The Human Microbiome and its defensive actions against AMR: Intestinal Microbiota Transplant (IMT) based therapies.

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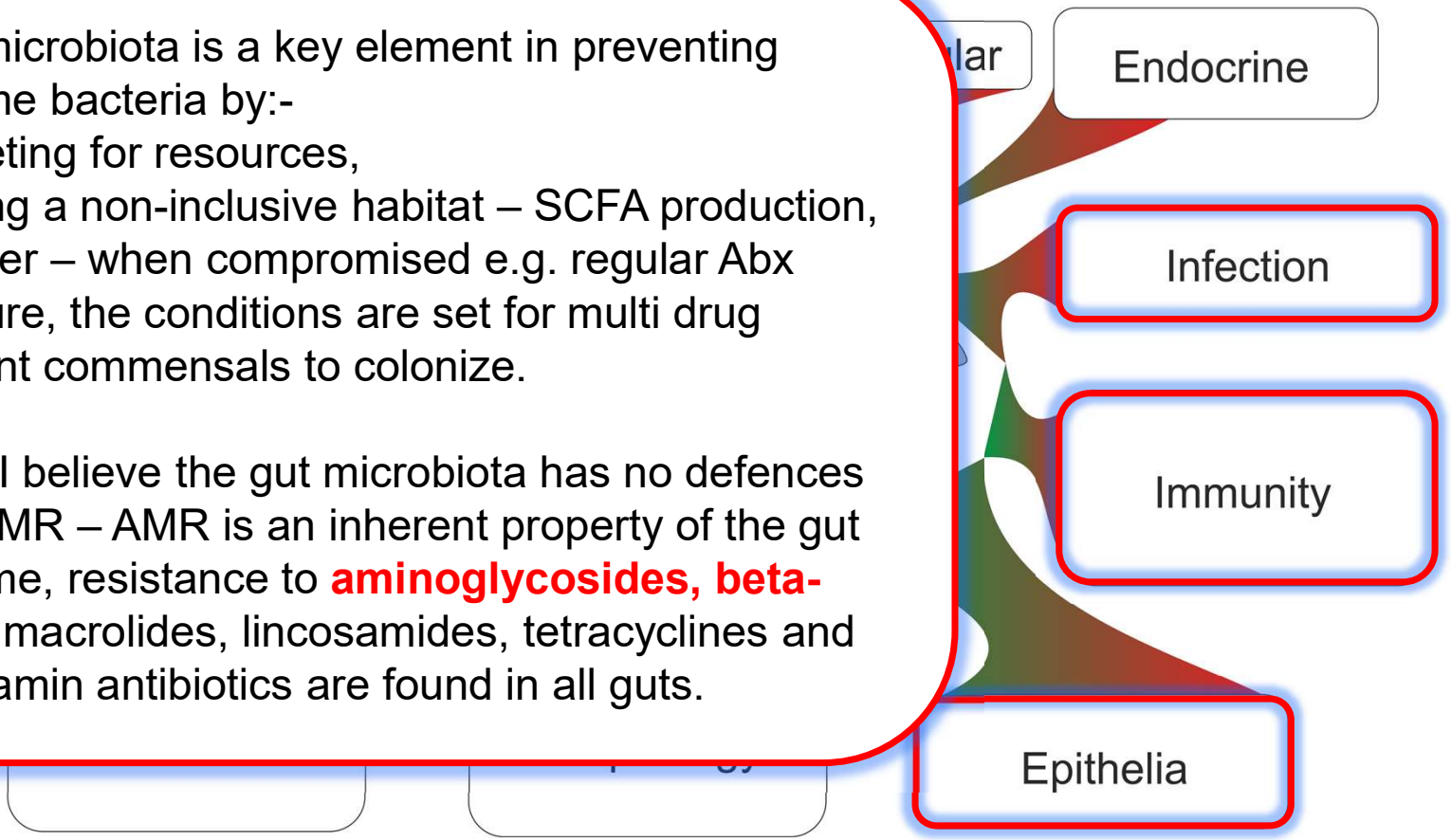
Evidence: The absence of a microbiome impacts the whole host

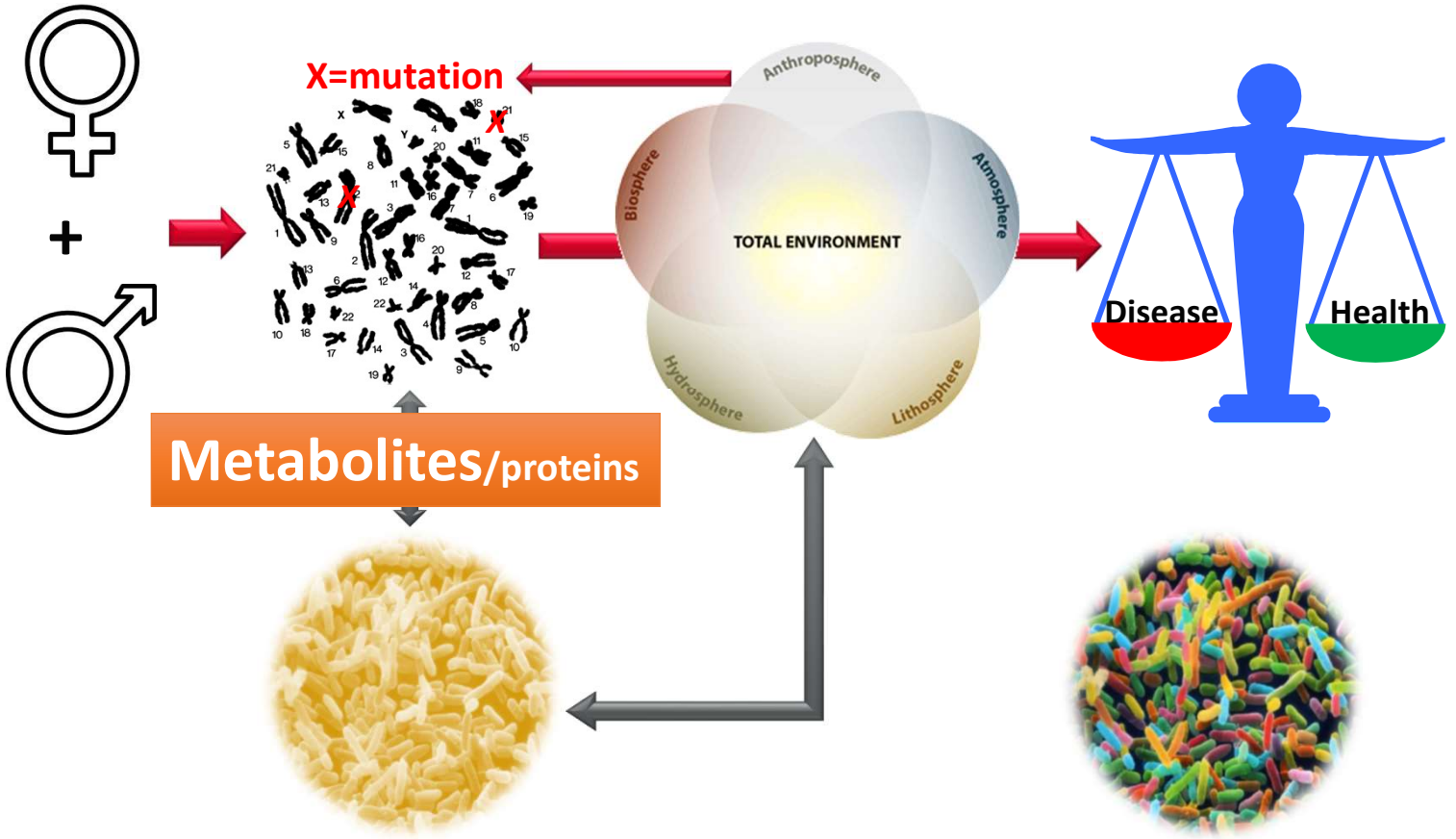
The gut microbiota is a key element in preventing unwelcome bacteria by:-

- Competing for resources,
- Creating a non-inclusive habitat – SCFA production,
- However – when compromised e.g. regular Abx exposure, the conditions are set for multi drug resistant commensals to colonize.

Morever, I believe the gut microbiota has no defences against AMR – AMR is an inherent property of the gut microbiome, resistance to **aminoglycosides, beta-lactams**, macrolides, lincosamides, tetracyclines and streptogramin antibiotics are found in all guts.



Gut Health: Intestinal microbiota transplantation to manipulate the gut microbiome and treat MDROs



Gut microbiome

"Healthy" donor

Over the last 5 years we have been exploring how intestinal microbiota transplantation (IMT) can control MDROs and associated complications

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We have been using a wide range of approaches to characterize an IMT's impact on the host and find mechanisms

- *Workflow:* Characterization of changes in the structure and metabolic function of the gut microbiota pre- and post-IMT:
  - Human samples.
  - Twin vessel chemostat ('Robogut').
  - Metataxonomics (16S rRNA genes).
  - Metabolite profiling (NMR/MS).
  - qPCR and enzymology.
  - Plate counts.
  - Batch cultures.
  - Mouse modelling.

In the setting of a *C. difficile* infection we believe a significant proportion of the way in which an IMT treats this disease is by restoring the bile metabolising function and the ability to produce valerate - we have shown this in mouse models of *C. difficile* infection.

We were approached by haematologists who had a microbiological headache.

- Their leukaemia patients awaiting stem cell transplant (SCT) were heavily colonized with multi-drug resistant bacteria – *E. coli* and *Klebsiella* spp.
- The last patient they gave an SCT to died of a bacteraemia due to an MDRO
- So they had stopped SCT due to risk of their MDRO colonized patients getting an untreatable MDRO and dying.

So we started to explore using IMT to modulate the gut with an aim to remove the MDROs and allow the SCT to proceed.

Bone Marrow Transplantation (2017) **52,** 1452–1454; doi:10.1038/bmt.2017.151; published online 17 July 2017

Case study: A 63-year-old man presented with a new diagnosis of Philadelphia-positive acute lymphoblastic leukaemia.

Table 1. Microbiological sample results/Timeline

Days post FMT	*− 224*	*− 209*	*− 203*	*− 177*	*− 168*	*− 164*	*− 30*	*− 30*	*− 30*	*-*	*0*	*14*	*16*	*16*	*19*	*23*	*29*	*36*
Sample source	*Blood cultures ×2*	*Stool*	*Blood cultures ×2*	*Stool*	*Rectal screen*	*Rectal screen*	*Blood cultures & line tip*	*Rectal screen ×2*	*Rectal screen ×2*		*Rectal screen*		*Rectal screen*	*Stool*	*Blood cultures*	*Rectal screen*	*Rectal screen*	*Rectal screen*
Organism	*E. coli*		*E. coli*		*K. oxytoca GES-5*	*K. oxytoca GES-5*	*S. aureus*	*E. coli*	*E. coli*		*E. coli*				*E. faecalis*			
Amikacin	S		S		S	S	--	S	S									
Amoxicillin	R		R		R	R	-	R	R									
Aztreonam	R		R		R	R	-	R	R									
Cefoxitin	R		R		R	R	-	R	R									
Ceftazidime	R		R		R	R	-	R	R									
Ceftriazone	R		R		R	R	-	R	R									
Cefuroxime	R		R		R	R	-	R	R									
Ciprofloxacin	R		R		R	R	S	R	R									
Co-Amoxiclav	R		R		R	R	-	R	R									
Collistin	S		S		S	S	-	S	S									
Ertapenem	S		S		R	R	-	S	S									
Gentamicin	R		R		R	R	S	R	R									
Meropenem	S		S		I	I	-	S	S									
Piperacillin-tazobactam	I		I		R	R	-	R	R									
Temocillin	R		R		R	R	-	R	R									
Tigecycline	S		S		S	S	-	S	S									
Tobramycin	R		R		R	R	-	R	R									
Trimethoprim	R		R		R	R	S	R	R									
Clindamycin	-		-		-	-	S	-	-									
Erythromycin	-		-		-	-	S	-	-									
Flucloxacillin	-		-		-	-	S	-	-									
Fusidic acid	-		-		-	-	S	-	-									
Oxacillin	-		-		-	-	S	-	-									
Penicillin	-		-		-	-	R	-	-									
Rifampicin	-		-		-	-	S	-	-									
Teicoplainin	-		-		-	-	S	-	-									
Tetracycline	-		-		-	-	S	-	-									
Vancomycin	-		-		-	-	S	-	-									

C. difficile PCR – positive

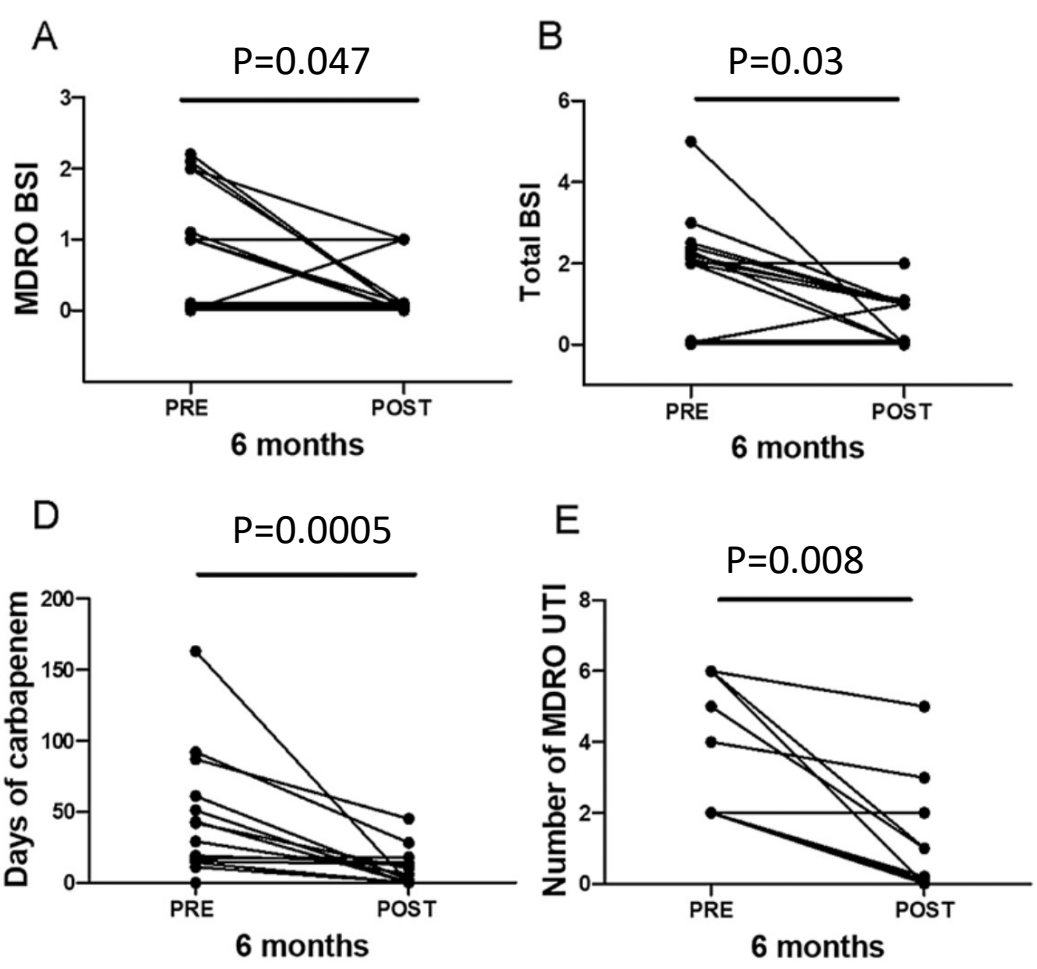
C. difficile PCR – positive

Neutrophil engraftment was achieved on day +25 and the patient was discharged from the hospital on day +29. At day +100 he was well, with no evidence of leukaemia, GvHD or MDRO by rectal screening. At 12-months post-transplant the patient remains well and in remission.

No XDRO identified

Abbreviations: *C. difficile* = *Clostridium difficile; E. coli* = *Escherichia coli; E. faecalis* = *Enterococcus faecalis;* HCT = haematopoietic cell transplantation; I = intermediate; *K. oxytoca* = *Klebsiella oxytoca;* PCR = polymerase chain reaction; R = resistant; *S. aureus* = *Staphylococcus aureus;* S = susceptible; XRDO = extensively drug-resistant organism.

We have used IMT to manipulate the gut microbiota of stem cell transplant and renal patients with multi drug resistance organisms.



Clinical outcomes.

Abbreviations:

- **BSI**, bloodstream infection; **FMT**, fecal microbiota transplantation;
- **MDRO**, multidrug-resistant organism;
- **UTI**, urinary tract infection.

Clinical Infectious Diseases

BRIEF REPORT

Disease Prevention Not Decolonization: A Model for Fecal Microbiota Transplantation in Patients Colonized With Multidrug-resistant Organisms

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Using IMT to control MRDOs in the gut microbiome

We are now starting to explore the potential of IMT as a rescue therapy, which can reset the gut microbiota to control the impact of MDRO bacteria, where their gut microbiomes have been shaped by regular antibiotic (Abx) exposure and subsequent colonization by MDROs opportunistic pathogens.

While I do not believe that the gut microbiota has a defence against AMR, I think in an ecosystem which is shaped by constant Abx exposure, which also allows MDROs to colonize, IMT can rescue the system and modulate the levels of MDRO such that the host is afforded some protection and be a viable alternative to more antibiotic use.

Thank you and I wish to thank my colleagues and collaborators, Frances Davies, Rohma Ghani, Andrew Innes, Julie McDonald, Ben Mullish and Jiri Pavlu.