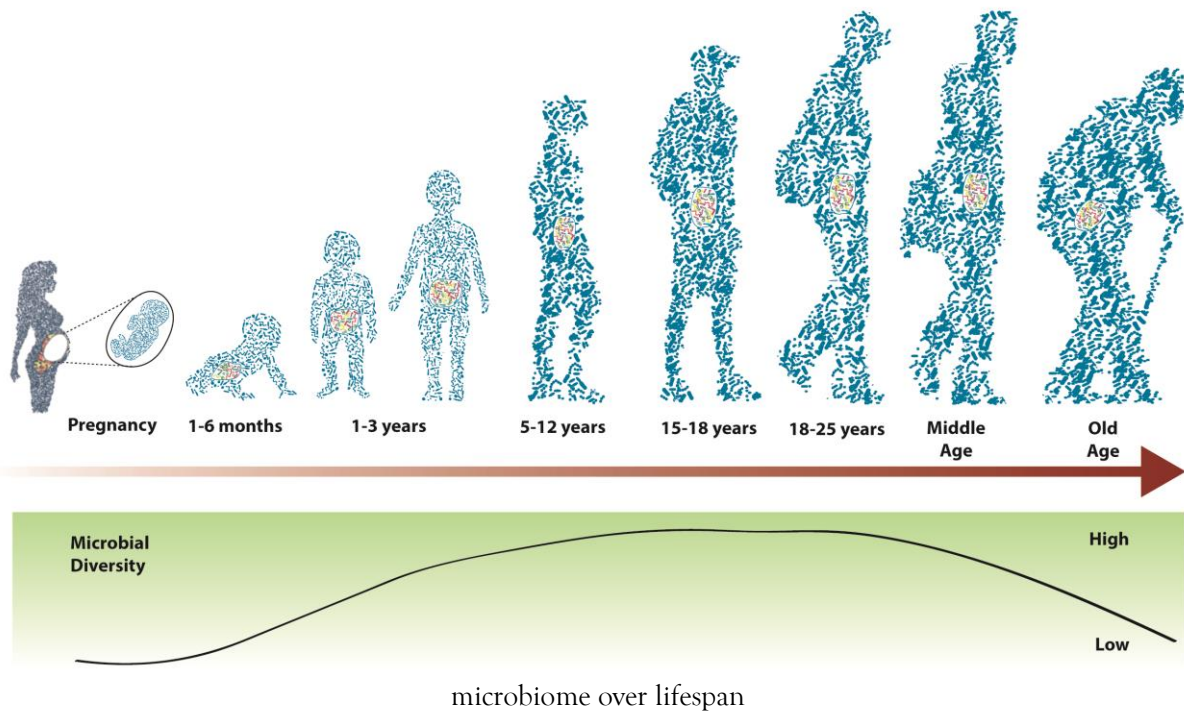


## Peter Pan: microbiota transplants to rejuvenate and slow the process of ageing

*Mum: Will we manage to stay young forever like Peter Pan?*



Thomaz F. S Bastiaanssen, Kenneth O’Riordan, John F. Cryan

APC Microbiome Ireland, University College Cork, Ireland

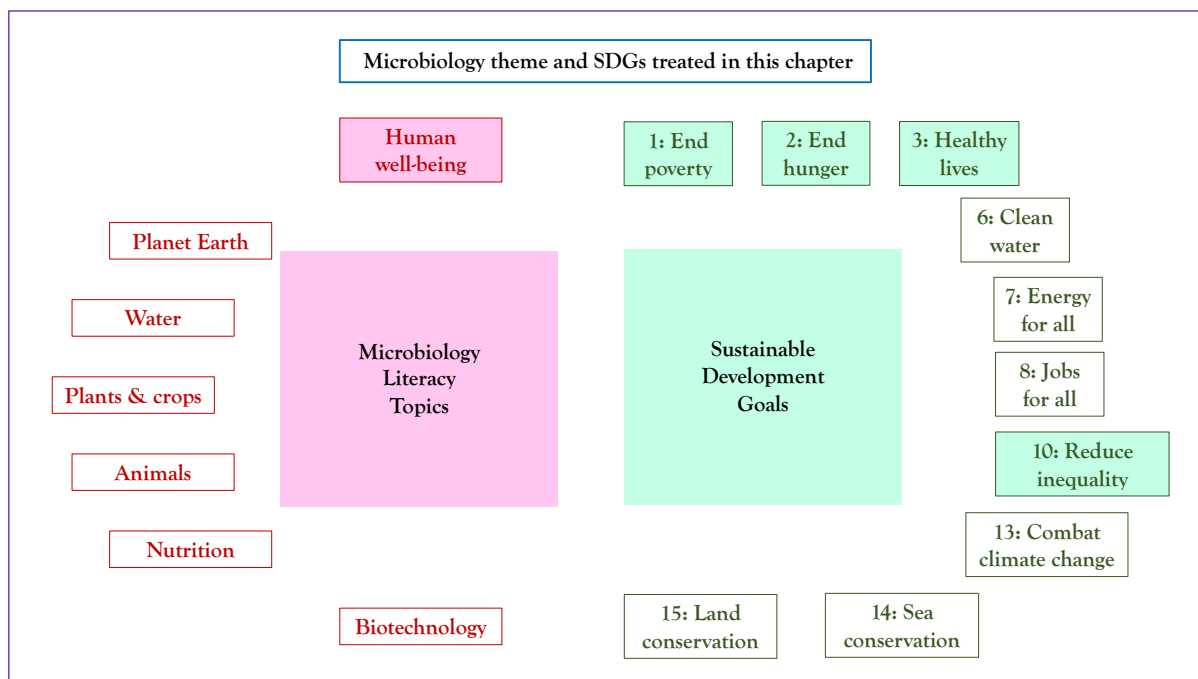
## Microbiota transplants to rejuvenate

### Storyline

The gut microbiome plays an important role in many aspects of our lives, both in health and disease, including ageing. Recently, there has been an increasing interest in therapies targeting the microbiome. Faecal Microbiota Transplantation (FMT) involves wiping out the microbiome of the host and replacing it with the microbiome of a healthy donor. In one such study, researchers were able to reverse some symptoms of ageing in mice by transplanting the microbiome from young mouse donors. While this technology is still in very early development, the concept of the microbiome-gut-brain axis, the ways in which the microbiome communicates with the host brain, has been widely reported on. Besides FMT, there are other ways in which we can improve our health by targeting our microbiome right now. By minding our dietary intake and lifestyle, we can steer our microbiome towards improving our physical and mental health and thus towards a healthier, longer and happier life.

### The Microbiology and Societal Context

*The microbiology:* The microbiome, microbiome enrichment and immune system development in infants; host-microbe communication, the microbiota-gut-brain axis, faecal microbiota transplantation. *Sustainability issues:* end poverty, end hunger; healthy lives; reduce inequality.



### Microbiota transplants to rejuvenate: the Microbiology

**1. A lifelong companion.** Microorganisms can be found almost everywhere, including in and on the human body. The largest collection of microorganisms in humans can be found in the gut and is referred to as the gut microbiome. Microbiomes were around long before humans or even eukaryotes evolved and they play a crucial role in the health and behaviour of the organism they inhabit, including humans.

We all know that humans undergo changes over their lifespan. We can roughly divide this into two phases. First, we develop from infants to adults, then we go from adults to middle-aged to elderly. But not only does our body change over time, our microbiome does too.

Typically, we get our microbiome from our mothers during birth. Our microbiome plays several important roles in our infant life, including keeping bad microbes out, training and regulating our developing immune system, and helping us digest food.

As we grow older and start eating solid foods, our microbiome evolves with us. Generally, our microbiome becomes more diverse over time, as our now more diverse diet allows new species to settle and thrive; new food in our diet feeds not only us but also new microbes able to digest it. Typically, a more diverse microbiome is considered healthy.

Then, during adulthood, the microbiome remains relatively stable for some time, though factors such as diet, medication, drugs, smoking and alcohol intake will influence it.

During ageing, microbial species tend to disappear and the microbiome will gradually become less diverse. Ageing is also associated higher levels of inflammation, which can lead to – and worsen – conditions like arthritis, type 2 diabetes and Alzheimer's disease.

One of the big questions that scientists are pondering, is whether the state of the microbiome could play a role in how we age. Indeed, going further, could it be possible to reverse certain aspects of ageing by modifying the microbiome? Could you rejuvenate yourself by wiping out your microbiome and replacing it by that of a young and healthy donor?

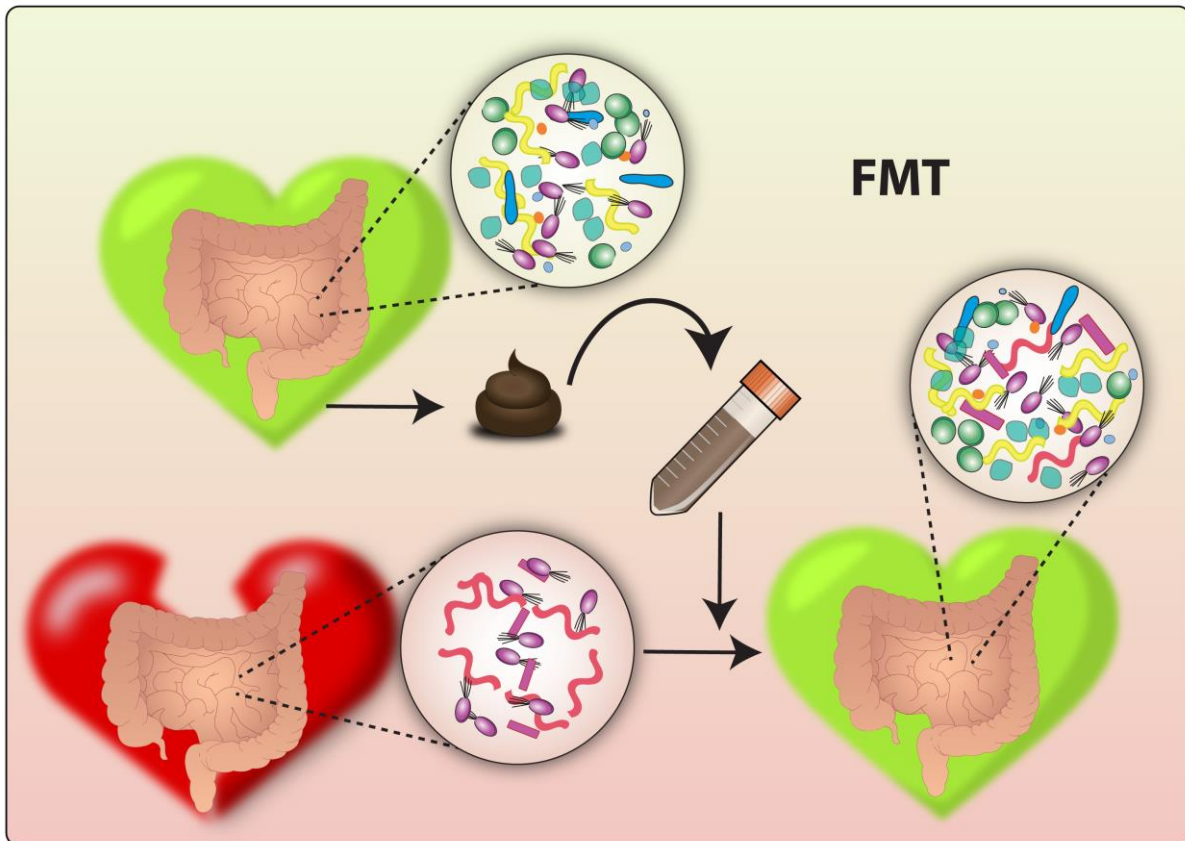
**2. Faecal Microbiota Transplantation.** Faecal Microbiota Transplantation, often abbreviated as *FMT*, describes the procedure of taking a microbiome from a donor, usually from a stool sample, in order to engraft it into a recipient. Bluntly speaking, yes, we take poop from one source and give it to someone else. While this may sound completely out there, there are ancient reports of comparable treatments throughout human history. For instance, we have a description of 'yellow soup' from a 16<sup>th</sup> century Chinese medical text, which is basically stool with water to treat certain gastrointestinal diseases. Delightful!

Nowadays, Faecal Microbiota Transplantation is sometimes used to treat some types of chronic diarrhoea. Strikingly, researchers have demonstrated that Faecal Microbiota Transplantations in rodents can also influence aspects of mental wellbeing, such as depression and social anxiety. In 2021, a group of researchers in Ireland demonstrated that transferring the microbiome from young mice to elderly mouse recipients could restore some - but not all - aspects of ageing, including their neurochemistry and cognitive behaviour. Can the fountain of youth be found in the gut?

**3. Disclaimer: Science vs Therapy.** Before we continue, it's important to mention that Faecal Microbiota Transplantation can be both a medical treatment and an experimental technique used by scientists to investigate the role of the microbiome. Like any medical intervention, clinical trials are crucial to determine the efficacy, safety and potential side-effects of a potential treatment.

## A child-centric microbiology education framework

Because some microbes can be very dangerous, it is crucial to know which microbes are present in a donor faecal sample. As an example of how things can go wrong if not regulated properly, sadly, in 2019, a 73-year-old man with a weakened immune system died after receiving FMT to treat chronic diarrhoea. Afterwards, it became clear that the donor sample contained a rare and dangerous strain of the usually harmless *E. coli*. Proper screening of donor samples for pathogenic and opportunistic microbes is clearly of utmost importance.



**4. Mind-altering organisms.** Besides playing an important role in normal gut function, it has become clear that the microbiome is also involved in a broad array of other bodily functions. Perhaps most strikingly, the microbiome is known to be in constant communication with the brain. This is known as the microbiota-gut-brain axis.

**Routes of communication:** the microbiome can communicate with the brain in at least four distinct ways.

a. First, certain microbes are known to produce and degrade compounds that are neuroactive, such as dopamine, tryptophan and serotonin. These compounds can then migrate into the bloodstream and reach the brain – affecting us directly.

b. Second, the gut microbiome can produce a specific group of small molecules called short-chain fatty acids. These molecules include acetate, propionate and butyrate and are famous for their strong smell and taste. Importantly, our gut cells can easily feed on these short-chain fatty acids, keeping them healthy. These molecules are known to help regulate the immune system and alleviate the effects of stress for the host.

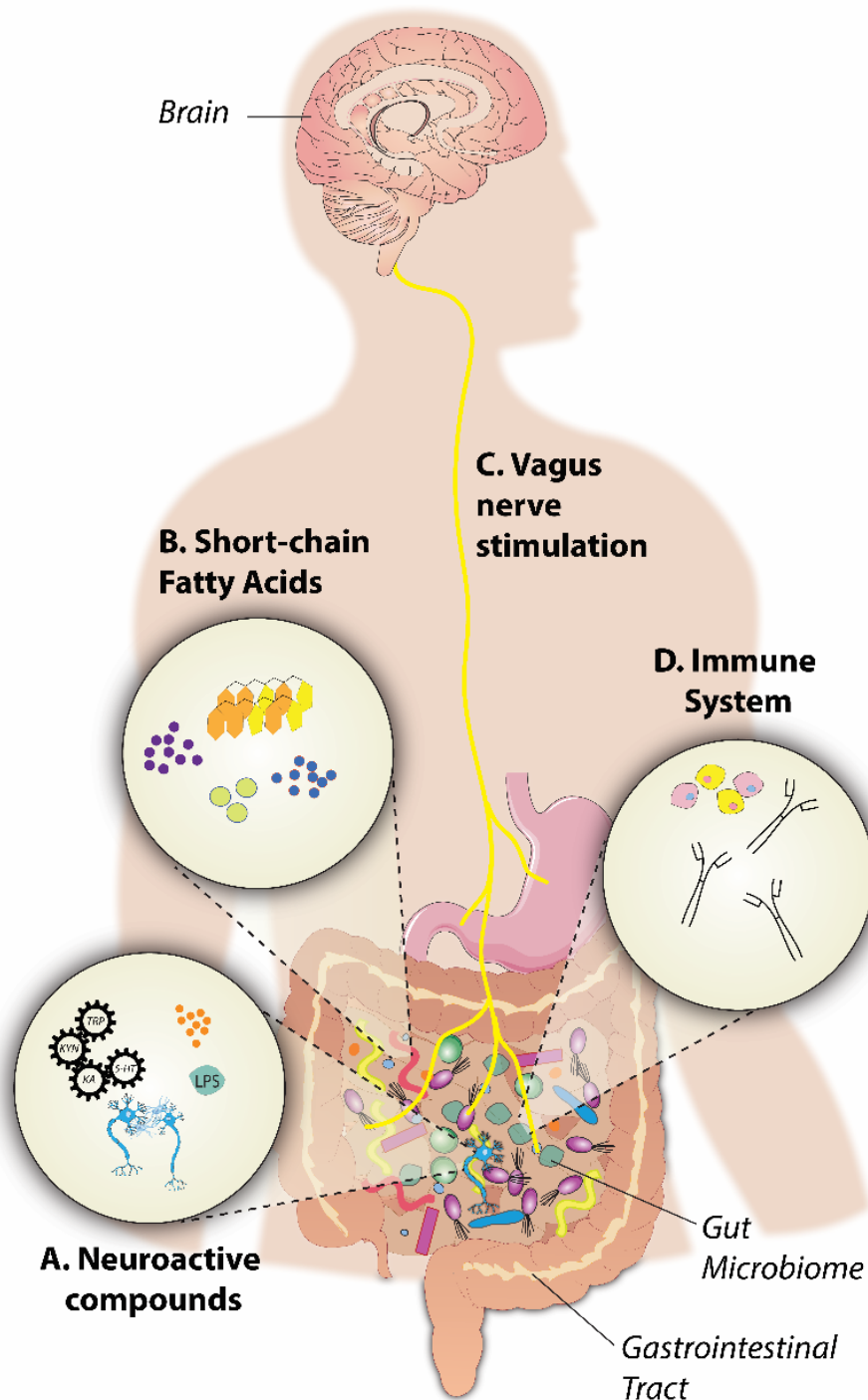
c. Third, microbes can communicate with the brain by stimulating certain nerves directly. Specifically, there is evidence that the microbiome can stimulate the *nervus vagus* (roughly

## A child-centric microbiology education framework

translated from Latin to English as the *wandering nerve*, because it is the longest nerve of the body and wanders all the way from the brain to the heart, lungs and digestive tract).

d. Fourth, microbes can communicate directly with immune cells. The human gut is densely packed with immune cells to protect us from potential infection. The microbiome is involved in setting up the immune system in early life and continues to communicate with it in adulthood.

All of these routes of communication will impact how and how well we age. If we play nice with our microbiome, it will help us stay healthy. If we give our microbiome too much punishment, it will leave us more vulnerable to stress, inflammation and general poor health.



**5. *Towards a longer and healthier lifespan.*** It is clear that a healthy microbiome is important for both physical and mental health. There are several ways in which we can improve our own health by sculpting our microbiome. As the microbiome typically feeds off what we eat, diet, medication, smoking, alcohol and drugs play a big role in this.

a. *Diverse diet.* One of the most effective ways of promoting a beneficial microbiome, and consequently its beneficial health effects, is a diverse diet. Generally, a more diverse microbiome is thought to be more beneficial for the host. Different microbes thrive on different nutrients, so if we eat a diverse diet, many different types of microbes will be able to thrive. Interestingly, this does not necessarily mean that you should eat something different every day, if you have the same few diverse meals every day that should work too.

b. *Fibre and fermented foods.* Fibre is a specific class of carbohydrates that humans struggle to digest. Our microbes, on the other hand, have no difficulty digesting them. Often, our microbiome will produce beneficial short-chain fatty acids as a by-product of digesting fibre. Some common foods that are rich in fibre include grains, fruits, sweet potato and leafy greens.

Many cultures also have fermented foods, such as sauerkraut, yoghurt, some cheeses, kefir and kimchi. Microorganisms were already involved in making these foods and typically many microbes thrive on them. Recently, an American research group reported that consuming a lot of fermented foods can decrease systemic inflammation by targeting the microbiome.

c. *Avoid antibiotics and processed foods.* On the other hand, some foods and medications have negative effects on the microbiome. For example, highly processed foods, typically high in preservatives, additives, saturated fats, processed sugars and salts, tend to hinder beneficial microbes from growing. Also, antibiotics can have a huge impact on the microbiome as they are designed to kill all sorts of microbes, including the beneficial ones in our gut. It is a good idea to avoid these products when possible and be kind to your microbiome whenever possible.

**6. *And will microbiota transplants be used to rejuvenate and slow the process of ageing?*** So, will we all take out yearly FMT in the future? Have scientists finally figured out how to beat ageing? Unfortunately, this is very unlikely to be the case. Ageing is a highly complex phenomenon that affects the body on countless levels. Some of these levels we understand pretty well, whereas others we may have not even discovered!

There are still many questions that need to be answered before we can consider FMT an effective therapy to rejuvenate and slow ageing. For instance, most of the current data is from animal experiments. While these results are promising, it would be crucial to also investigate the effect and efficacy of FMT to combat ageing in human volunteers. Second, it is still unclear what aspects of the young microbiome specifically drive the rejuvenating effects. Are some young microbiomes more efficient than others? There are plenty of open questions yet.

It seems much more likely that the microbiome is the key to one aspect of ageing. By targeting the microbiome and keeping it working with us rather than against us, we can reduce inflammation and keep the microbiome-gut-brain axis functioning to our benefit.

Together with other methods that we know improve healthy ageing, such as managing stress levels and regular exercise, targeting the microbiome with FMT could be one piece in the puzzle of how to slow and perhaps eventually even stop aspects of ageing.

## A child-centric microbiology education framework

### Relevance for Sustainable Development Goals and Grand Challenges

There are several ways in which alleviating the symptoms of ageing by targeting the microbiome is related to the Sustainable Development Goals.

- **Goal 1. End poverty in all its forms everywhere.** The poor are disproportionately affected by the negative health outcomes associated with ageing. In many parts of the world, healthcare is not universal and older people are more likely to require it. Altering our diet represents a relatively cheap way to target the microbiome and improve the symptoms of ageing.
- **Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture.** It is clear that the microbiome is intimately linked to diet. A better understanding of and education about which foods are beneficial and why, can lead to a population that makes better choices on nutrition. Fortunately, most foods that benefit the microbiome are unprocessed, like grains and vegetables, also tend to be more affordable.
- **Goal 3. Ensure healthy lives and promote well-being for all at all ages.** A better understanding of how our microbiome interacts with us will help us improve our general health and well-being.
- **Goal 10. Reduce inequality within and among countries.** The poor are disproportionately affected by the negative health outcomes associated with ageing. Many people cannot afford expensive medical treatment. Developing cheap and effective strategies to improve our health by targeting the microbiome through diet will help level the playing field and encourage people to eat a healthy diet.

### Potential Implications for Decisions

#### 1. *Individual*

- a. Weighing up the various microbial and non-microbial factors and aligning them with personal convictions (How to find a balance between long term health and short term delicious but unhealthy food?).
- b. What decisions can you make now that will affect you when you're much older?

#### 2. *Community policies*

- a. Accessibility of affordable and healthy alternatives to fast food, the existence of food deserts.
- b. Health costs associated with unhealthy ageing. Support for local businesses that work with probiotics and fermented, often traditional foods.

#### 3. *National policies relating to the ageing population*

- a. Healthcare economics of ageing and associated diseases, and positive influence on mental health
- b. Safety regulations regarding microbiome-targeted treatments
- c. Regulate to incentivise healthy diets?

## A child-centric microbiology education framework

### Pupil Participation

1. **Class discussion:** Would you ever consider taking a Faecal Microbiota Transplantation as a treatment if a medical doctor suggested it? How about as a supplement from the pharmacy?

2. **Pupil stakeholder awareness:** In some particularly poor, often densely populated areas, it can be practically impossible to access affordable, healthy food. This is known as a *food desert*. In fact, obesity is more common in the poor because they often can't access healthy foods – they are all but forced to get their nutrition from highly processed junk food.

- a. How do you think living in such a food deserts would impact the microbiome?
- b. Can we think of ways in which to help alleviate these problems?

3. **Exercise:** Throughout the text, we have taken it for granted that most heavily processed foods will negatively impact the gut microbiome, but it will thrive on more 'natural' foods, like grains, vegetables and oats. Keeping in mind that the microbiome has been around for way longer than humans have, can you come up with a (micro)biological reason why this may be the case?

### The Evidence Base, Further Reading and Teaching Aids

#### Books:

*There's A Zoo in My Poo* – Prof. Felice Jacka

*The Psychobiotic Revolution: Mood, Food and the New Science of the Gut-Brain Connection* – Scott C. Anderson, Prof. John F. Cryan, Prof Ted G Dinan

#### Scientific articles:

*The Microbiota-Gut-Brain Axis* – Prof. John F. Cryan *et al.*  
(<https://doi.org/10.1152/physrev.00018.2018>)

*Microbiota from young mice counteracts selective age-associated behavioral deficits* – Dr. Marcus Boehme *et al.* (<https://doi.org/10.1038/s43587-021-00093-9>)