Gut microbiome - its role in child health and development.

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Some definitions

• **Microbiota** (*microflora*) – the qualitative and quantitative information about the different microbes present in a system – so who is there and how abundant.

• **Microbiome** – the entire habitat, including the microorganisms (bacteria, archaea, lower and higher eukaryotes, and viruses), their genomes (i.e., genes), and the surrounding environmental conditions.

• **Metagenome** – the functions that these microbiota have, e.g. bile metabolism – their gene catalogue.

• **Metaxonom**e – a **16S rRNA** gene inventory, used to define the **microbiota**.

• **Metabonome** – a catalogue of the metabolites in a sample.

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The main focus in human biology has been to explain how it functions in terms of the genome. The human microbiome is host specific and can be changed by diet, drugs, pregnancy & surgery.
We should not view the gut solely as a tube involved in extracting nutrients from food.

Examination of the output from this tube indicates that it is also an ecosystem that microbes have successfully colonised.

50-55% of a stool sample is microbial biomass – 50 – 250 g.

Born sterile???

36-60 mnths

Established community
The absence of a microbiome impacts the whole host

We have a dearth of mechanisms and only a few have been identified.

- Intestinal
- Exocrine
- Vascular
- Endocrine
- Hepatic
- Infection
- Nutritional
- Biologics e.g. anti-CTLA-4
- Metabolism
- Morphology
- Epithelia
All these diseases have evidence for a role of a microbiome
Ecological interactions between members of different species

+ positive (win); - negative (loss); 0 neutral

Species 1/Microbiota; Species 2 = host

- **Pathogen**
  - e.g. *E. coli* or *Mycobacterium avium* subspecies *paratuberculosis* (MAP)

- **Amensalism**
  - Microbes which cause inadvertent damage to the host

- **Commensalism**
  - e.g. FMT for CDAD
  - e.g. probiotic microbes which do not reproduce in the host *L. lactis*.

- **Mutualism**
  - Parasitism/predation
  - Pathologies not associated with a pathogen

This is the modern issue for microbiome studies.
Who’s responsible for the first hit?

**Classical model**
- E. coli
- MAP

**Virulence factors**
- Microbe

**Amensalistic?**

**first “hit” driving uncontrolled inflammation**

**Inflammation**

**Diet**
- H₂S, phenols?

**Microbiome**
- Microbe

**Surgery**

**Diet**
- H₂S, phenols?
Variability clouds the issue of a healthy vs unhealthy microbiota.

We have no idea of the consequences of position on this continuum.

What can be considered a dysbiosis?

ELDERMET data

& biogeography complicates the story.

De Filippo et al PNAS 2010,107(33):14691-6
We have some preliminary evidence that B:F ratio matter. B:F ratio in pregnant women.

A high Bacteroidetes to Firmicutes ratio does have a real impact on host metabonome.
An important link is the proteome

Why?

Bacterial proteases are a potential virulence factor in colorectal cancer and IBD. They have also been shown to compromise tight junction integrity.

Does the bacterial exoproteome, i.e. free proteases in the gut lumen, play a role in inflammatory bowel disease?

- **Casein**: 
P = 1.405e-4

- **Collagen**: 
P = 0.08213

- **Keratin**: 
P = 1.929e-5

(n=10) (n=13)
Use of targeted proteases inhibitors to understand the degradome in IBD and healthy samples
The microbiome and IBD

- **PROTEASE**
- **INTESTINAL ALKALINE PHOSPHATASE**
- **LPS**
- **BACTERIAL ALKALINE PHOSPHATASE**

Diet, Smoking, Abx, Appendectomy, Vit D status, Caucasian vs Asian, CD vs UC

Tight junction integrity

INFLAMMED → IBD

NOT INFLAMMED → IBD

This concept can be transferred to IBD and the drugs used to treat it.
What role for the microbiome in IBD drug efficacy

Azo-reductases in the gut microbiome

**Thioguanine (TG) ➔ Thioguanine nucleotides (TGN)**

**ORIGINAL ARTICLE**

**Colonic microbiota can promote rapid local improvement of murine colitis by thioguanine independently of T lymphocytes and host metabolism**

I Oancea,¹,² R Movva,¹,²,³ I Das,¹ D Aguirre de Cárcer,⁴ V Schreiber,¹,² Y Yang,¹,⁵ A Purdon,¹,² B Harrington,¹,² M Proctor,¹,² R Wang,¹,² Y Sheng,¹,² M Lobb,⁶ R Lourie,¹,² P Ó Cuív,²,⁷ J A Duley,⁴,⁶ J Begun,¹,²,⁸ T H J Florin¹,²,⁸
Molecularly, it was associated to elevated levels of IL-10 and VEGF and low levels of TGF-b1 from the beginning of the healing process.
In summary

• Application of multi modal “omic” tools is definitely helping us to determine the roles of the gut bacteria in IBD, cancer, general inflammation, auto-immune disease and other NCDs.

• Newer ecologic concepts, such as ammensalism will help guide us to a better understanding of the role of the microbiome.

• The microbiome will need to be considered in relation to drug efficacy.

• Can we harness knowledge of the microbiome to treat and understand NCDs?

• Thank you and I wish to thank my labs at Imperial and Cardiff and the funders of my research.