Exploration of the microbiota in inflammatory diseases

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Research Computing Day

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We're surrounded by bugs

- Human body contains 100 trillion microbes
  - Out-number human cells 10:1
- Human gut alone:
  - ~ 99% of all of the microbiota
  - 3 pounds of bacteria
    - 50% of fecal volume
  - ~ 1000 different species
  - 3 million different genes (100x human host)

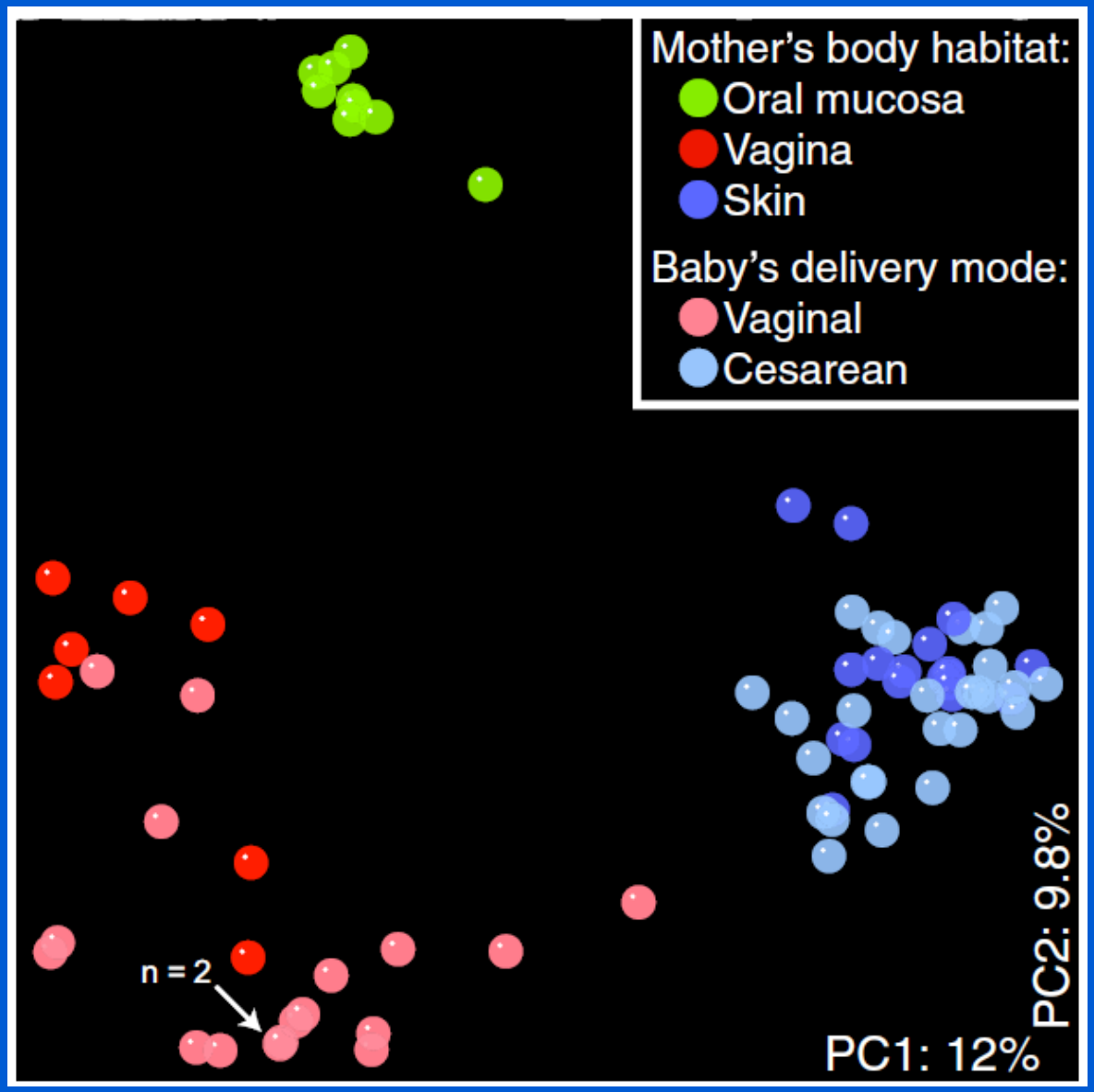
Scher, *Nat Rev Rheumatol* 2011;7:569
De Cruz, *Inflamm Bowel Dis* 2012;18:372

Influences of microbiota composition

- Infant specific factors
  - Mode of delivery
  - Food source (breast vs bottle)
  - Maternal composition
- Diet
- Geography
- Antibiotic use

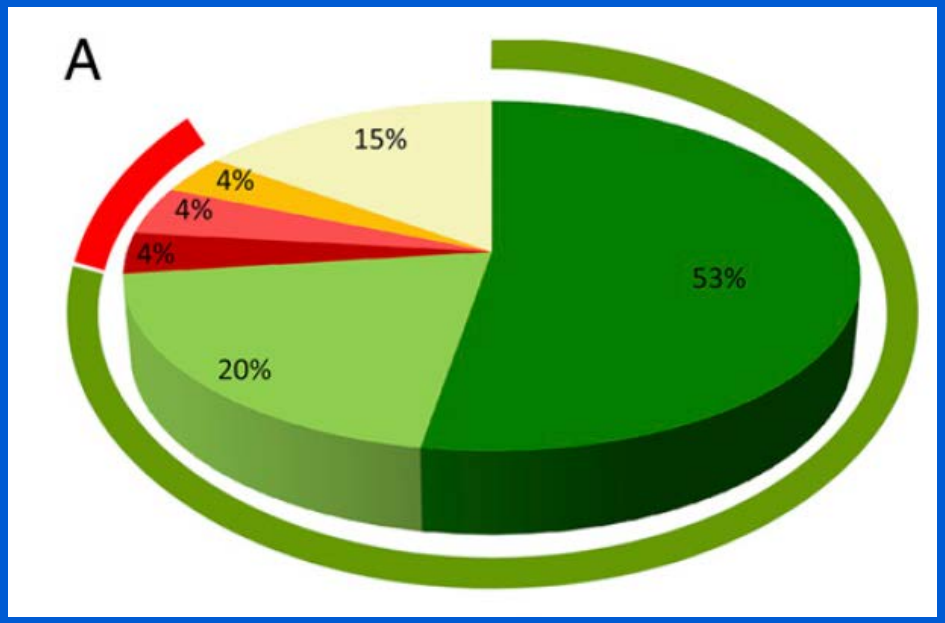
Palmer *PLoS Biol* 2007;5:e177

Delivery mode and neonatal flora



Domingues-Bello *PNAS* 2010;107:11971

Microbiota and diet / geography



Children age 1 – 6 years

Burkina Faso (rural Africa)

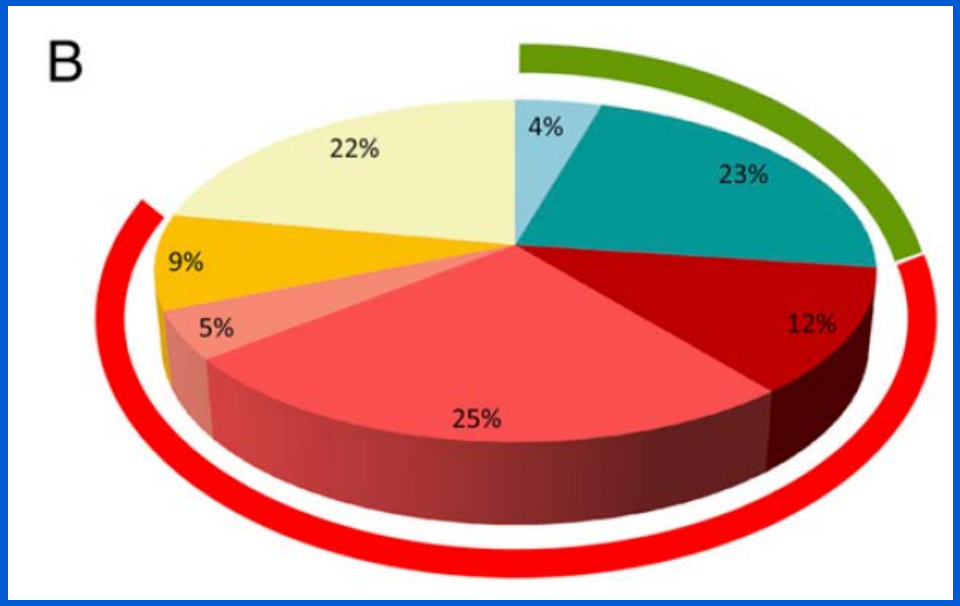
- Prevotella
- Xylanibacter

Bacteroidetes

- Acetitomaculum
- Faecalibacterium
- Subdoligranulum

Firmicutes

- Others



Florence, Italy

- Alistipes
- Bacteroides

Bacteroidetes

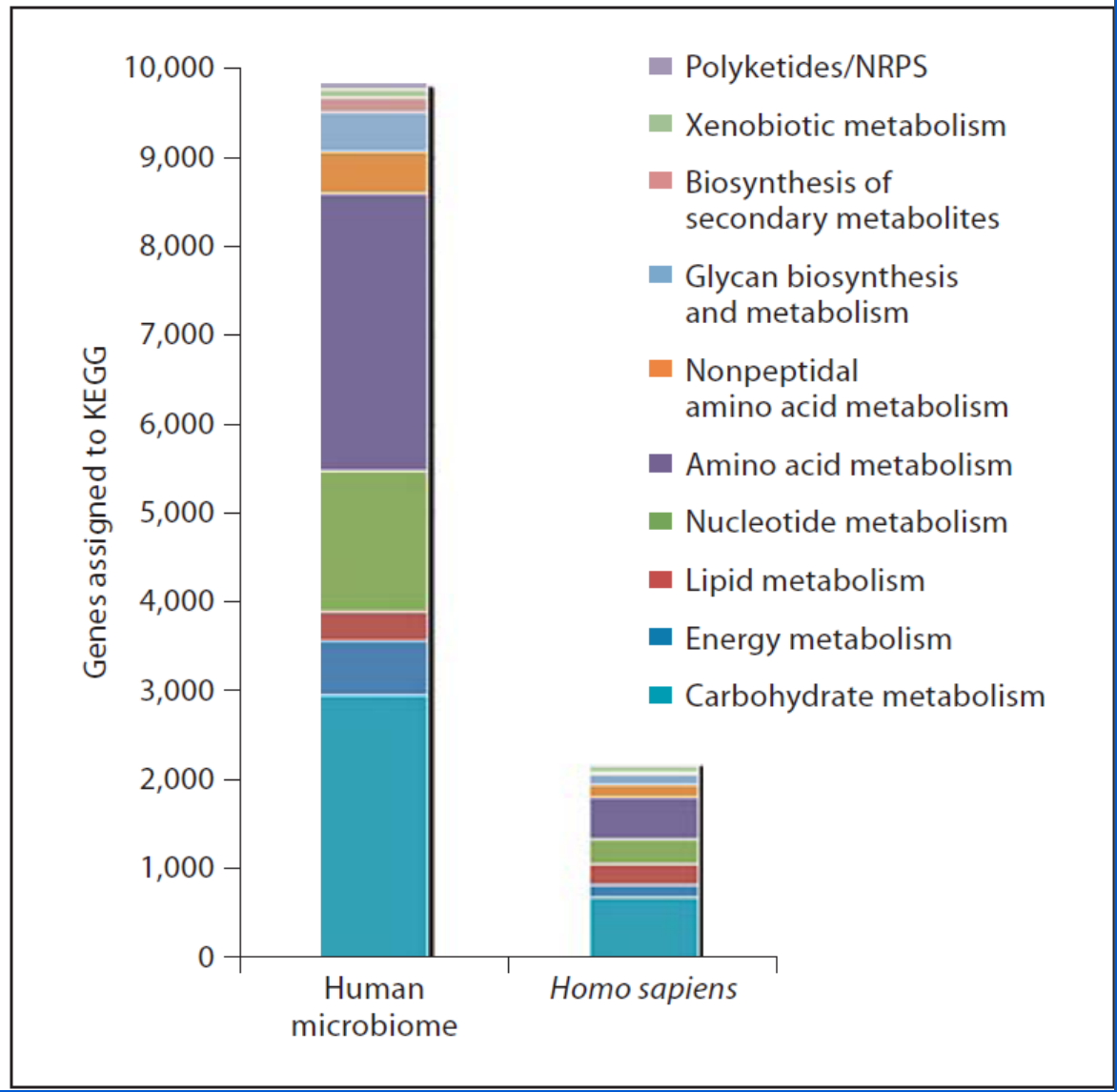
- Acetitomaculum
- Faecalibacterium
- Roseburia
- Subdoligranulum

Firmicutes

- Others

De Filippo, PNAS 2010;107:14691

These bacteria do stuff



Maccaferri *Dig Dis* 2011;29:525

Important metabolic functions

- Sugar / starches
- Drug metabolism
- Vitamin synthesis
- Bile acid deconjugation
  - Affects on triglycerides, cholesterol

Microflora appear to have a profound impact on a variety of diseases

Immunology and gut bacteria

- **Mice raised in GF conditions show:**
  - **Defective T, B, and innate cells in mucosal lymphoid tissue**
  - **Smaller mucosal LNs**
  - **Fewer CD4 cells in peripheral LN**
  - **Th2 bias, with few Th17 cells**
  - **Decreased IgG and IgA levels**

Mathis, *Cell Host & Microbe* 2011;10:297

Hygeine hypothesis

- Recent increases in
  - Inflammatory bowel disease
  - Atopy (allergies, asthma)
  - Type I diabetes
- Attributed to cleaner environments

Strachan, *Jrnl Allergy Clin Immunol* 1999;104:554

Germ-free humans, cont.

- Temporal: pre / post Industrial Revolution
- IBD, atopy risk increase with income
  - Across continents
  - Within countries
- Other markers of infectious burden
  - Day care attendance
  - Family size (increased # of sibs is protective)

Bach, Cell Immunol 2005;233:158
Blanchard, Am J Epidemiol 2001;154:328
Werner, Br Jrnl Dermatol 2002;147:95

Flora and animal models of disease

- **Germ-free state results in altered / absent disease expression in several models of autoimmune diseases.**
  - **IBD**
  - **Spondyloarthritis with colitis**
  - **Rheumatoid arthritis**
  - **Type I Diabetes**
  - **Multiple sclerosis**

Wu, *Gut Microbes* 2012;3:1

Disease transfer: TRUC model

- Colitis develops in double k/o mice:
  - RAG2
  - T-bet (transcription factor)
- Role for flora evidenced by
  - Response to broad-spectrum abx
  - Absence of disease in progeny of abx-Tx mice
  - Development of colitis in wt mice housed with TRUC mice

Garrett, *Cell* 2007;131:33

Microbiota and inflammatory diseases

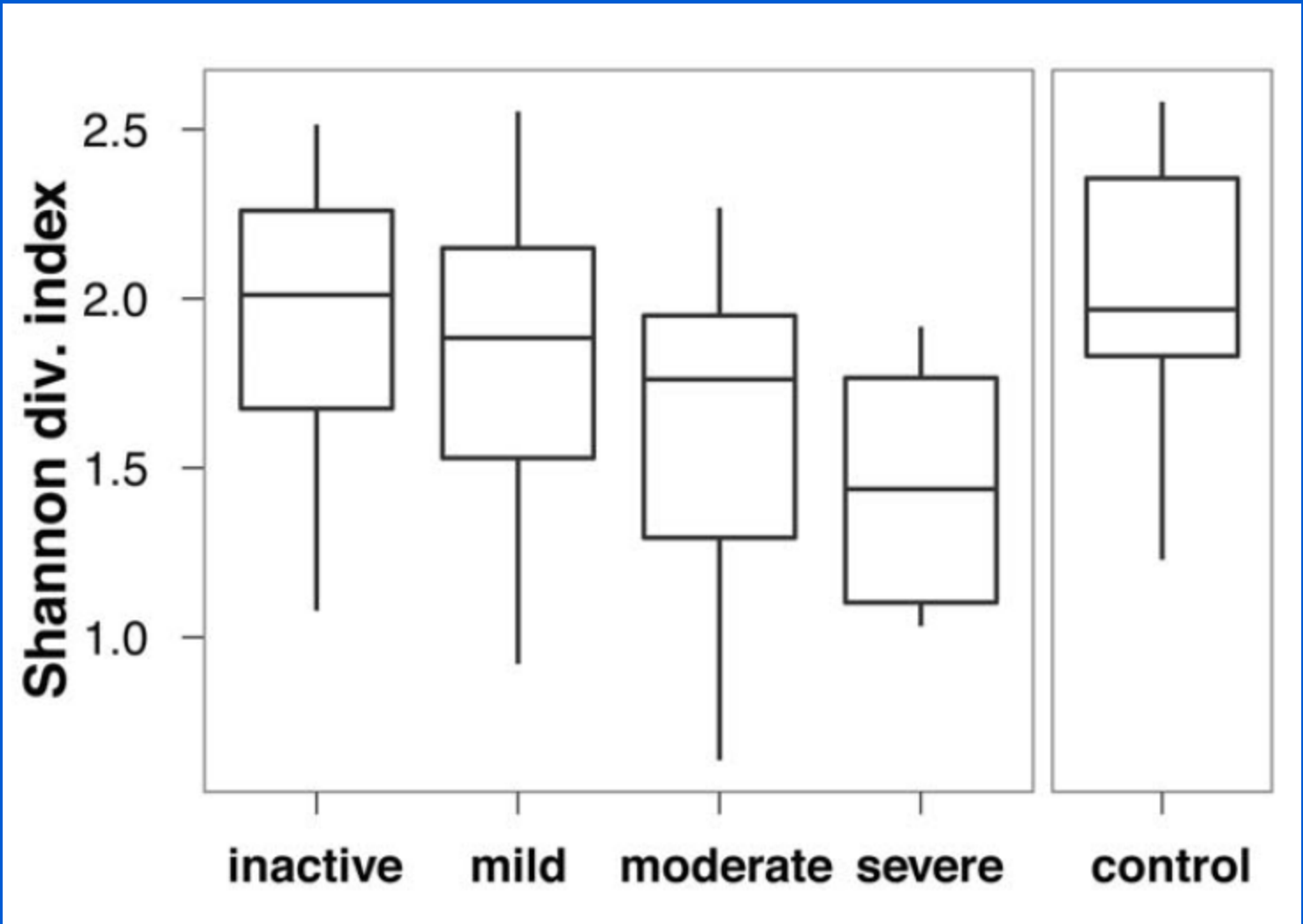
- Inflammatory bowel disease (IBD)
- Insulin-dependent (Type I) diabetes
- Arthritis?

Microbiota and IBD: indirect evidence

- Altered flora in multiple studies
- Decreased diversity

De Cruz, *Inflamm Bowel Dis* 2012;18:372
Comito, *International Jrnl Inflam* 2012;ePub

Diversity of flora in peds IBD



Papa, PLoS *One* 2012;7:e29242

Microbiota and IBD: therapeutic response to alterations in flora

- Antibiotics routinely used
- Probiotics may be effective
- Fecal microbiota transplantation
  - Used extensively in chronic C. diff
  - Case reports in IBD
- Gnotobiotic facility at UAB can permit further study of microbiota transfer

Borody, *Expert Rev Gastroenterol Hepatol* 2011;5:653

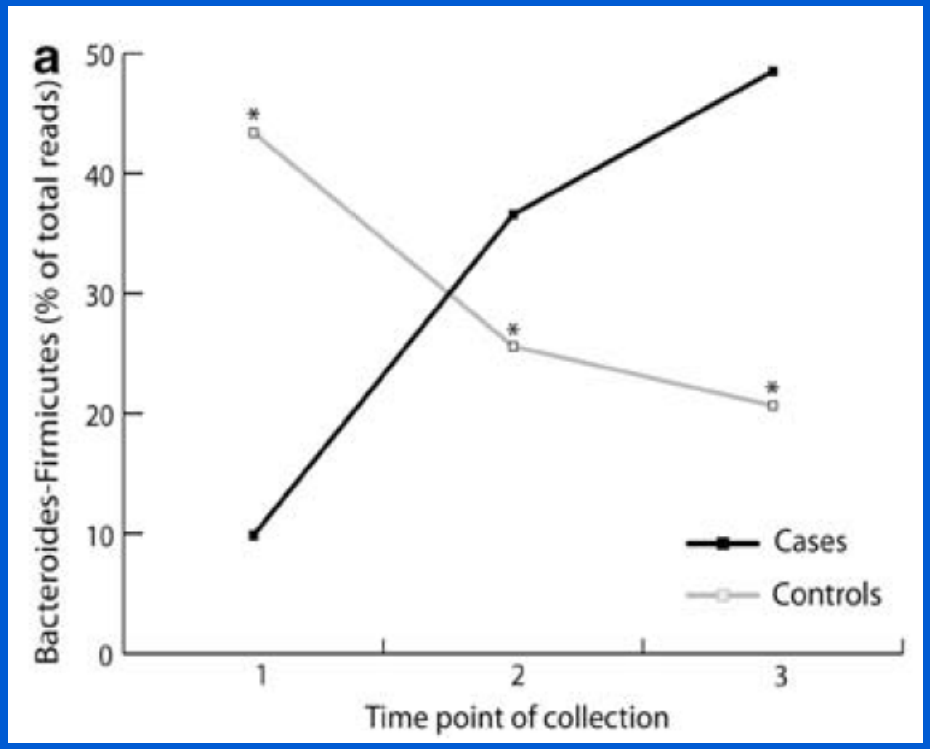
Microbiota and Type I DM

- Diabetes Prediction and Prevention Study
- Serial stool collections on high-risk infants
- Case defined as pos. autoantibodies
  - Ultimately dx with diabetes
- Matched controls

Giongo, *ISME* 2011;*5*:82

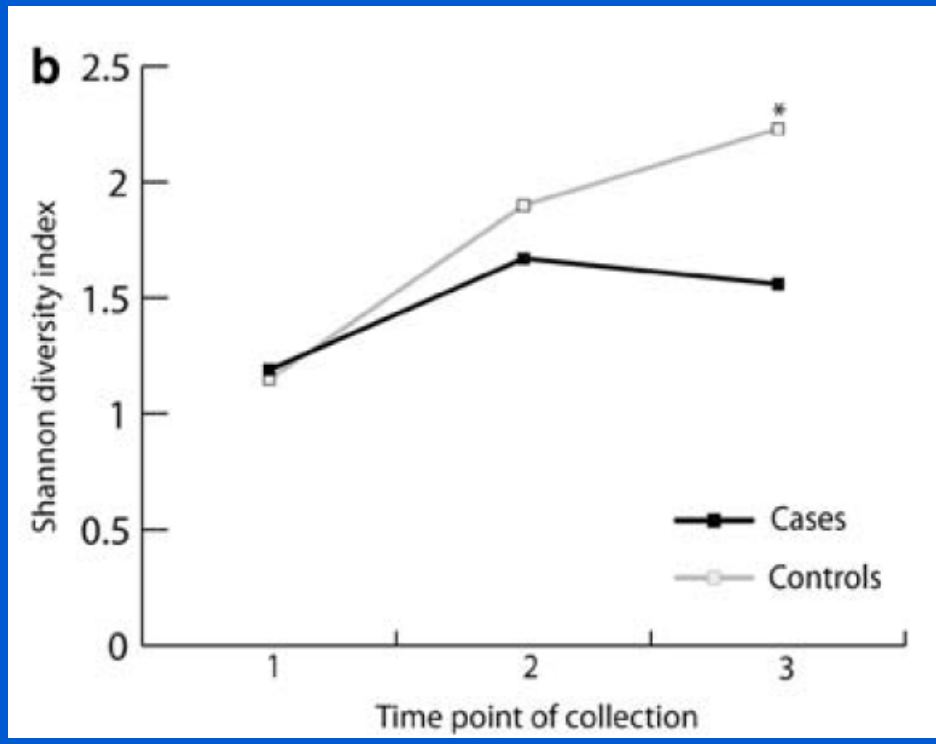
Microbiota changes precede onset of Type I diabetes

Increase in Bacteroides



Onset

Decreased diversity



Onset

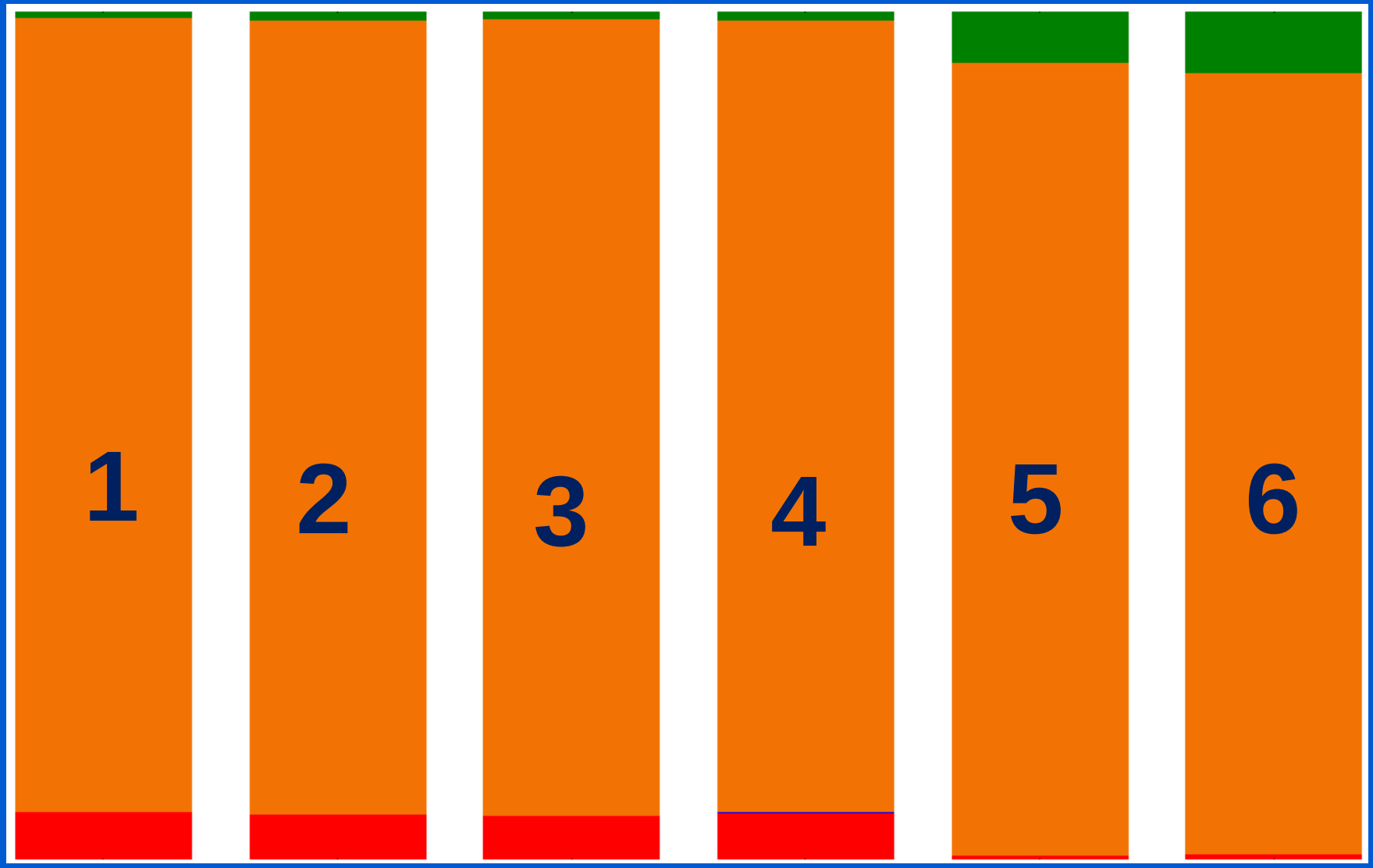
Giongo, *ISME* 2011;*5*:82

Juvenile arthritis: preliminary study

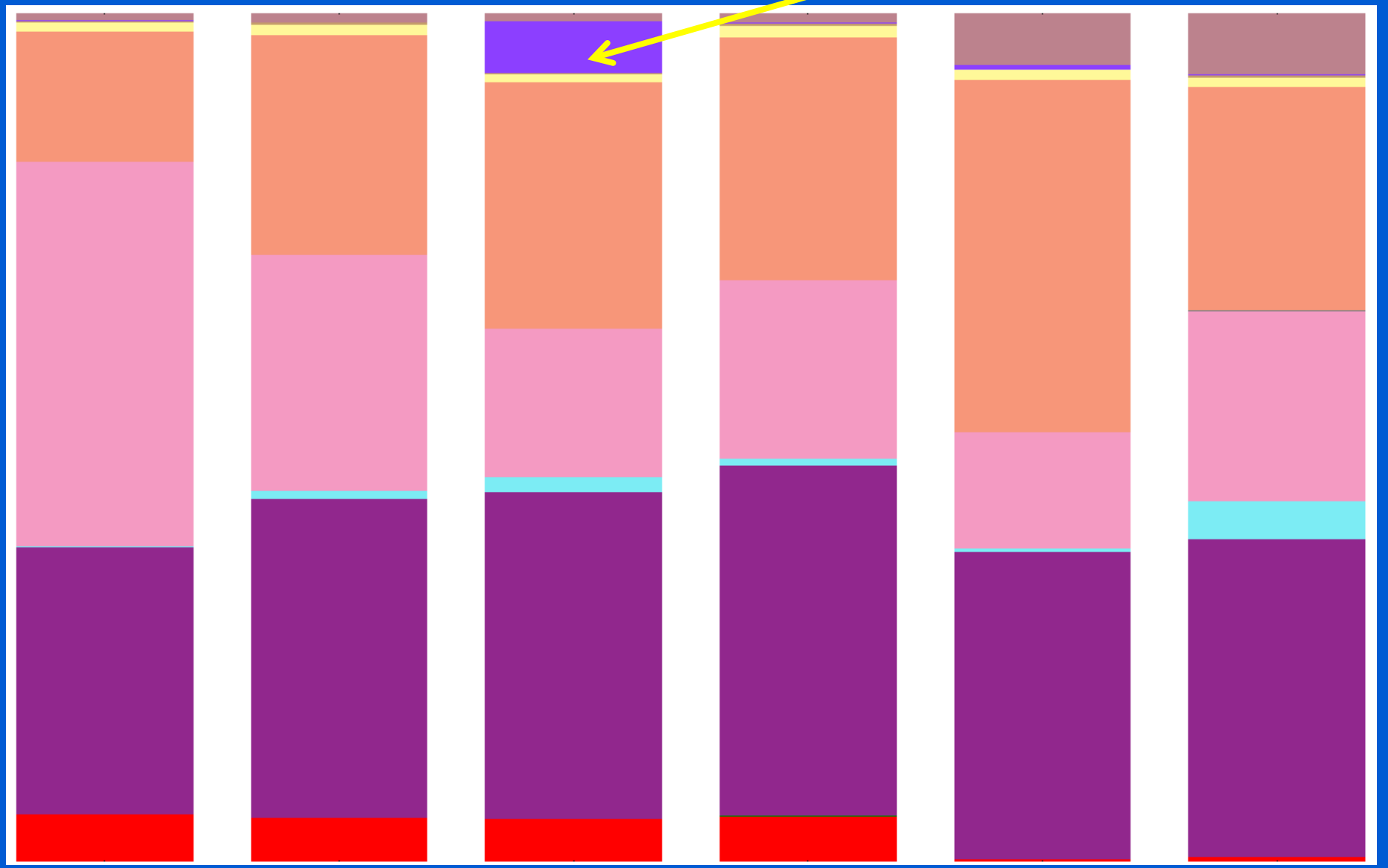
- Stool collected from
  - Three children with juvenile arthritis
  - One with psoriasis + joint pain
  - Two adult controls

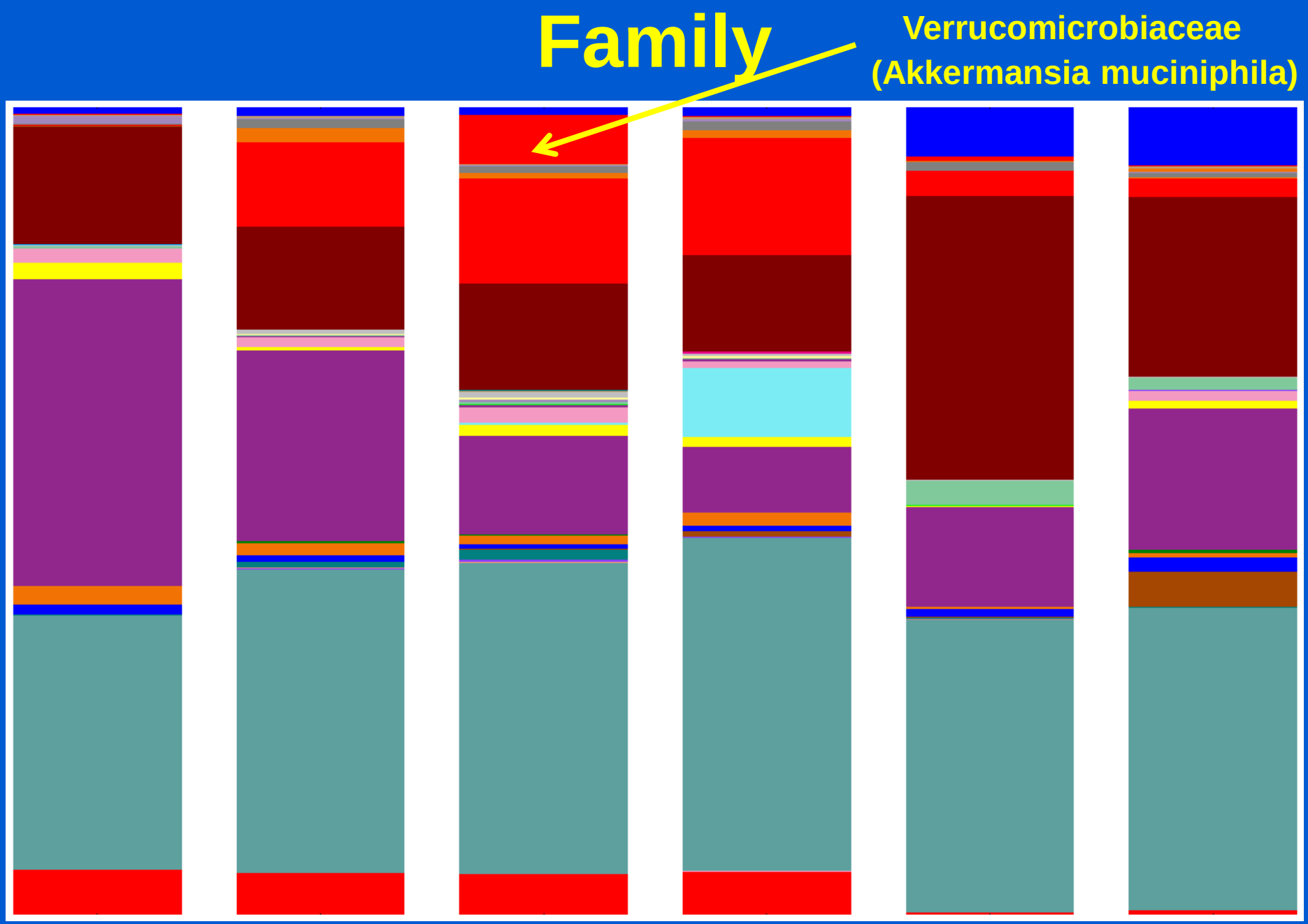
- 16S sequencing performed

Kingdom



Phylum




Family
Verrucomicrobiaceae
(Akkermansia muciniphila)
JIA
JIA
Psor.
JIA
Ctrl
Ctrl

Start of a story…

- 6 yo female with psoriasis and joint pain
- Subsequently developed abdominal pain
  - Diagnosed with IBD
- *A. muciniphila* chews up protective mucin layer in intestines

Hmmm…..

Microbiota may impact non-inflammatory diseases

- Obesity
- Metabolic syndrome

Obesity

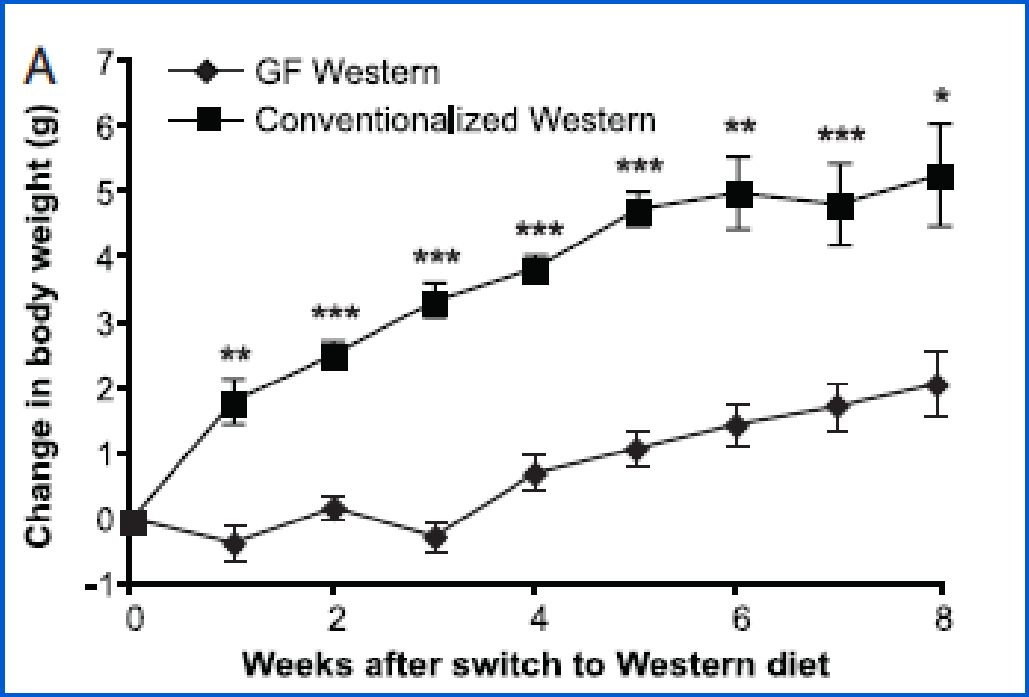
- Differences in obese vs lean microbiome
  - Not universally detected
- Even if so, cause or effect?
  - Weight loss results in altered microbiome
  - Bacteria adapt to our diet
    - Vegetarians enriched for bugs that can metabolize monosaccharides and disaccharides

Harris, *Jrnl Obesity* 2012;ePub
Angelakis, *Future Microbiol* 2012;7:91

However, in mice…

- **Germ-free mice showed less weight gain on Western diet**

Backhed, *PNAS* 2007;104:979



- **Transplantation of microbiota from leptin-deficient mice resulted in increased body fat compared to recipients of microbiota from wt mice** Turnbaugh, *Nature* 2006;444:1027

And in humans…

- Infant abx use is associated with increased BMI during childhood[1]
- Infant microbiota is associated with future weight gain:
  - *B fragilis* correlates with BMI at age 3[2]
  - Low *bidifobacter* predicts overweight at age 7[3]
- Upregulation in obese subjects of genes involved in phosphotransferase, which is involved in putting sugars into cells[4]

[1]Trasande, Int Jrnl Obesity 2012;ePub
[2]Vael, *Gut Pathogens* 2011;3:8
[3]Kalliomaki, *Am J Clin Nutr* 2008;87:534
[4]Greenblum, *PNAS* 2012;109:594

Moreover…

- 18 adults with metabolic syndrome underwent small bowel lavage, with either:
  - Allogenic microbiota transfer (lean donors)
  - Autologous microbiota transfer
- Results
  - Increased microbial diversity
  - Increased insulin sensitivity
  - Weight changes not reported

Vrieze, *Gastroenterol* 2012; in press

Summary

- New technology enables collection of previously unattainable amounts of data
- Analysis would not be possible without high-power computing platforms discussed throughout today
- Areas of research include:
  - Ontogeny of microflora, factors that influence it
  - Effect of flora on inflammatory diseases
  - How to alter the flora to improve human health