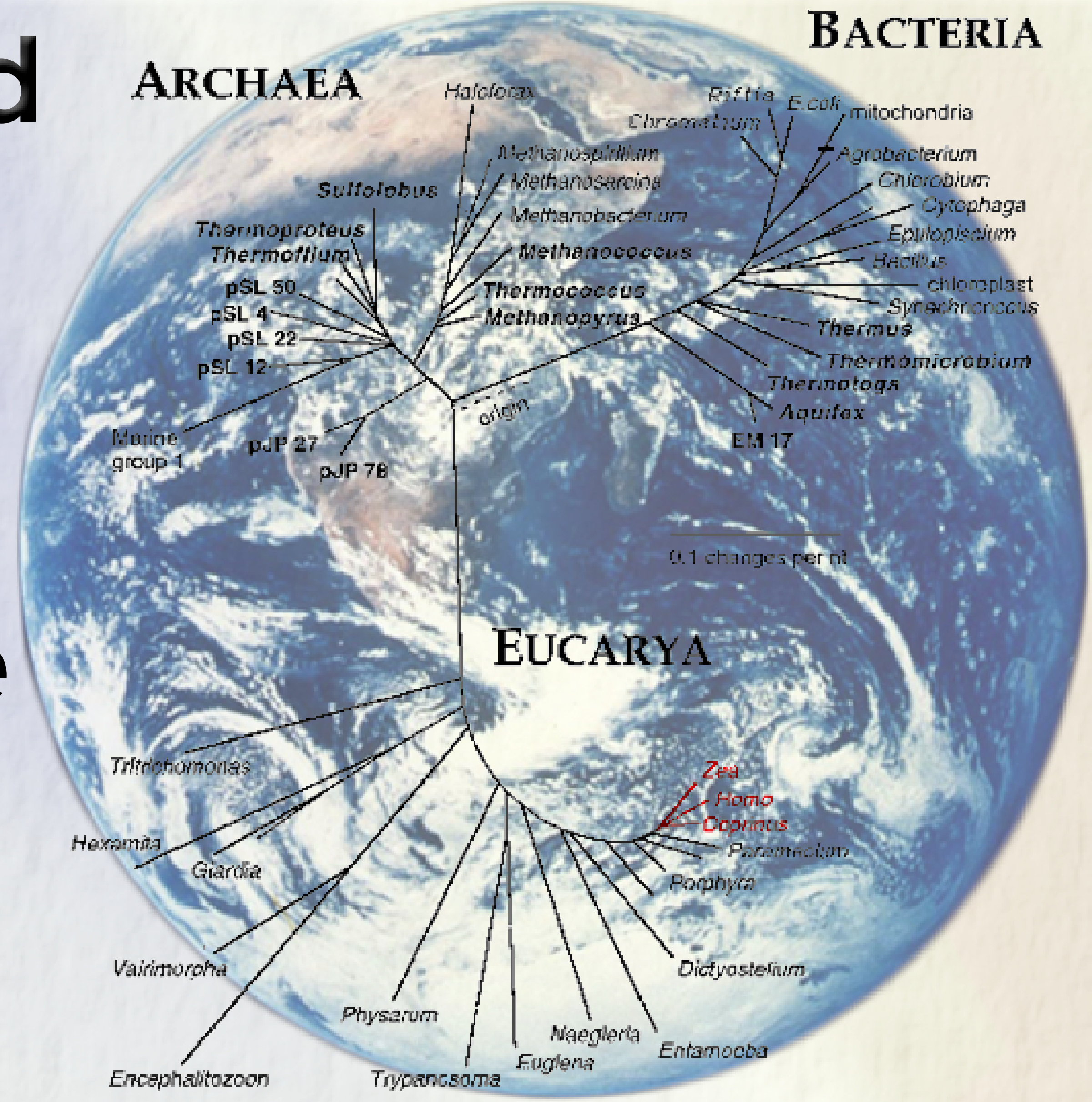
Why you should care about microbial community ecology (in the context of bioinformatics)



Rob Knight

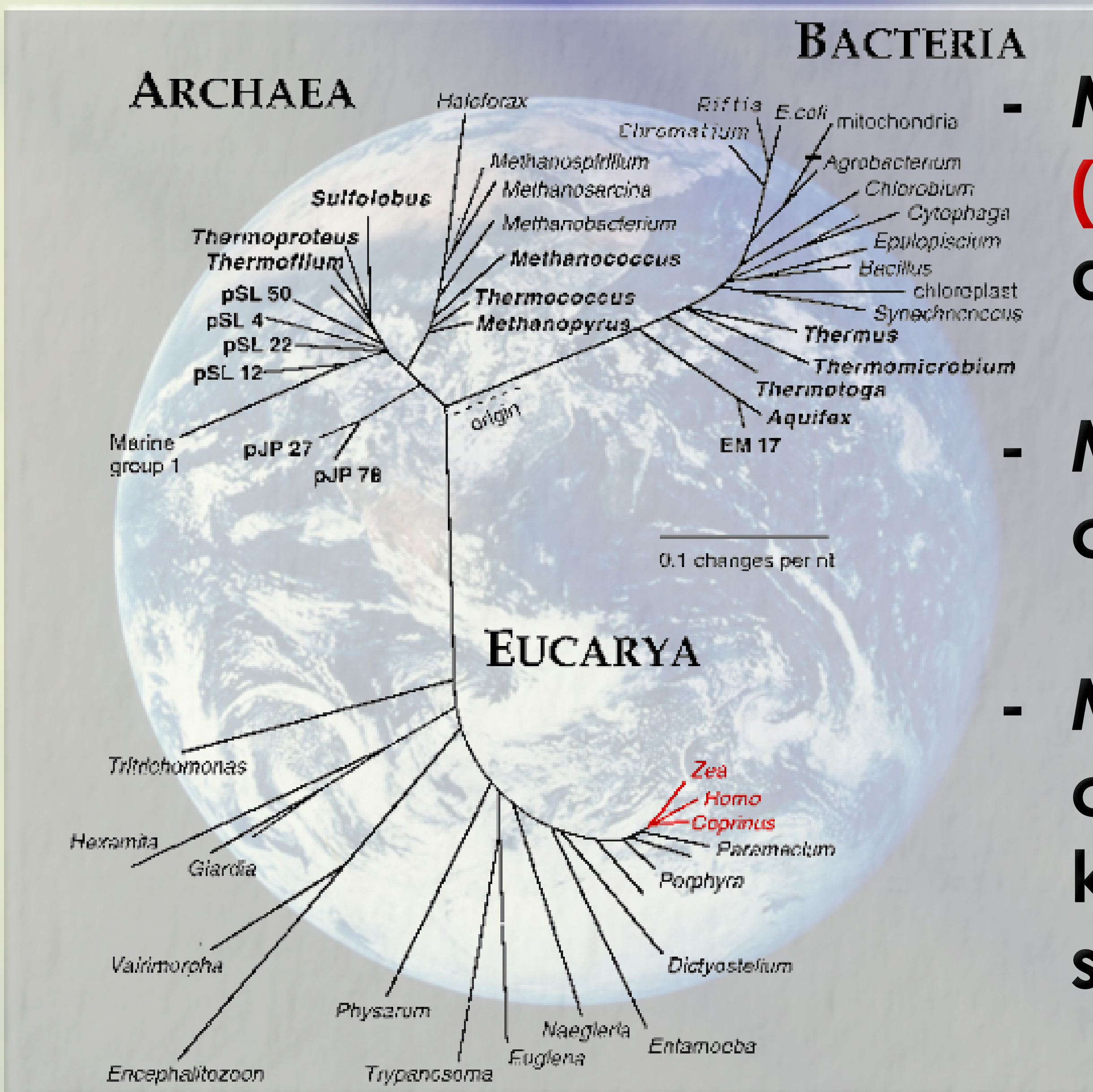
HHMI, and Dept. Chemistry & Biochemistry

University of Colorado, Boulder

It's important to remember that our world...

NASA: Earth from Apollo

...is a microbial world



- Multicellular lineages (red) rare, not diverse as measured by SSU rRNA
- Most molecular diversity can be found in microbes
- Most (99%+) microbes can't be cultured: known only from sequences

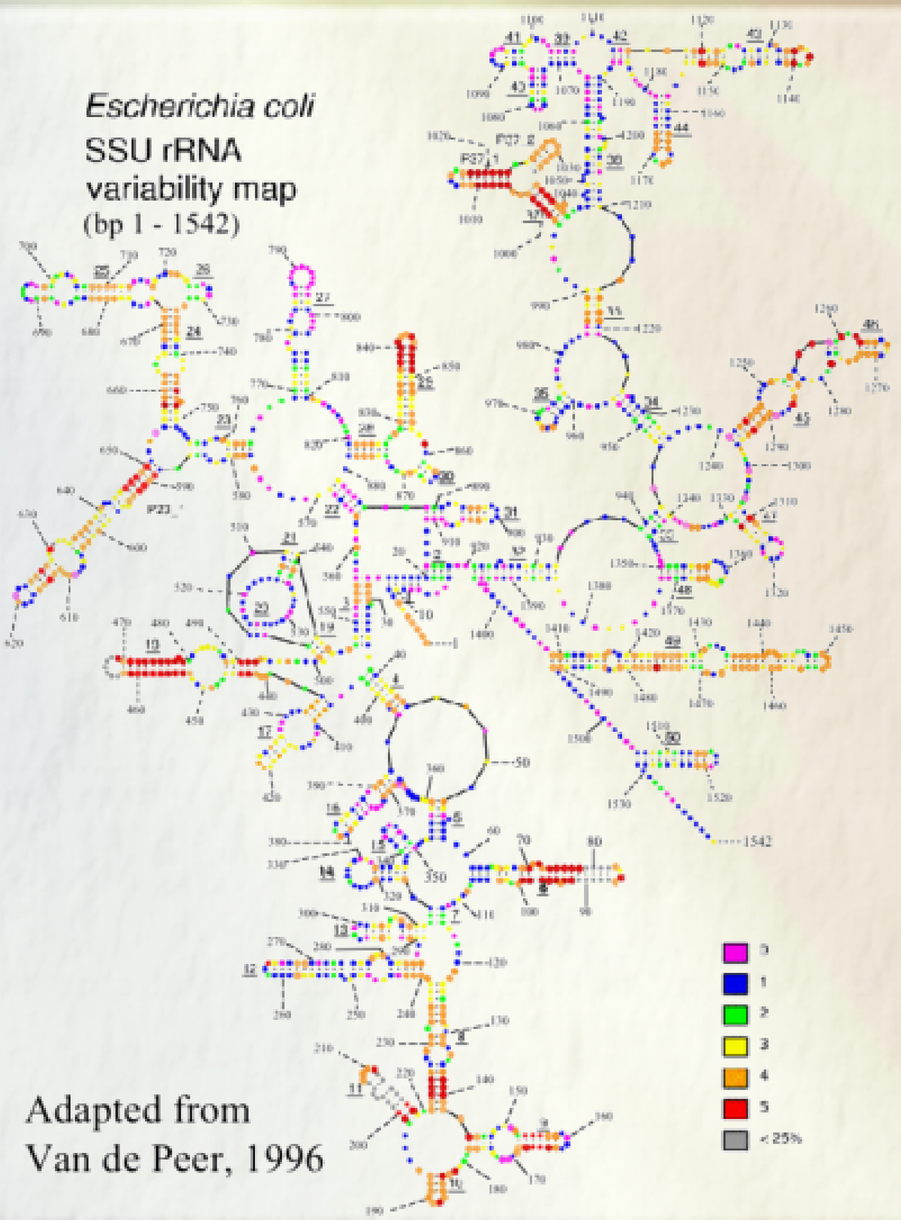
Tree adapted from Pace 1997 Science 276:734-740.

Ribosomal RNA is an excellent phylogenetic marker

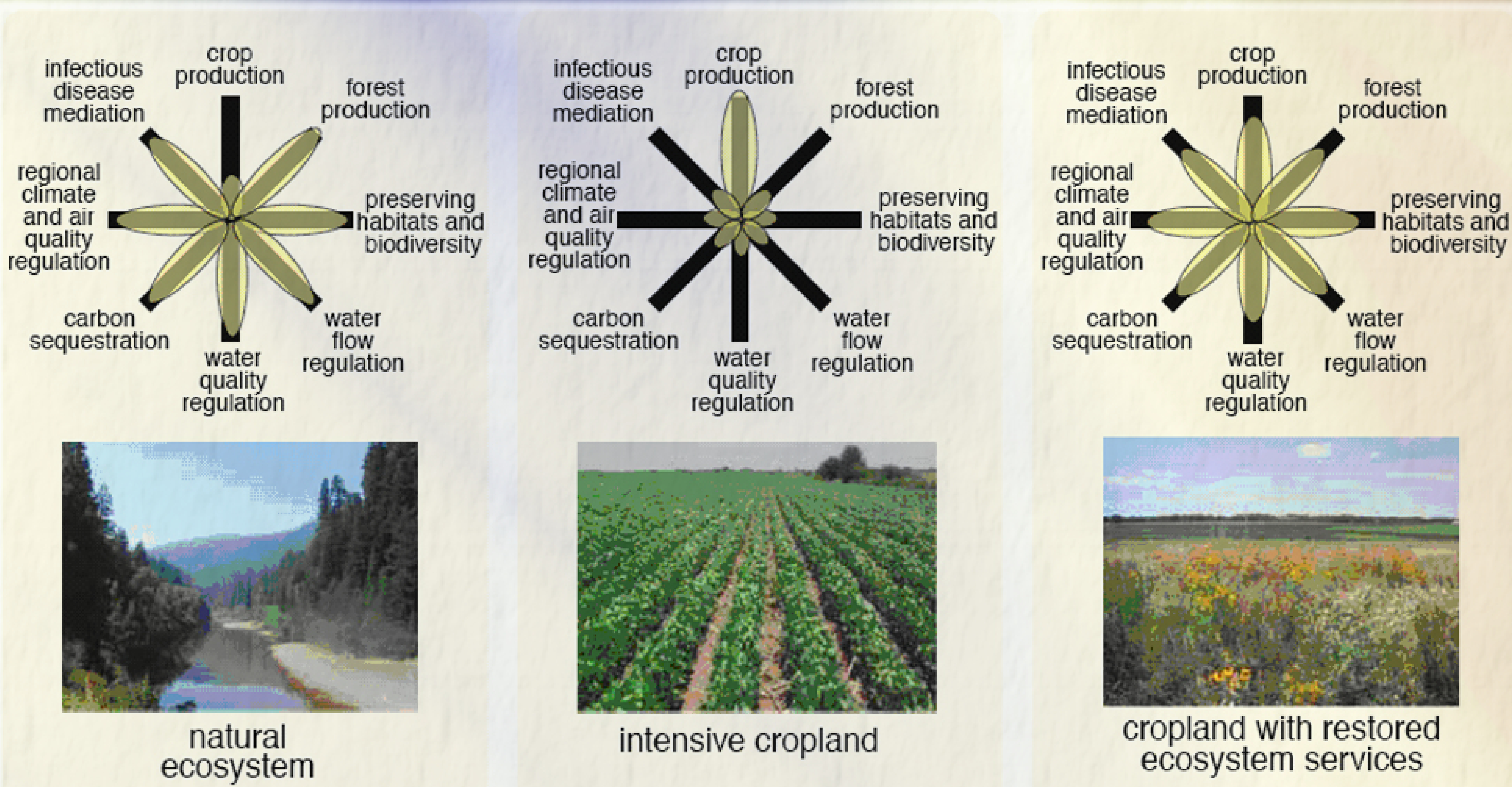
- Found in all species

- Has fast- and slow-evolving regions so can reconstruct relationships at different depths

- Large pre-existing databases for comparison



Microbes are ubiquitous, provide key ecosystem services



http://www.epa.gov/ncer/rfa/2009/2009_star_usda.jpg

Early observations: body teeming with microbial life

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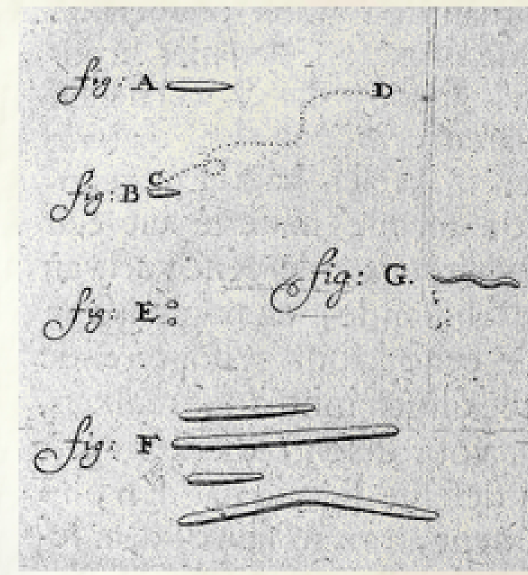

"...animalcules were in such enormous numbers, that all the water...seemed to be alive." — van Leeuwenhoek (1683)

Early observations: body teeming with microbial life

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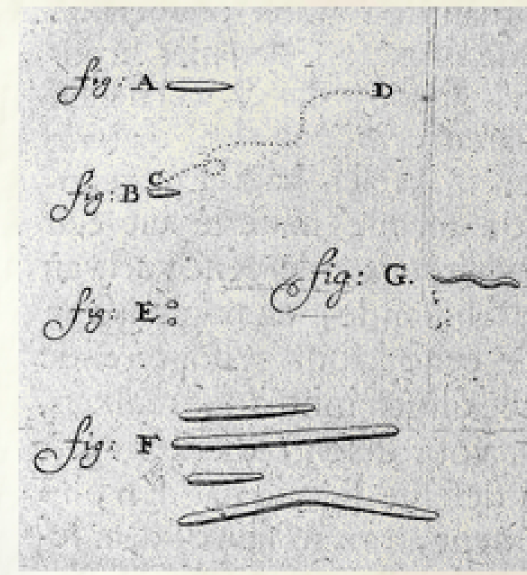
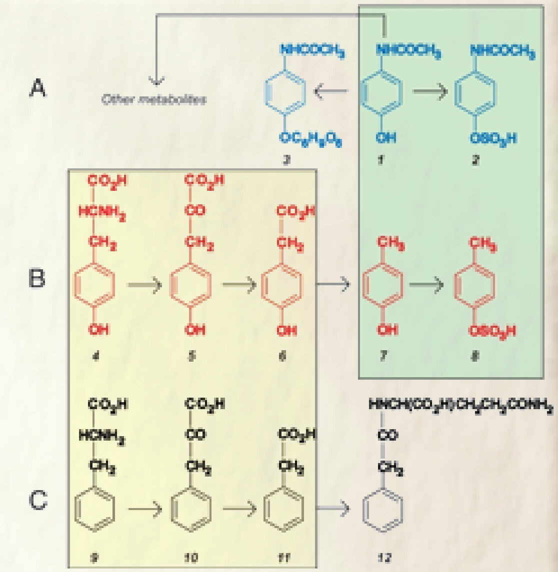


"...animalcules were in such enormous numbers, that all the water...seemed to be alive." — van Leeuwenhoek (1683)

Why should you care about your microbes?

Why should you care about your microbes?

They determine whether Tylenol is toxic to your liver...



PNAS

Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism

T. Andrew Clayton[a], David Baker[b], John C. Lindon[a], Jeremy R. Everett[c], and Jeremy K. Nicholson[a,1]

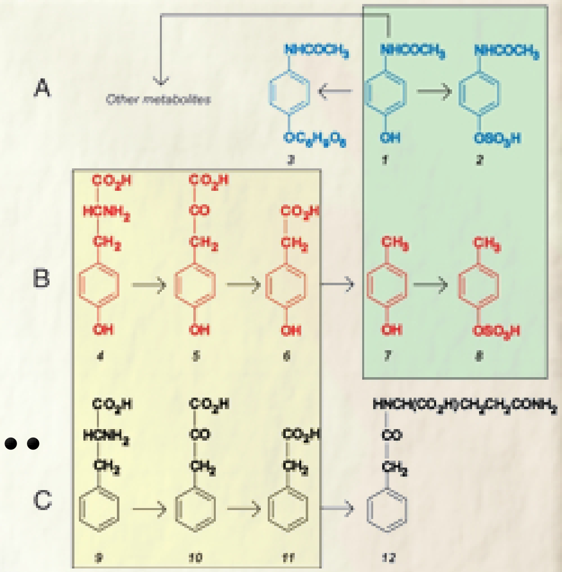
[a]Biomolecular Medicine, SORA Division, Faculty of Medicine, Sir Alexander Fleming Building, Imperial College London, South Kensington, London SW7 2AZ, United Kingdom; [b]Pfizer Inc., 50 Pequot Avenue, New London, CT 06320; and [c]Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

Communicated by Burton H. Singer, Princeton University, Princeton, NJ, April 29, 2009 (received for review December 8, 2008)

Why should you care about your microbes?

They determine whether Tylenol is toxic to your liver...

...they tell you who to have sex with (if you're a fruit fly)...



Pharmacometabonomic identification of a significant

Commensal bacteria play a role in mating preference of *Drosophila melanogaster*

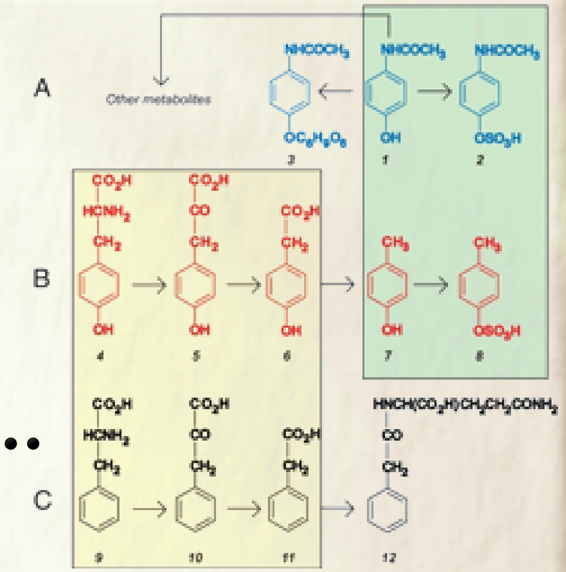
Gil Sharon[a], Daniel Segal[a], John M. Ringo[b], Abraham Hefetz[c], Ilana Zilber-Rosenberg[d], and Eugene Rosenberg[a,1]

[a]Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv 69978, Israel; [b]School of Biology and Ecology, University of Maine, Orono, ME 04469; [c]Department of Zoology, Tel Aviv University, Tel Aviv 69978, Israel; and [d]18 Rachavat Ilan St., Givat Shmuel 51905, Israel

Edited by R. John Collier, Harvard Medical School, Boston, MA, and approved September 28, 2010 (received for review July 12, 2010)

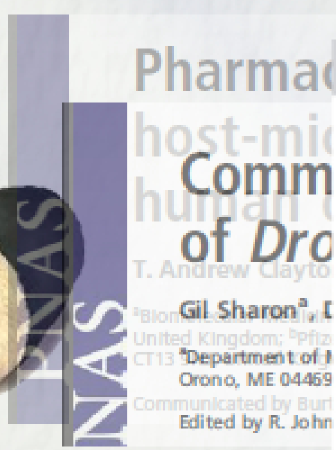
Why should you care about your microbes?

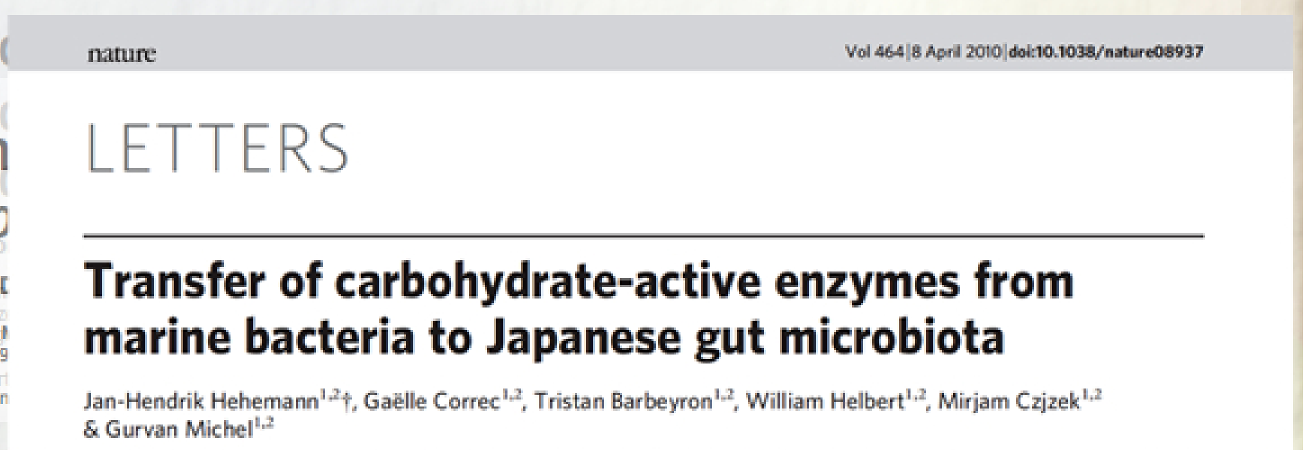
They determine whether Tylenol is toxic to your liver...



...they tell you who to have sex with (if you're a fruit fly)...

...and they steal genes from your food to help you digest it





nature Vol 464|8 April 2010|doi:10.1038/nature08937

LETTERS

Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota

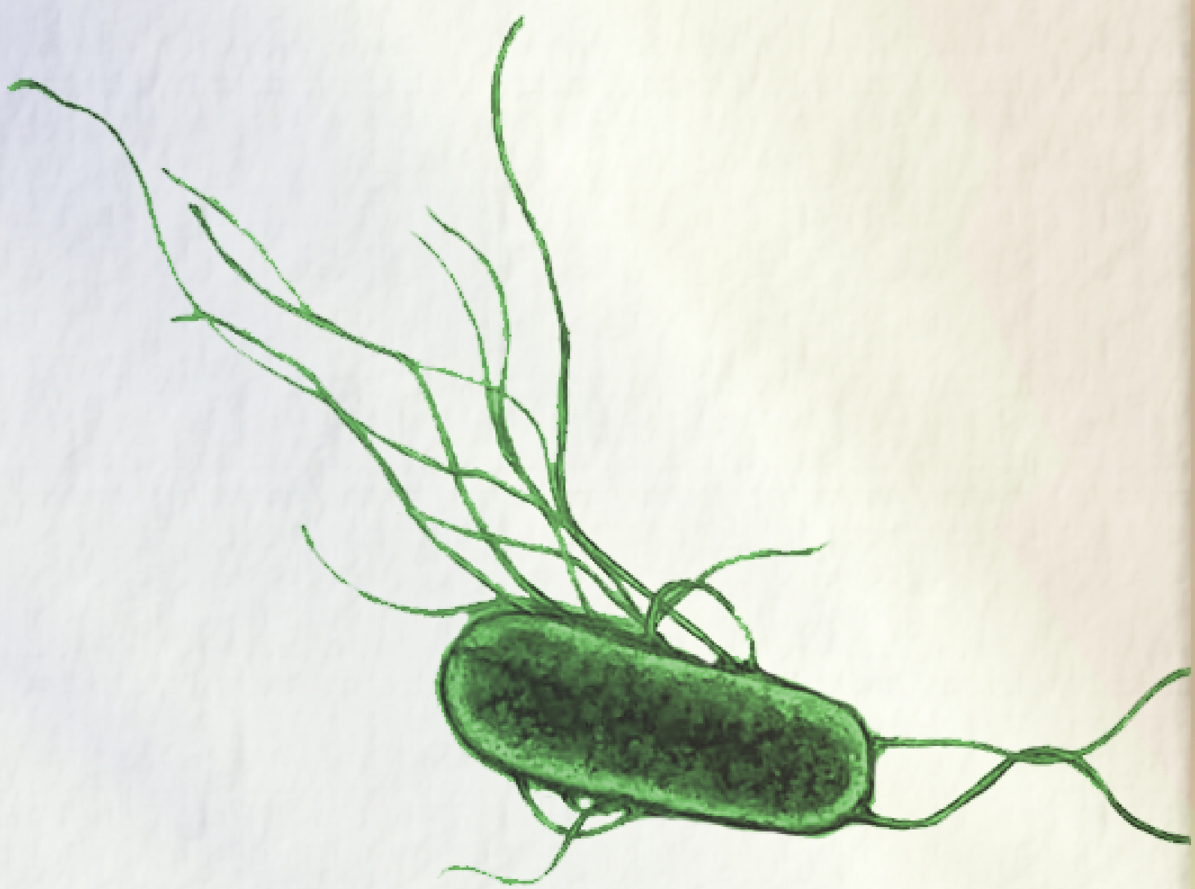
Jan-Hendrik Hehemann[1,2]†, Gaëlle Correc[1,2], Tristan Barbeyron[1,2], William Helbert[1,2], Mirjam Czjzek[1,2] & Gurvan Michel[1,2]

There are about as many *E. coli* in your gut...

...as there are humans on Earth!

=

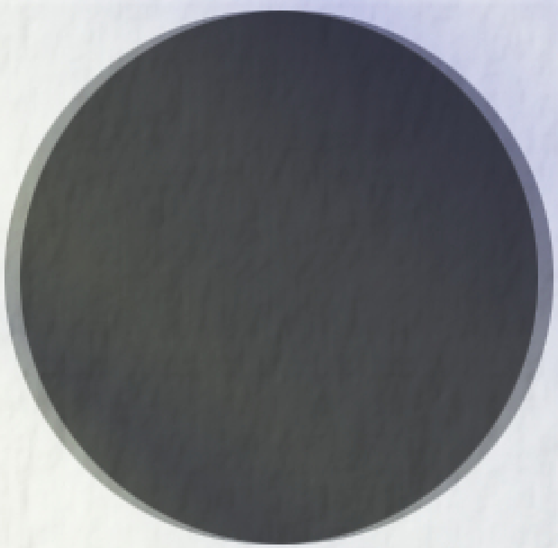
We think of *E. coli* as a classic gut microbe...

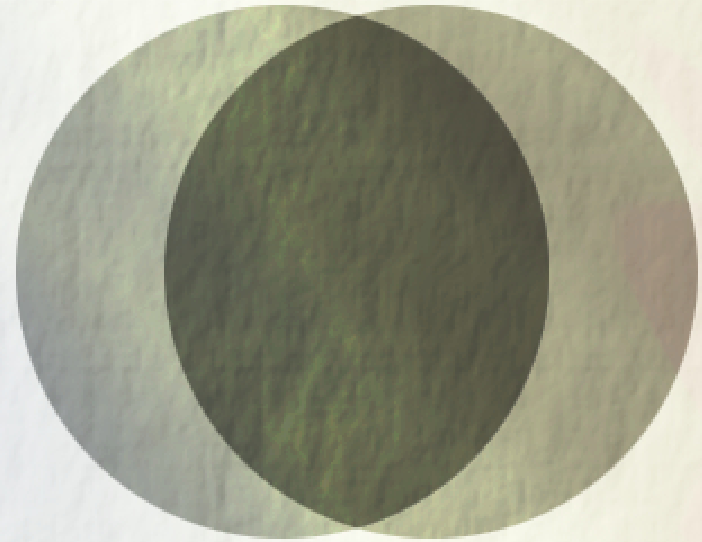


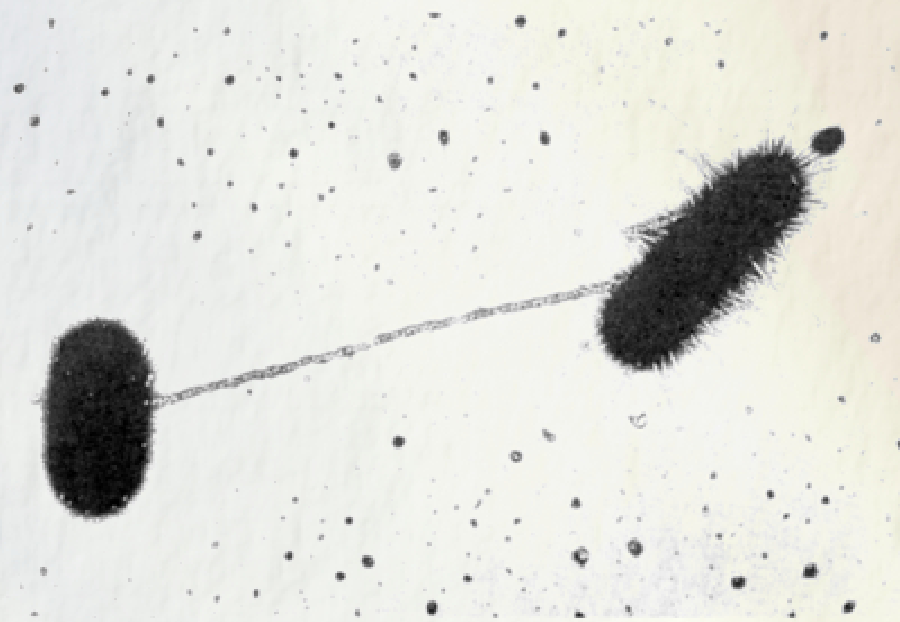
....but only because it is easy to grow in captivity, unlike most

...and any two humans you pick have 99.9% identical genomes...

...but two E. coli cells can have genomes that are 40% different.

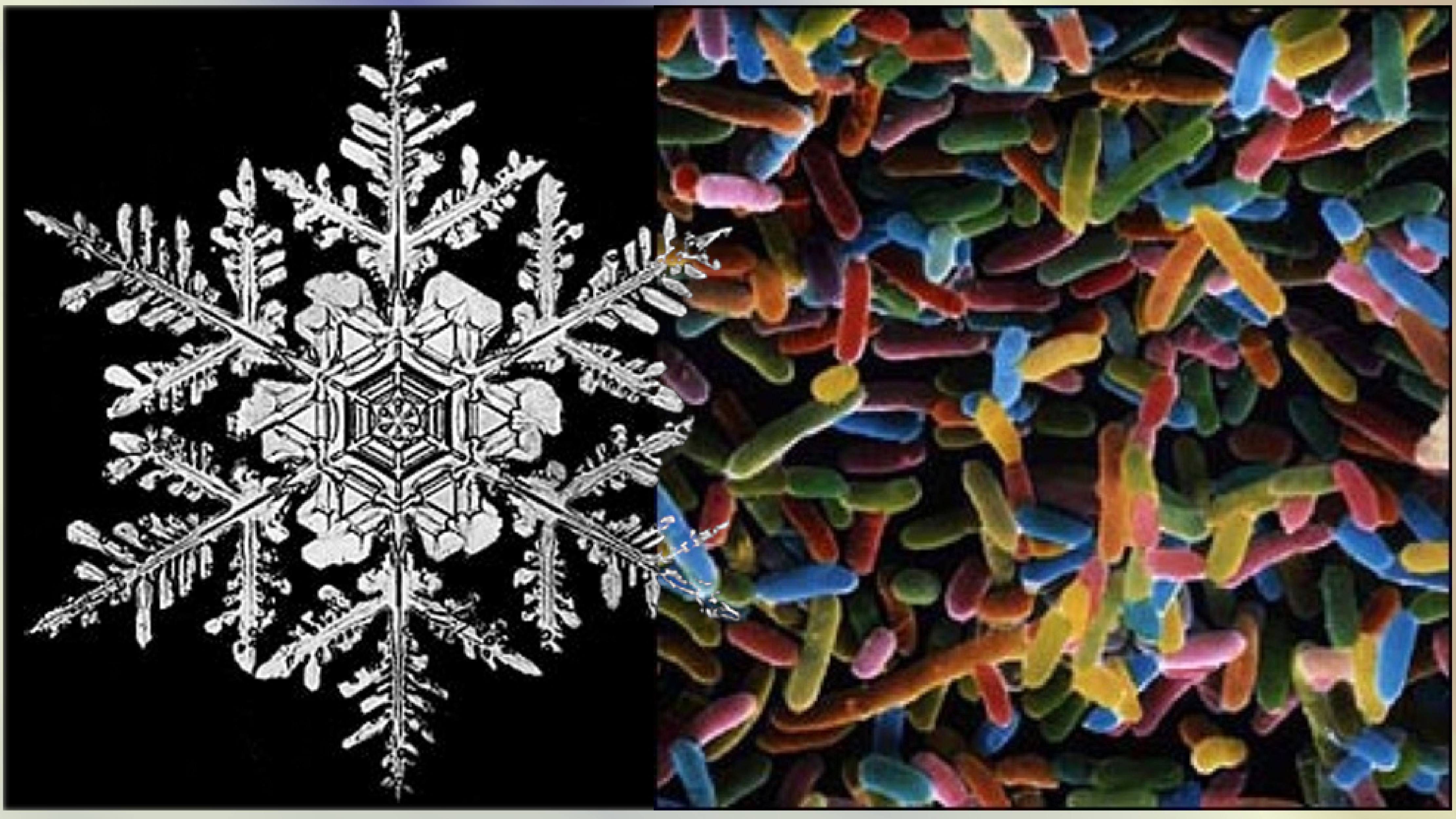




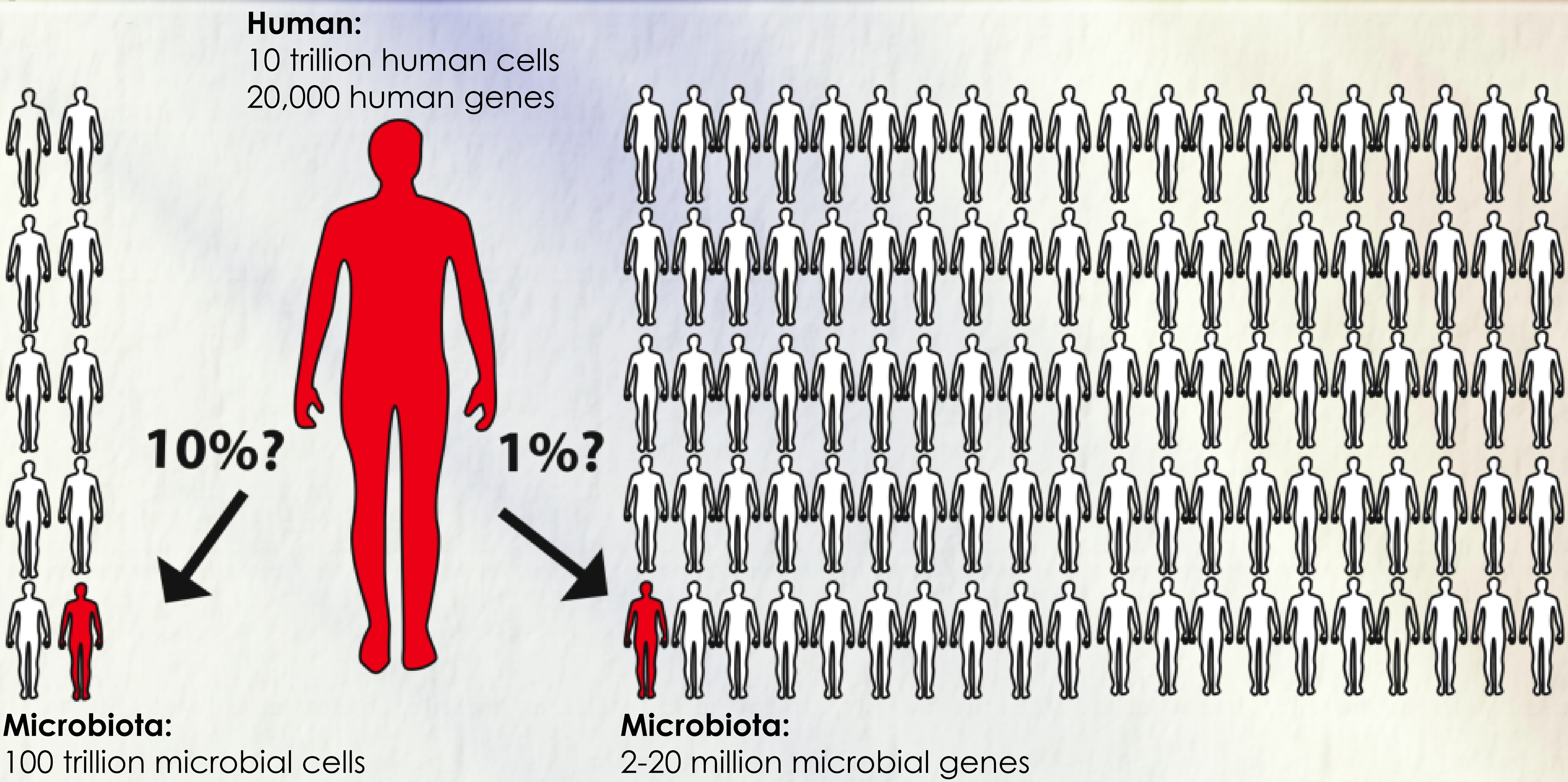


So you are not a beautiful and unique snowflake...

...but your microbial symbionts are!



All this microbial diversity raises question: how human are we?



99.9% of our genomes the same, but our microbes...?

Micah Hamady, PhD thesis, 2009

We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

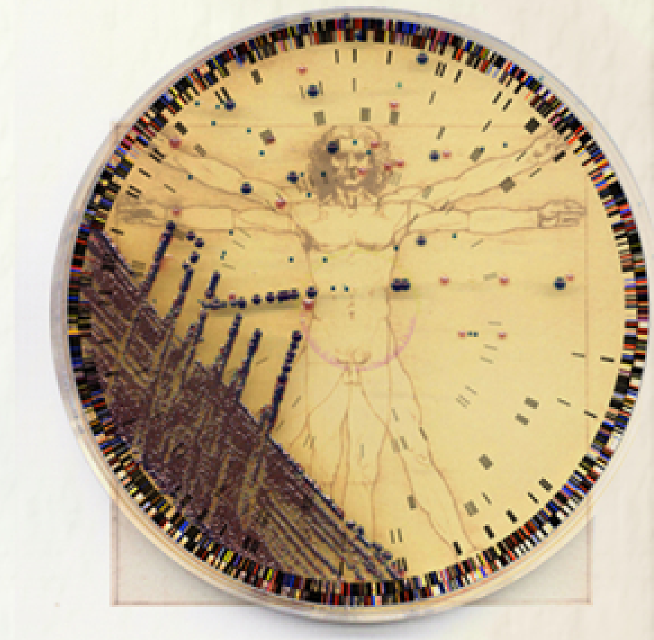
We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

- **How are microbes distributed over our bodies?**

We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?



- **How are microbes distributed over our bodies?**

- **How do our microbes change over time?**

We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

- How are microbes distributed over our bodies?

- How do our microbes change over time?

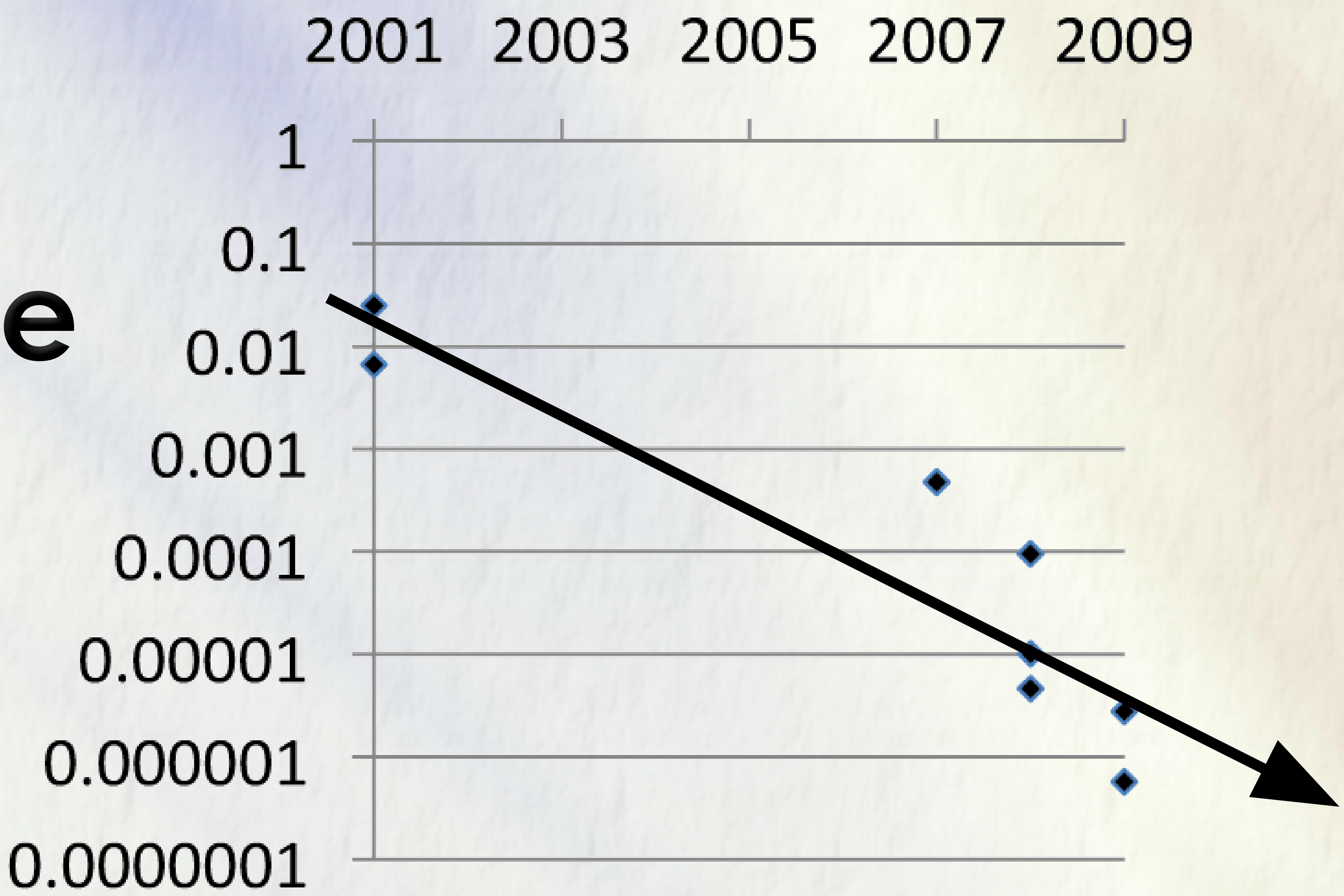
- How can we translate between humans and animal models?

Microbiome studies motivate a broad range of bioinformatics

- Homology search
- Sequence alignment
- Phylogenetic trees
- Assembly
- Functional assignment
- Distance metrics
- Dimensionality reduction
- Supervised and unsupervised classification
- Networks (interaction, biochemical, regulatory)
- Data visualization

Sequencing is getting so cheap...

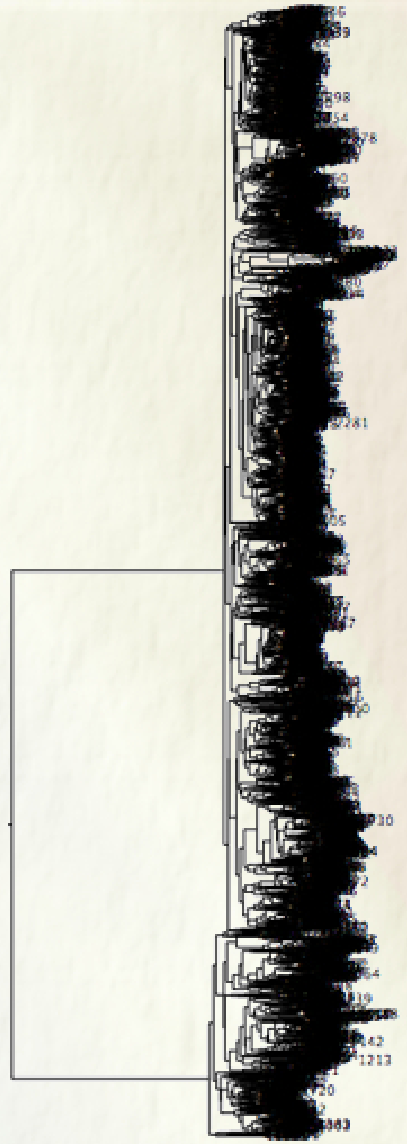
$/base



The issue: need to interpret vast amounts of sequence/tree data

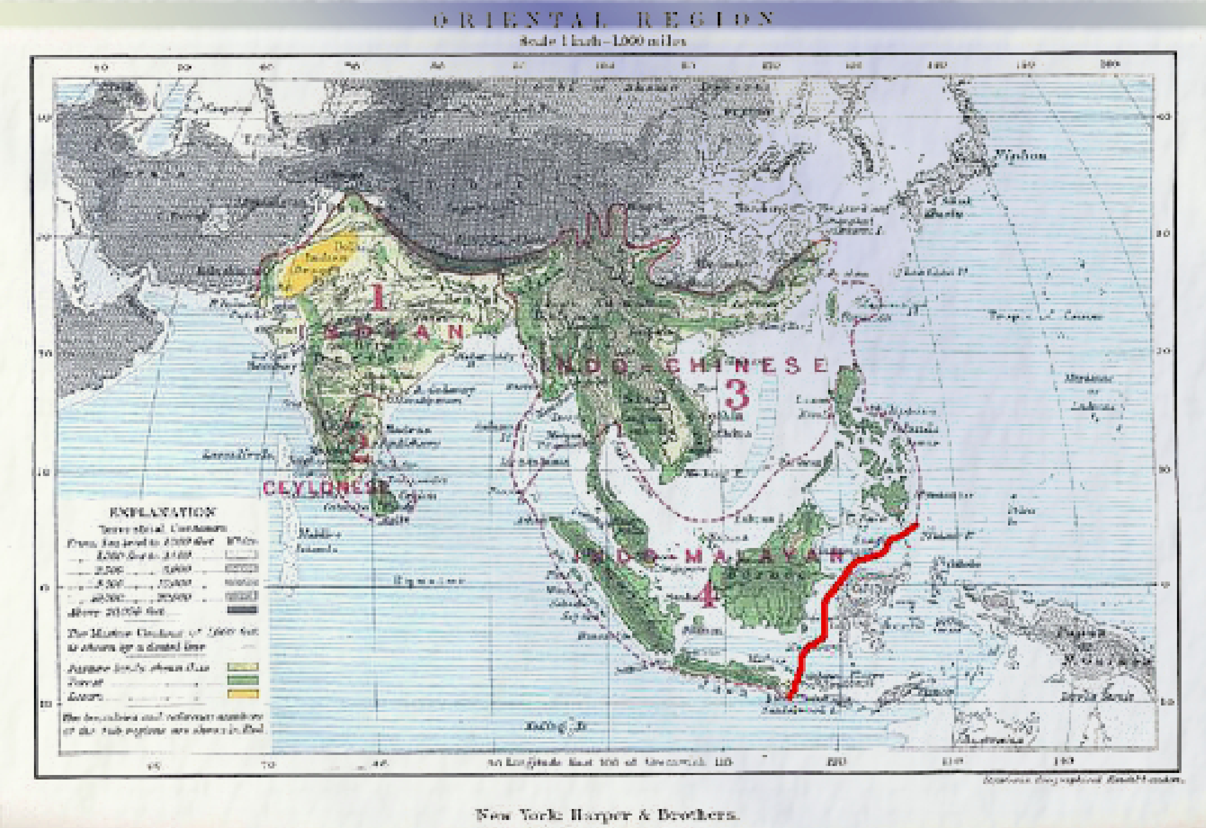
first 9 of 130,000 sequences

~0.1% of the tree file



naive visualization of tree...

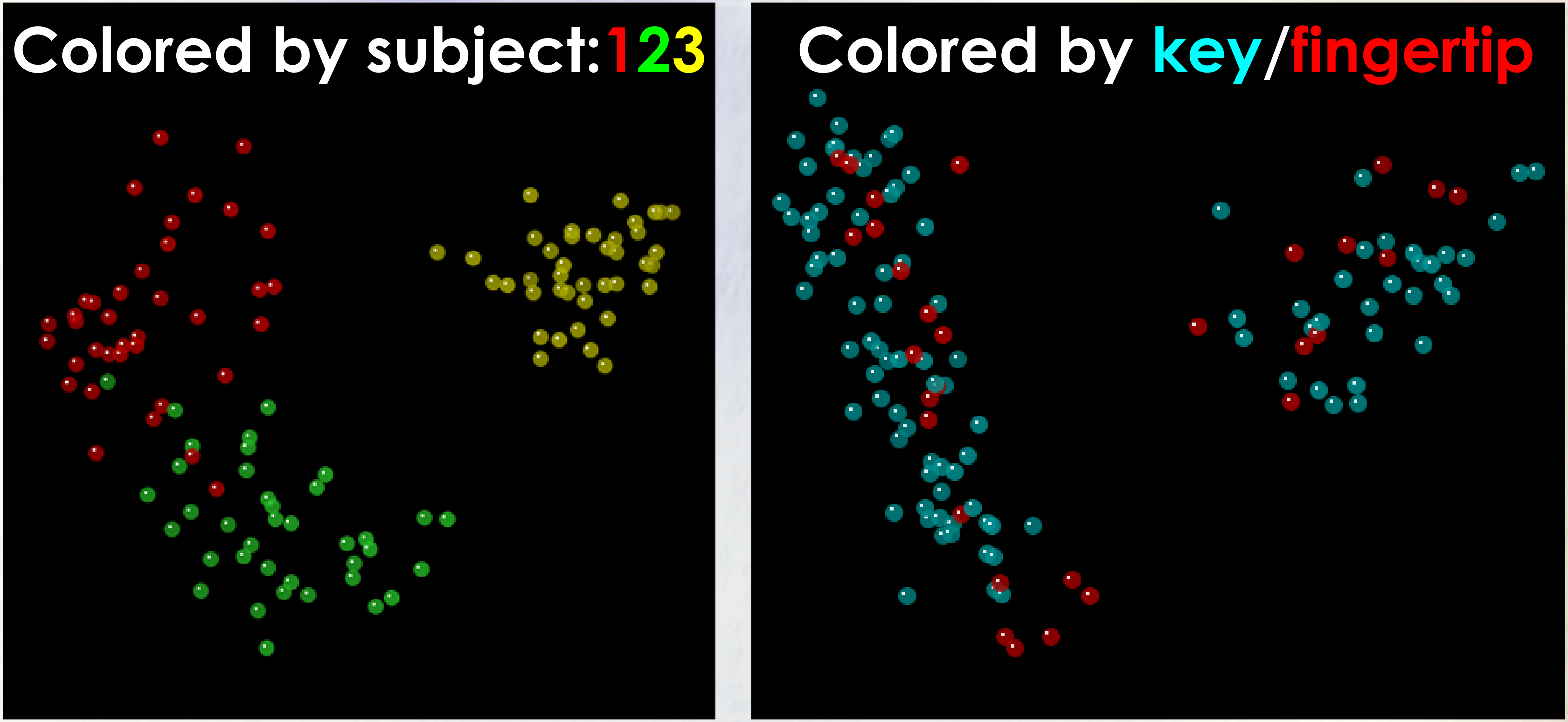
Microbial biogeography on the keyboard?



- Sample keys and fingertips: are keys a desert where few microbes survive?
- Is there a “Wallace line” between G and H? etc.

Fierer et al. 2010 PNAS

Two other views of these same data make patterns clear…



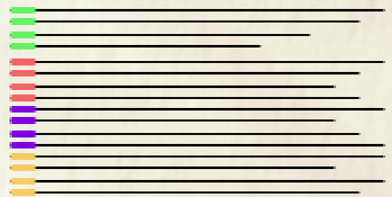
…i.e., each individual has a unique skin community that is transferred from fingertips to keyboards

QIIME: integrating analysis of hundreds of samples

Tag 16S genes from hundreds of samples with DNA barcode

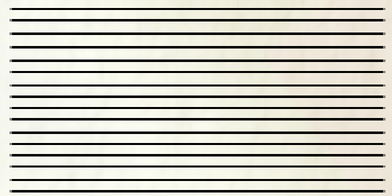
454: short sequence + added barcode

Mix samples and sequence on 454's GS FLX instrument

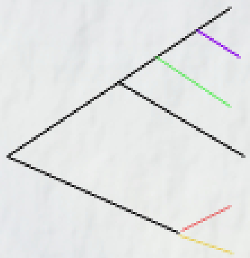


Because each sequence has a barcode, can tell which sample each is from

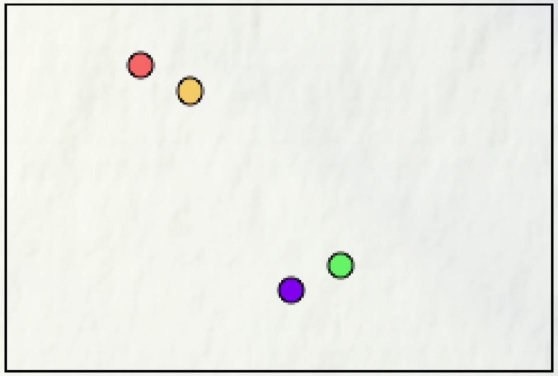
Clip off barcodes



Align sequences to identify taxon-specific regions



Use the sequences to build phylogenetic tree with samples on branches



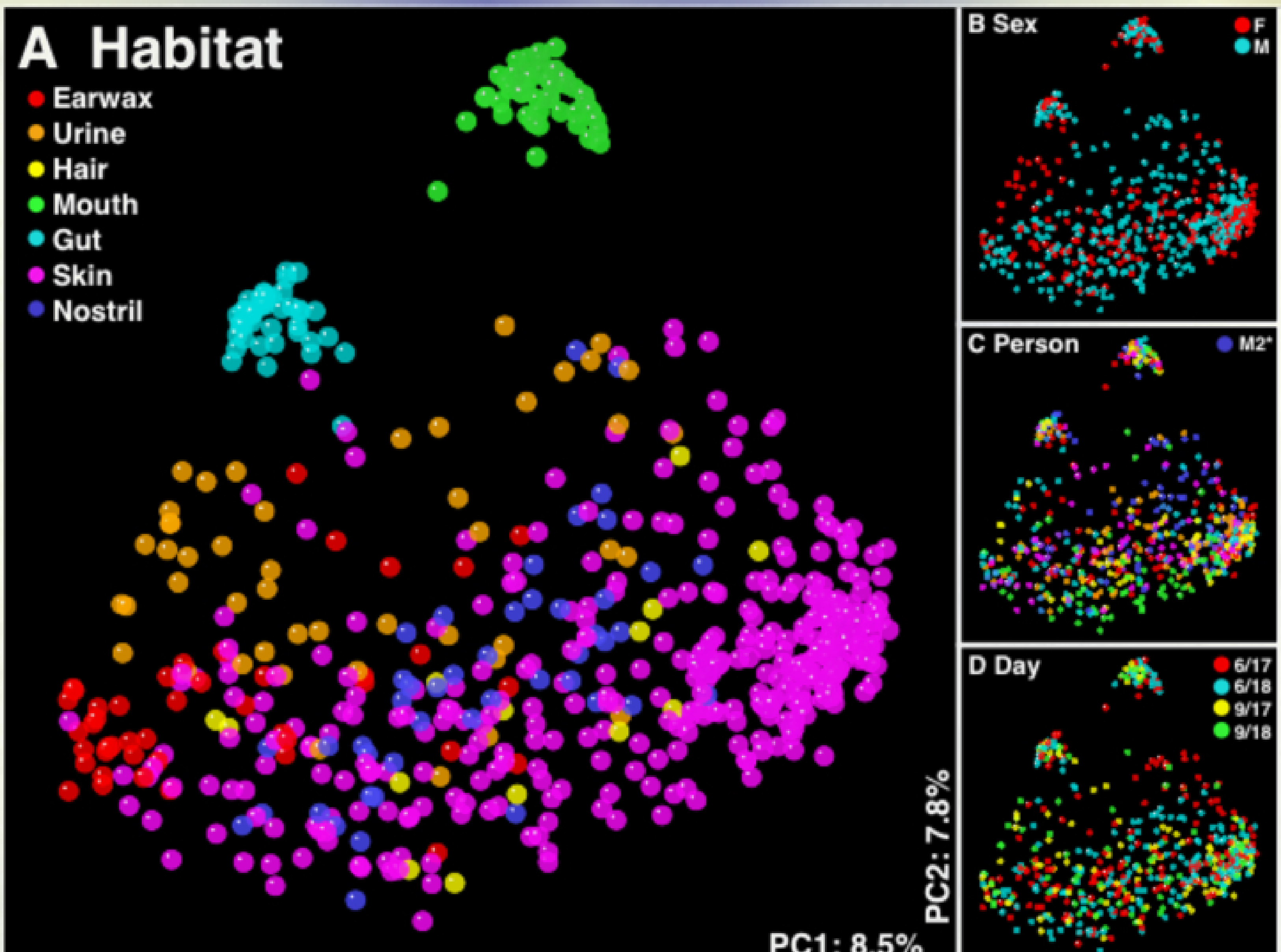
Use the tree to cluster the samples, e.g. healthy/diseased samples cluster?

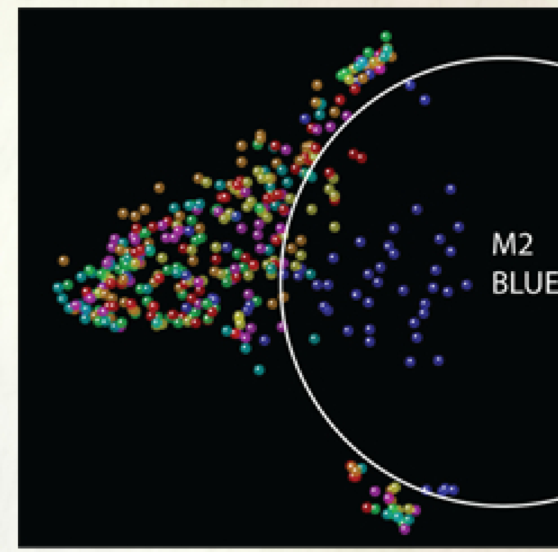
Hamady et al. 2008 Nature Methods 5:235; Caporaso et al. 2010 Nature Methods 7:335

Why is it called “454”?

Why is it called "454"?

Different body habitats are very different from one another

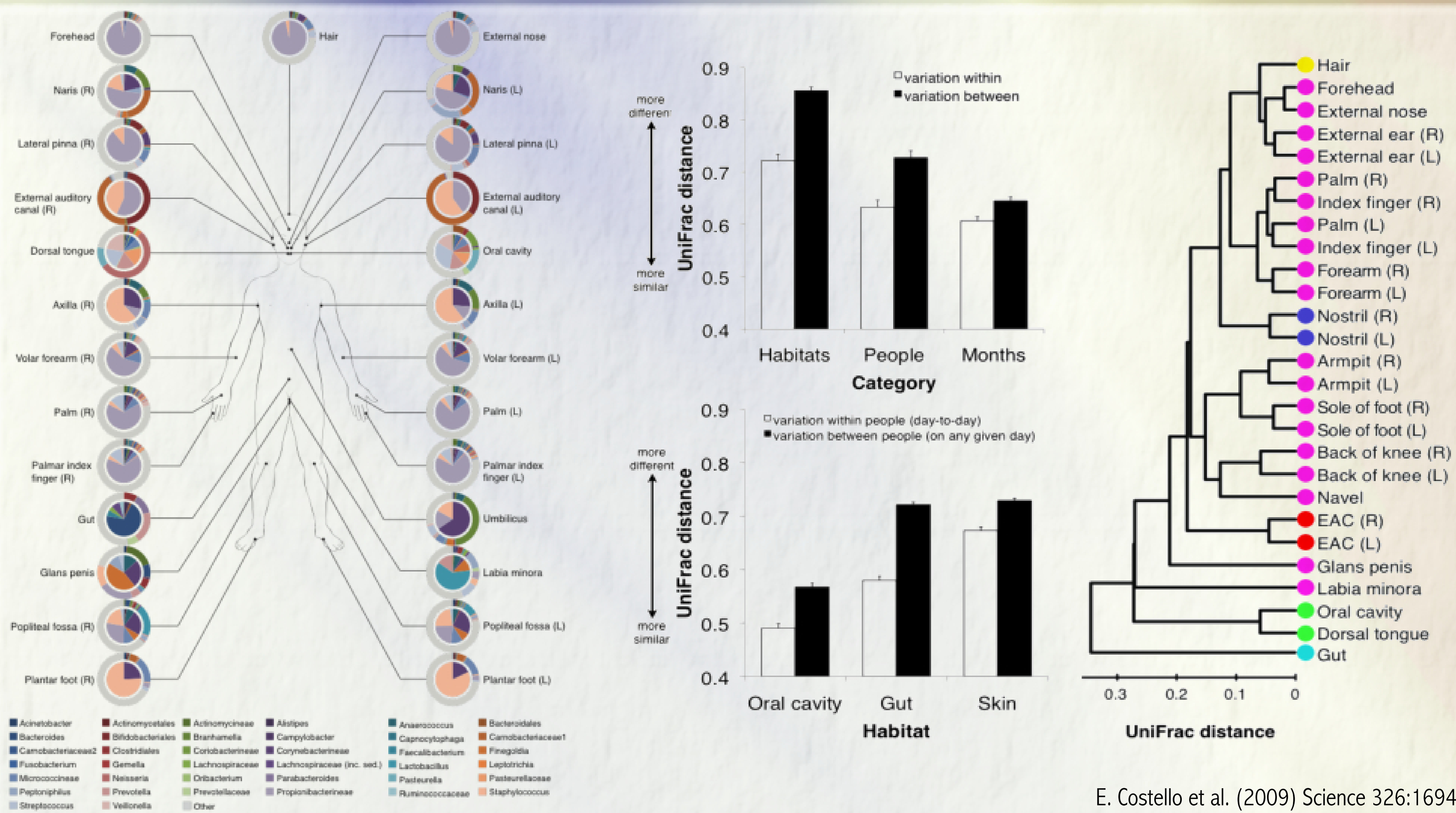




M2 on antibiotics: all body habitats change

Costello et al. (2009), Science 326:1694

Now getting first picture of overall human microbiome variability

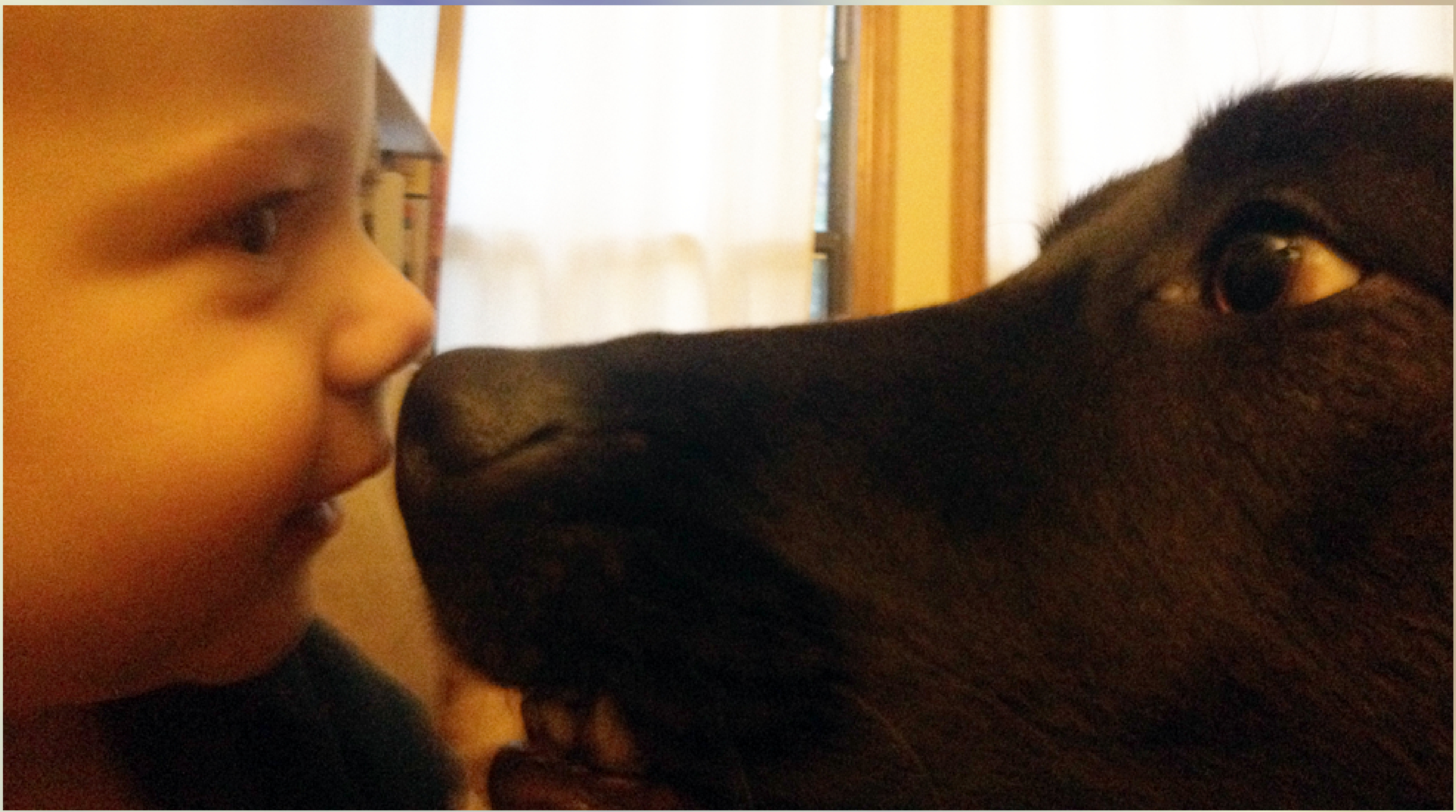


E. Costello et al. (2009) Science 326:1694

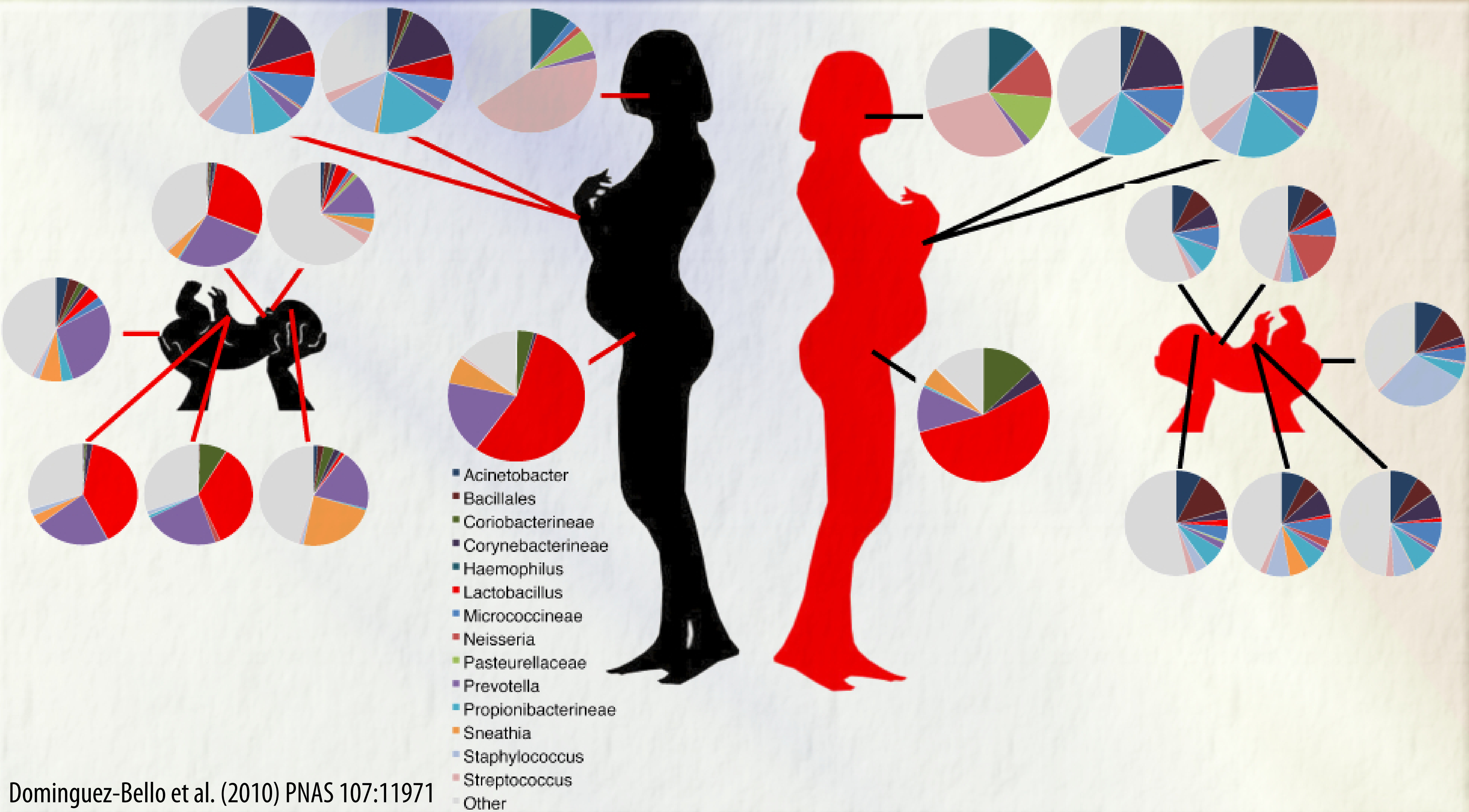
But a handful of timepoints isn't really sufficient...

So where do our microbes come from?

So where do our microbes come from?

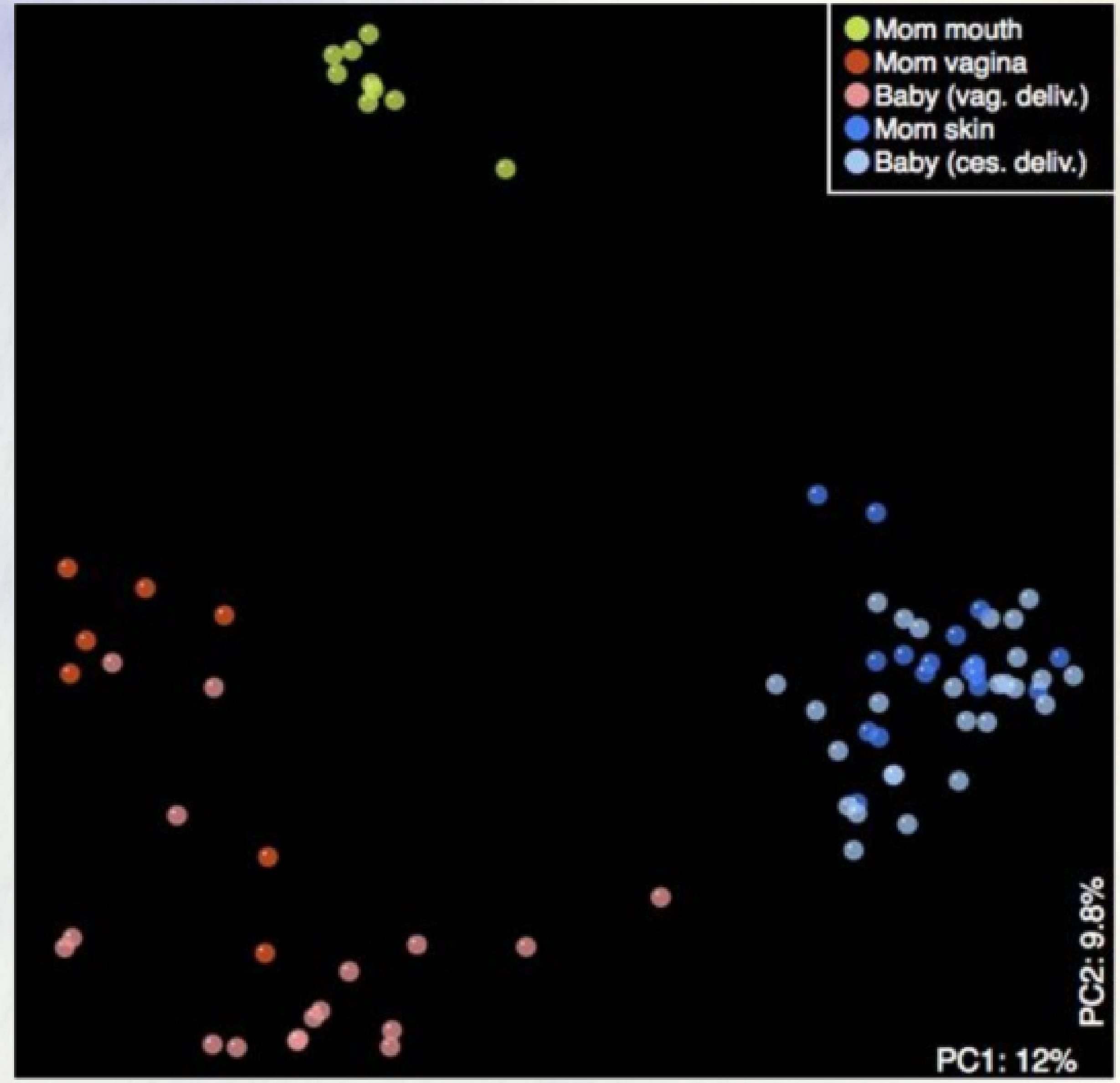


Sampling of the microbiota 20 minutes after birth



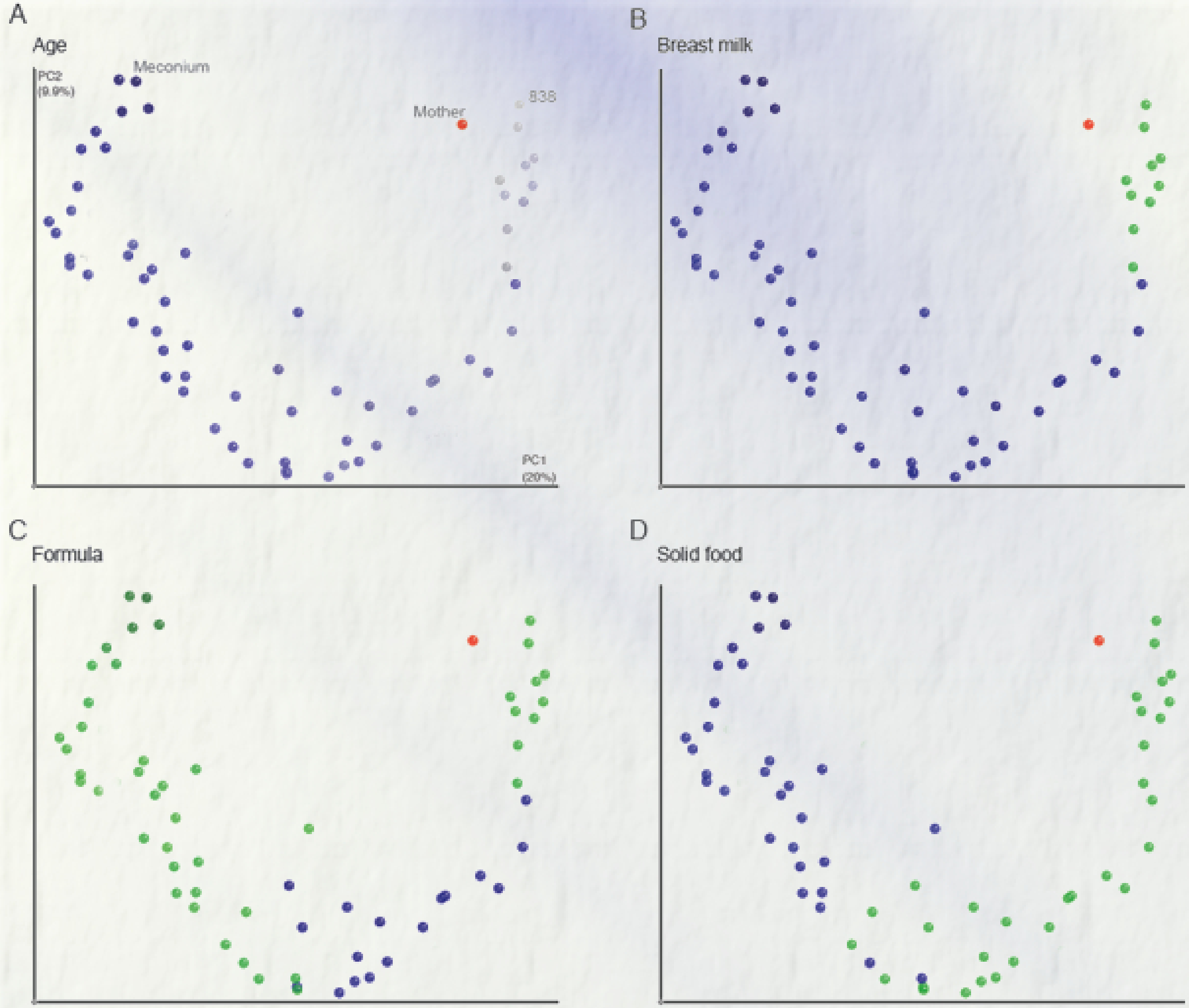
Dominguez-Bello et al. (2010) PNAS 107:11971

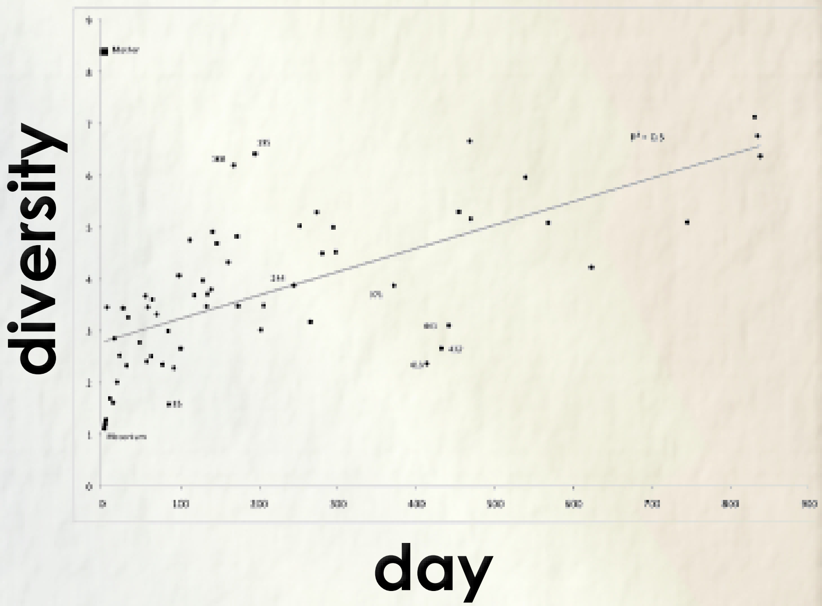
Sampling of the microbiota after birth... (alternative view)



Dominguez-Bello et al. (2010) PNAS 107:11971

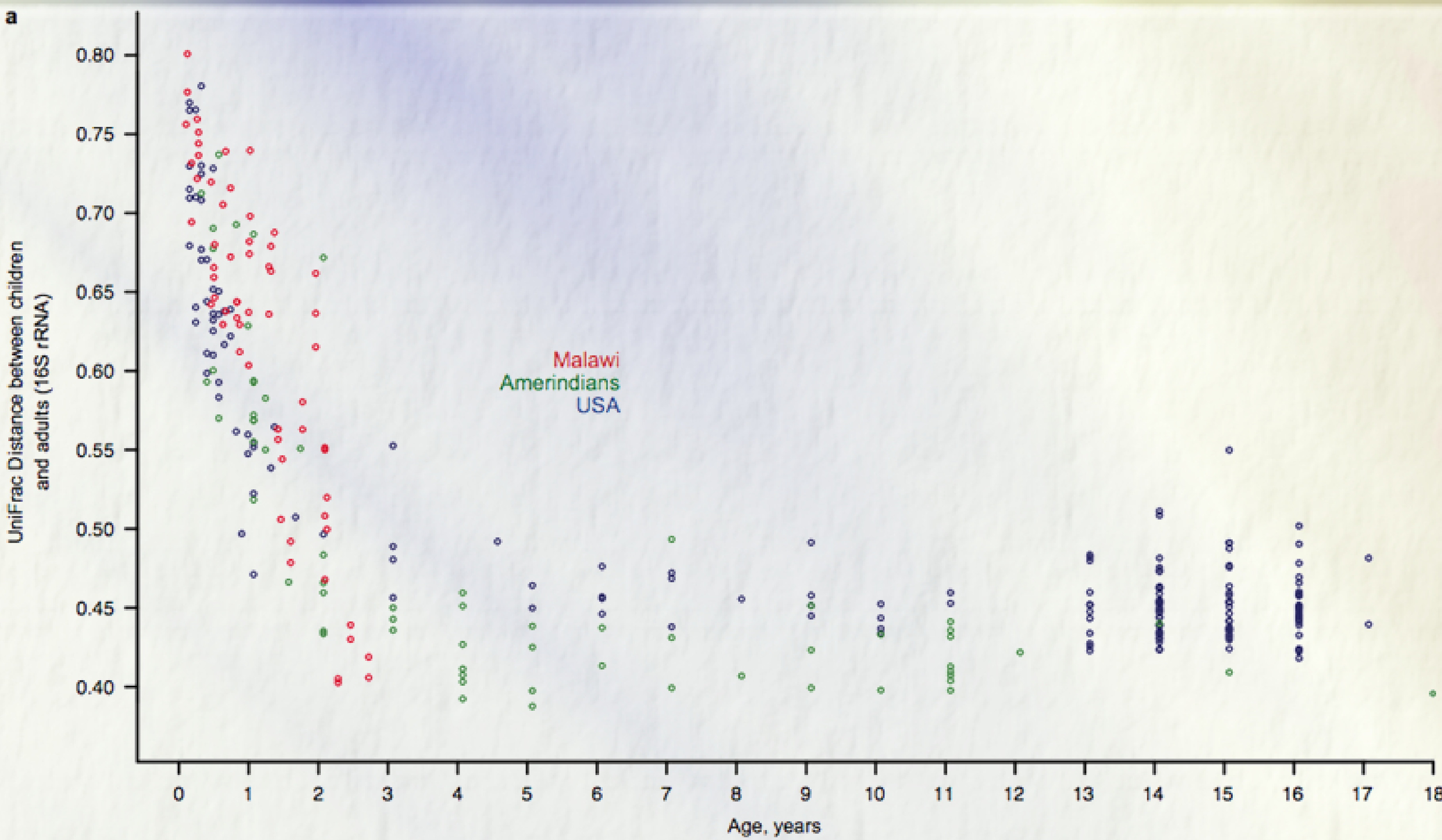
We can understand how the microbiome develops in infants...





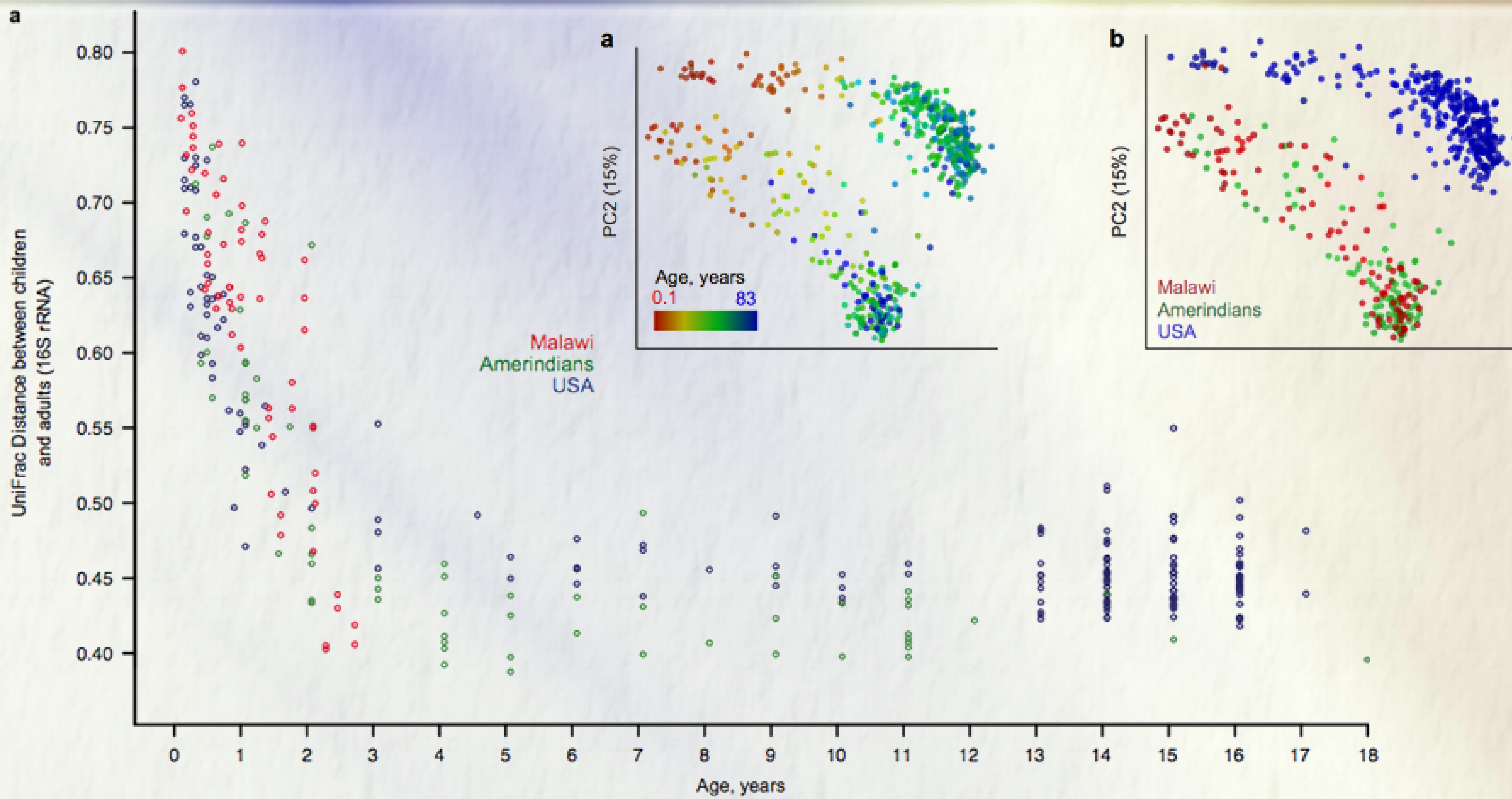
Koenig et al. PNAS 2011 108 suppl 1:4578

...and across cultures...



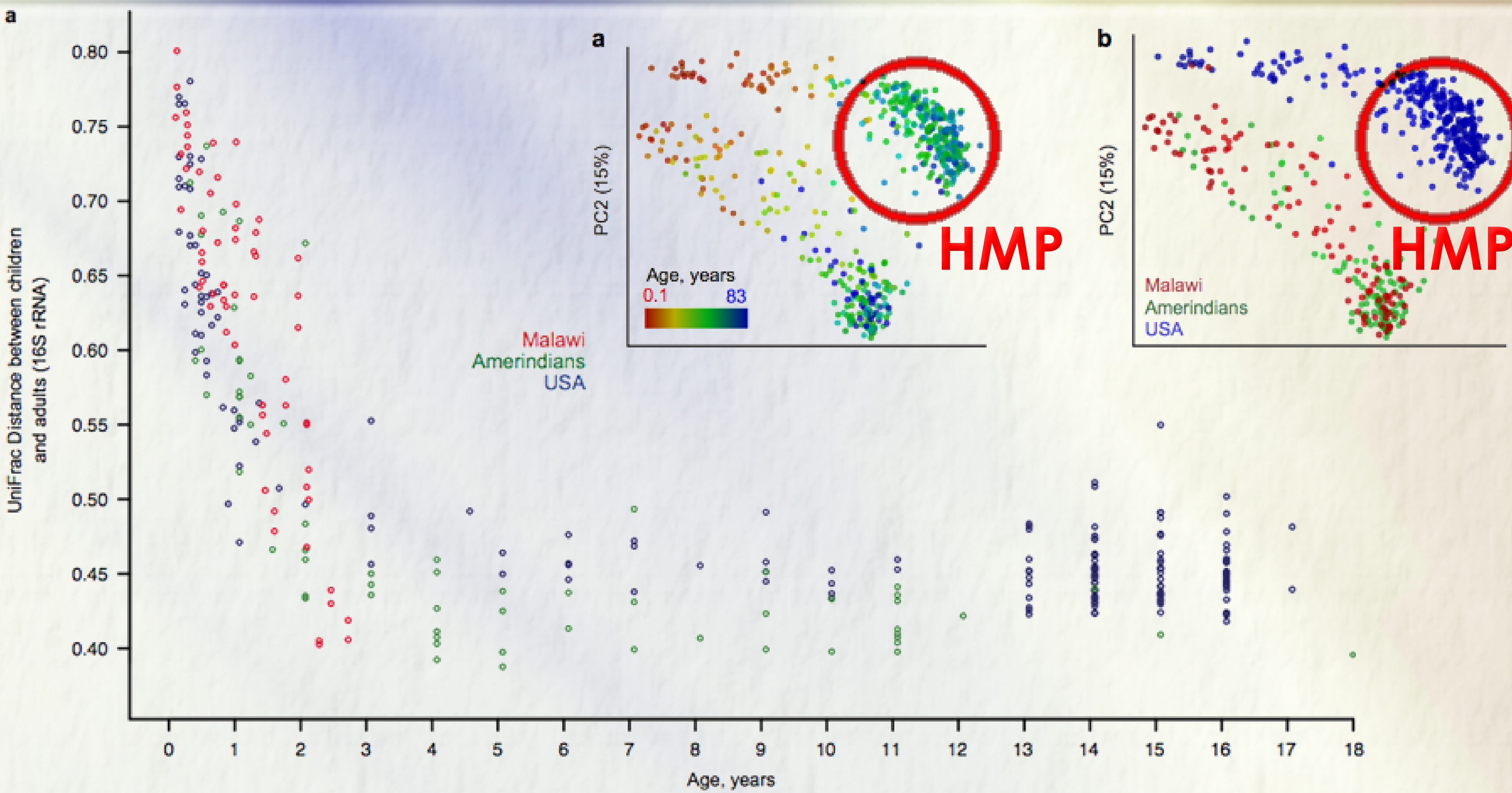
Yatsunenko et al. 2012 Nature 486:222

...although converging on very different endpoints!



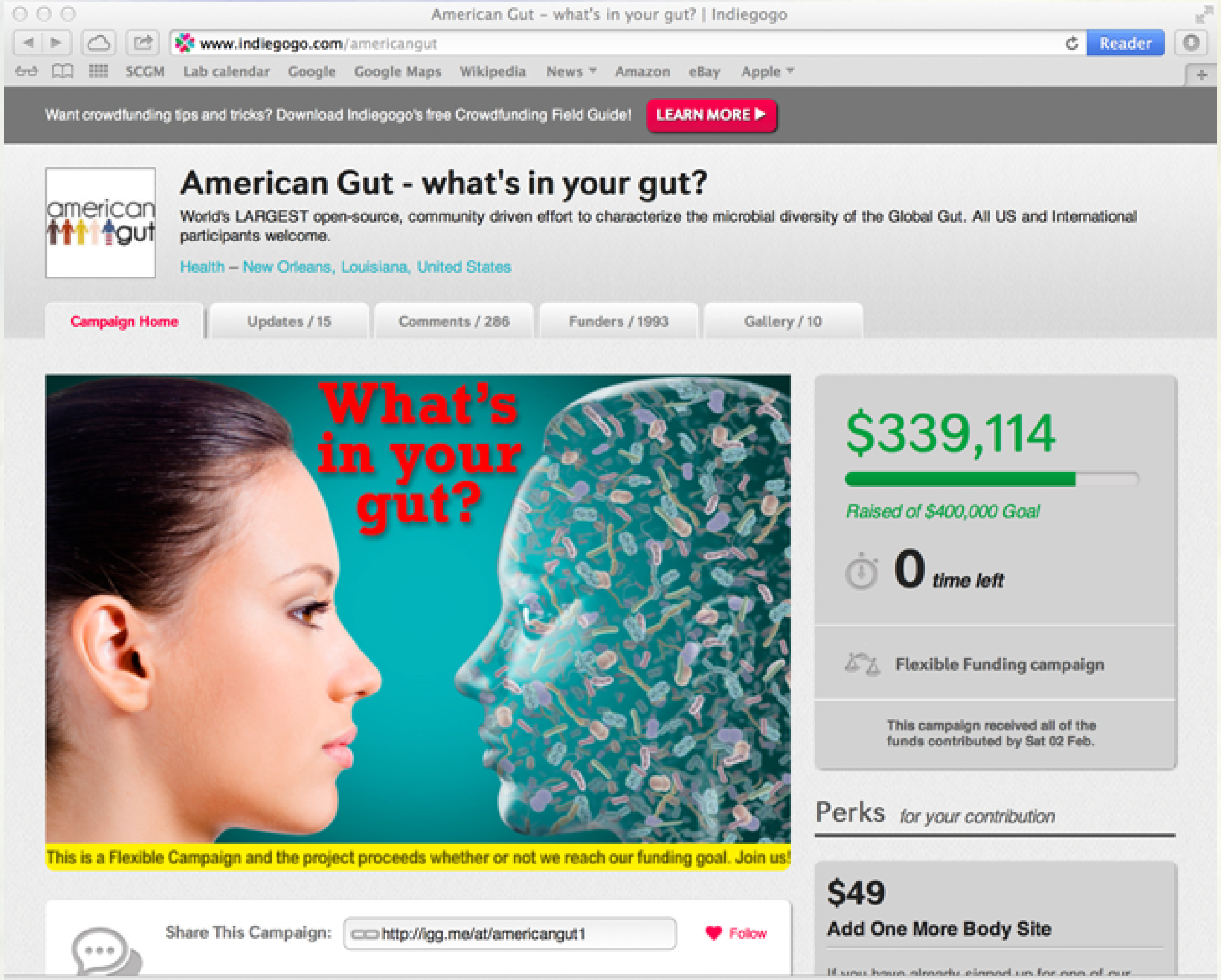
Yatsunenko et al. 2012 Nature 486:222

And the HMP only covers the start of this diversity



Yatsunenko et al. 2012 Nature 486:222

Starting to cover rest of diversity by crowdfunding, with American Gut



American Gut: you can get involved!

>$500k
>6000 people
>1200 kits returned incl 400 PGP samples...

...but we need more!

Of course, not everyone wants to know what's in there...

Data just released into EBI for first 1080 American Gut samples

Preliminary Characterization of the American Gut Population

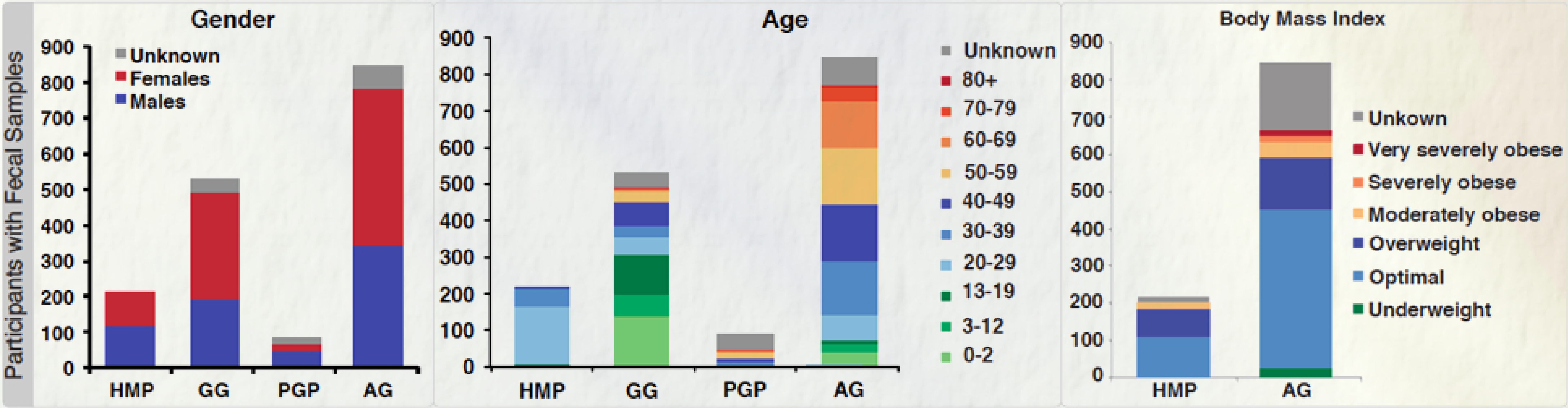
We have, as of September 5, 2013, completed sequencing and quality control of the gut bacteria from the first 1080 samples from 844 participants in the American Gut study. This document gives a first look at results for the whole population. Your individual results (if your sample is among these first 1080 samples) will be available shortly.

Here we compare the American Gut population to other populations who have had their gut bacteria characterized, describe the participants in the study, show the major kinds of bacteria in the gut microbiota of the American Gut population, and provide some information about what affects the gut bacteria (as well as show that some variables such as sex have surprisingly little effect).

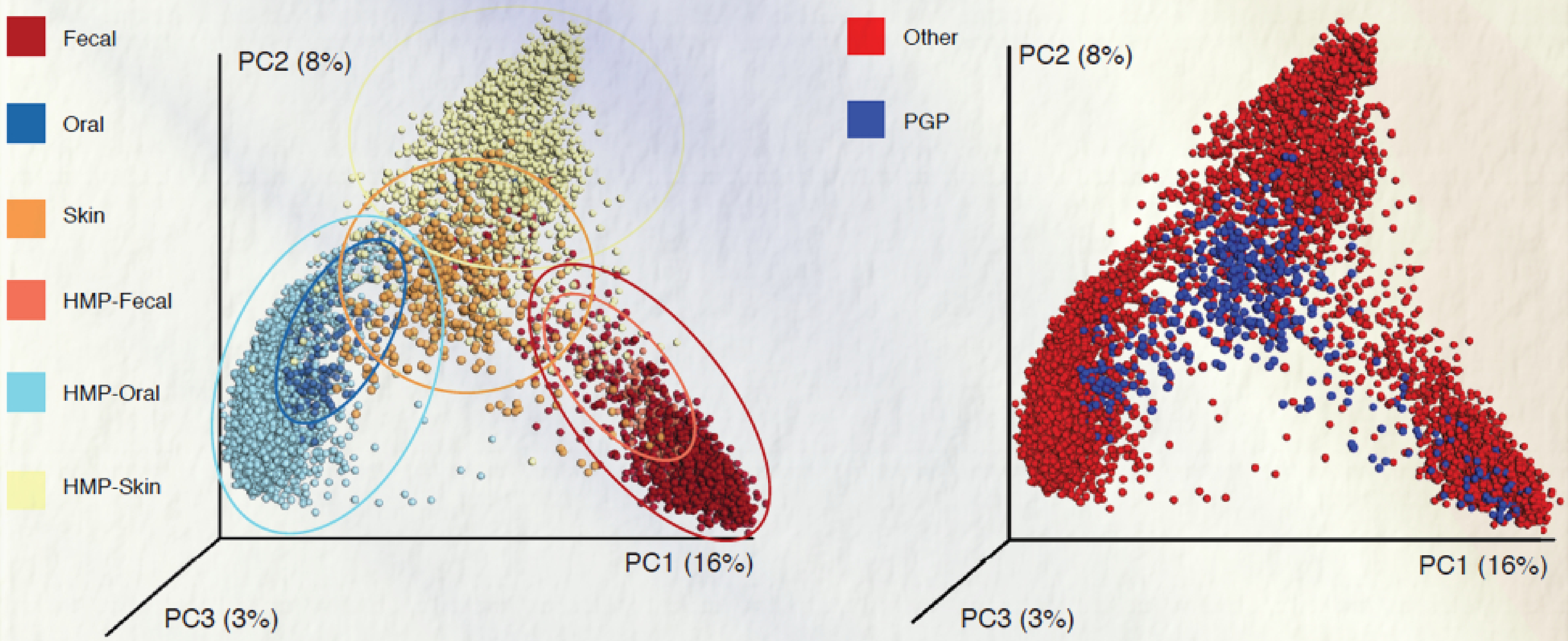
Technical note: "microbiota" refers to a particular community of microbes, including bacteria (e.g. the human gut microbiota); "microbiome" refers to the genes those microbes contain (e.g. the human gut microbiome). Most participants in American Gut have signed up for characterization of the microbiota.

Demographics cover more range than previous studies

	HMP	GG	PGP	AG
Study Subjects	Adults USA	Adults, Children Venezuela, Malawi, USA	Adults	Adults, Children USA
Total Samples	4,788[a]	531[b]	439*	1,080*
Total Participants	242	531	86	844
Sequences	36,797,226	1,093,740,274	9,509,776	45,389,415

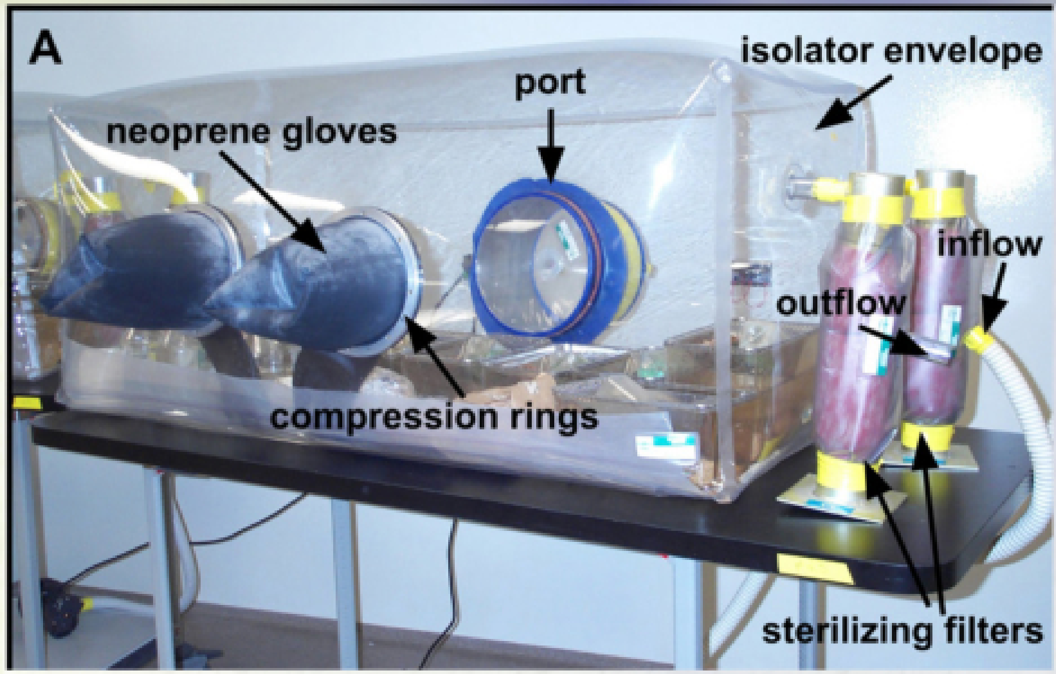


Overall results very consistent with prior studies at overall level...



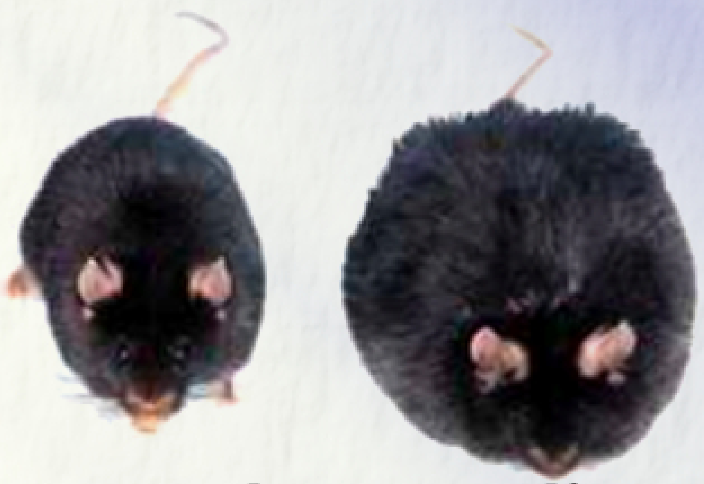
How can I tell cause from effect?

Can’t do Koch’s Postulates in humans, but can use mice



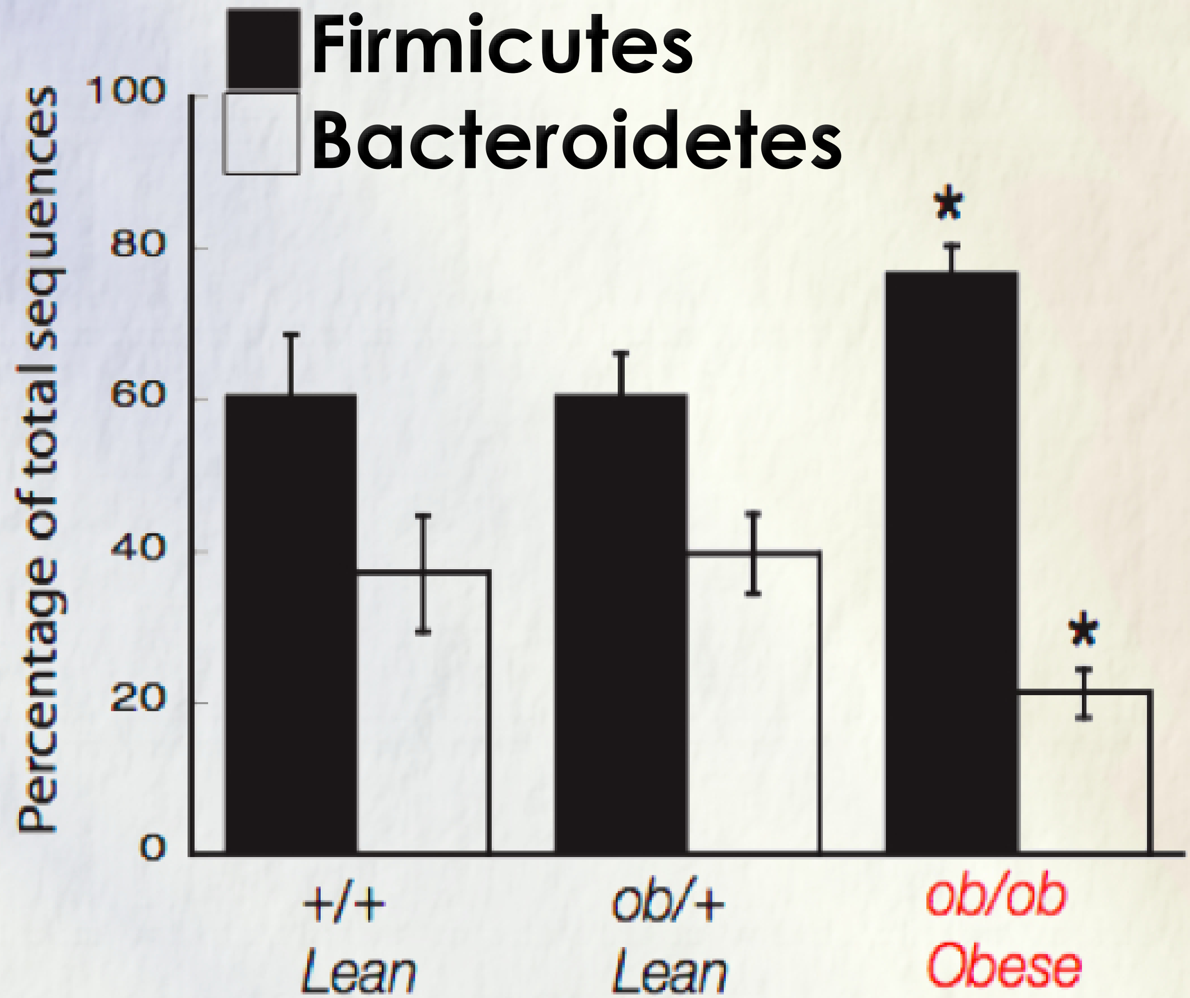
Gnotobiotic isolation units in Jeff Gordon’s lab at Wash U

Do differences in the microbiome matter? Ask a fat mouse...



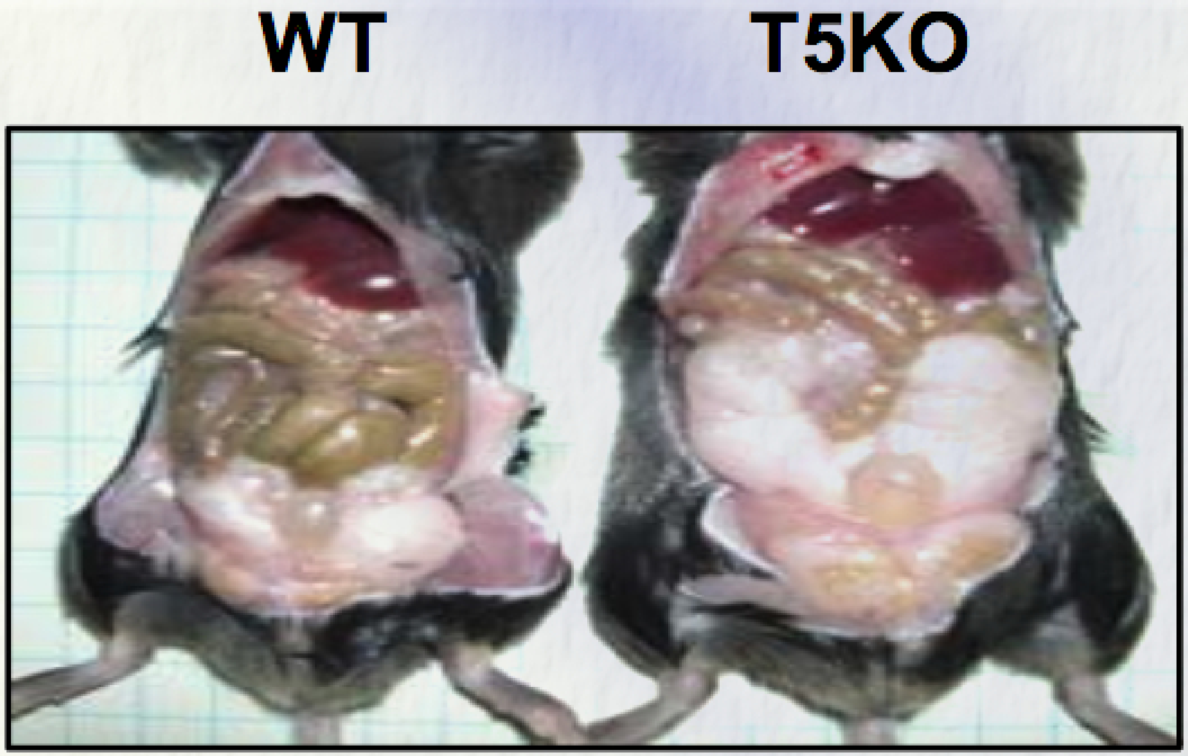
Normal mouse (+/+)

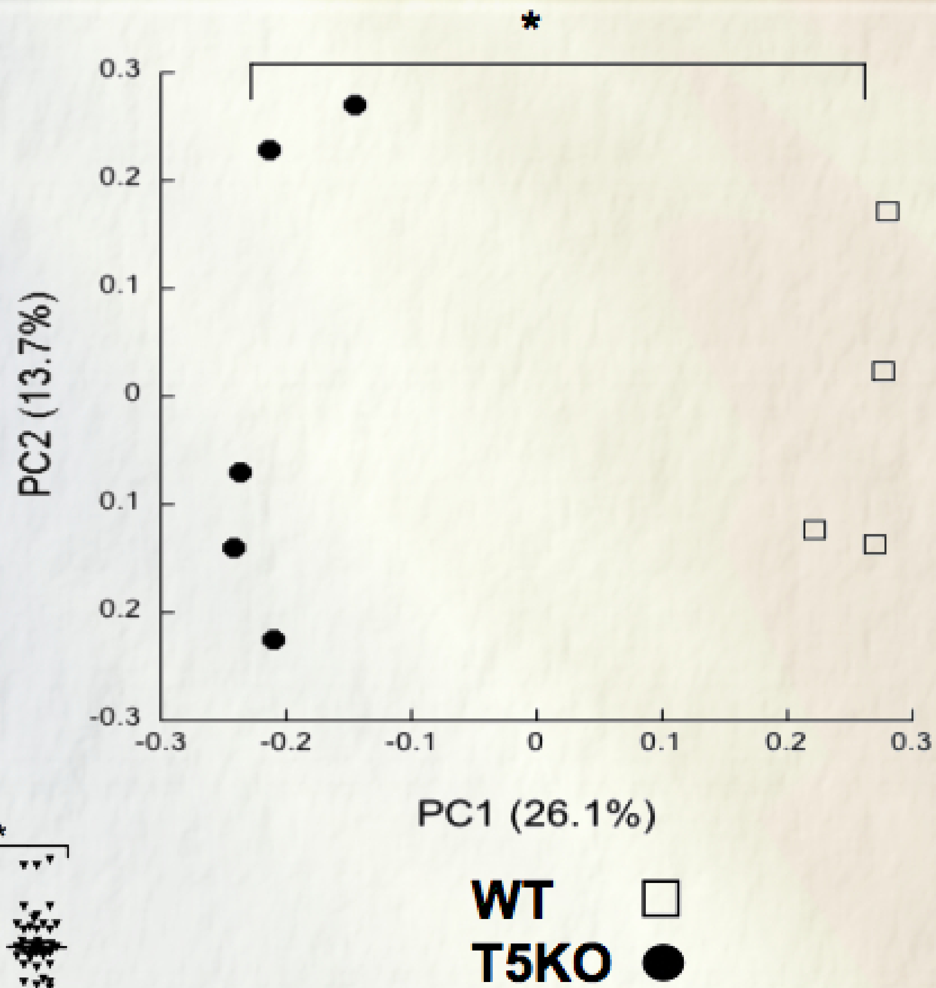
Leptin mutant (*ob/ob*)

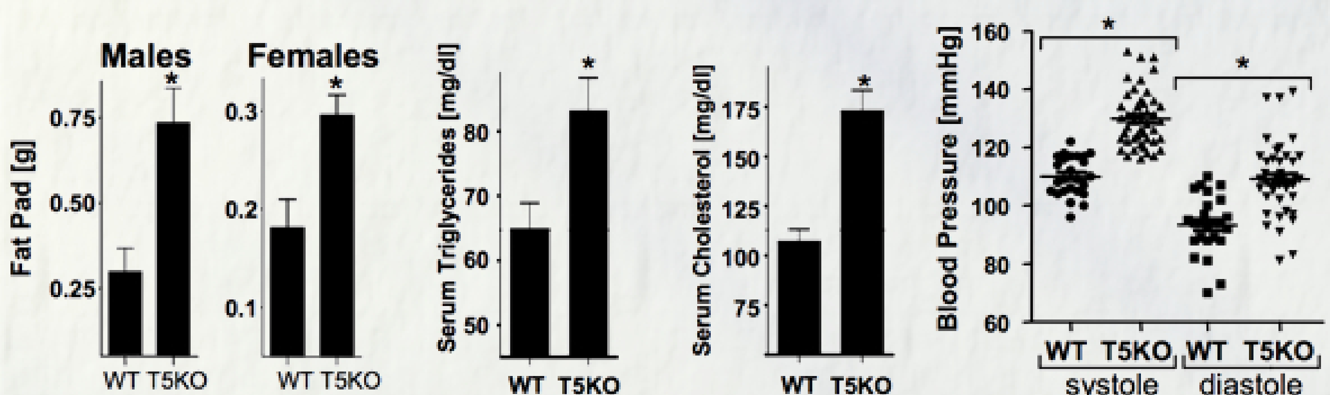


Ley et al. 2005 PNAS 102:11070

TLR5 mutant mice get fat for a different reason...

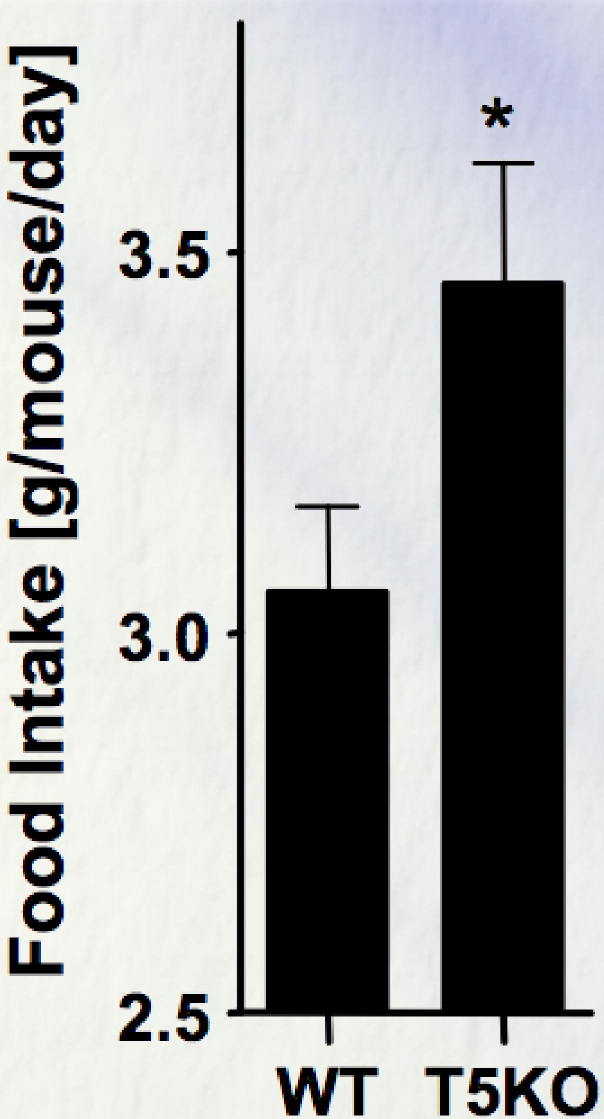






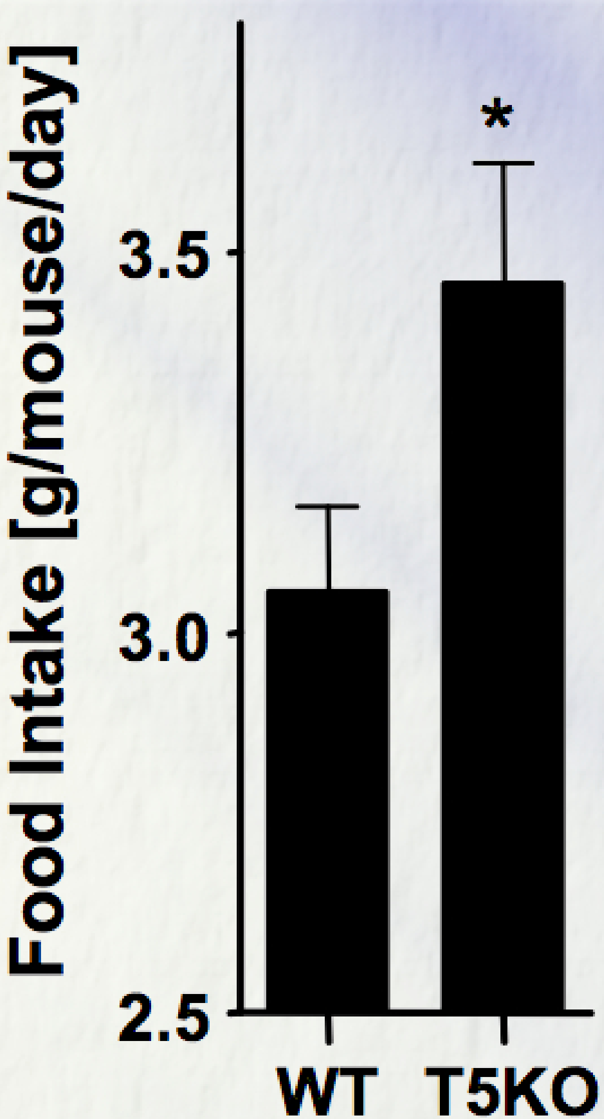
Vijay-Kumar et al. 2010 Science

...their transmissible gut microbes make them want to eat more!

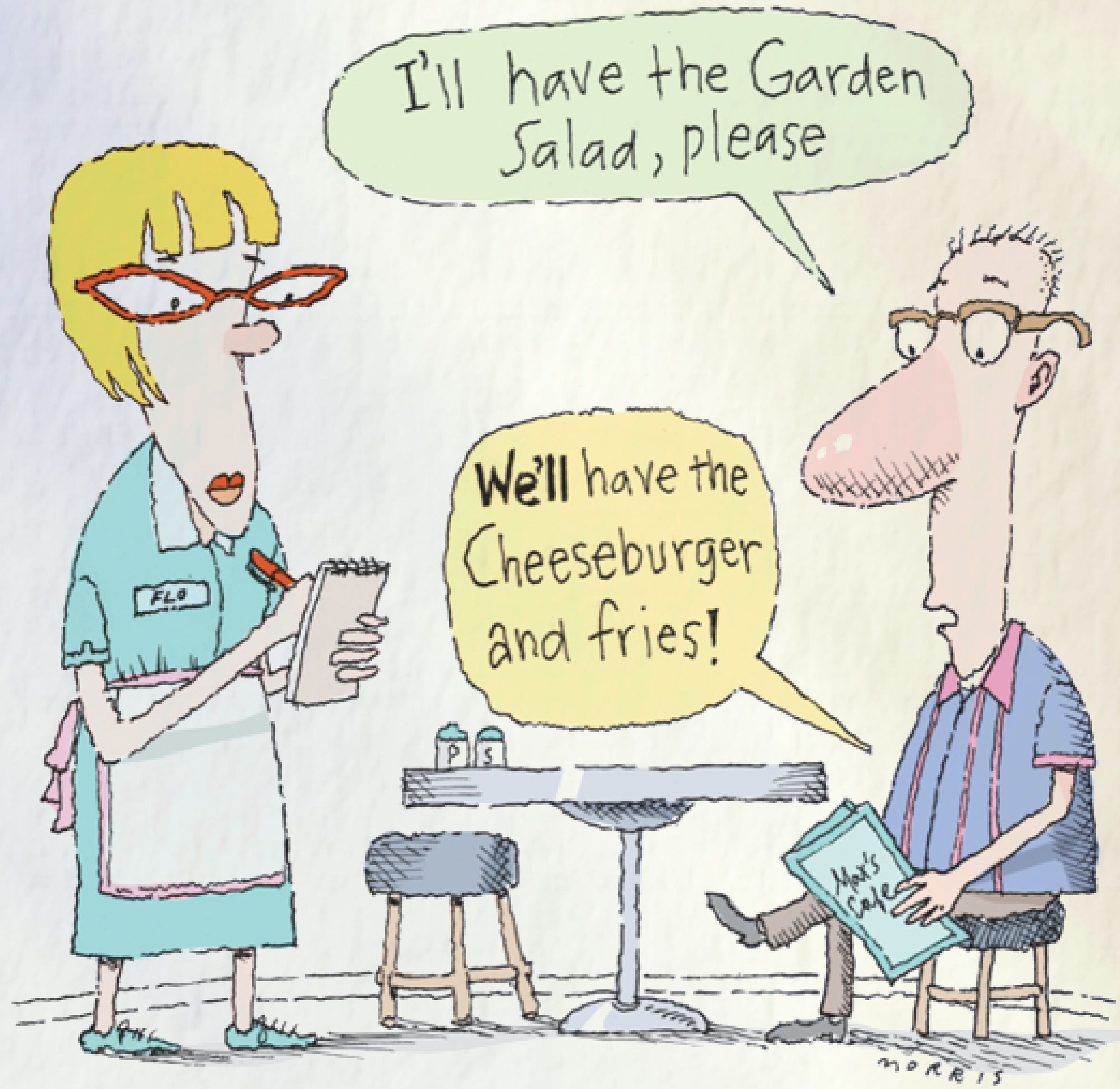


Vijay-Kumar et al. 2010 Science

...their transmissible gut microbes make them want to eat more!



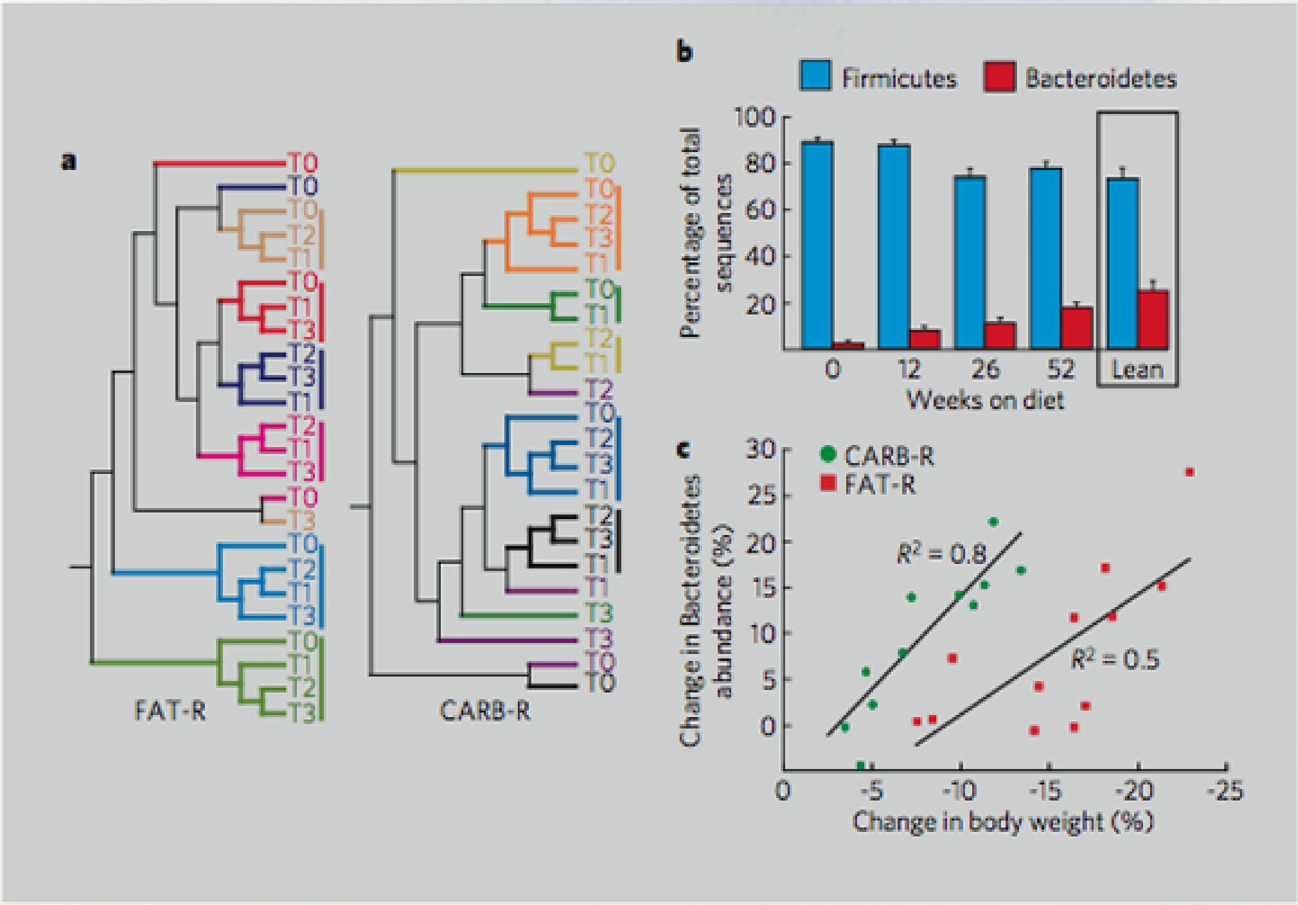
Vijay-Kumar et al. 2010 Science



Do the results extend to humans? Apparently so...

MICROBIAL ECOLOGY

Human gut microbes associated with obesity



Ruth E. Ley, Peter J. Turnbaugh, Samuel Klein, Jeffrey I. Gordon

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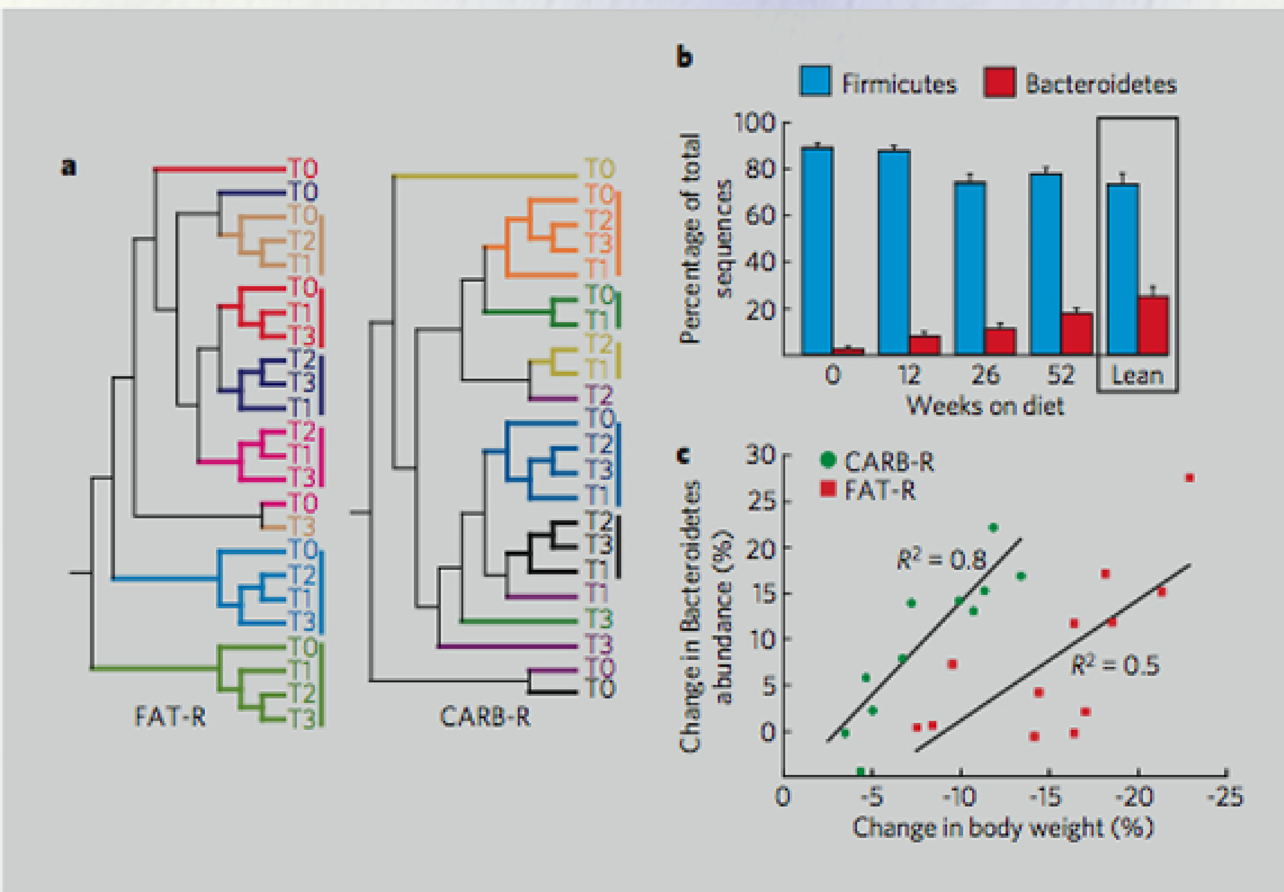
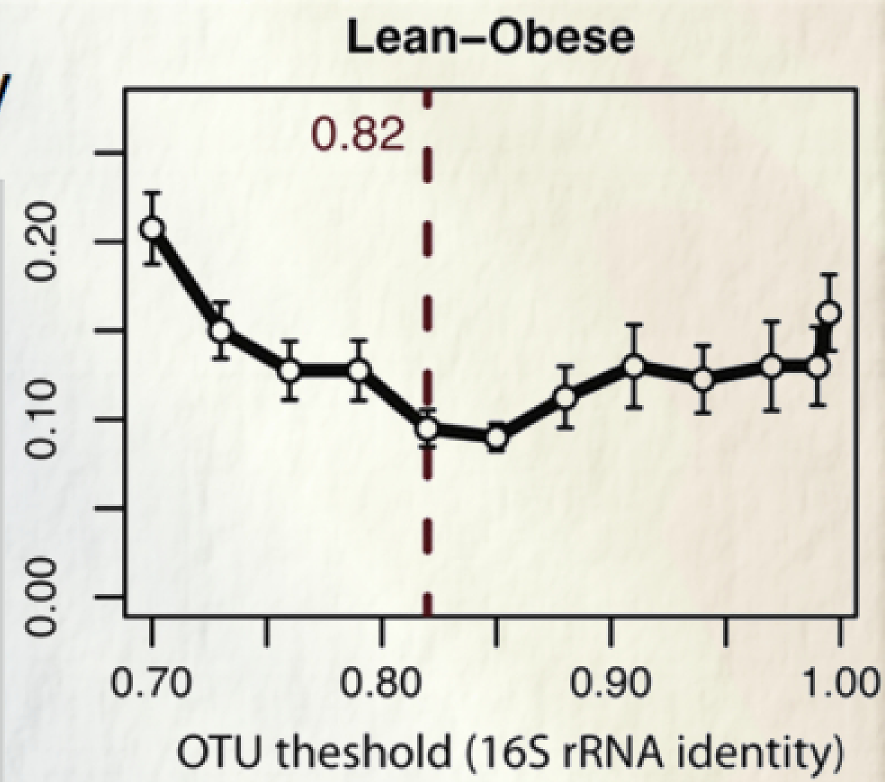


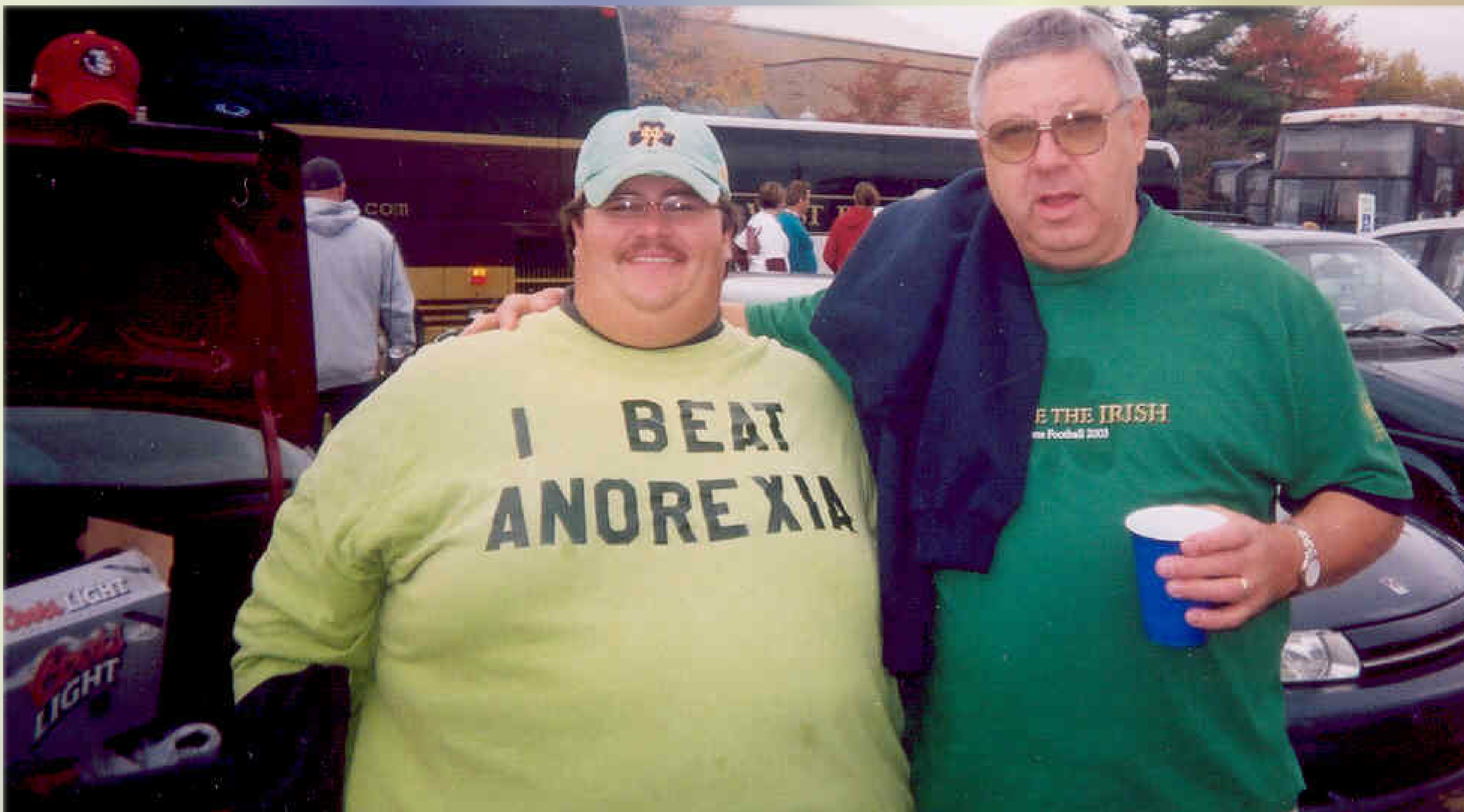
Ruth E. Ley, Peter J. Turnbaugh, Samuel Klein, Jeffrey I. Gordon



Classify lean/obese with 90% accuracy by microbiome

Knights et al. 2011 Cell Host & Microbe

...so can we change the microbiome to cure disease...?



Future directions: personalized medicine in developing nations?

Future directions: personalized medicine in developing nations?

Cell phones ubiquitous in Malawi due to Moore's Law...

Future directions: personalized medicine in developing nations?

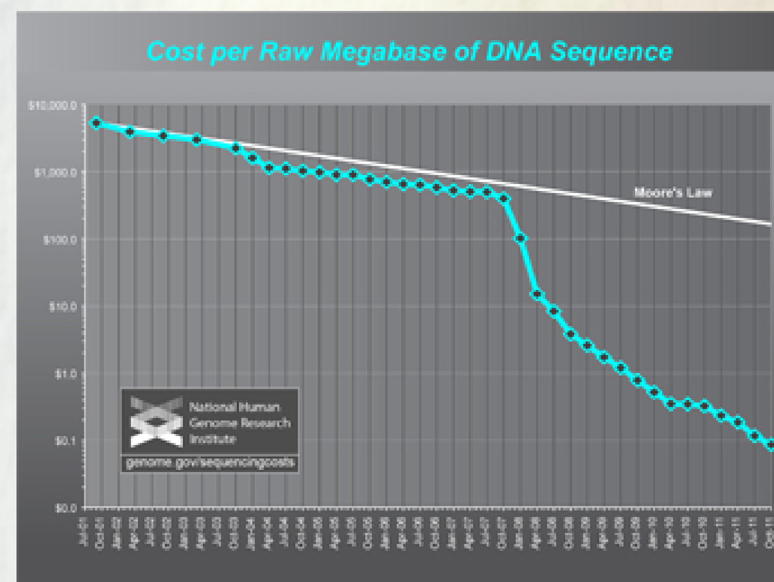
Photo: Tanya Yatsunenko, Malawi 2009

Cell phones ubiquitous in Malawi due to Moore's Law...

...and not just in Malawi, but everywhere...

Future directions: personalized medicine in developing nations?

Cell phones ubiquitous in Malawi due to Moore's Law...



...will DNA sequencing follow?

Pilot studies in humanized mice

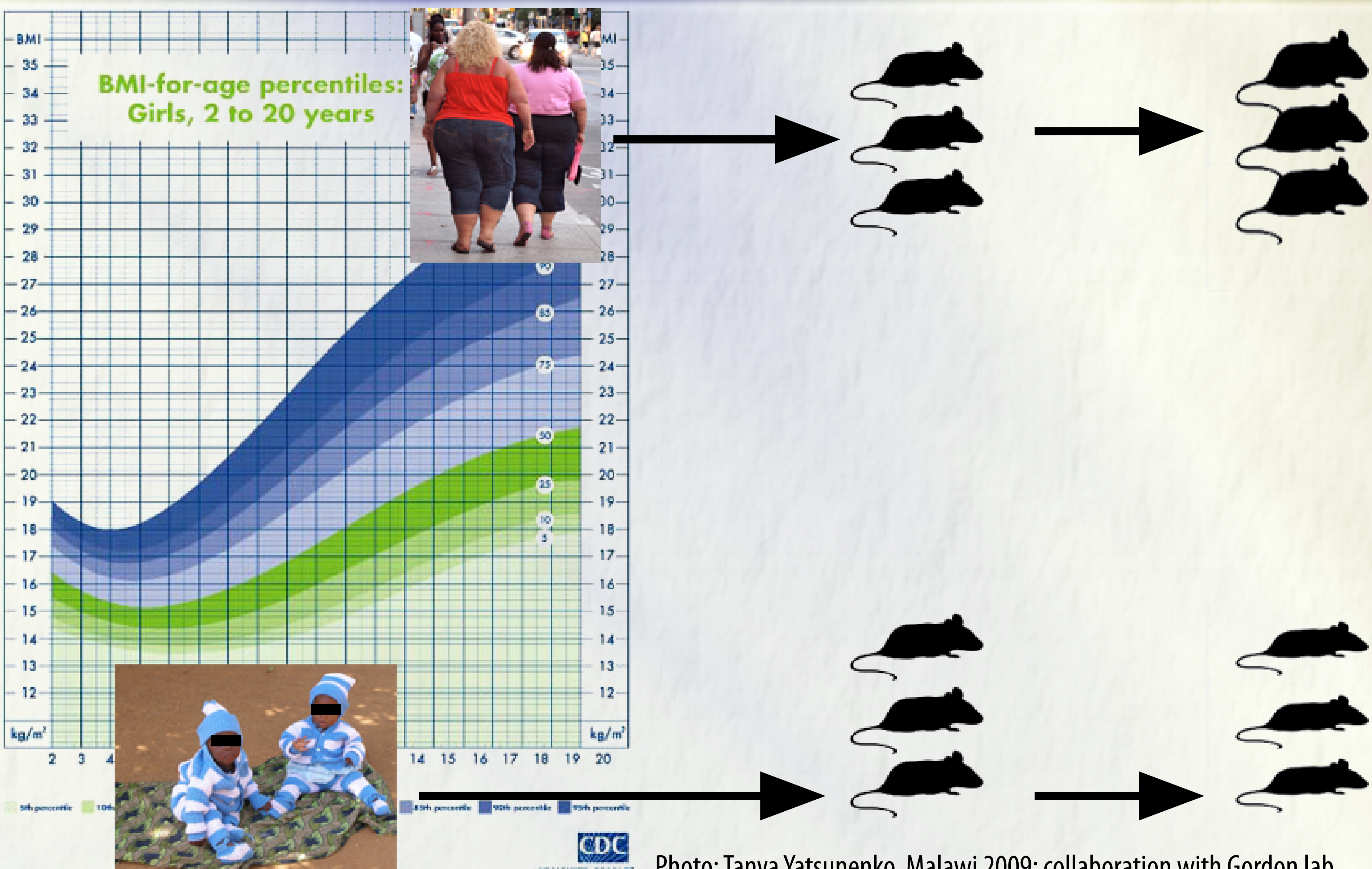


Photo: Tanya Yatsunenko, Malawi 2009; collaboration with Gordon lab

Pilot studies in humanized mice: input microbes, diet change BMI

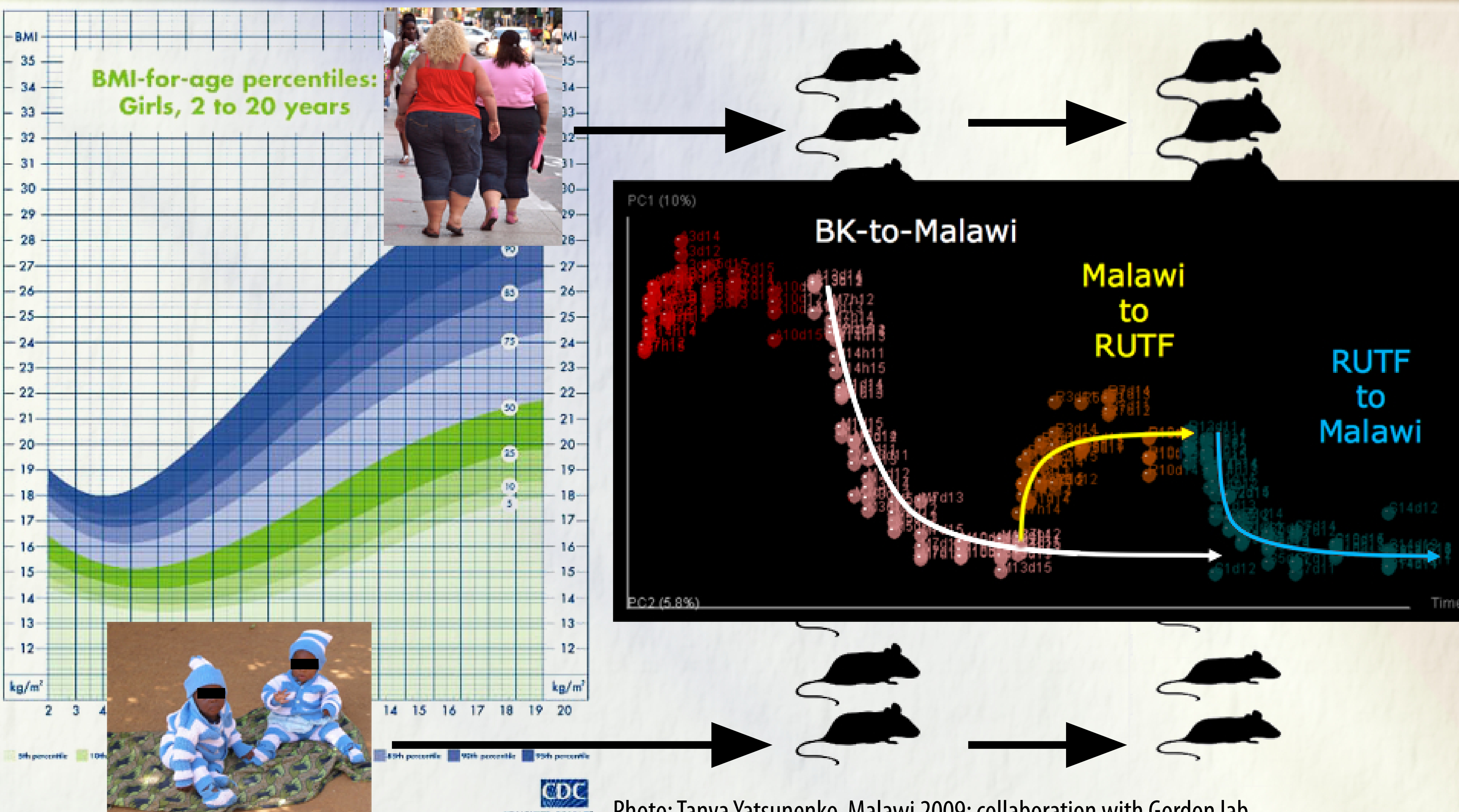
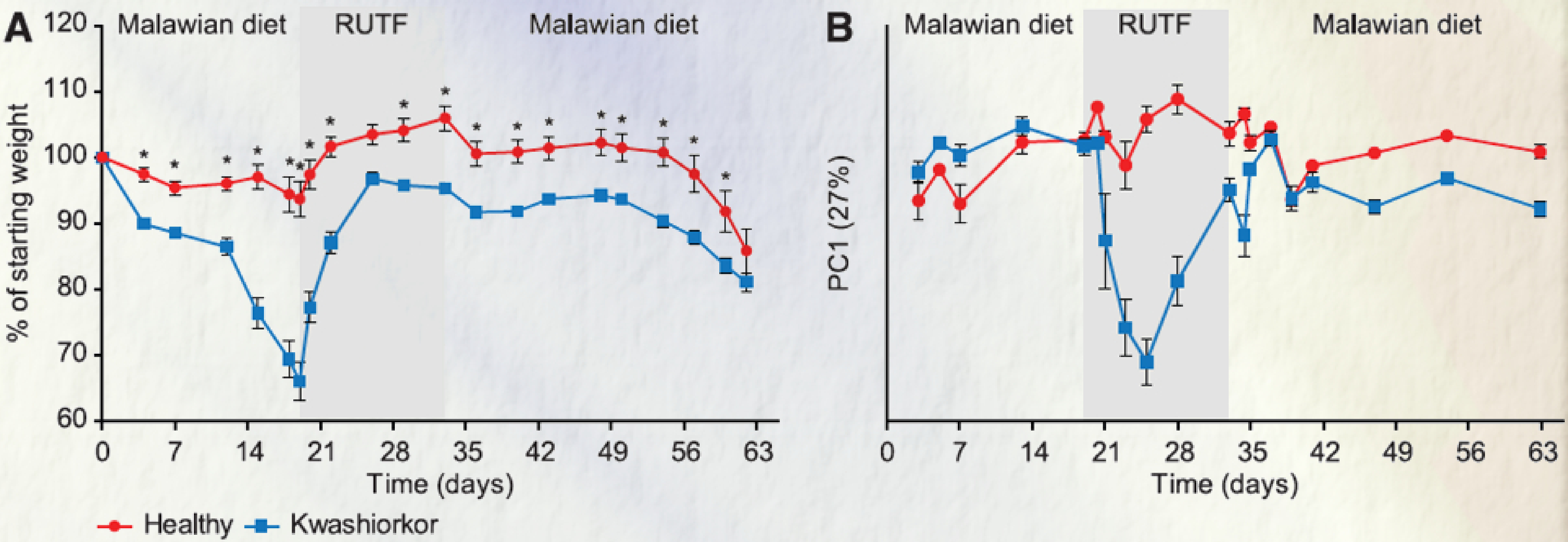


Photo: Tanya Yatsunenko, Malawi 2009; collaboration with Gordon lab

...and individual phenotypes can be transplanted into mice



Smith et al. (2013) Science 339:551

Culture collections permit mechanistic hypothesis tests

PNAS

Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice

Andrew L. Goodman[1], George Kallstrom, Jeremiah J. Faith, Alejandro Reyes, Aimee Moore, Gautam Dantas, and Jeffrey I. Gordon[2]

Center for Genome Science and Systems Biology, Washington University School of Medicine, St. Louis, MO 63108

Contributed by Jeffrey I. Gordon, February 24, 2011 (sent for review January 21, 2011)

The Long-Term Stability of the Human Gut Microbiota

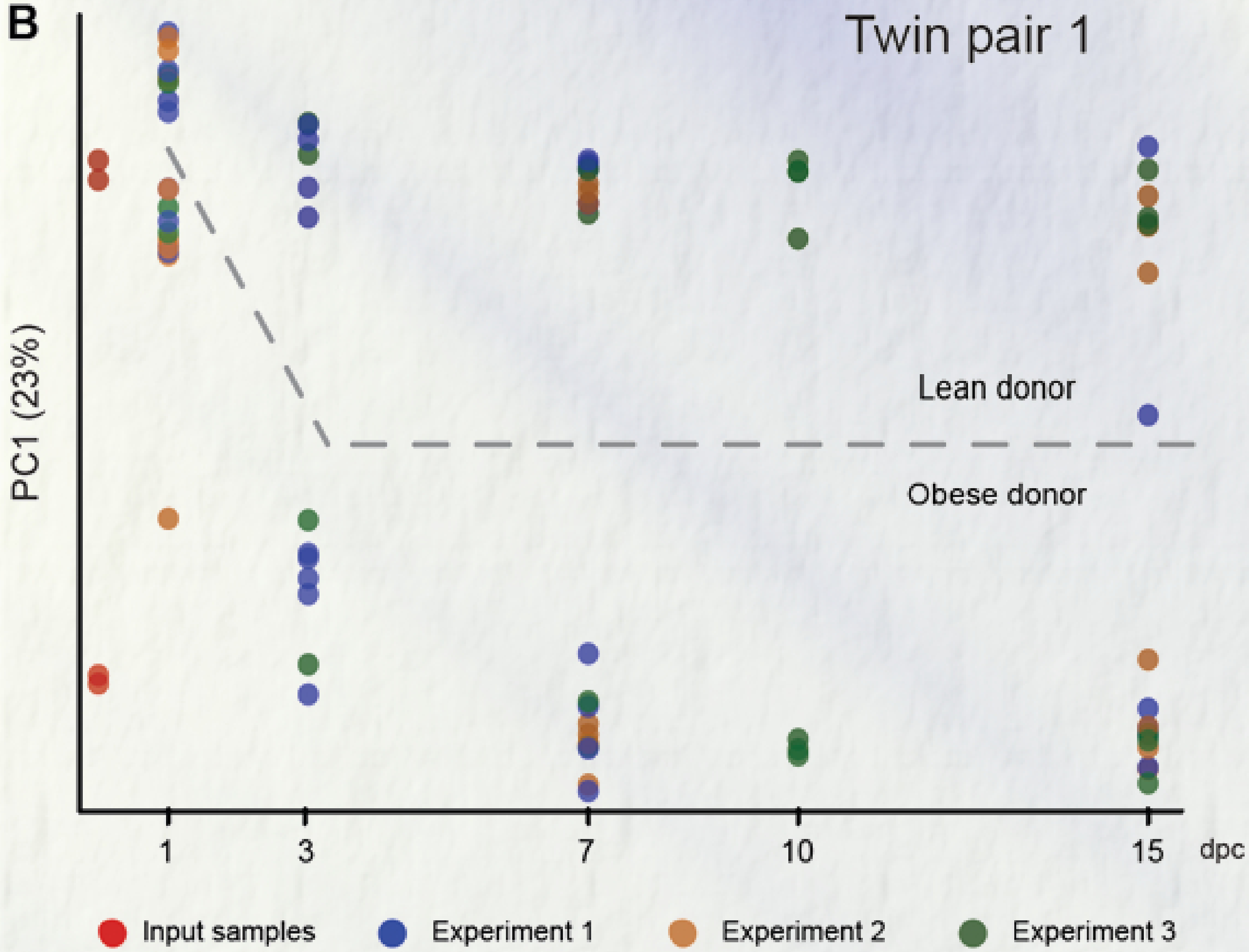
Jeremiah J. Faith,[1*] Janaki L. Guruge,[1] Mark Charbonneau,[1] Sathish Subramanian,[1] Henning Seedorf,[1] Andrew L. Goodman,[1†] Jose C. Clemente,[3*] Rob Knight,[3,4,5] Andrew C. Heath,[2] Rudolph L. Leibel,[6] Michael Rosenbaum,[6] Jeffrey I. Gordon[1‡]

The same type of transplant also works for obesity phenotypes

A

Twin Pair	1 (DZ)		2 (DZ)		3 (DZ)		4 (MZ)	
BMI (kg/m²)	23	32	25.5	31	19.5	30.7	24	33

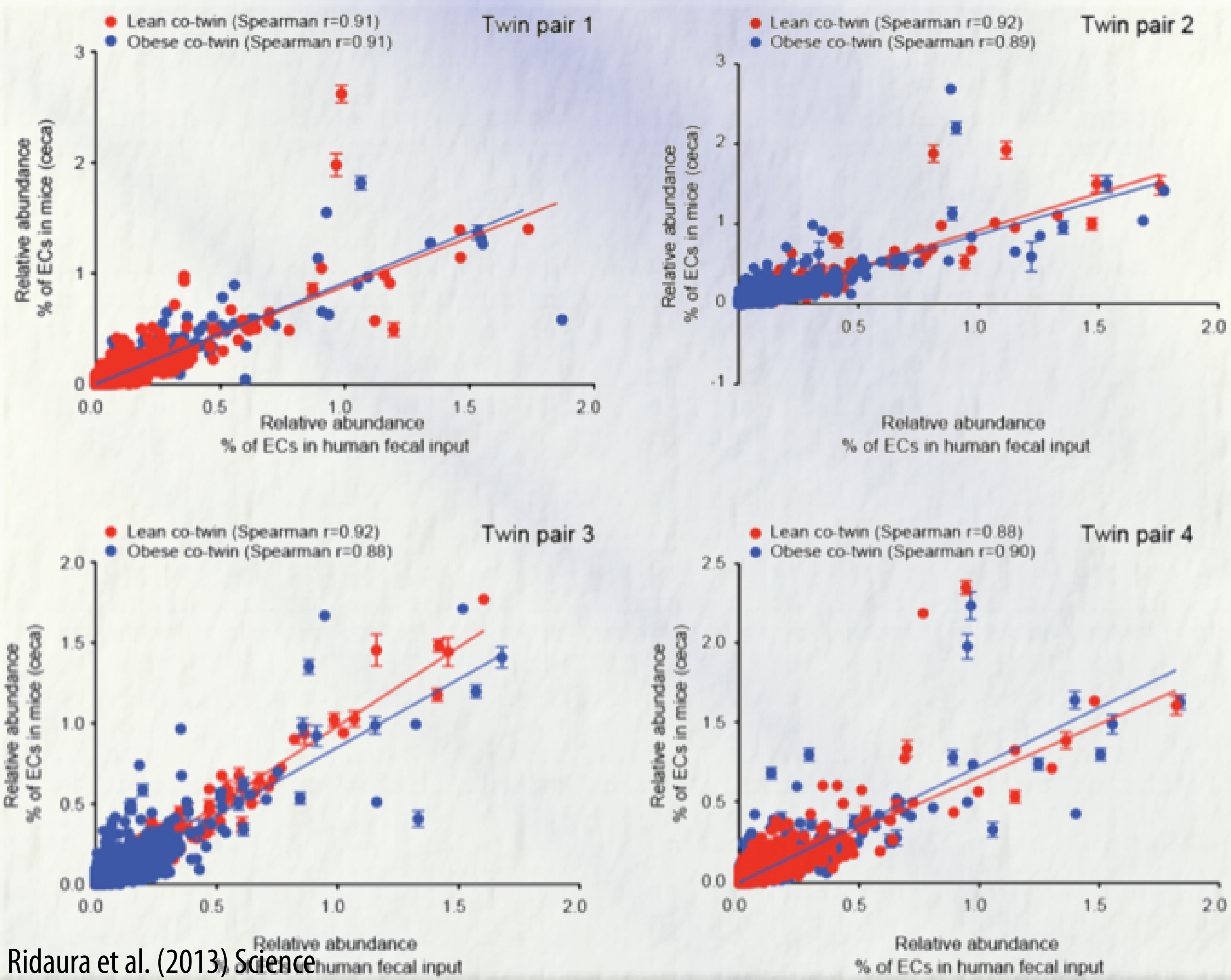
B



Ridaura et al. (2013) Science

Twins discordant for obesity stably transplant different microbes into germ-free mice

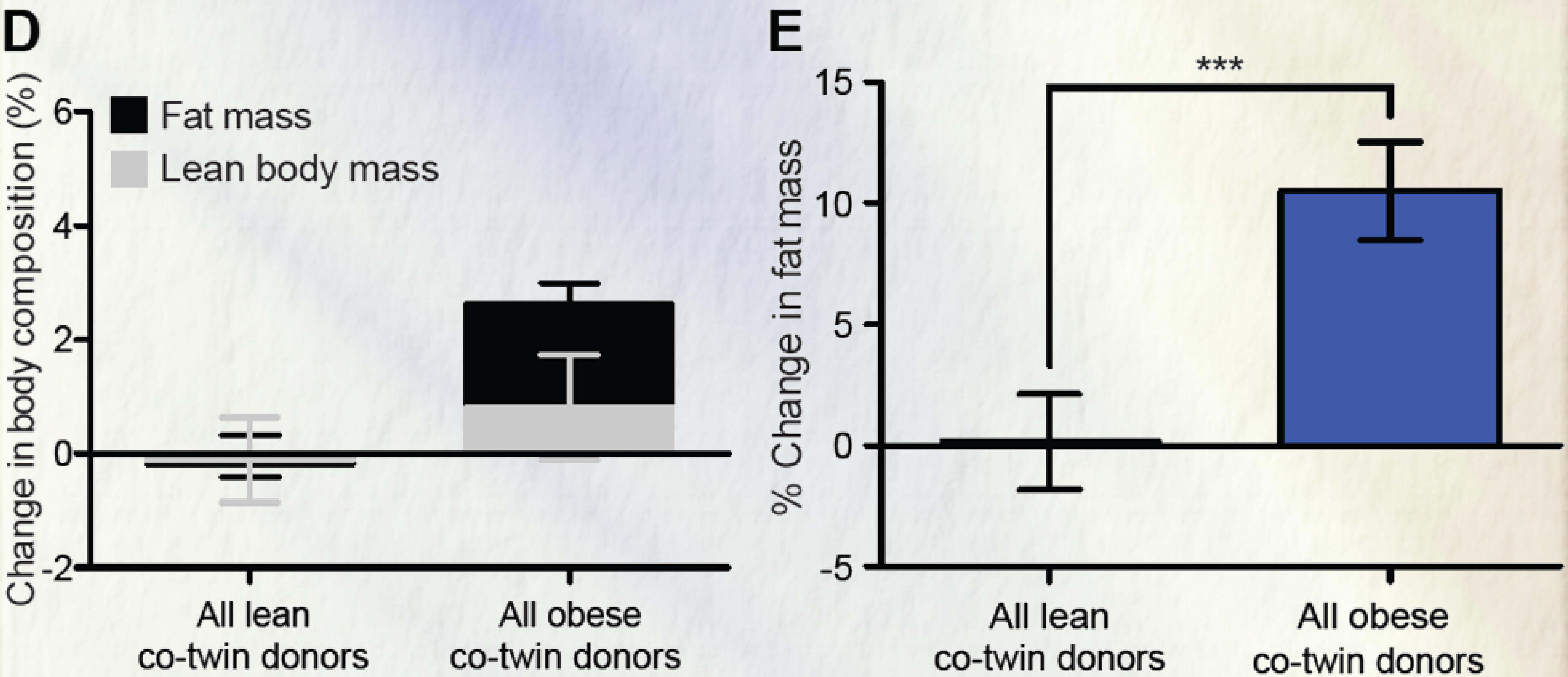
The functional stability of the transplant is excellent



ECs are highly correlated in donor and recipient for all individuals

Ridaura et al. (2013) Science

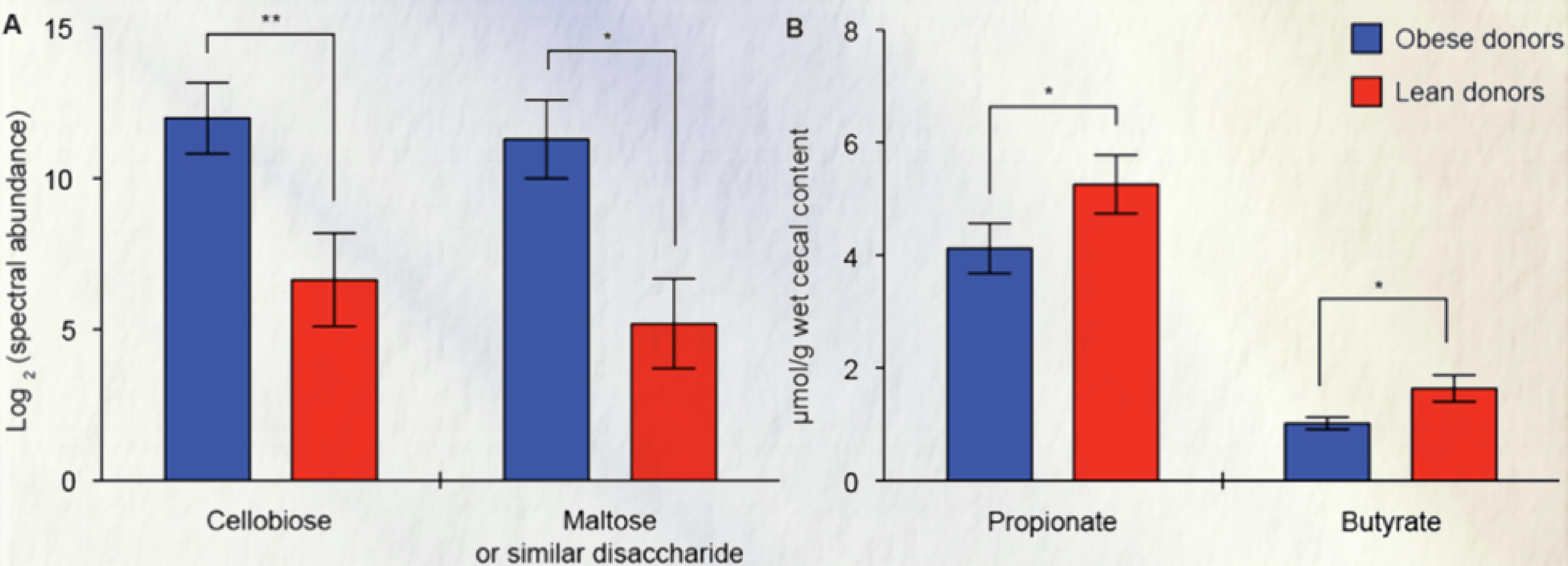
Body composition and fat mass depend on donor



* Two-Way ANOVA, significant donor effect driven by the difference in adiposity

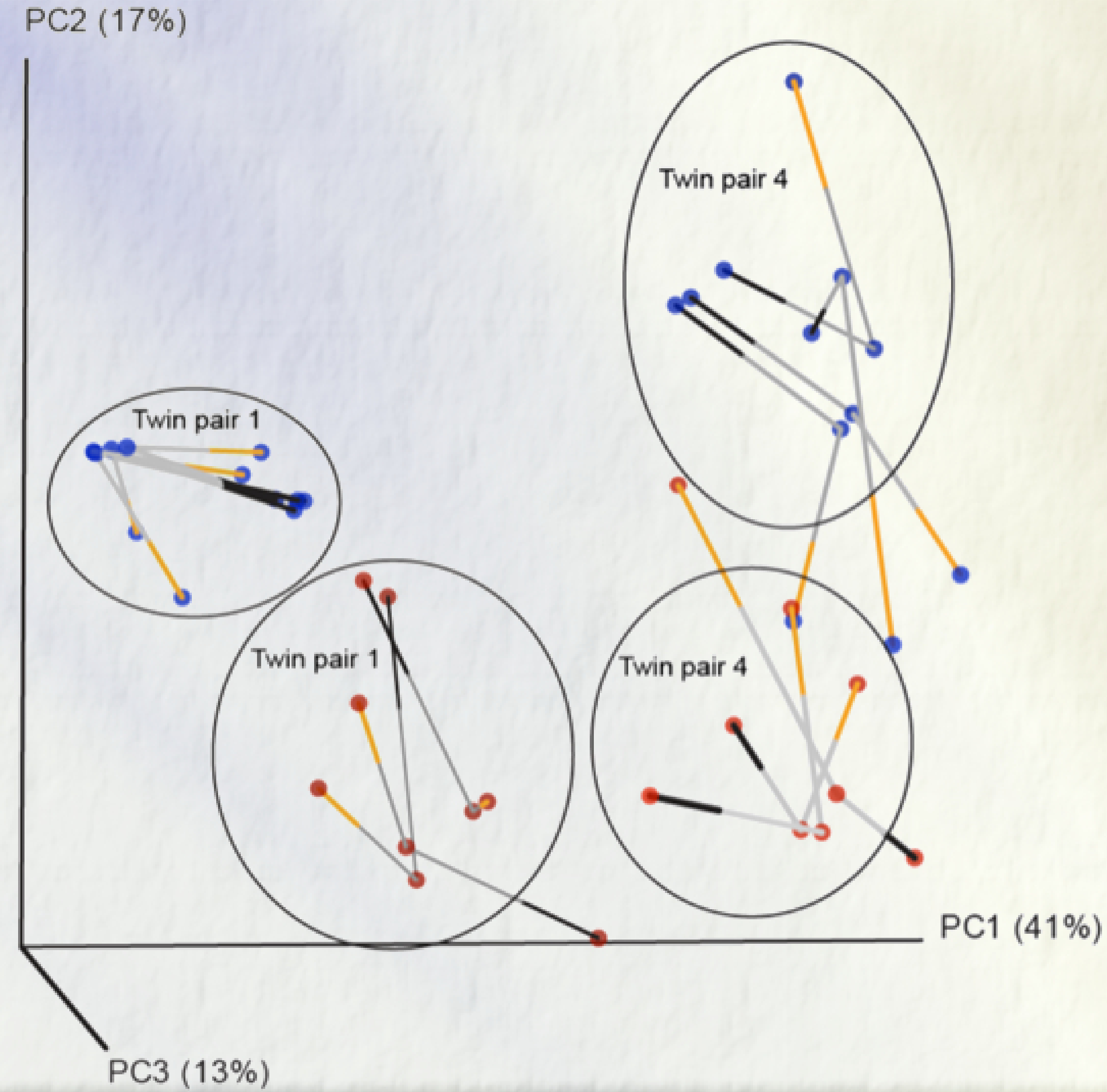
Ridaura et al. (2013) Science

SCFAs upregulated in mice with lean donor



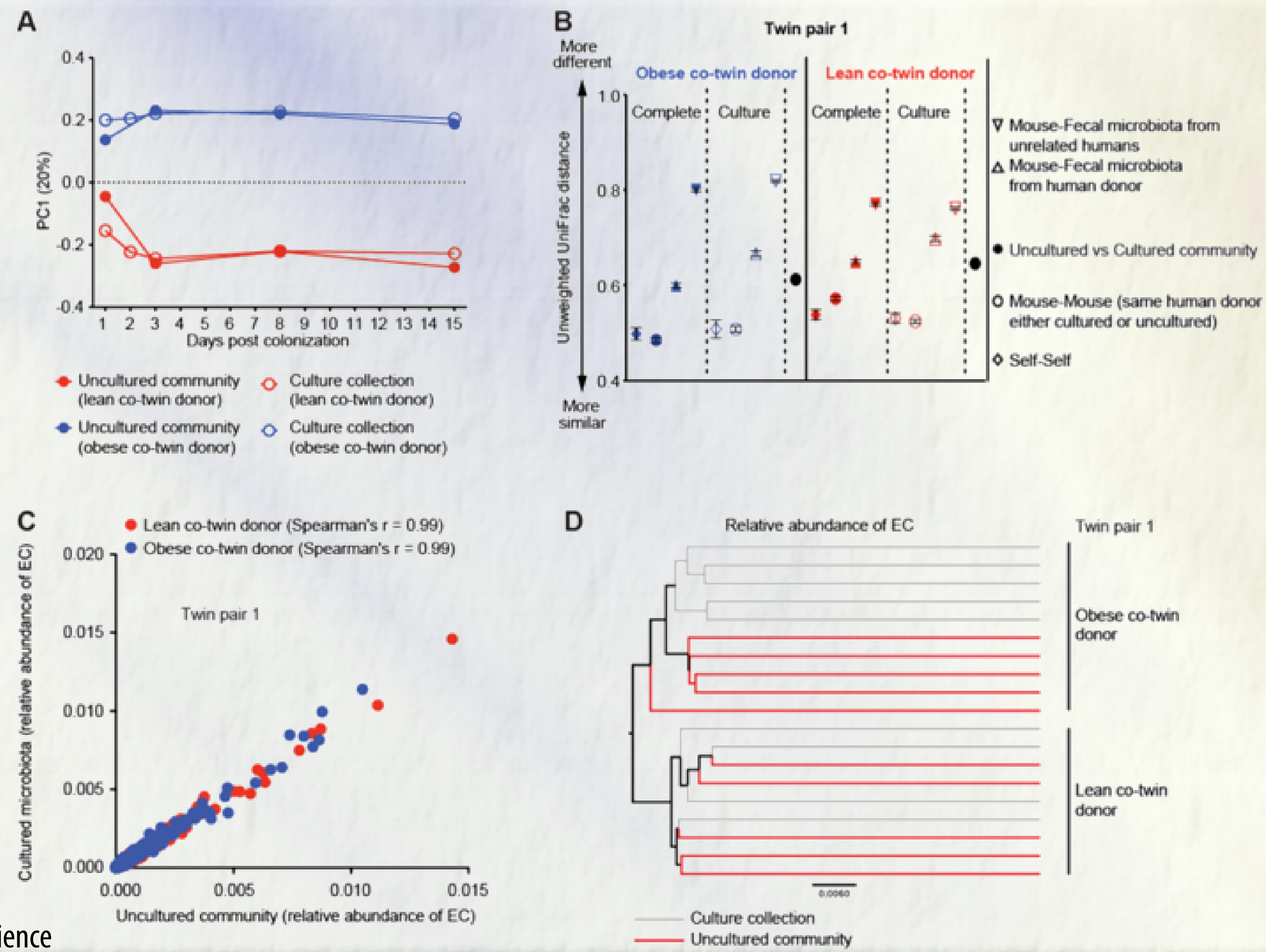
Ridaura et al. (2013) Science

Multi-omics levels agree with each other to surprising degree



Ridaura et al. (2013) Science

Results from culture collections agree with primary specimens



Ridaura et al. (2013) Science

How can we extend this vision to the entire microbial world?

How can we extend this vision to the entire microbial world?

G. Evelyn Hutchinson

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Fig. 1. Generalized lacustrine food-cycle relationships (after Lindeman, '41b).

Niche space: hypervolume

How can we extend this vision to the entire microbial world?

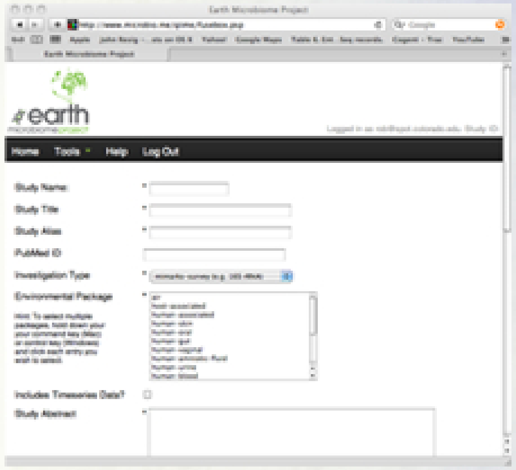
G. Evelyn Hutchinson

Niche space: hypervolume

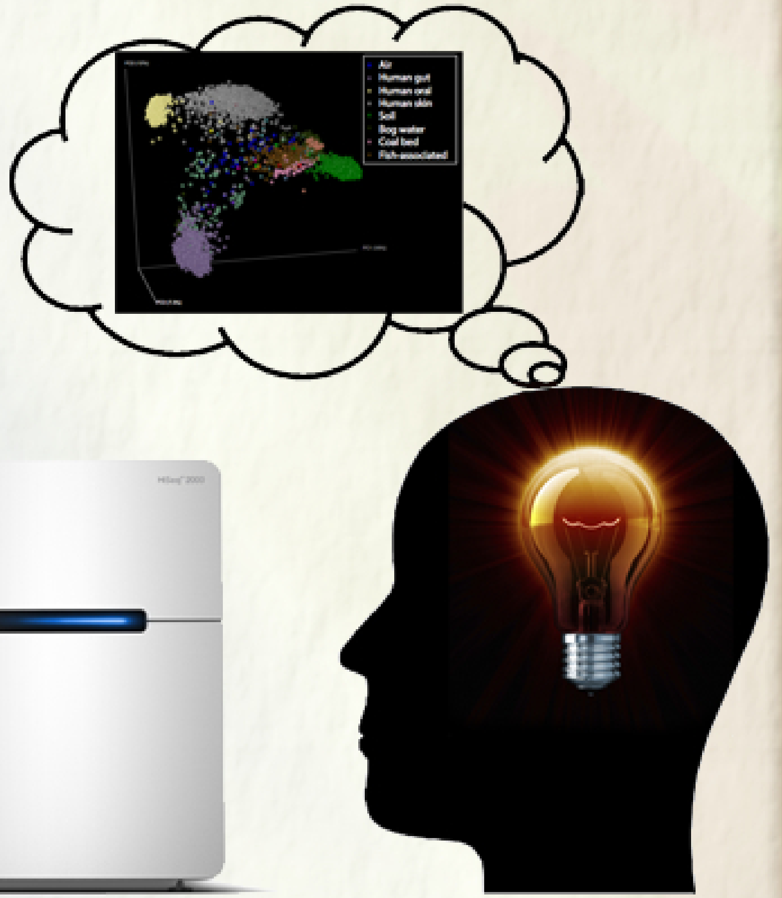
Predict dynamics

To address these questions, we held series of EMP meetings

EMP now provides framework for samples through data analysis



+



Sample submission → DNA extraction → DNA sequencing → Ecological insights

The community response to the EMP has been truly inspiring

EMP Structure:

earth microbiome project

>100 members, 30 institutes, 12 countries

Steering committee (10 members)

Advisory committee (45 members)

Participants (>100 members)

Janet Jansson, Rob Knight, Jack A. Gilbert, Bin Hu, Noah Fierer, Folker Meyer, Rick Stevens, Jonathan A Eisen, Jed Furhman, Mark Bailey, Jeff Gordon, Norman Pace, Jeroen Raes, James Tiedje, Ruth Ley, Noah Fierer, Dawn Field, Nikos Kyrpides, Frank-Oliver Glockner, Hans-Peter Klenk, K. Eric Wommack, Elizabeth M. Glass, Kathryn Docherty, Rachel Gallery, George Kowalchuk, Mark Bailey, Dion Antonopoulos, Pavan Balaji, C. Titus Brown, Christopher T. Brown, Narayan Desai, Dirk Evers, Wu Feng, Daniel Huson, James Knight, Eugene Kolker, Kostas Konstantindis, Joel Kostka, Rachel Mackelprang, Alice McHardy, Christopher Quince, Alexander Sczyrba, Ashley Shade,

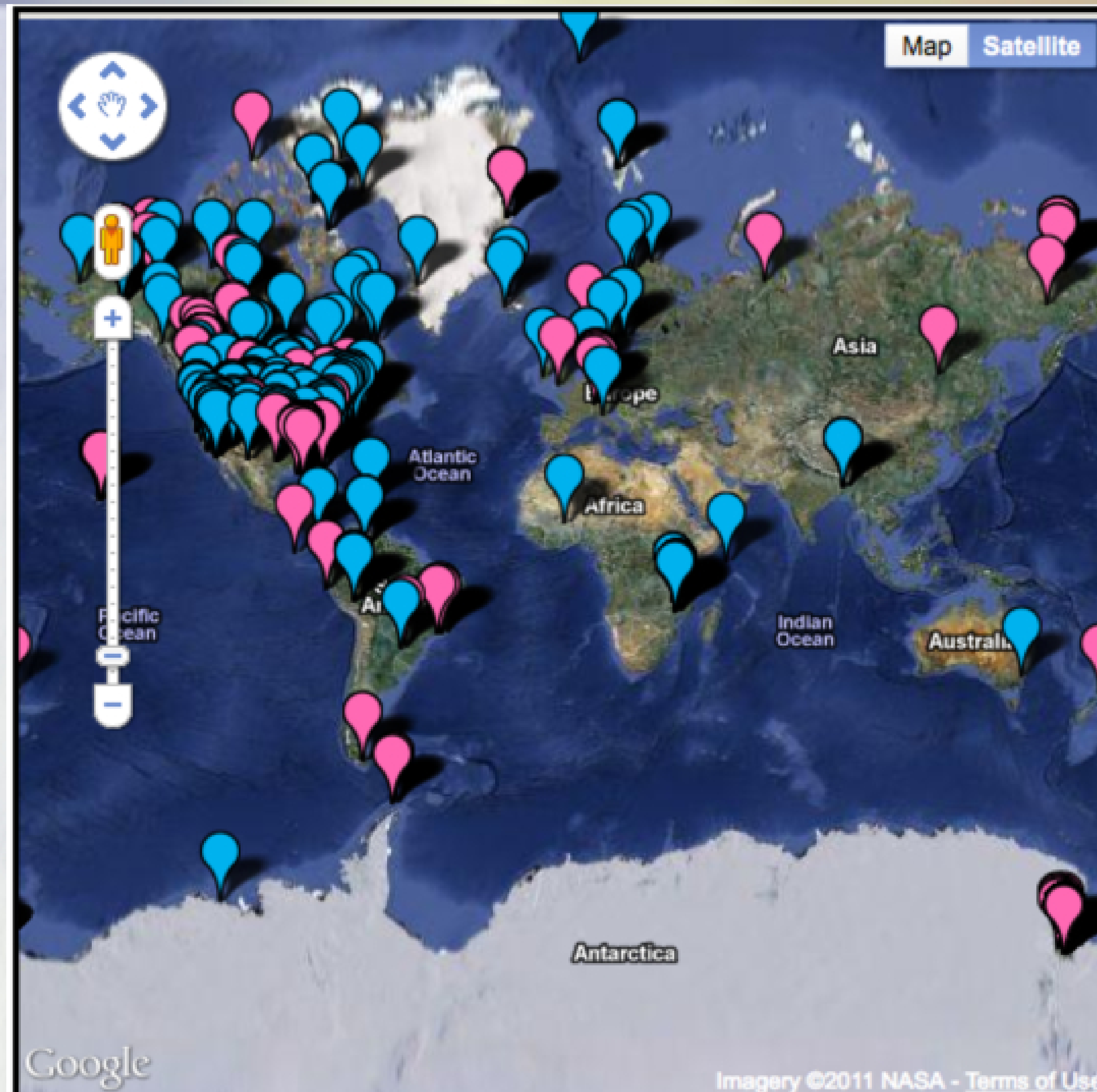
….. And you?

UF University of Florida IFAS; University of Glasgow; Florida State University 1851; The University of Chicago; Argonne National Laboratory; Berkeley Lab; Department of Energy United States of America; Davis College; ESD Earth Sciences Division; Colorado University of Colorado at Boulder; CEH Centre for Ecology & Hydrology Natural Environment Research Council; University of Southern California; Washington University in St. Louis 1853; Yale; Michigan State; VIB; mpii max planck institut informatik; Eberhard Karls Universität Tübingen; Max-Planck-Institut für Marine Mikrobiologie; DSMZ; Cornell University; Roche 454 Sequencing; JGI DOE Joint Genome Institute; University of Delaware; neon National Ecological Observatory Network, Inc.; NIOO; illumina; Virginia Tech Invent the Future; Seattle Children's

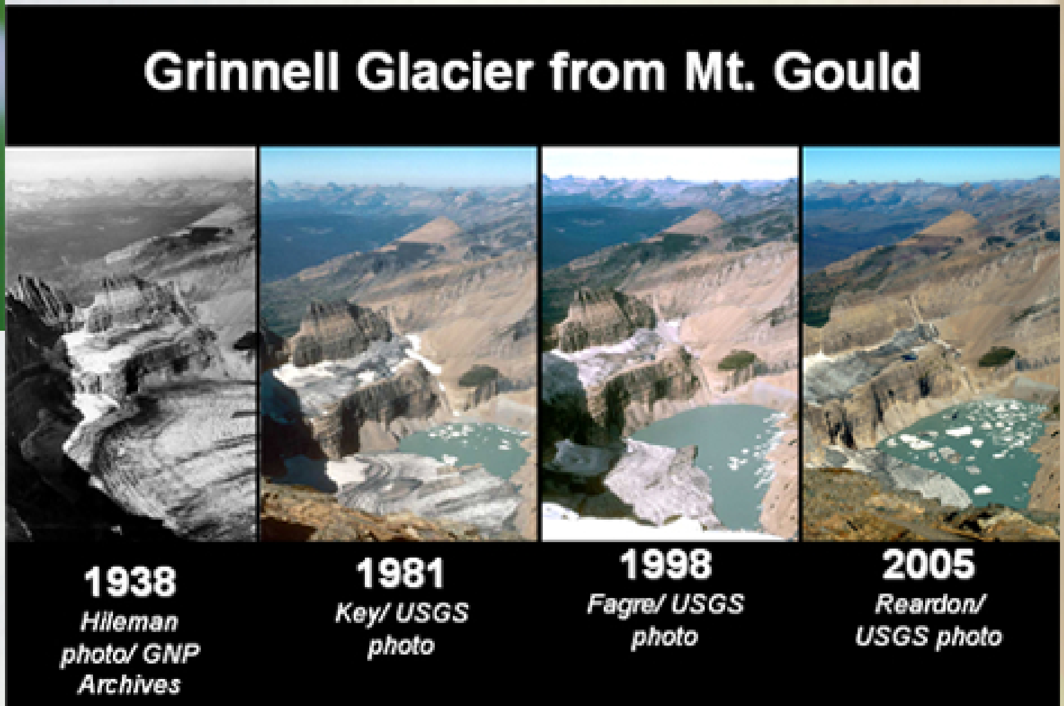
We have processed thousands of samples from around the world

Currently >60,000 samples pledged from >100 researchers

Selected based on rich standards-compliant metadata, ability to inform about processes on different spatial and temporal scales



...what principles can we derive that cross systems and scales?

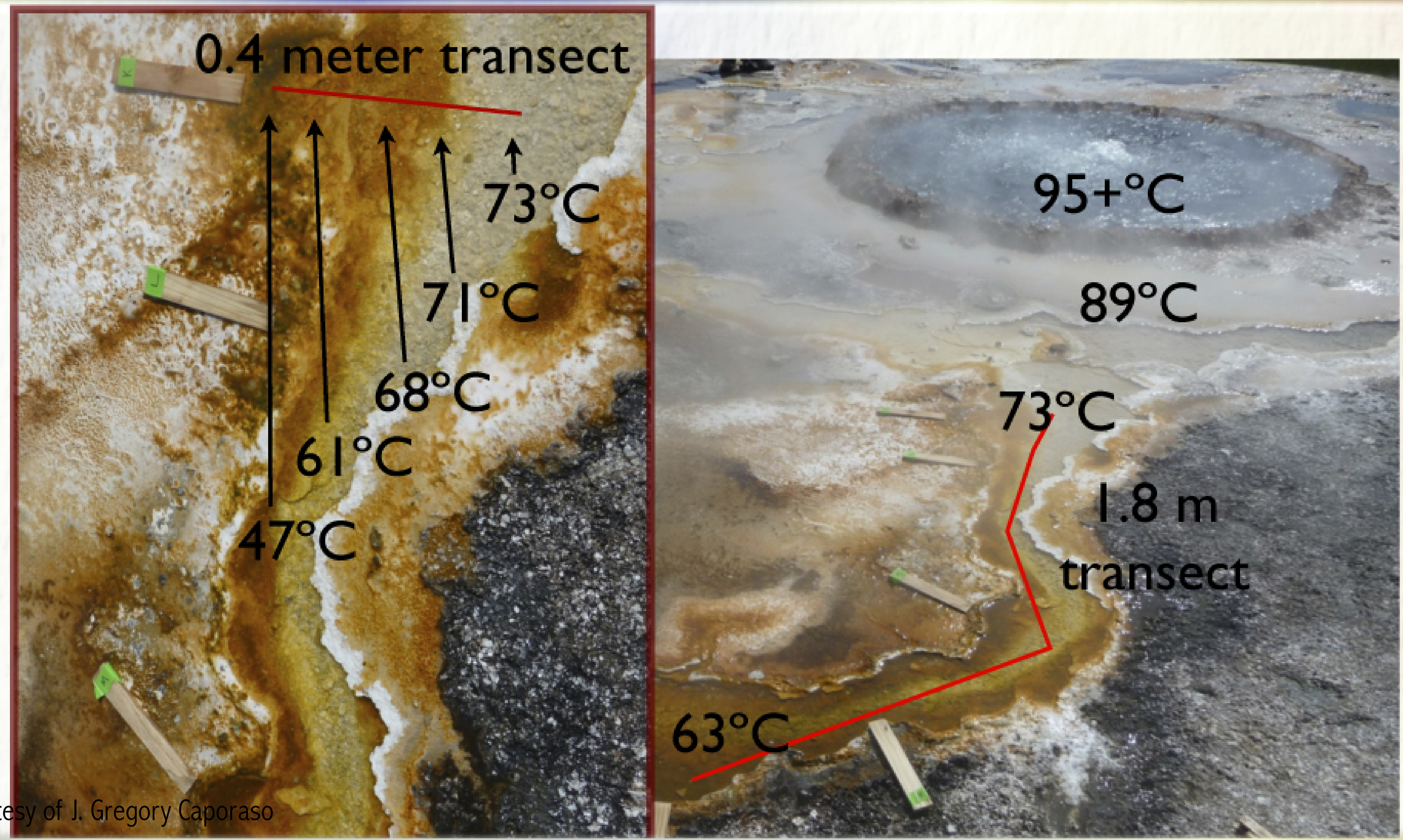


http://www.flickr.com/photos/terrabella/2713519265/; http://www.earthmaps.com/Grinnellquad_frMtGould_color.jpg

Gradients in environments such as Yellowstone...


Courtesy of J. Gregory Caporaso

...are reproducible across highly variable spatial scales...



Courtesy of J. Gregory Caporaso

...including the scale transformations critical for translational medicine

GSC standards and EMP allow unprecedented data integration

gsc genomic STANDARDS consortium

MIGS
MIMS
MIMARKS

GENOME 10K

earth microbiome project

Yilmaz et al. 2011, Nature Biotech 29:415

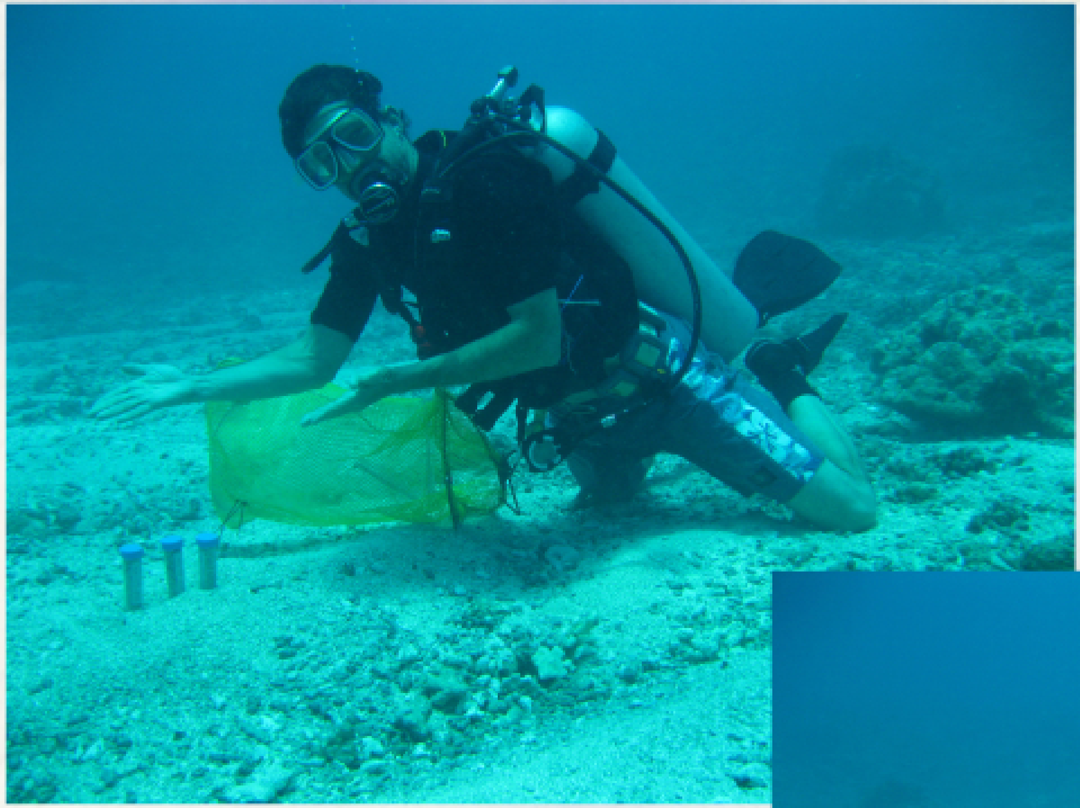
EMP pilot studies

EMP pilot studies

Extreme environments:
Acidic hot springs, Yellowstone–
contributed by Greg Caparoso

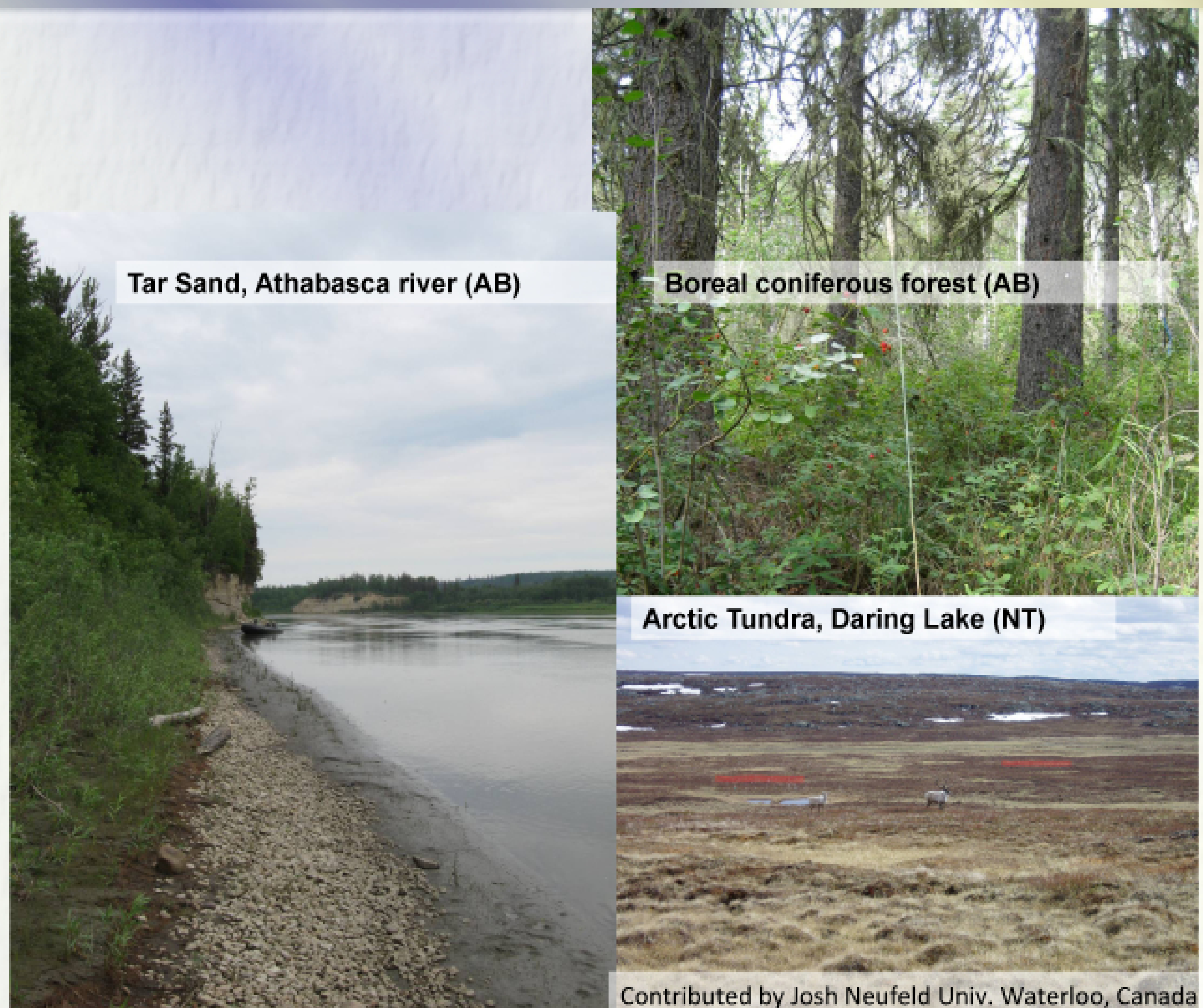
Merlot Microbiome:
High school volunteers
Long Island

EMP pilot studies



Chris Meyer, French Polynesia, sampling water and sediment at the LTER sites on the tropical island and reefs of Moorea.

EMP pilot studies



EMP pilot studies


Thar Desert (Great Indian Desert)


Arctic Permafrost

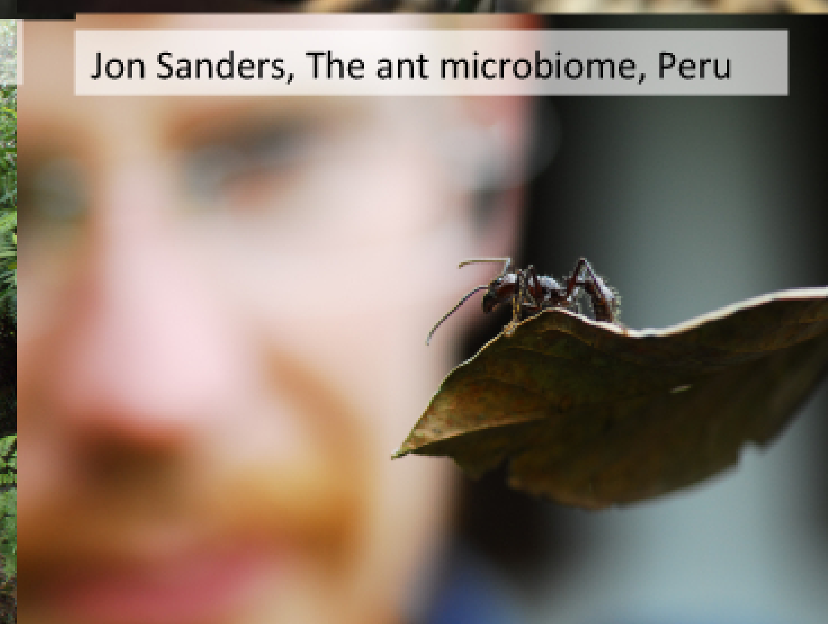

Sampling desert sand, Subramanya Rao


Antarctica Dry Valleys

EMP pilot studies

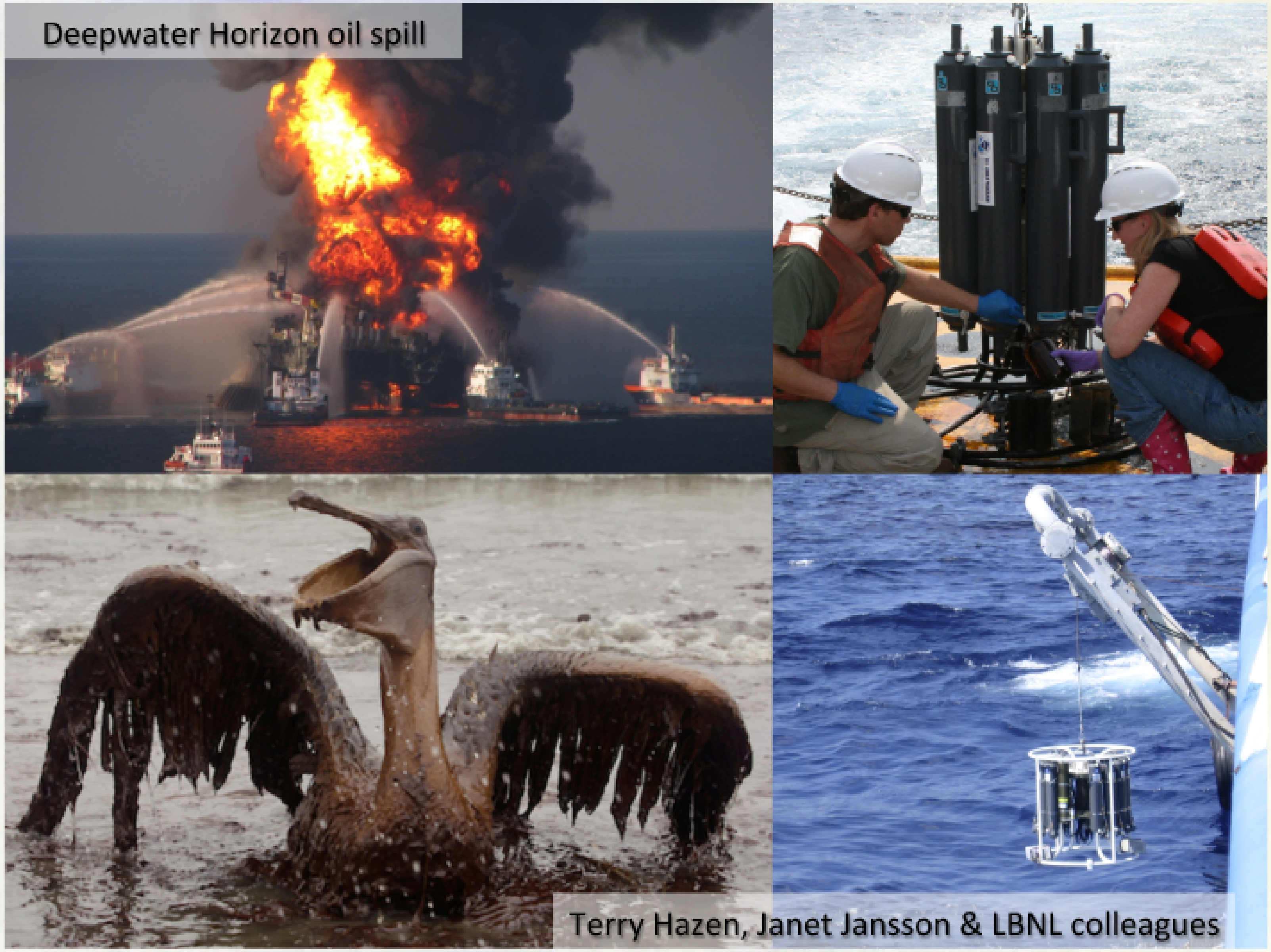
Beck Wehrle, The Iguana Microbiome

Corrie Moreau, Tne ant microbiome - Brazil

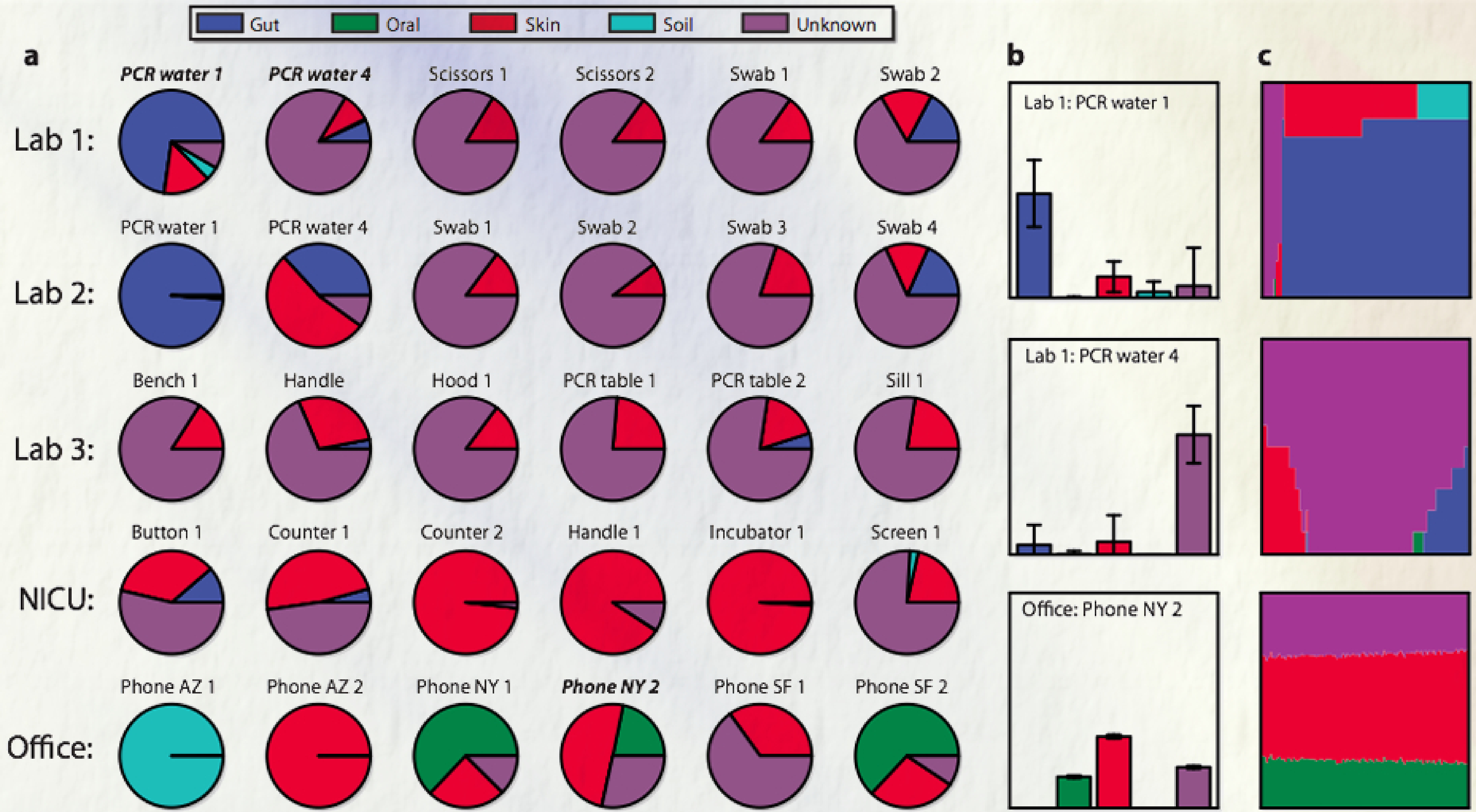


Jon Sanders, The ant microbiome, Peru

EMP pilot studies

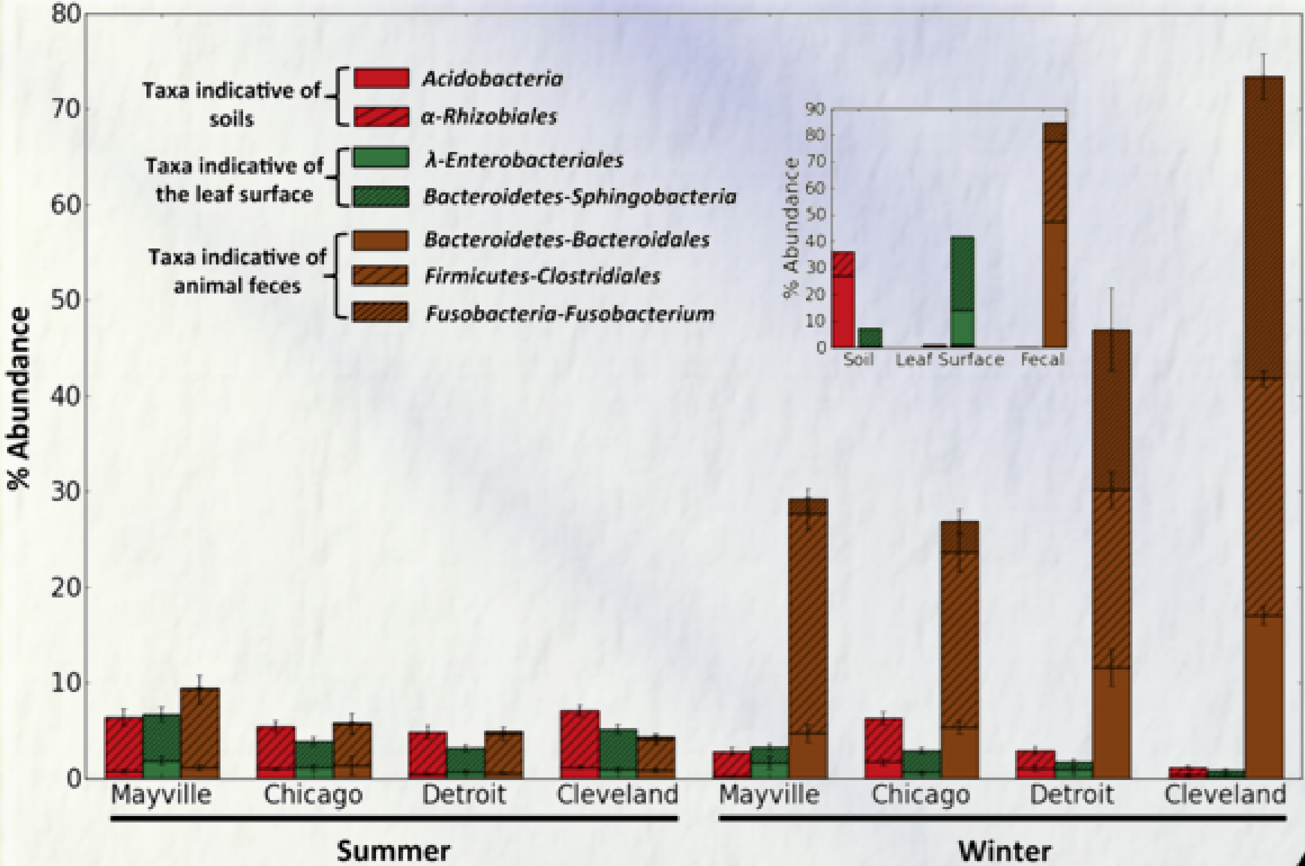


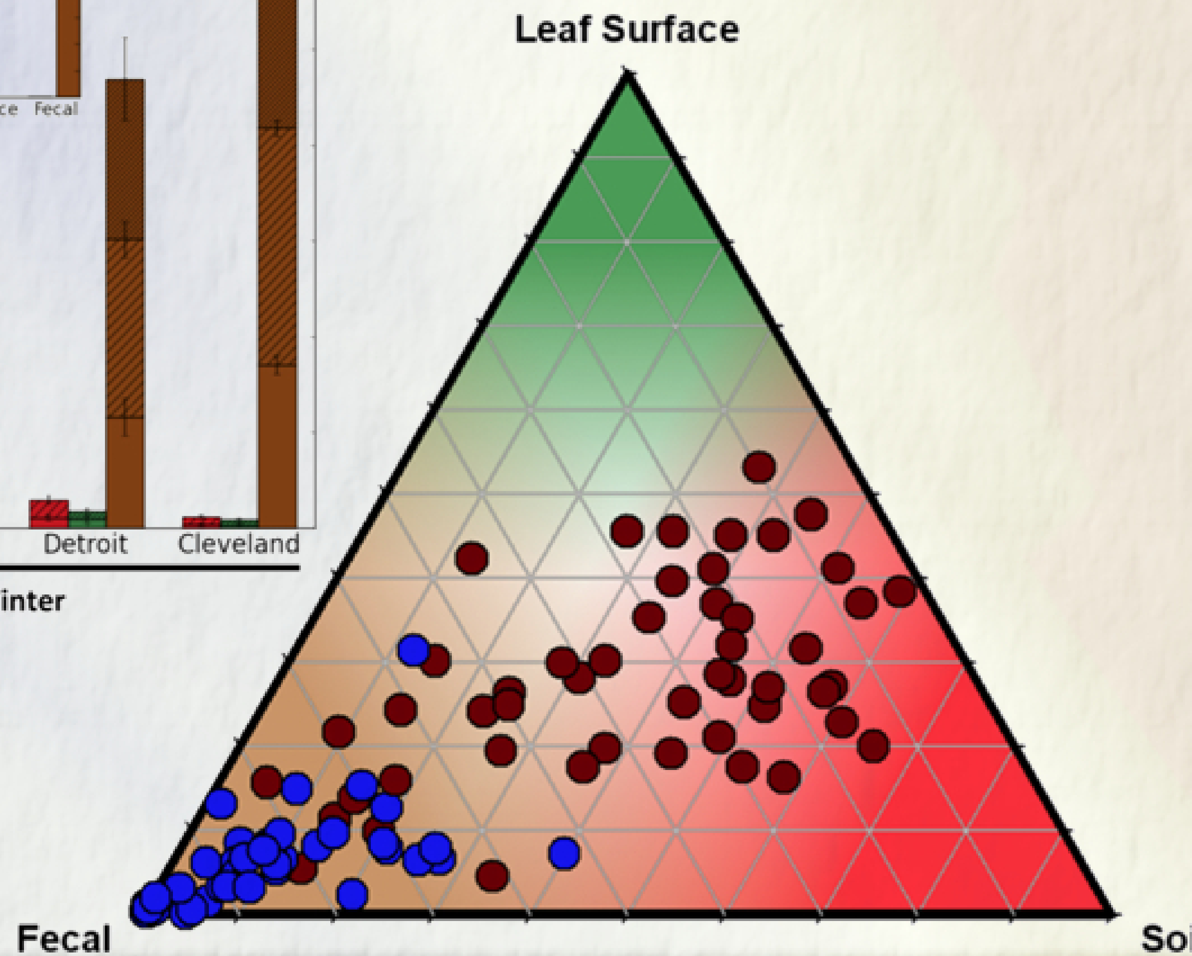
Database enables unanticipated benefits, e.g. source tracking



Knights et al. 2011 Nat Meth

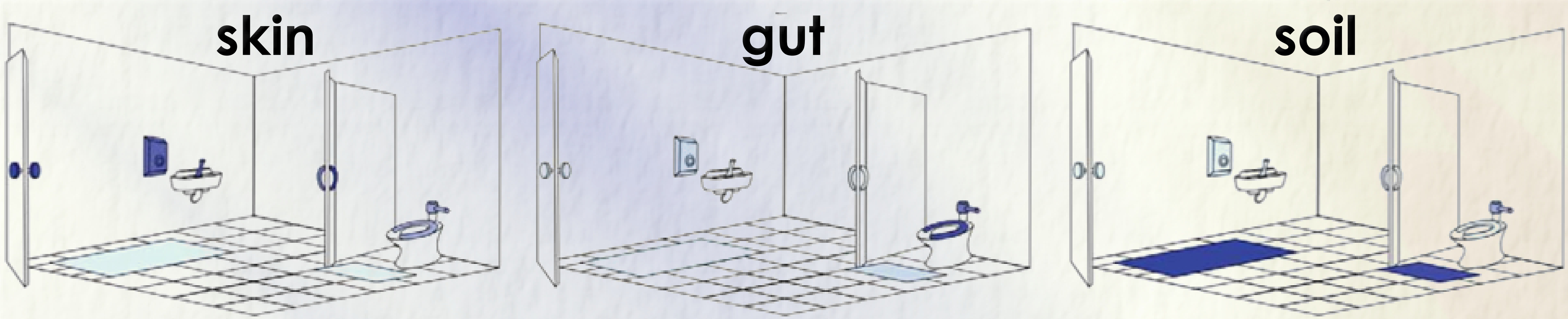
...to outdoor air...

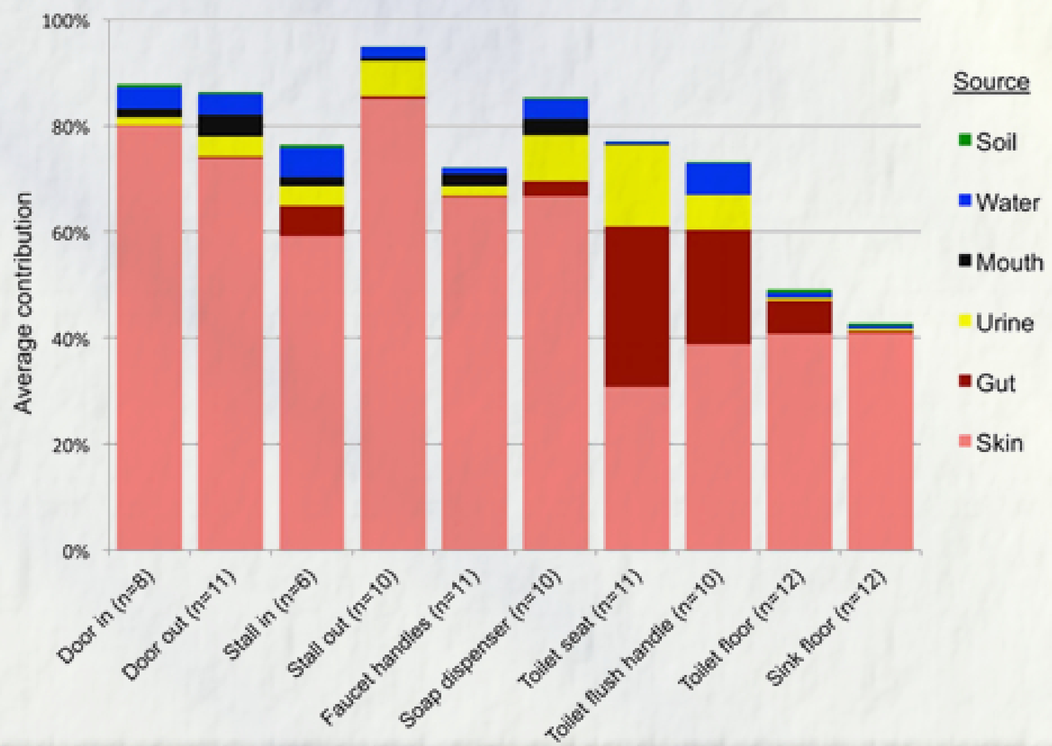




Bowers et al. 2011 AEM

...to public restrooms





Flores et al. 2011 PLoS ONE

Wolves have profound effect on Yellowstone ecosystem...

Before & After Wolves

Restoring wolves to Yellowstone after a 70-year absence as a top predator—especially of elk—set off a cascade of changes that is restoring the park's habitat as well.

YELLOWSTONE WITHOUT WOLVES 1926-1995

ELK overbrowsed the stream side willows, cotton-woods, and shrubs that prevent erosion. Birds lost nesting space. Habitat for fish and other aquatic species declined as waters becam broader and shallower and, without shade from streamside vegetation, warmer.

ASPEN trees in Yellowstone's northern valleys, where elk winter, were seldom able to reach full height. Elk ate nearly all the new sprouts.

COYOTE numbers climbed. Though they often kill elk calves, they prey mainly on small mammals like ground squirrels and voles, reducing the food available for foxes, badgers, and raptors.

ART BY FERNANDO G. BAPTISTA, NG STAFF; AMANDA HOBBS, NG STAFF
SOURCES: ROBERT L. BESCHTA AND WILLIAM J. RIPPLE, OREGON STATE UNIVERSITY; DOUGLAS W. SMITH, YELLOWSTONE NATIONAL PARK

YELLOWSTONE WITH WOLVES 1995-PRESENT

ELK population has been halved. Severe winters early in the reintroduction and drought contributed to the decline. A healthy fear of wolves also keeps elk from lingering at streamsides, where it can be harder to escape attack.

ASPENS The number of new sprouts eaten by elk has dropped dramatcally. New groves in some areas now reach 10 to 15 feet tall.

COYOTES Wolf predation has reduced their num bers. Fewer coyote attacks may be a factor in the resurgence of the park's pronghorn.

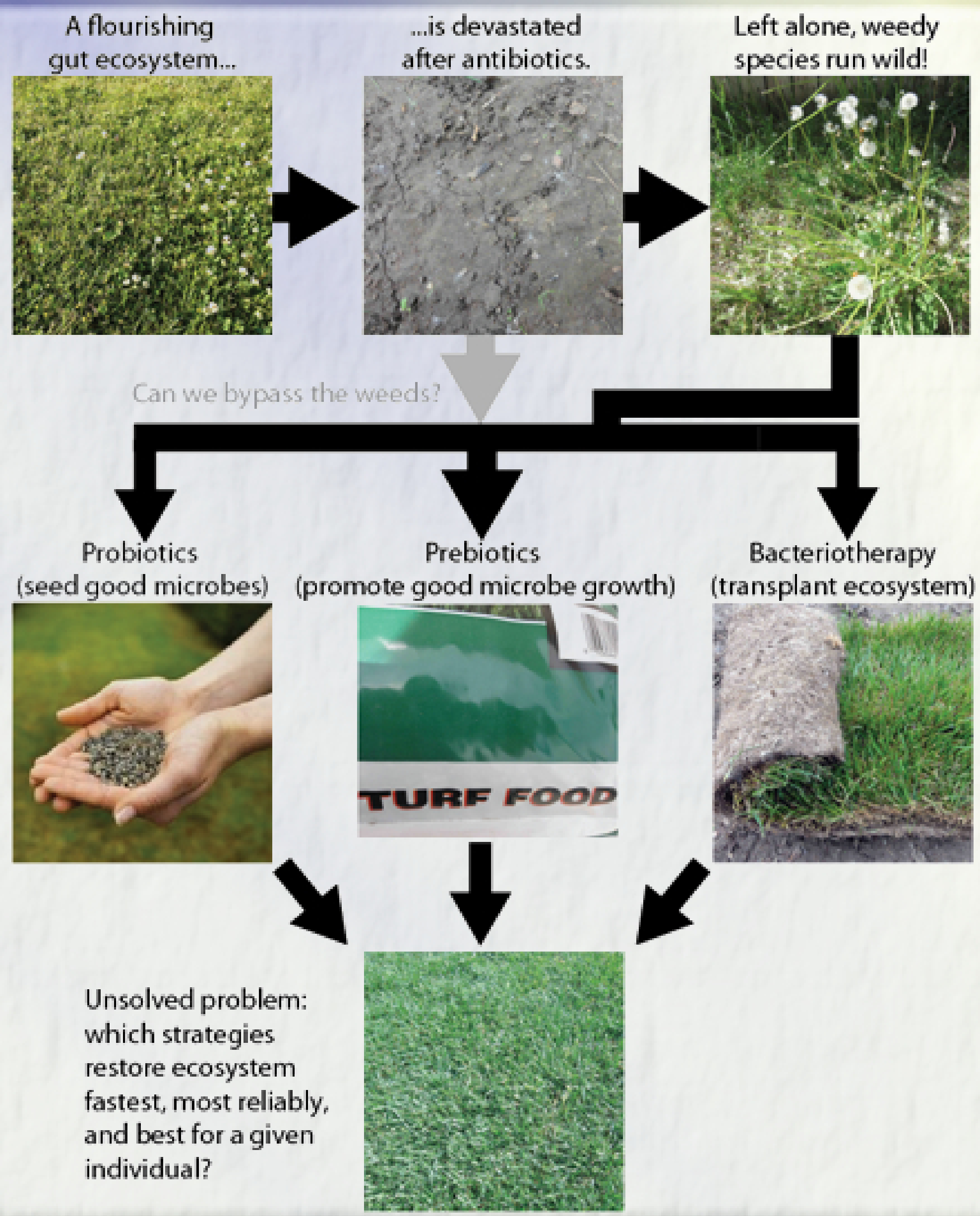
WILLOWS, cottonwoods, and other riparian vegetation have begun to sta bilize stream banks, helping restore natural water flow. Overhanging branches again shade the water and welcome birds.

BEAVER colonies in north Yellowstone have risen from one to 12, now that some stream banks are lush with vegetation, especially willows (a key beaver food). Beaver dams create ponds and marshes, supporting fish, amphiians, birds, small mammals, and a rich insect population to feed them.

CARRION Wolves don't cover their kill, so they've boosted the food supply for scavengers, notably bald and golden eagles, coyotes, ravens, magpies, and bears.

Nat. Geo.
Mar 2010

Can we develop a restoration ecology for microbes?



Lozupone et al. 2012, Nature 489:220

Acknowledgments

Knight lab:
Cathy Lozupone
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Doug Wendel
Antonio Gonzalez
Jeremy Widmann
Meg Pirrung
Tony Walters
Daniel McDonald
Nigel Cook
Dan Knights
Jesse Zaneveld -> Oregon State
Jens Reeder -> Genentech
Julia Goodrich -> Cornell
Ryan Kennedy -> Penn
Zongzhi Liu -> Yale
Micah Hamady -> world travels
Jerry Kennedy
Greg Humphrey
Jose Clemente
Will van Treuren
Jess Metcalf
Laura Parfrey-Wagner
Bharath Prithiviraj
Gail Ackermann
Luke Ursell

[a few of the] Collaborators using UniFrac/QIIME:
Noah Fierer (CU, EEB), Jeff Gordon (Wash U), Ruth Ley (Cornell), Peter Turnbaugh (Harvard),Andrew Gewirtz (Emory), Maria Gloria Dominguez (UPR), Rick Bushman, Gary Wu, Jim Lewis (Penn), Scott Kelley (SDSU), Marty Blaser (NYU), Jacques Ravel (U Maryland), Allan Konopka (PNNL), David Relman (Stanford), Laura Katz (Smith), Norm Pace (CU), Andy Goodman (Yale), Jo Handelsman (Yale), Lars Angenent (Cornell), George Church (Harvard)
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PyCogent: Gavin Huttley (ANU) + many others
Methods: Joe Jones (USC), Eric Nawrocki (HHMI), Sean Eddy (HHMI), Phil Hugenholtz (UQ), Henry Tufo (CU, CS), Manuel Lladser (CU, APPM), Andy Martin (CU, EEB), Alexis Stamatakis (Munich), Steven Brenner (Berkeley), Folker Meyer (ANL), Chris Quince (Glasgow), Pawel Gajer (U Maryland), Eytan Ruppin (TAU)
HMP: DACC: Owen White, Jennifer Wortman, Todd Desantis, Gary Andersen, Nikos Kyrpides, Victor Markowitz; Centers: WashU, Broad, BCM, JCVI; Integration: Curtis Huttenhower, Dirk Gevers, Joe Petrosino, HMP Consortium
ICDDR,B: Tahmeed Ahmed, Rashidul Haque, Dinesh Mondal, Mukul Sarker
EMP:Jack Gilbert (Argonne), Janet Jansson (LBNL), Rick Stevens (Argonne), Folker Meyer (Argonne), Jed Fuhrman (USC),Jonathan Eisen (UC Davis), many, many sample donors
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