The microbiome in health and disease

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SAHMRI
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INFECTION & IMMUNITY
Microbiome Research

Flinders UNIVERSITY
Rise of the microbiome
Culture-independent microbiology

Clinical sample

Culture-based microbiology

DNA

Sequence-based microbiology

Sequence data (GAT AAAT CT GGT TATT TCC)

Diagram showing the analysis of microbial composition through sequence-based microbiology.
The sequencing revolution

Human Genome Project
Completed 2003
Cost: $2,700,000,000

January, 2014
Human genome sequence <$1000
Less than the cost of a chest X-ray

Sequencing costs

Publications featuring "microbiome"
The human superorganism

Microbial Cells
-100 trillion
(-70-90%)

Human Cells
-30 trillion

Microbial Genes
-2,000,000
(-39%)

Human Genes
-23,000

http://www.amnh.org
What has the microbiome ever done for us?

- Prevention of infection
- CNS function
- Immune regulation
- Nutrition
- Lipid and glucose metabolism
- Circadian rhythm

**Transkingdom Control of Microbiota Diurnal Oscillations Promotes Metabolic Homeostasis**

Christoph A. Thaiss,1 David Zeaivi,2 Maayan Levy,1 Gilli Zilberman-Schapira,1 Jotham Suez,1 Anouk C. Tengeler,1 Lior Abramson,1 Meirav N. Katz,1,2 Tal Koren,1,2 Niv Zmora,1,2,3 Yael Kuperman,1 Inbal Biton,1 Shlomit Gilad,1 Alon Harmelin,1 Hagit Shapiro,1 Zarnir Halpern,1,4 Eran Segal,1 and Eran Elinav1,4
Dysbiosis and chronic inflammatory diseases

- **Depression**
  doi: 10.1038/mp.2016.46

- **Atherosclerosis**

- **Cirrhosis**

- **Type 2 diabetes**
  *Nature*. 2015; 10;528:262-6

- **Obesity**
  *Science*. 2013; 341; 6150

- **Rheumatoid arthritis**

- **Cancer**
Is dysbiosis really to blame?

Cultured gut microbiota from twins discordant for obesity modulate adiposity and metabolic phenotypes in mice

Vanessa K. Ridaura¹, Jeremiah J. Faith¹, Federico E. Rey¹, Jiye Cheng¹, Alexis E. Duncan², ³, Andrew L. Kau¹, Nicholas W. Griffin¹, Vincent Lombard⁴, Bernard Henrissat⁴, ⁵, James R. Bain⁶, ⁷, ⁸, Michael J. Muehlbauer⁶, Olga Ilkayeva⁶, Clay F. Semenkovich⁶, Katsuhiko Funai⁷, David K. Hayashi⁸, Barbara J. Lyle⁹, Margaret C. Martini⁹, Luke K. Ursell¹², Jose C. Clemente¹², William Van Treuren¹², William A. Walters¹³, Rob Knight¹², ¹⁴, ¹⁵, Christopher B. Newgard⁹, ⁷, ⁸, Andrew C. Heath², and Jeffrey I. Gordon¹.*

Early life determinants of disease

Antibiotic exposure <12 months associated with increased risk of

- Allergy and asthma at 6 years of age
- Wheezing and eczema at 8 years of age
- Inflammatory bowel disease
- Obesity, central adiposity, and type 2 diabetes
- Type 1 diabetes
- Depression, anxiety, or psychosis
Early life determinants of autoimmunity

Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans

Tommi Vatanen,1,2,3 Aleksandar D. Kostic,1,3,4,5,6 Eva d’Hennezel,5,22 Heil Slijenders,5,7,8 Eric A. Franzosa,1,4 Moran Yassour,1 Raivo Kolde,1 Hera Vlamakis,1 Timothy D. Arthur,1 Anu-Maria Hämäläinen,2 Aleksandr Post,10 Valio Tillmann,10 Raivo Uibo,11 Sergei Mokryov,12 Natalya Dorshakova,13 Jorma Ilonen,14,15 Suvi M. Virtanen,15,17,18 Susanne J. Szabo,10 Jeffrey A. Porter,1 Hari Lähdesmäki,6 Curtis Huttenhower,10 Dirk Gevers,1,23 Thomas W. Cullen,5,23 Mikael Knap,5,7,8,18,23 on behalf of the DIABIMMUNE Study Group, and Ramnik J. Xavier16,20,21,23*

Cell 165, 842–853, May 5, 2016

Diagram showing the variation in Microbiome LPS Immunogenicity and its contribution to autoimmunity in Finland, Estonia, and Russia.
The prenatal influence of the microbiome

Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites

Maternal fibre intake influences acetate levels

Maternal acetate levels during pregnancy influence rates of allergic airways disease in offspring
Microbiome and treatment outcomes

Determinants of microbiome composition

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

Ayelet Sivan, Leticia Corrales, Nathaniel Hubert, Jason B. Williams, Keston Aquino-Michaels, Zachary M. Earley, Franco W. Benyamin, Yuk Man Lei, Bana Jabri, Maria-Luisa Alegre, Eugene B. Chang, Thomas F. Gajewski

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**IMPrecision Medicine**

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. **Abilify** (arispiprazole) - Schizophrenia
2. **Nexium** (esomeprazole) - Heartburn
3. **Humira** (adalimumab) - Arthritis
4. **Crestor** (rosuvastatin) - High cholesterol
5. **Cymbalta** (duloxetine) - Depression
6. **Advair Diskus** (fluticasone propionate) - Asthma
7. **Enbrel** (etanercept) - Psoriasis
8. **Remicade** (infliximab) - Crohn’s disease
9. **Copaxone** (glatiramer acetate) - Multiple sclerosis
10. **Neulasta** (pegfilgrastim) - Neutropenia

Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at gcnature.com/446798.
Using microbiome analysis to guide therapy

“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?”

- President Obama, January 30, 2015
A precision approach to respiratory medicine

**Disease course**

*A Novel Microbiota Stratification System Predicts Future Exacerbations in Bronchiectasis*

Geraint B. Rogers, Nur Masriah M. Zain, Kenneth D. Bruce, Lucy D. Burt, Alice C. Chen, Damian W. Rivett, Michael A. McGuirk, and David J. Sentsler

*AnnalsATS Volume 11 Number 4 | May 2014*

**Treatment efficacy**

*The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial*

Geraint B Rogers, Kenneth D Bruce, Megan I Martin, Lucy D Burt, David J Sentsler

**Adverse outcomes**

*Inhaled Corticosteroids and the Risk of Pneumonia in People With Asthma*  
*A Case-Control Study*

Tricia McKeeve, PhD; Timothy W. Harrison, MD; Richard Hubbard, MD; and Dominick Shaw, MD

*Chest 2013; 144(6):1788–1794*
Challenges and opportunities

How do we balance treatments for discrete conditions against their impact on other physiological systems?

Can we manage the human microbiome to influence patient health and therapeutic efficacy?

Thank you