cutting Initiatives

III. Support Microbiome Technology Development & Innovation

Analytical

• blood microbiome protocol
• room temp protocols for tissue collection/storage
• *in situ* sampling device for gut microbiome
• HTP cultivation of novel microbes
• HTP analysis of novel microbial products
IV. Build Microbiome-Based Isolate and Microbial Products Resource

A library of human gut bacterial isolates paired with longitudinal multiomics data enables mechanistic microbiome research.


Proposed HRA Cross-Cutting Initiatives

Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking

Mingxin Wang, Jeremy J. Carver, [...] Nuno I.
Proposed HRA Cross-Cutting Initiatives

V. Develop a Global Microbial Isolate Vault

Microbiology

Preserving microbial diversity
Microbiota from humans of all cultures are needed to ensure the health of future generations

By Maria G. Dominguez Bello¹, Rob Knight², Jack A. Gilbert³, Martin J. Blaser⁴

Support to date:
Rutgers University, Karolinska Institutet, Seerave Foundation, Norwegian Institute of Public Health, New England Biolabs, Kiel Life Science, Calonste Gulbenkian Foundation

Feasibility study currently underway
1. Thousands of different kinds of microbial species*, possessing millions of genes, known as the microbiome or metagenome, live with humans.

<table>
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<th>Abundance (approx.)</th>
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<tr>
<td>Lungs</td>
<td>$\approx 10^{3-5}$</td>
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<tr>
<td>Vagina</td>
<td>$\approx 10^{8-9}$</td>
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<tr>
<td>Skin</td>
<td>$\approx 10^{9-10}$</td>
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<tr>
<td>Oral</td>
<td>$\approx 10^{10-11}$</td>
</tr>
<tr>
<td>GI tract</td>
<td>$\approx 10^{14}$</td>
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2. The microbiome develops like an organ system over the first few years of life and maintains our immune system and our organs throughout our lifetimes.

3. Changes in the microbiome due to modern practices may be associated with disease and the role of the microbiome is now being studied in 100+ disease classes.

4. HRA cross-cutting initiatives could involve a. developing research resources, b. creating cohort registries, c. building stool/tissue biobanks, d. funding technology development and innovation, e. supporting standardization activities (and so on) to catalyse microbiome research and treatments.

* bacteria, fungi, viruses, phage, archaea, protozoa, (helminths)
Questions?

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