Human Microbiome

Marcel R.M. van den Brink, MD, PhD

September 29th, 2020

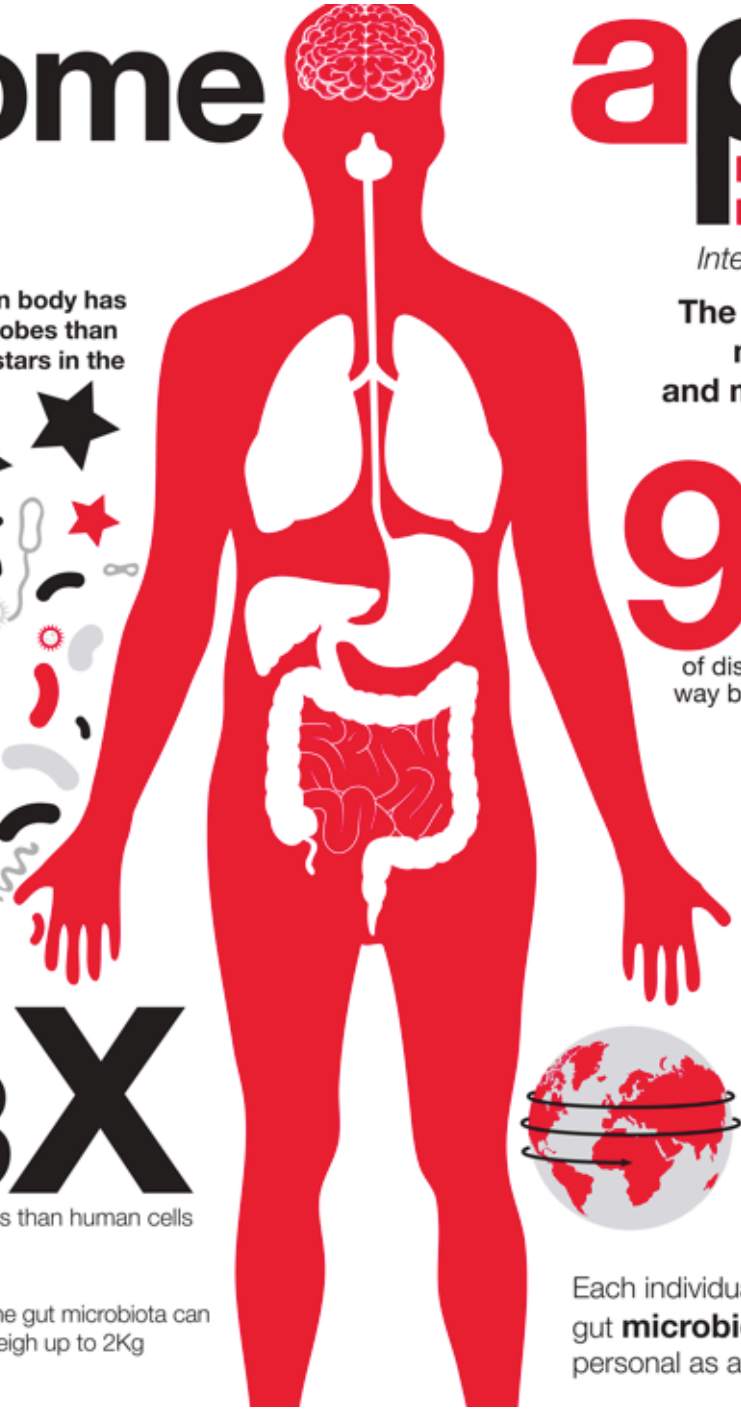
Memorial Sloan Kettering Cancer Center

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

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

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 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

Microbiome Ireland
Interfacing Food & Medicine

The microbiome is more medically accessible and manipulable than the human genome

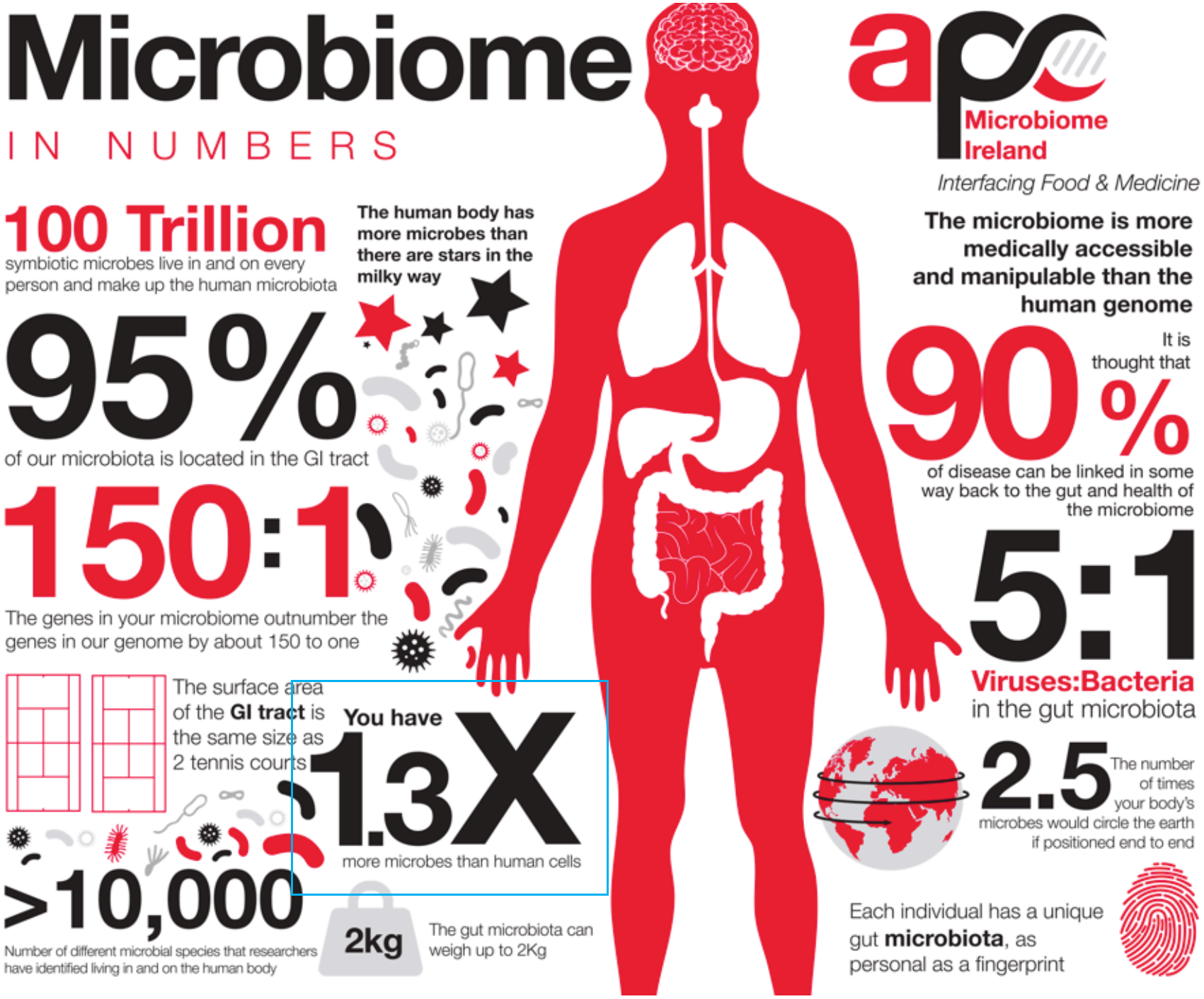
It is thought that **90%** of disease can be linked in some way back to the gut and health of the microbiome

5:1
Viruses:Bacteria in the gut microbiota

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

worldmicrobiomeday.com/human-microbiome



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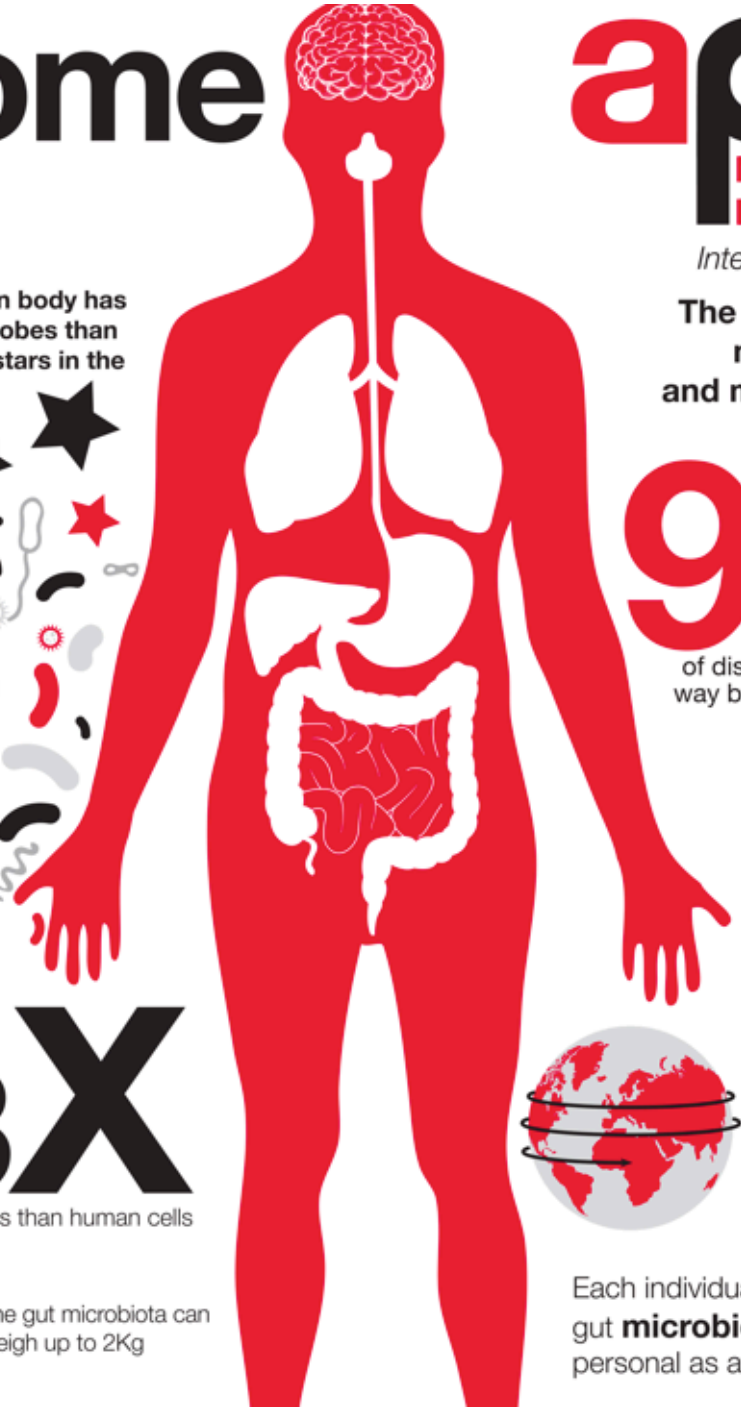

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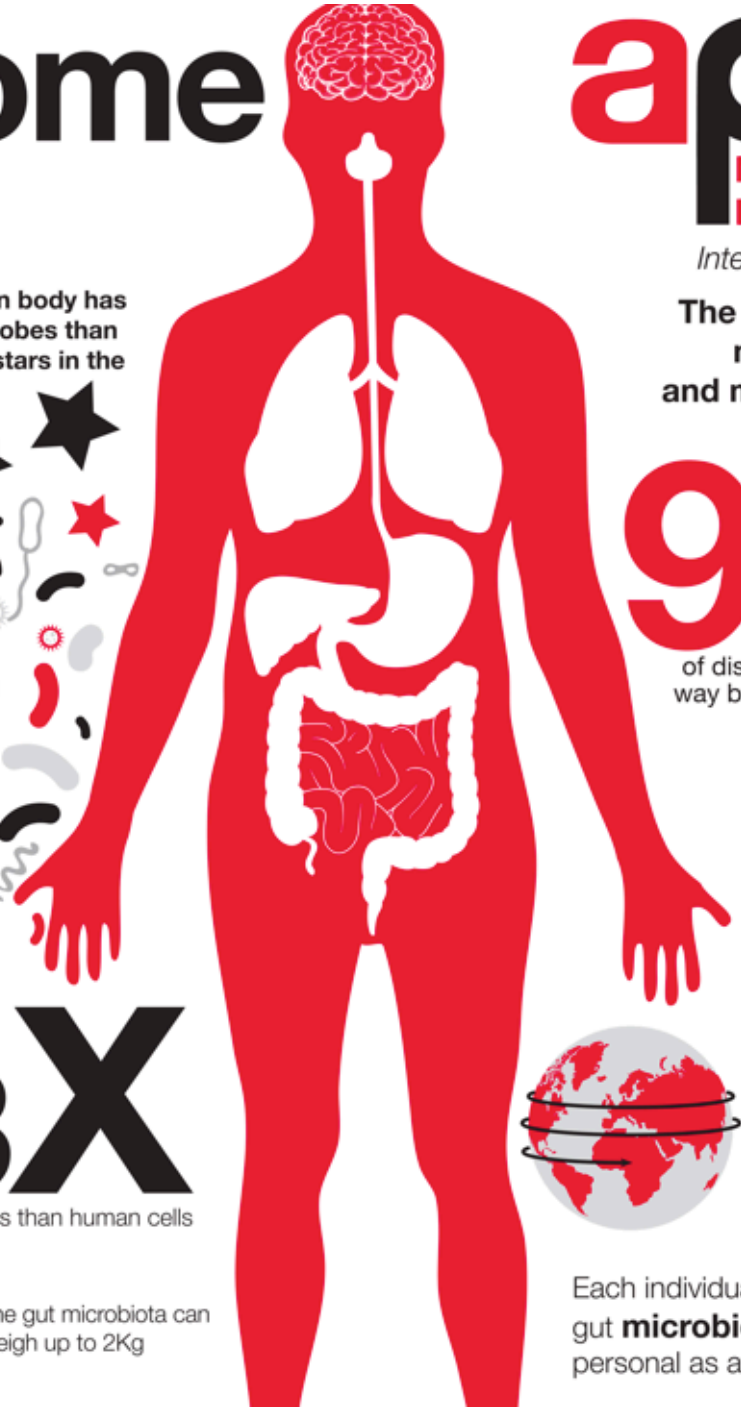

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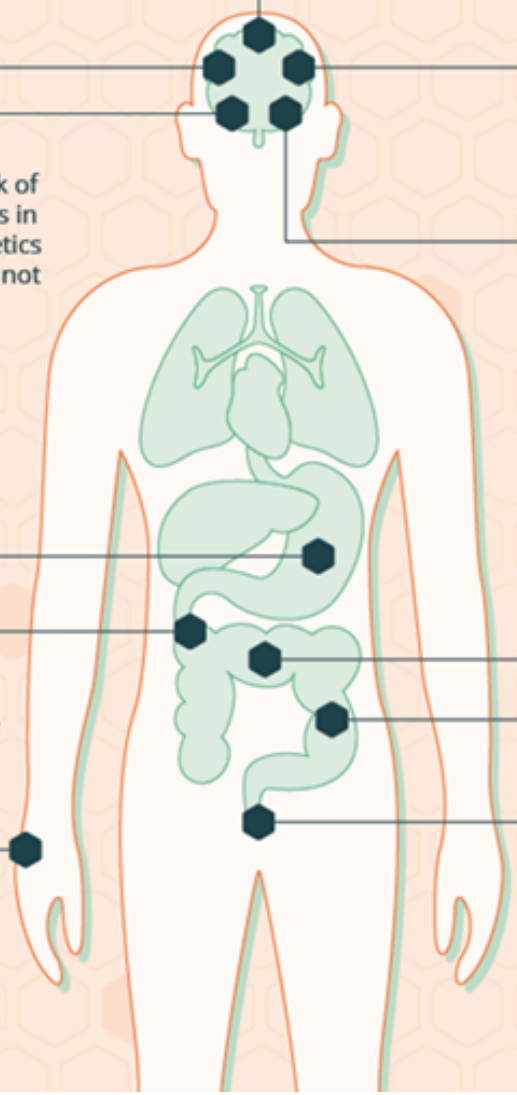
HOW GUT BACTERIA AFFECTS THE BRAIN AND BODY



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

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.

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.

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

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

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

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.

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

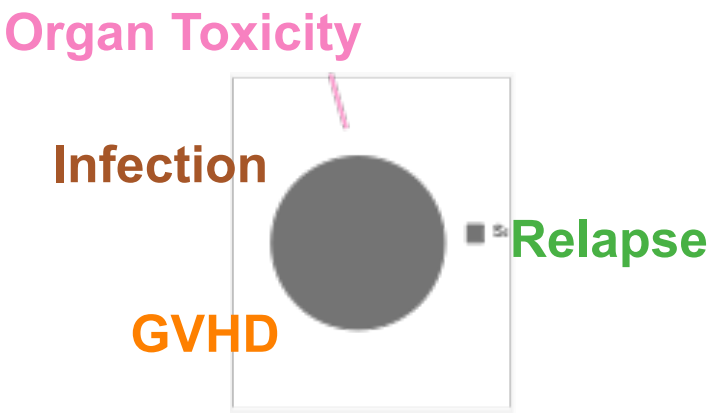
RHEUMATOID ARTHRITIS
Studies have found a link between low levels of certain good gut bacteria, high levels of unhealthy Prevotella copri bacteria, and autoimmune joint disease.

IRRITABLE BOWEL SYNDROME
There is a definitive link between IBS and an overgrowth of bacteria in the small intestines.

Huffington Post

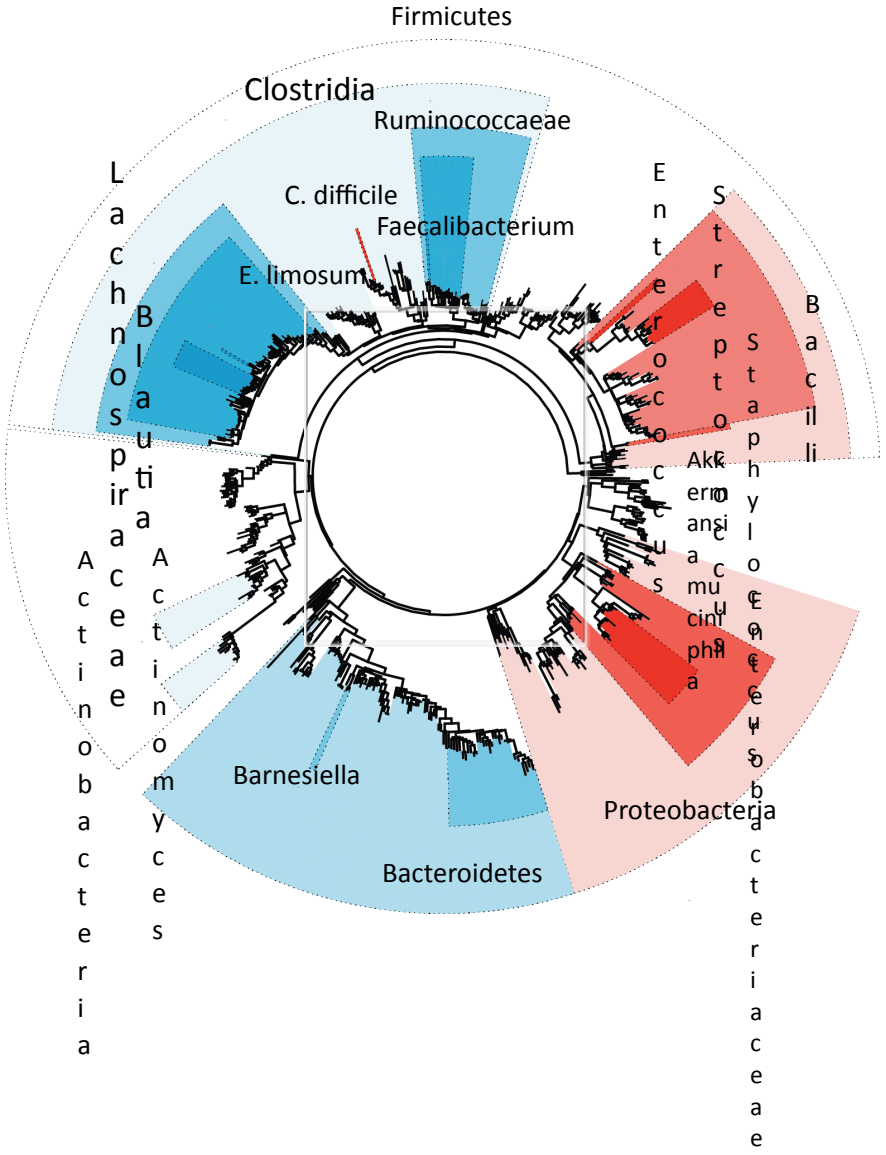
Gut bacteria associated with allo-HCT outcomes

Causes of Death after allo-HCT



Schematized from CIBMTR Summary Slides

Gut bacteria associated with allo-HCT outcomes



Adapted from Taur 2016

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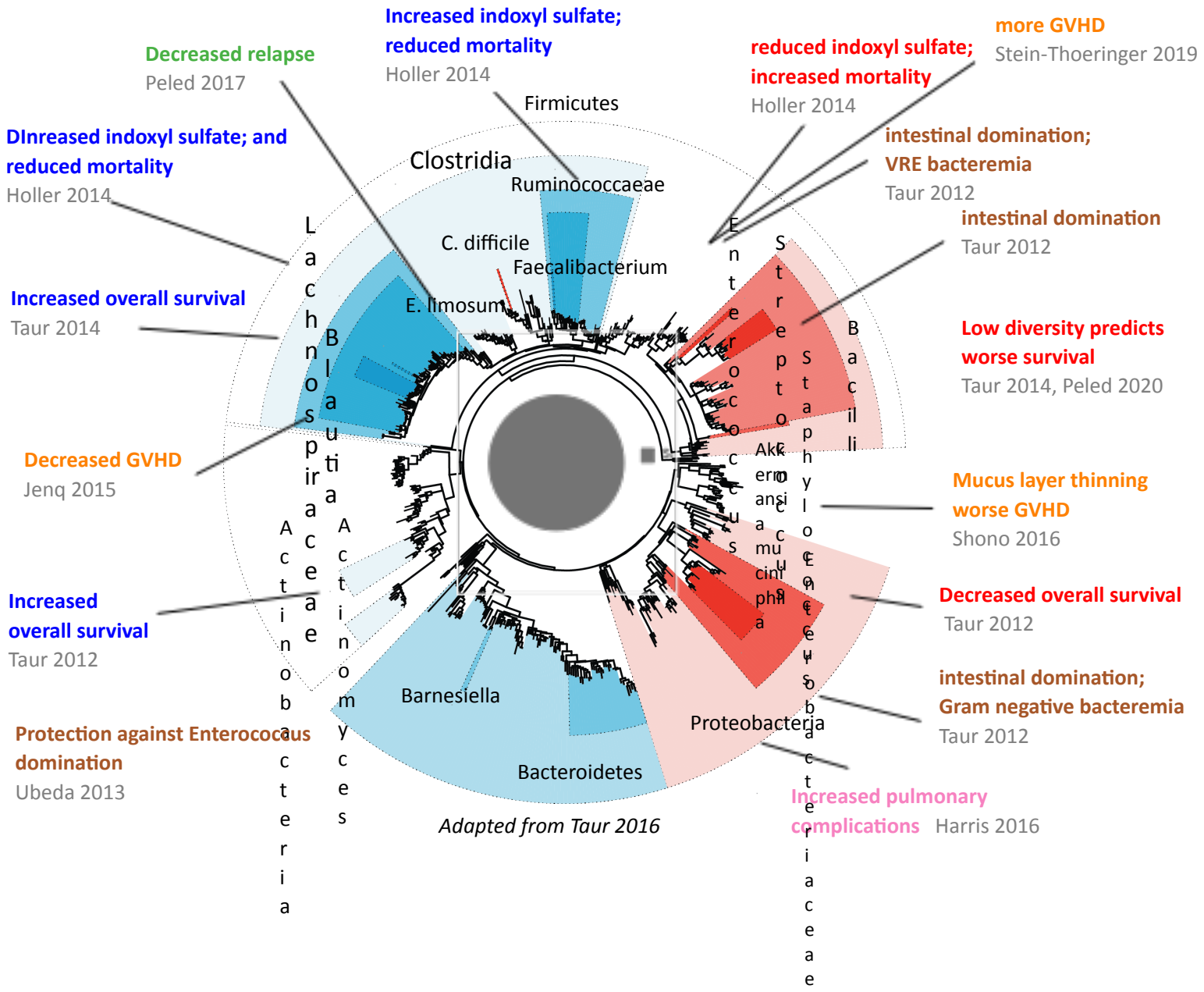
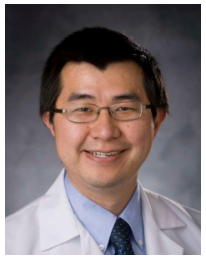


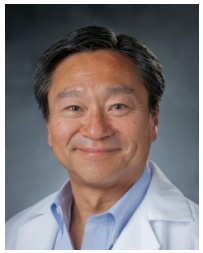
Microbiota as Predictor of Mortality in Allogeneic Hematopoietic Cell Transplantation

New England Journal of Medicine (2020)

Duke



Anthony Sung



Nelson Chao

Hokkaido University

Daigo Hashimoto

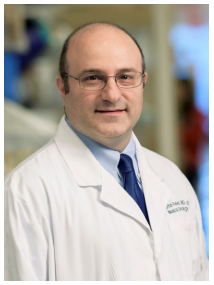
Takanori Teshima

University Hospital Regensburg

Ernst Holler

Daniela Weber

Memorial Sloan Kettering Cancer Center



Jonathan Peled

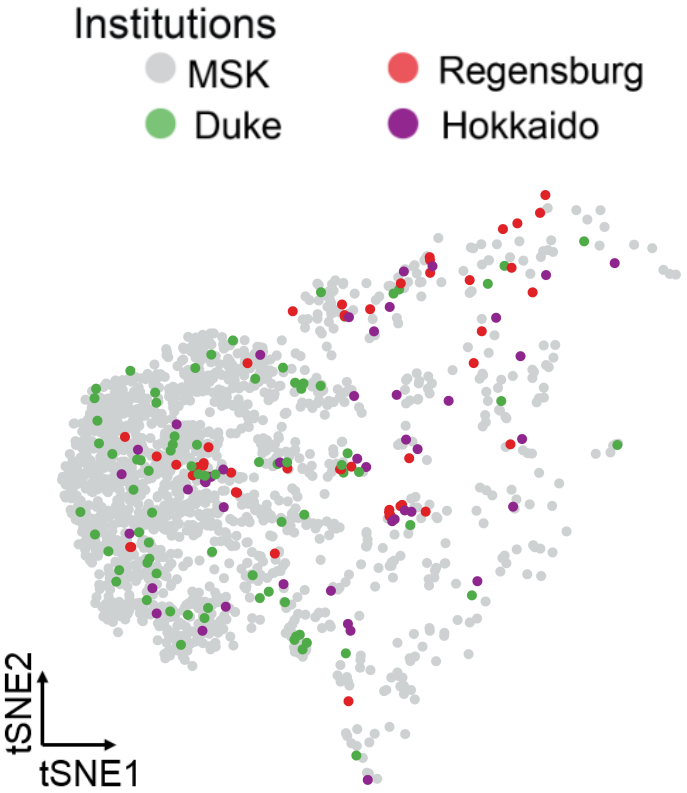
Antonio Gomes

8,691 samples from 1,361 HCT recipients from 4 international transplantation centers

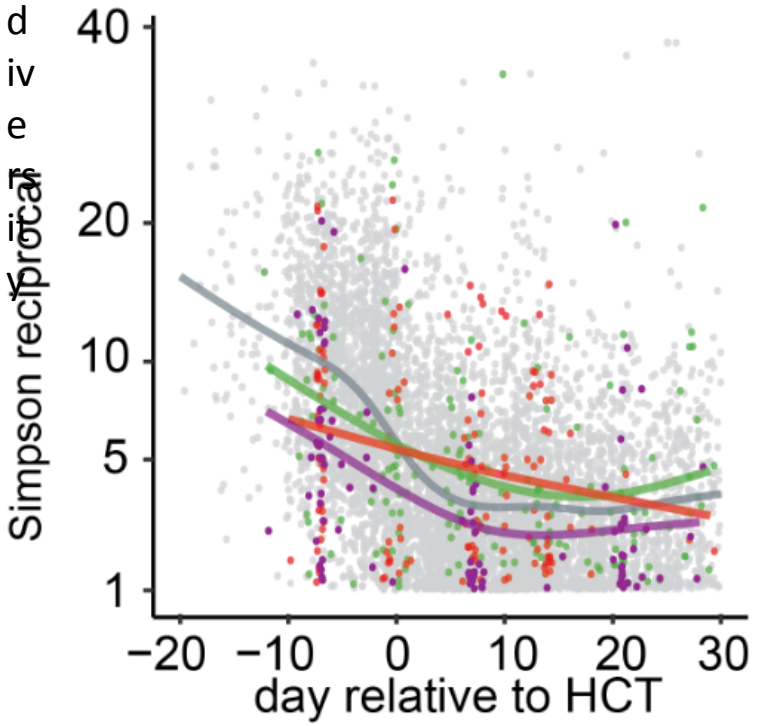
	Overall	MSKCC	Regensburg	Duke	Hokkaido
N = 1361					
MSKCC	1121 (82.4)	1121			
Regensburg	76 (5.6)		76		
Duke	98 (7.2)			98	
Hokkaido	66 (4.8)				66
Disease (%)					
AML	496 (36.4)	390 (34.8)	41 (53.9)	33 (33.7)	32 (48.5)
MDS/MPN	242 (17.8)	208 (18.6)	8 (10.5)	19 (19.4)	7 (10.6)
NHL	207 (15.2)	182 (16.2)	12 (15.8)	8 (8.2)	5 (7.6)
ALL	129 (9.5)	100 (8.9)	6 (7.9)	8 (8.2)	15 (22.7)
Myeloma	111 (8.2)	99 (8.8)	3 (3.9)	8 (8.2)	1 (1.5)
other	77 (5.7)	61 (5.4)	0 (0.0)	13 (13.3)	3 (4.5)
CLL	33 (2.4)	30 (2.7)	3 (3.9)	0 (0.0)	0 (0.0)
Hodgkins	31 (2.3)	27 (2.4)	0 (0.0)	4 (4.1)	0 (0.0)
CML	29 (2.1)	24 (2.1)	1 (1.3)	3 (3.1)	1 (1.5)
AA	5 (0.4)	0 (0.0)	2 (2.6)	2 (2.0)	1 (1.5)
Hodgkin's	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Graft Source (%)					
BM unmodified	112 (8.2)	85 (7.6)	11 (14.5)	10 (10.3)	6 (9.1)
cord	217 (16.0)	187 (16.7)	0 (0.0)	16 (16.5)	14 (21.2)
PBSC T-cell Depleted	450 (33.1)	450 (40.1)	0 (0.0)	0 (0.0)	0 (0.0)
PBSC unmodified	581 (42.7)	399 (35.6)	65 (85.5)	71 (73.2)	46 (69.7)
Conditioning Intensity (%)					
Ablative	763 (56.1)	615 (54.9)	10 (13.2)	91 (92.9)	47 (71.2)
Reduced Intensity	472 (34.7)	387 (34.5)	66 (86.8)	0 (0.0)	19 (28.8)
Nonmyeloablative	126 (9.3)	119 (10.6)	0 (0.0)	7 (7.1)	0 (0.0)
sex = M (%)	828 (60.8)	682 (60.8)	46 (60.5)	63 (64.3)	37 (56.1)

Peled, NEJM 2020

No apparent clustering of baseline samples by geography
Diversity declines with similar kinetics across centers



baseline samples (d-30 to d-6)

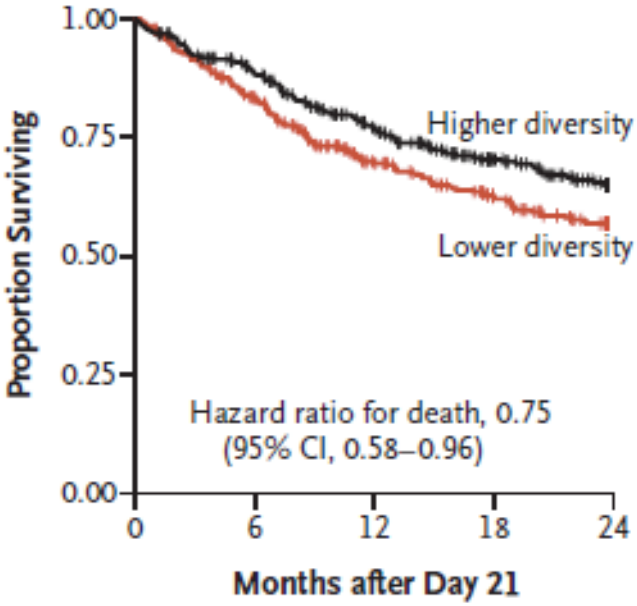


	Duke	Hokkaido	MSK	Regensburg
patients	93	66	1079	98
samples	310	217	7997	167

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

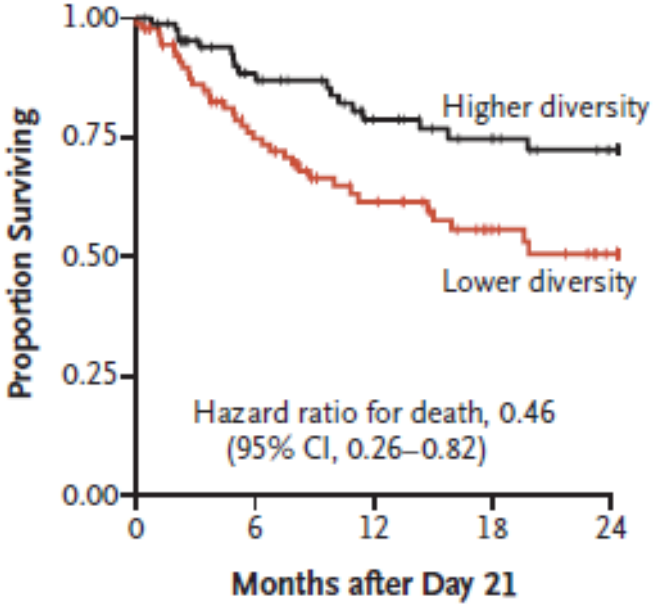
Low Intestinal Diversity at neutrophil engraftment is associated with decreased overall survival

Discovery Cohort (MSK)



No. at Risk					
Higher	354	289	220	159	116
Lower	350	281	204	164	129

Validation Cohort
(Duke+Regensburg+Hokkaido)



No. at Risk					
Higher	87	60	44	34	26
Lower	92	57	37	24	15

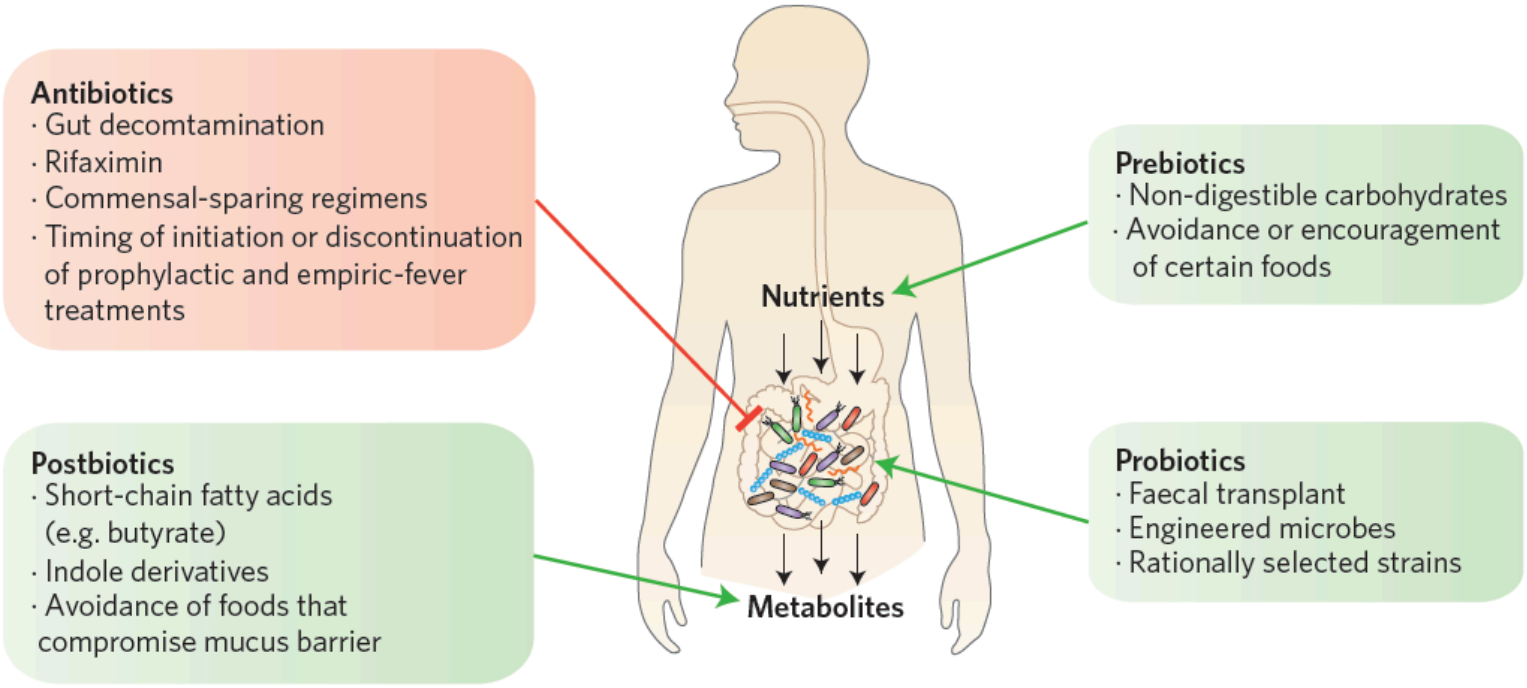
stratified by above- and below-median Simpson Reciprocal Index in each cohort
single sample per patient, collected day 14 +/- 7

Peled, NEJM 2020

Factors that affect the intestinal microbiota composition

- Antibiotics
- Conditioning regimen
- Diet
- Other drugs

Therapeutic approaches targeting microbiota



Peled et al. Nature Microbiology 2016

Probiotic Therapy - History

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

Ebers papyrus

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

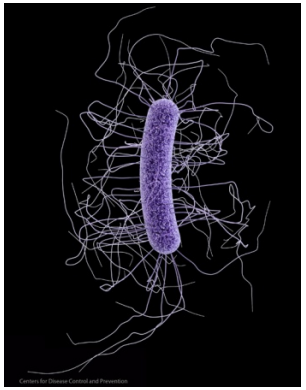
Fabricius ab Aquapendente

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

Ge Hong

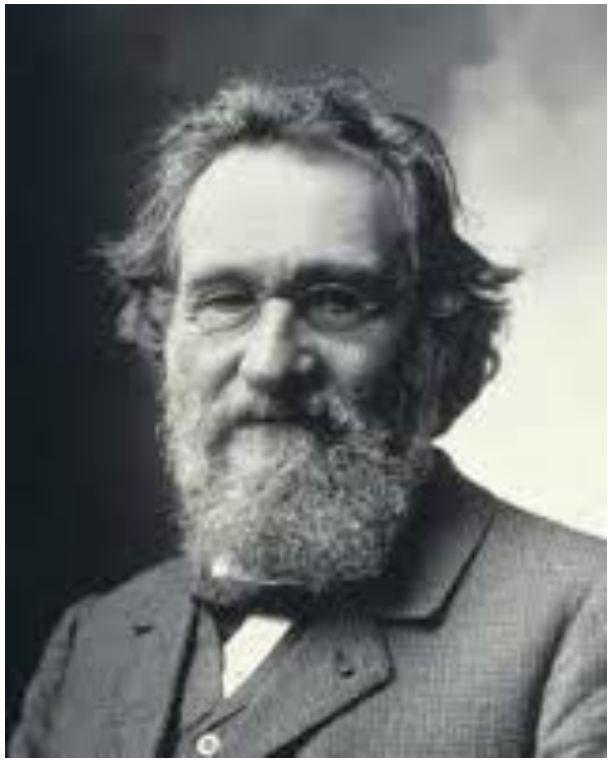
• **USA 1958:** Fecal matter transplant for *C difficile*

Ben Eiseman



Clostridium difficile

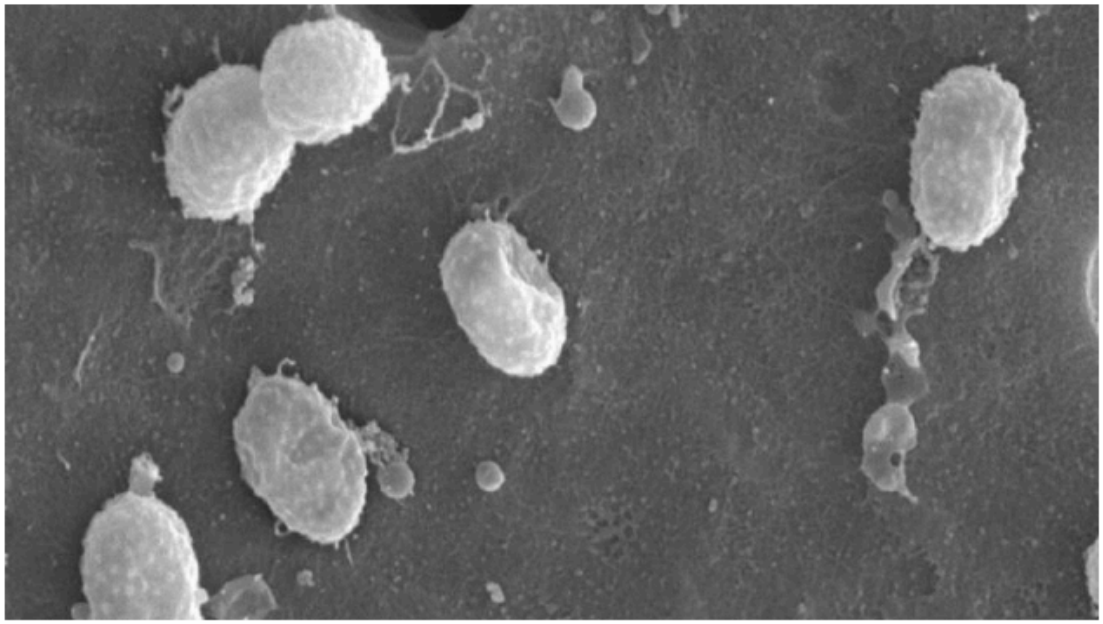
Elie Metchnikoff (1845-1916)



- 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, 2004

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

NIH National Institute on Aging

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

NATIONAL CANCER INSTITUTE

National Institute of Allergy and Infectious Diseases

NIH National Heart, Lung, and Blood Institute

Tri-Institutional Stem Cell Initiative

- **The Susan and Peter Solomon Family Fund**
- **The Lymphoma Foundation**
- **Parker Institute for Cancer Immunotherapy**
- **Tri-Institutional Stem Cell Initiative**

Acknowledgements

van den Brink Laboratory:
Yusuke Shono
Jennifer Tsai
Melissa Docampo
Jonathan Peled
Melody Smith
Marina Burgos da Silva
Lia Palomba
Scott James
Kimon Argyropoulos
Lorenz Jahn
Antonio Gomes
Harold Elias
Emmanuel Dwomoh
Kate Markey
Gabriel Armijo
John Slingerland
Annelie Clurman
Nicole Lee
Katarina Piasevoli
Sheena Kapoor
Pamela Hatfield
Peter Adintori
Susan Dewolf
Anqi Dai
Chi Nguyen

Regensburg:
Daniela Weber
Ernst Holler

Duke:
Anthony Sung
Nelson Chao

Fred Hutchinson:
Jarrod Dudakov

Seres:
Matt Henn

Ludwigs-Maximilians-University:
Hendrik Poeck
Gabriel Eisenkolb

University of Georgia:
Nancy Manley

University of Chicago:
Eric Pamer

Hokkaido University:
Daigo Hashimoto
Takanori Teshima

Continued:
Brandon Ng
Oriana Miltiadous

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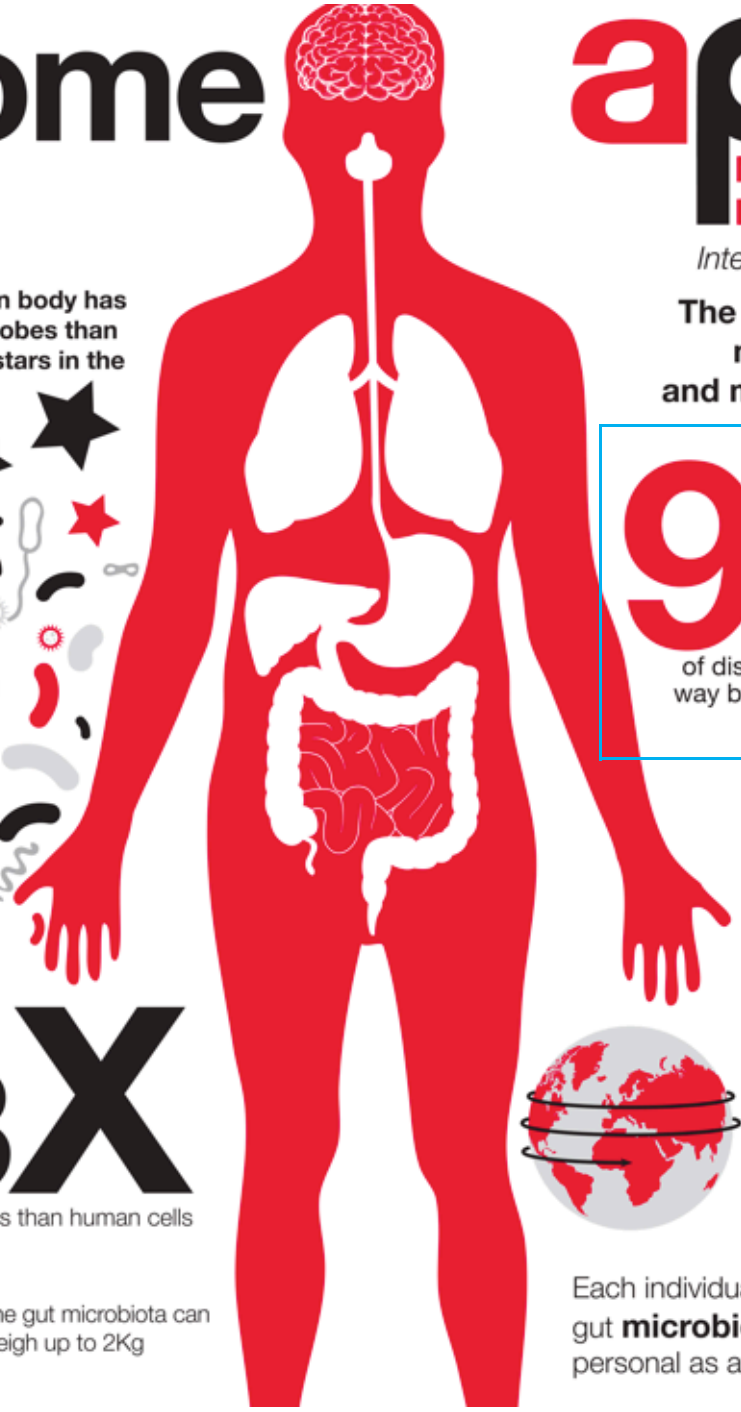

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