# Microbiome – Success Stories

Alimentary Pharmabiotic Centre
http://apc.ucc.ie

- Therapeutic Target
- Biomarkers
- Therapeutic asset

Fergus Shanahan

University College Cork, National University of Ireland

# Publications on the Microbiota

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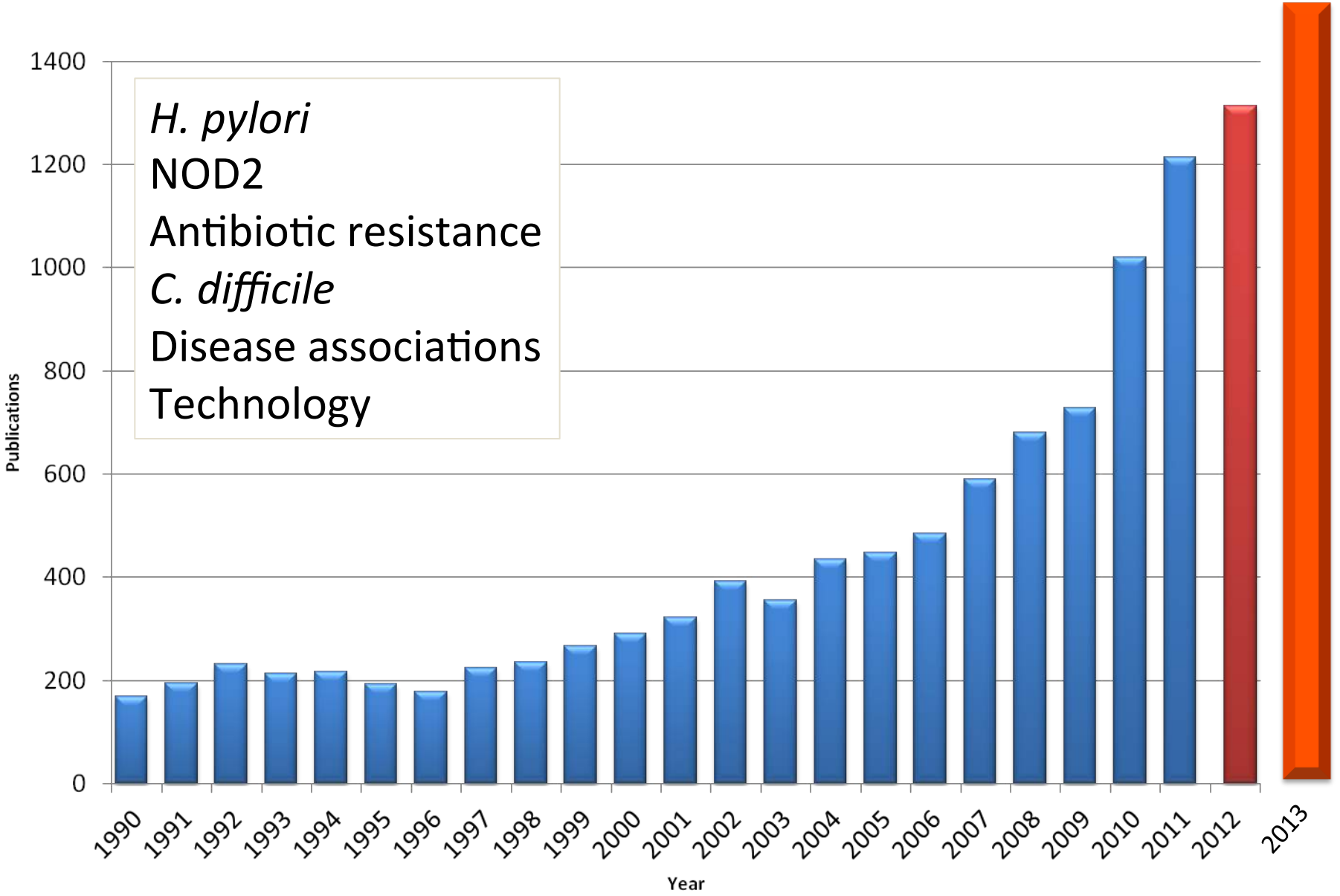

# Microbiome-Host Genome Interactions

Alimentary Pharmabiotic Centre

## April 2003

- Completion of
  "The Human Genome Project"
  - ↓ sequencing costs

Human Genome ⟶ 30k genes/1 million SNPs

**Microbiome** ⟶ 10 million genes/1 zillion SNPs

sfi Science Foundation Ireland

Alimentary Pharmabiotic Centre
Interfacing Food & Medicine

# Microbes & Man - Evolution

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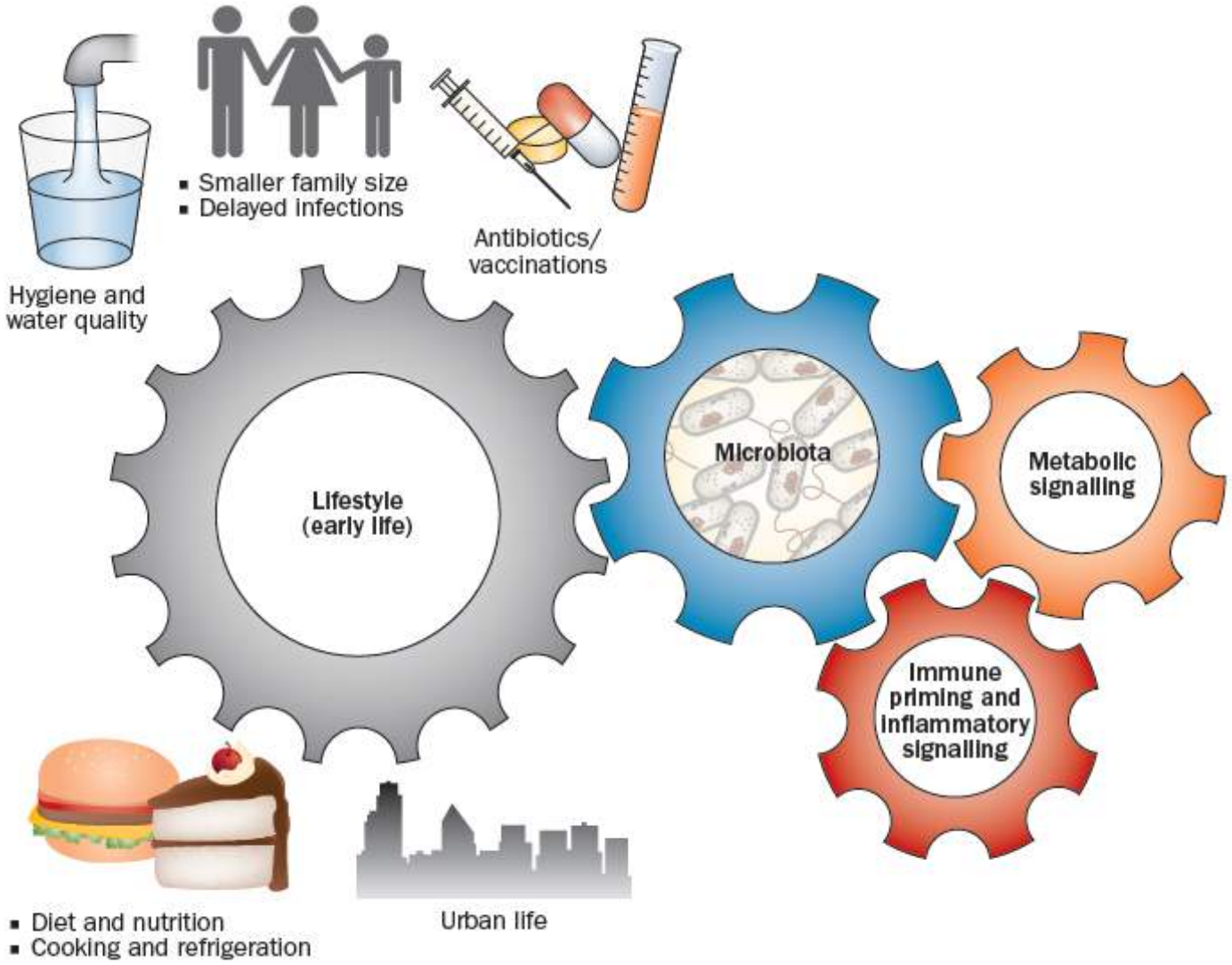
- Diet
- Sanitation & hygiene
- Refrigeration
- Urban life on concrete
- Decline in prevalence of *H. pylori*
- Decline in endemic parasitism
- Increased antibiotic usage
- Vaccinations
- Smaller family size
- Delayed exposure to mucosal infections
- Sedentary lifestyle - obesity

# Early life events




Shanahan *Nature Rev Gastro Hepatol* 2012

# Microbial Man

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# Therapeutic Armamentarium

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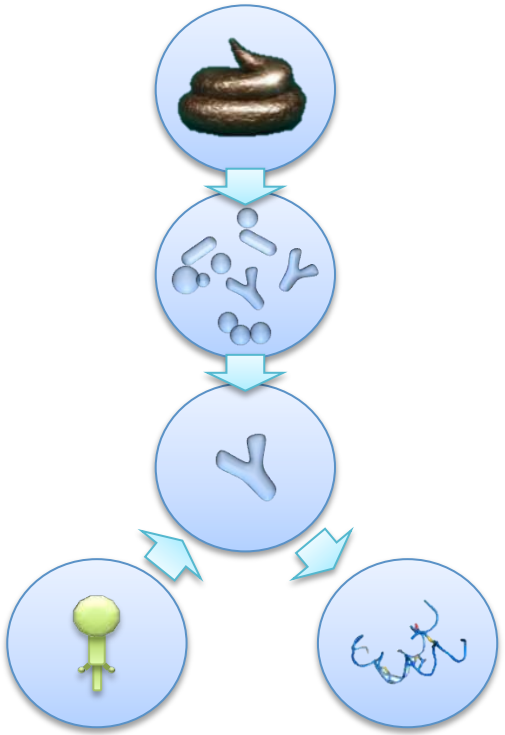
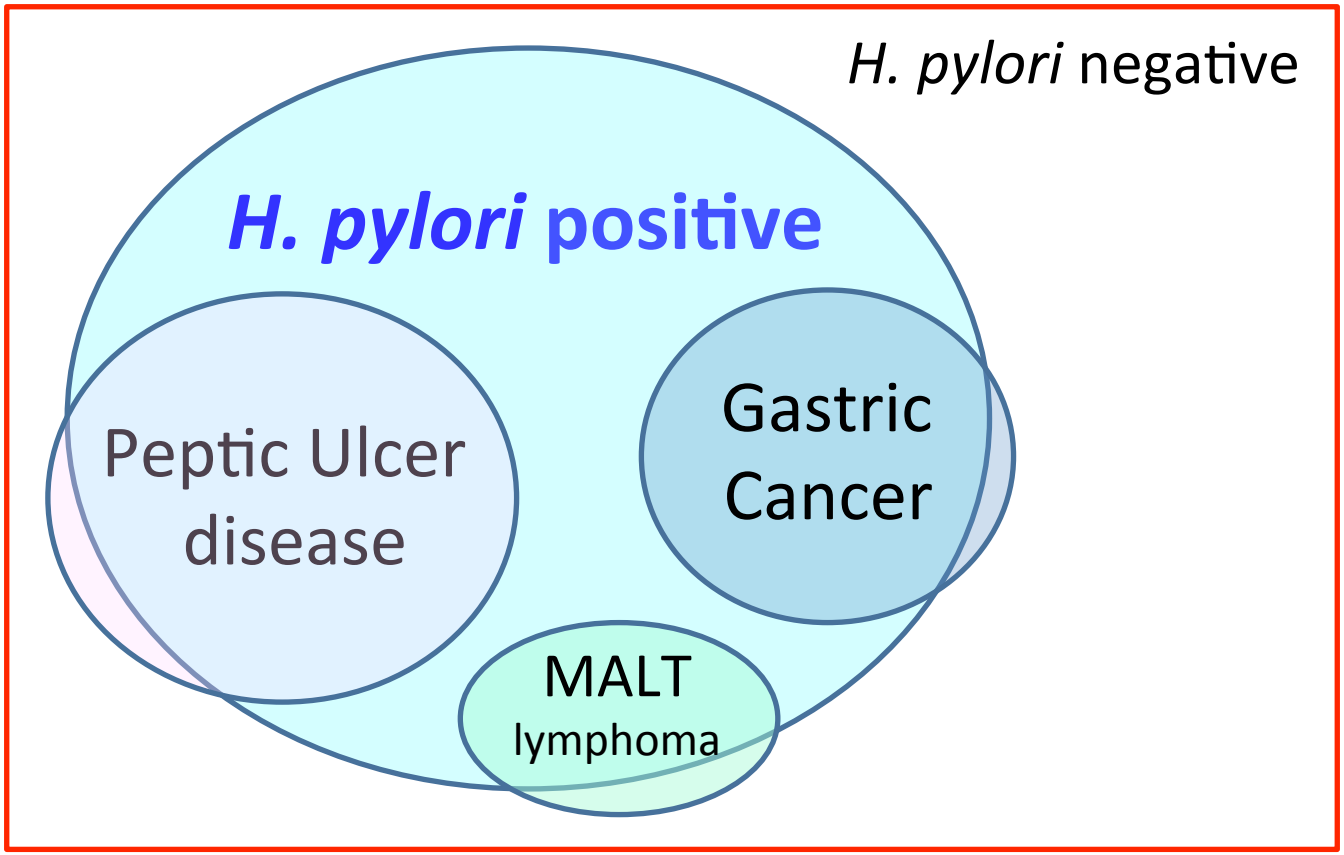
- fecal transplants
- microbial consortia
- probiotics
- bacteriophage
- pharmabiotics

(bioactives, bacteriocins.)



# Lessons




Barry Marshall & J. Robin Warren
Nobel Prize 2005

# What is a healthy gut?

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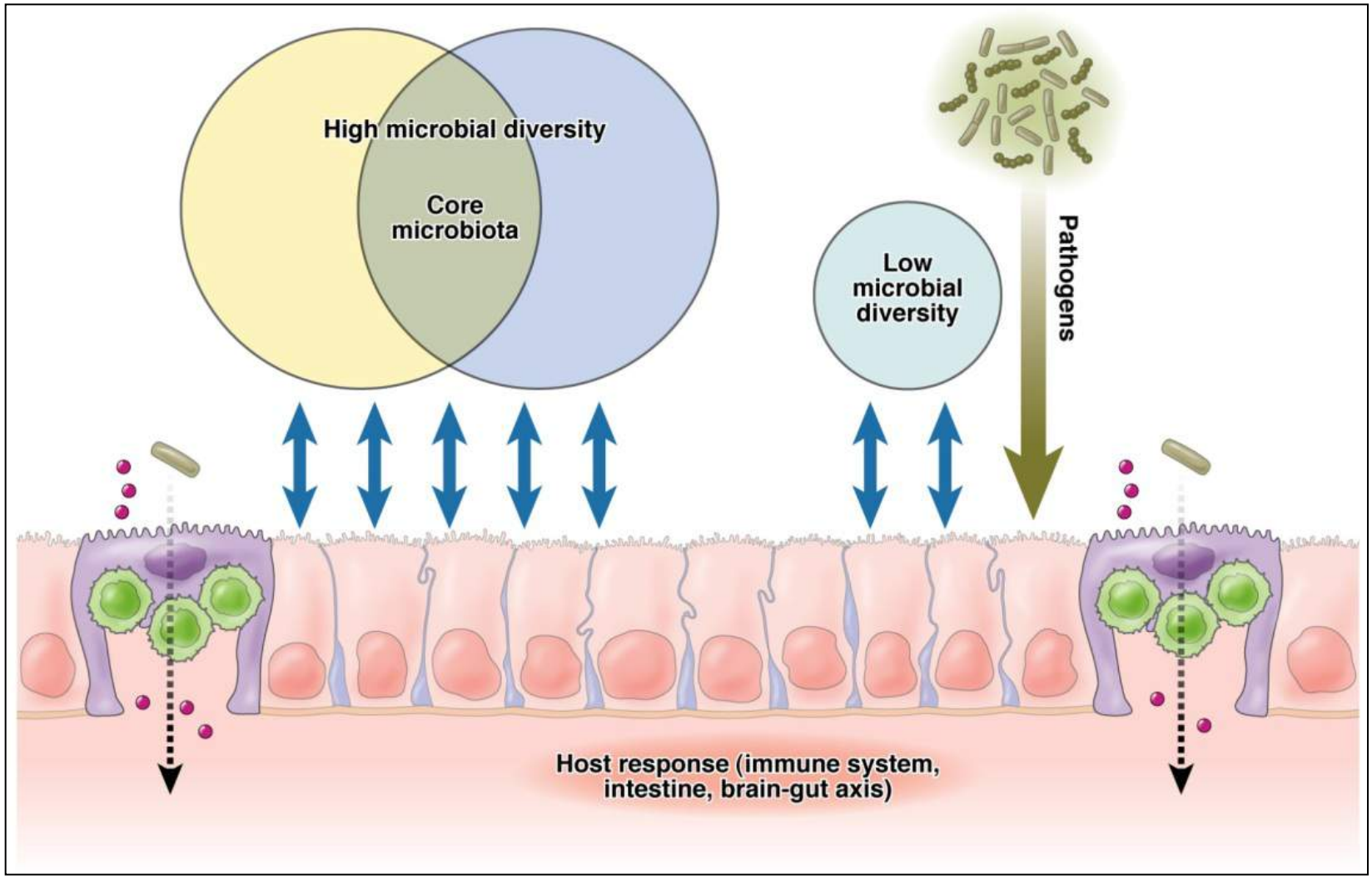


Shanahan *Gastroenterology* 2010;139:1808-12

# Antibiotic-associated disease

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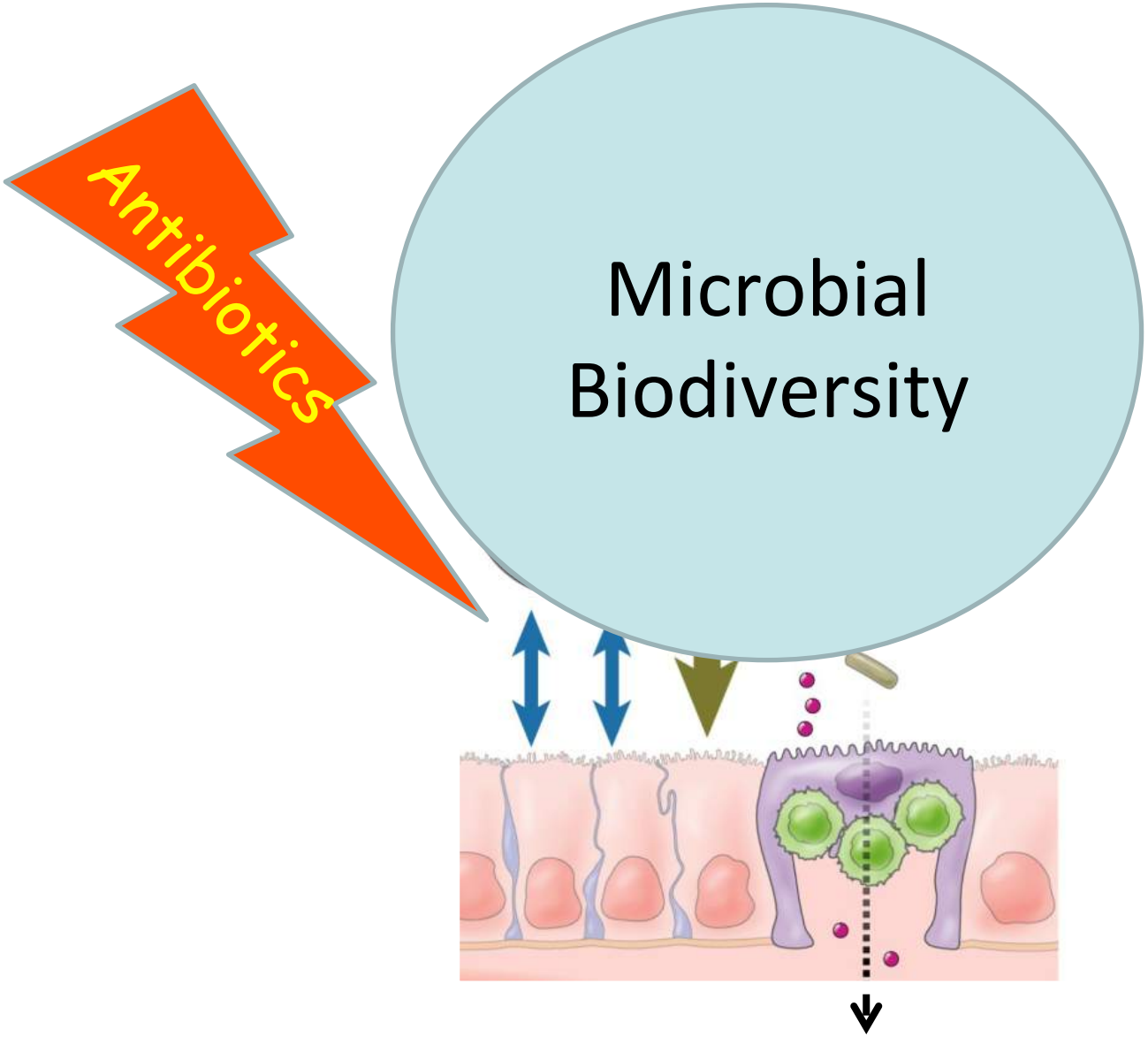
http://apc.ucc.ie




# Microbial Transplantation

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1. Transmissible pathogen

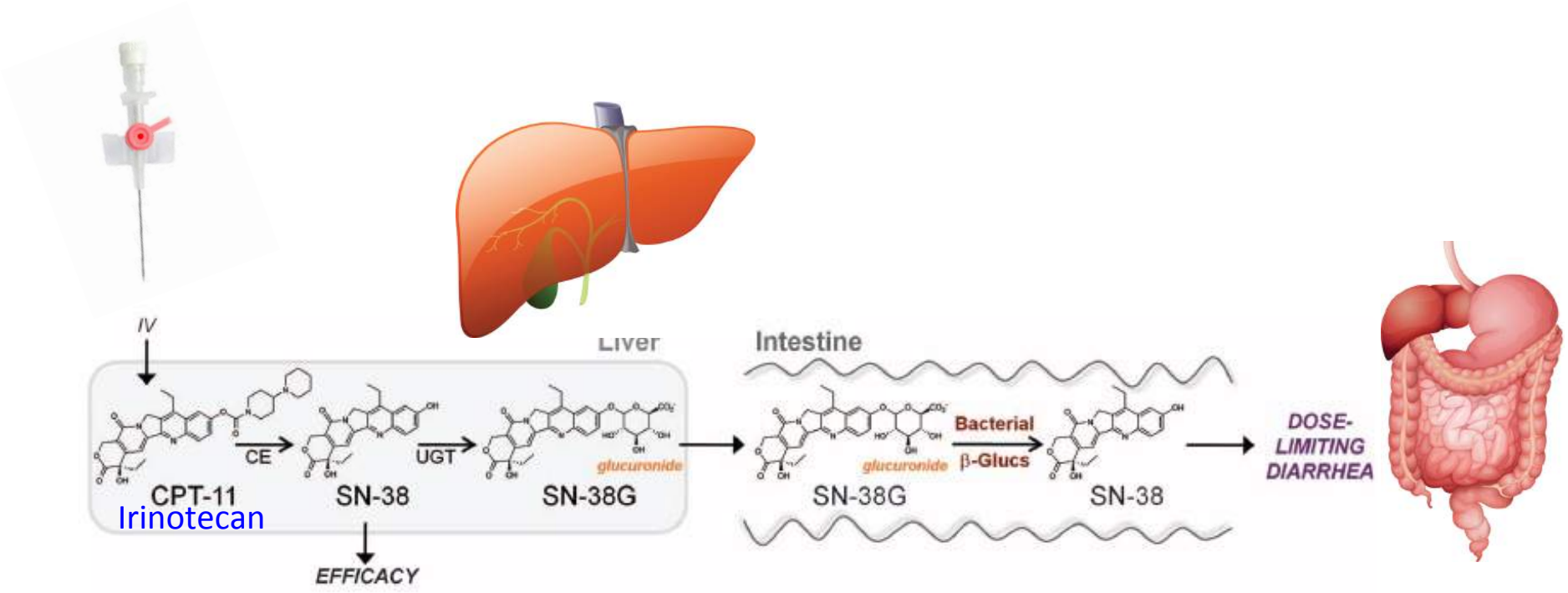
2. Translocation

3. Transferable phenotypes
   (inflammatory, metabolic, behavioural, ?carcinogenic)

# Harnessing microbial enzymes



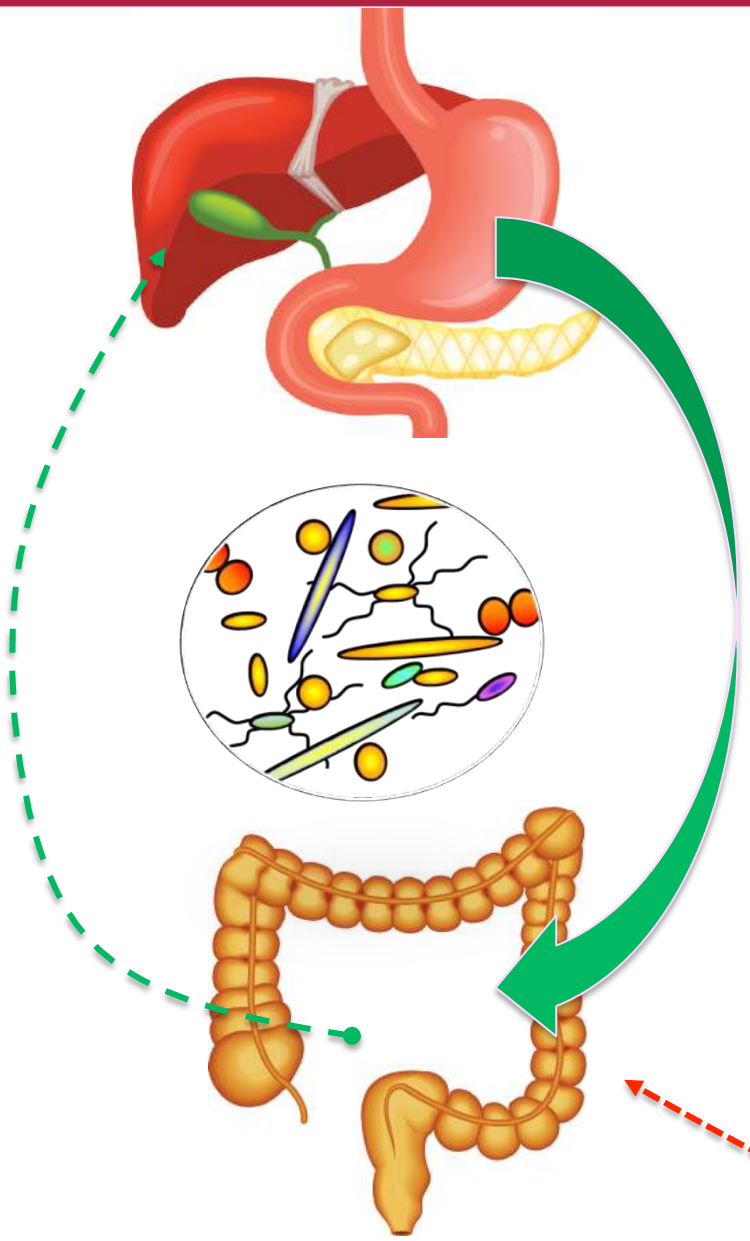
Alimentary Pharmabiotic Centre



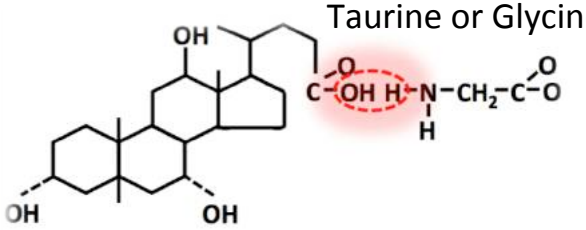

Prodrug → Active drug → Inactive drug → Reactivated drug

Wallace BD et al *Science* 2010

# Bile acid metabolism



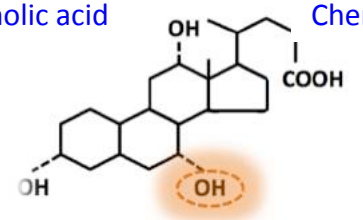
Taurine or Glycine



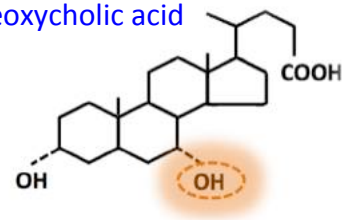
**Bile salt hydrolase (BSH)**

$1^0$

Cholic acid



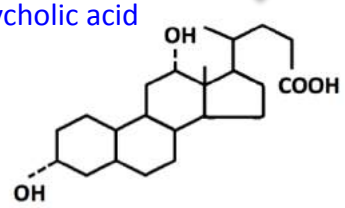
Chenodeoxycholic acid



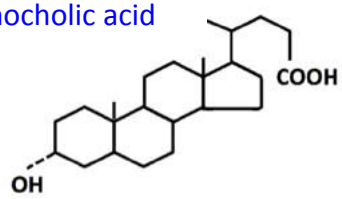
**7-α-dehydroxylase**

$2^0$

Deoxycholic acid

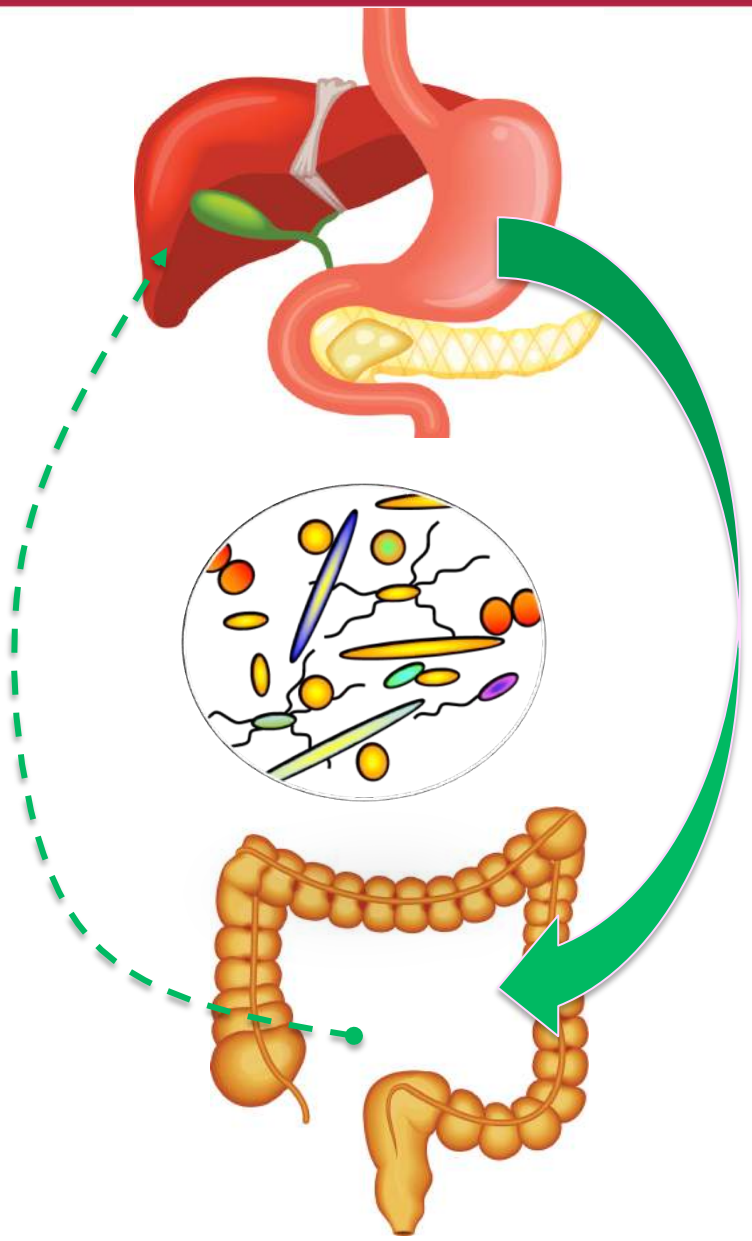


Lithocholic acid



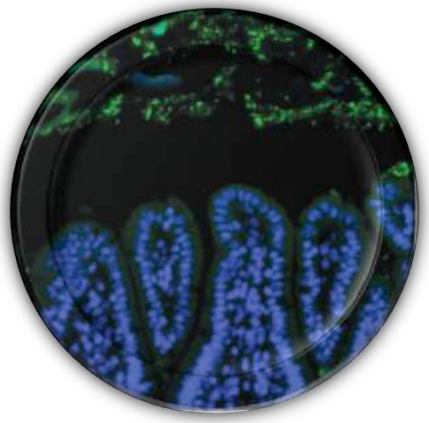
Mutagenic
Pro-inflammatory

# Bile acid metabolism

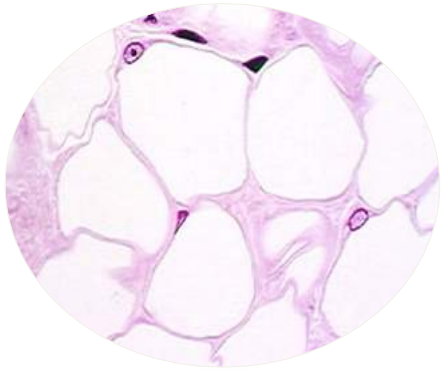


Bile acid signalling

Microbial composition
Cholesterol metabolism
Energy metabolism
Immune homeostasis
Circadian Rhythm



Reg IIIγ



Joyce et al. *PNAS* 2014
Joyce et al. *Gut Microbes* 2014

# Diet, Microbe-Host co-metabolism

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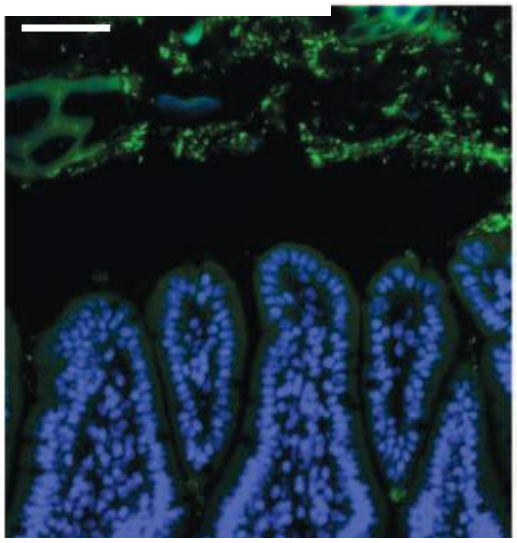
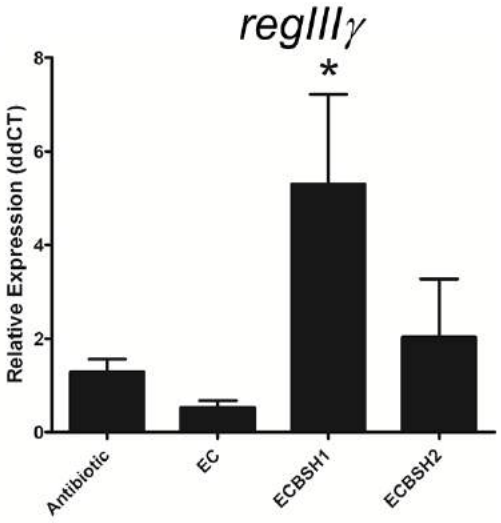
High Fat Diet Obesity

Reg IIIγ




Joyce et al. *PNAS* 2014

# Microbial Man

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# Dietary Diversity & Microbial Diversity

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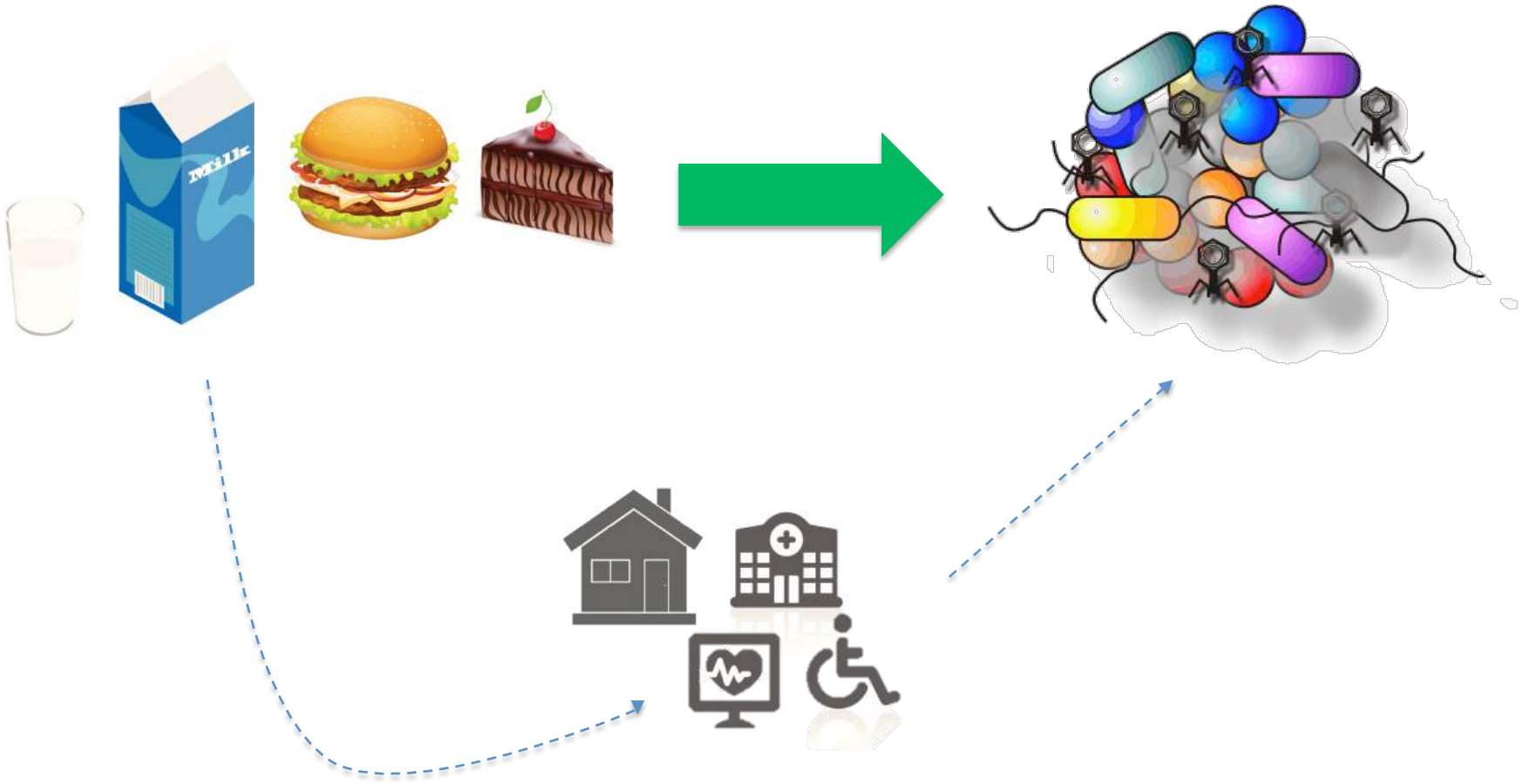
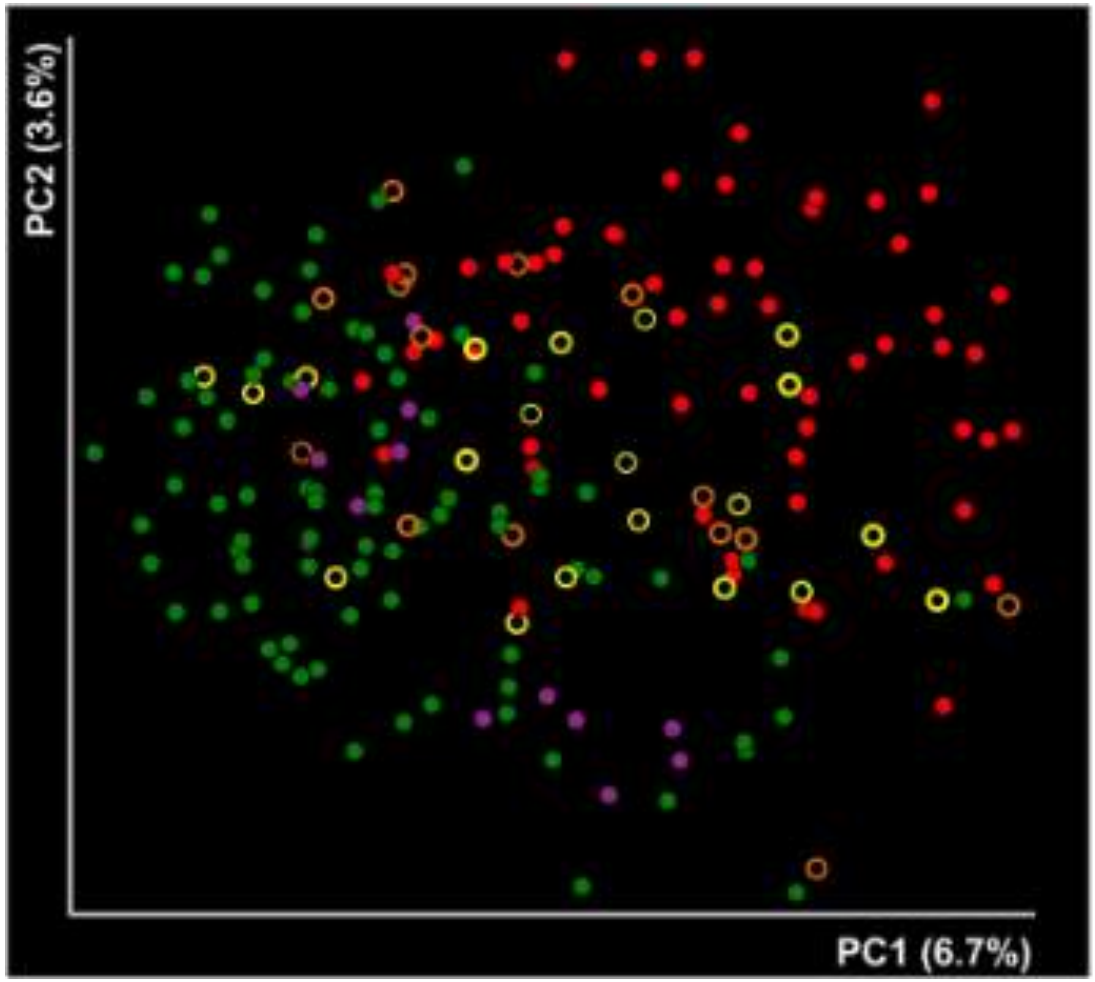



Claesson M et al. *Nature* 2012

# Gut bacteria vary with where you live

Alimentary Pharmabiotic Centre




Community Day Hospital Rehab Long-stay Young control

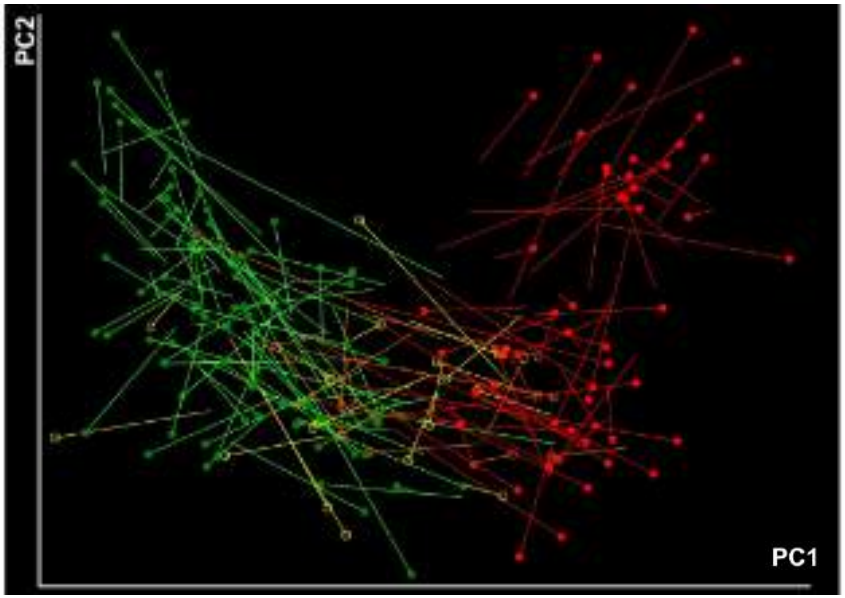
Elderly

Claesson M et al. *Nature* 2012

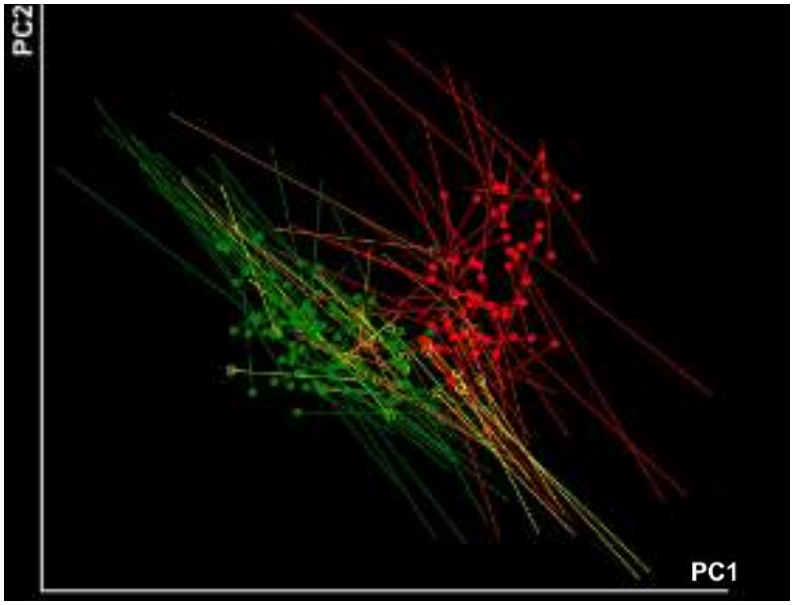
# Gut bacteria vary with diet

Alimentary Pharmabiotic Centre

**Unweighted UniFrac PCoA vs. FFQ PCA**




**Weighted UniFrac PCoA vs. FFQ PCA**

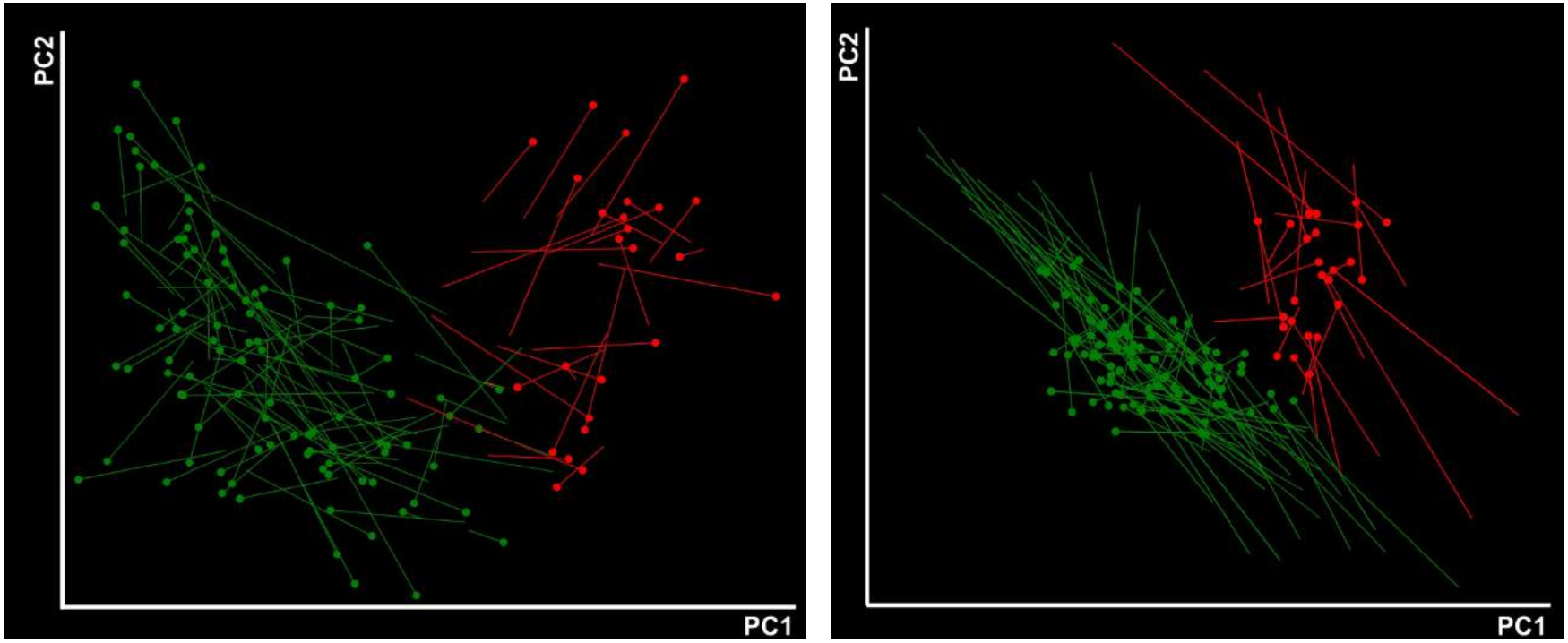



FFQ ——— Microbiota

Community Day Hospital Rehab Long-stay

Claesson M et al. *Nature* 2012

# Microbiota & diet correlation by duration in long-stay care




FFQ — Microbiota

N/A (C+DH) Week 0to6 (Rehab) Week 6 to Year 1 Year 1+

Claesson M et al. *Nature* 2012

# In praise of… the microbiota

Alimentary Pharmabiotic Centre

Editorial
guardian.co.uk, Monday 16 July 2012

**Researchers in Cork report in *Nature*** that they examined the intestinal products of 178 people with an average age of 78 and found microbial diversity correlated with their strength and health. Since this diversity also correlated with diet, **the lesson is clear: variety is not just the spice of life, but its staple. We are what we eat, and so are our inner friends.**

http://www.guardian.co.uk/commentisfree/2012/jul/16/in-praise-of-microbiota-editorial

# Microbial Man

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- Therapeutic Target
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# Why we need new antibiotics

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## A Perfect Storm

As bacterial infections grow more resistant to antibiotics, companies pull out of antibiotic research and fewer new antibiotics are approved

**1980 to 2010**

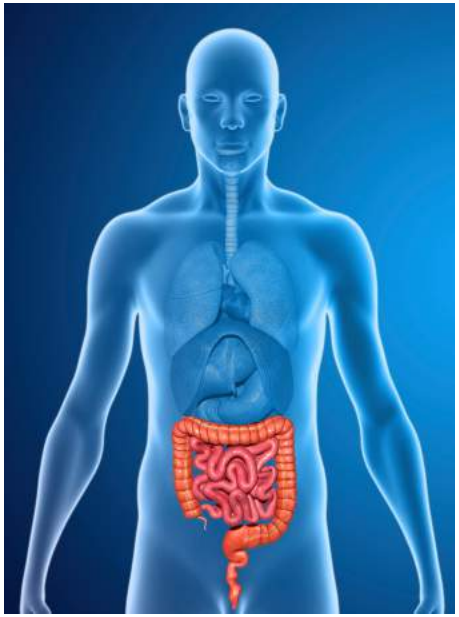
- ↑ Antibiotic resistance (MRSA, VRE, FQRP)
- ↓ Antibiotic research
  - (18 companies doing research in 1990; only 4 in 2011)
- Collateral damage
- Long term impact

Cooper MA & Shales D. Nature 2011

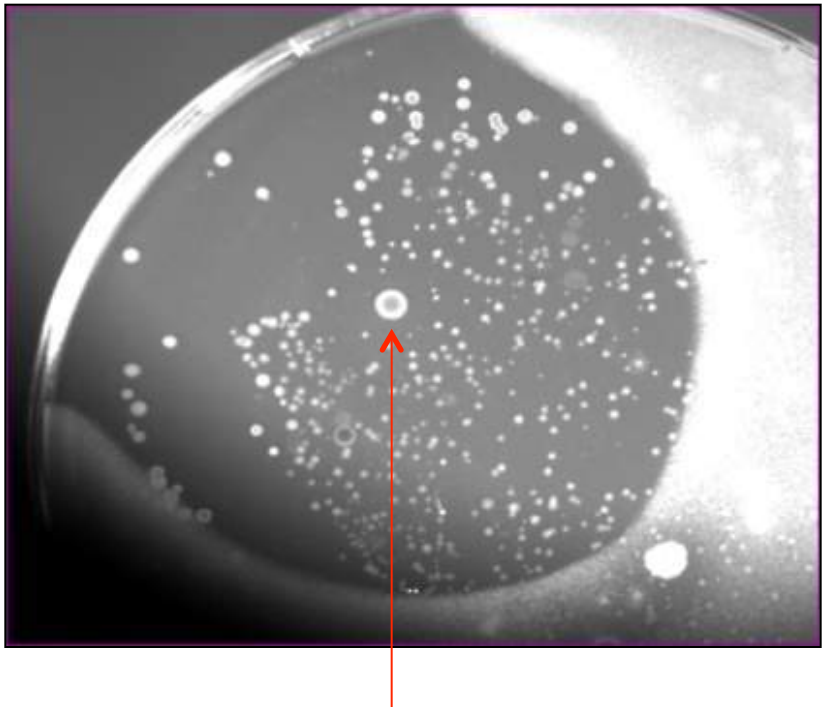
# A narrow spectrum bacteriocin against *C. difficile*

Alimentary Pharmabiotic Centre

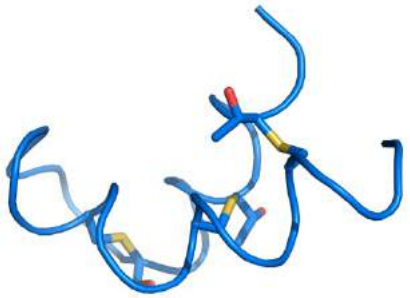
Overlaid with *Clostridium difficile*



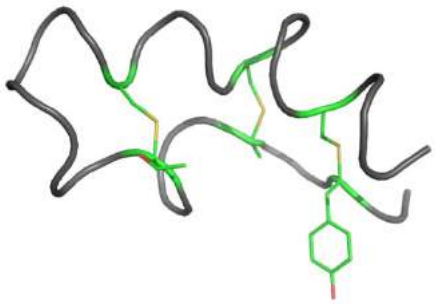
Isolated >30,000 spore-formers from faecal specimens



*Bacillus thuringiensis*



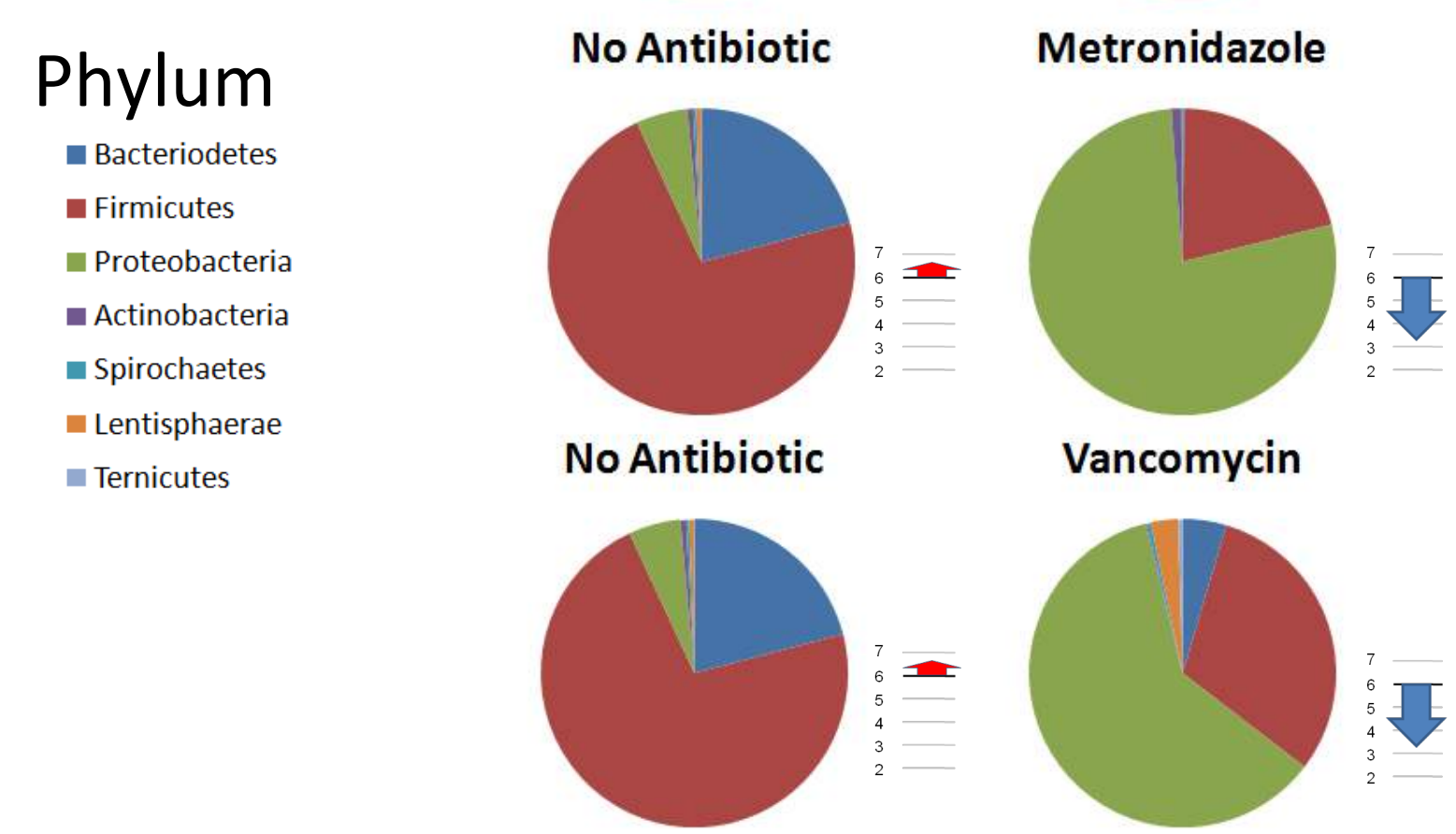
Thuricin CD



Rea M *et al*. *PNAS* 2011;107:9352-58

# Collateral damage

## 16S profiling




Rea et al. *PNAS* 2011

# Phage virus *vs* *C. difficile*

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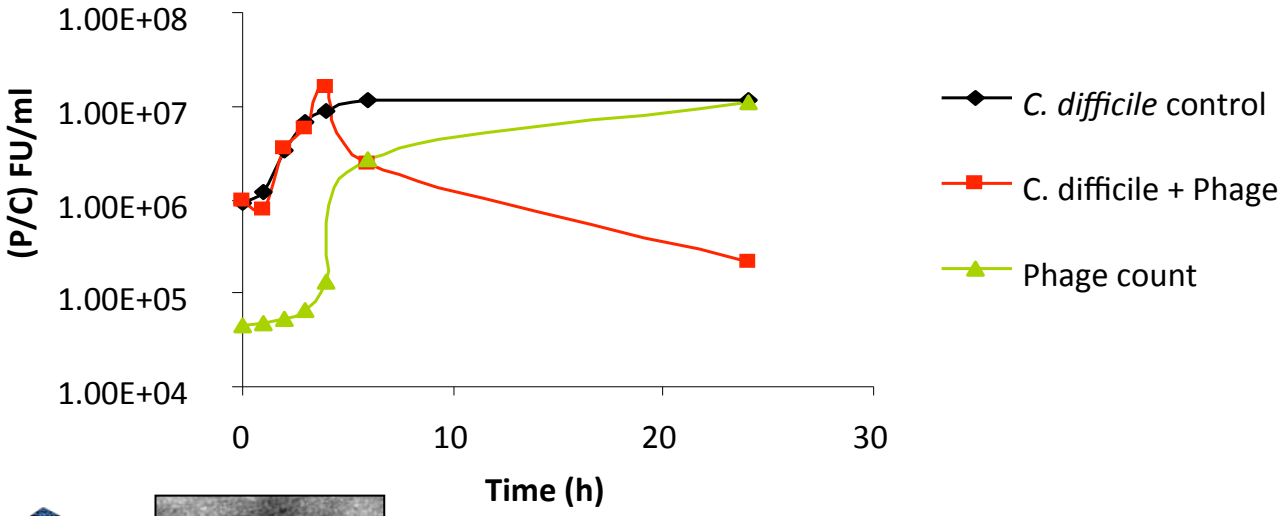
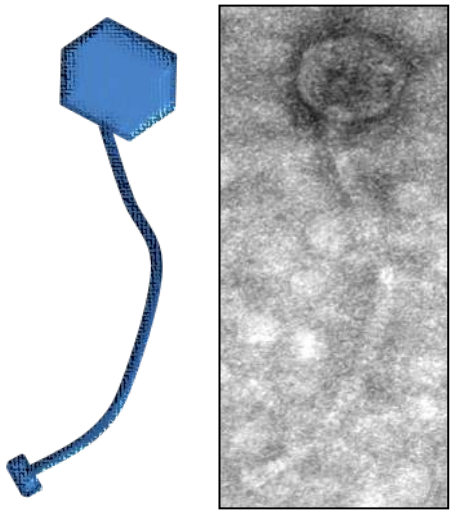
## Phage CD6356 in faecal fermentation



φCD6356 (37kb)

# Putting phage viruses to work

Alimentary Pharmabiotic Centre
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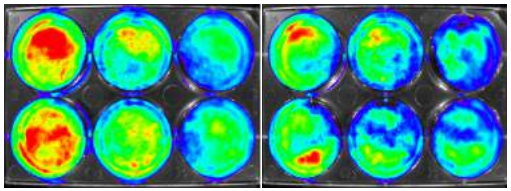
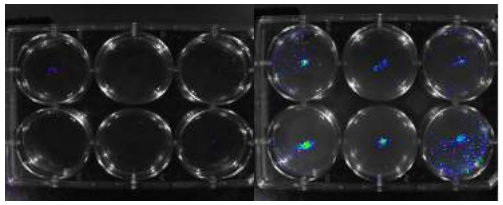
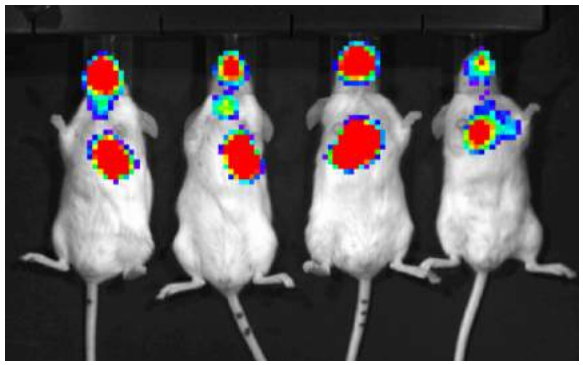
Lux-tagged *P. aeruginosa* biofilm on pulmonary cell line



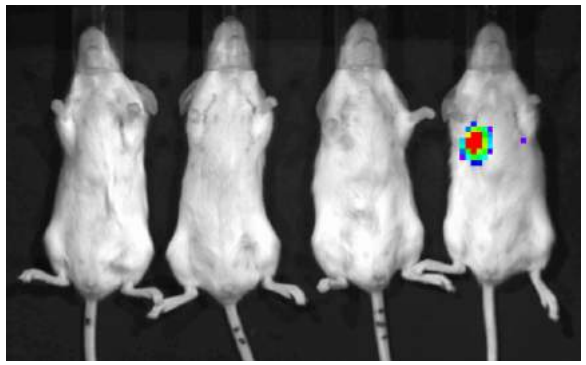
Phage added



Mice nasally infected with *P. aeruginosa*



30 min after receiving phage



Alemayehu D et al *MBio* 2012

# Microbial Man = Successful Man

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