EVOLUTIONARY INSIGHTS INTO *E. COLI*

Adding to research focused on the overall composition of the gut microbiome, biologist Isabel Gordo will use her Global Grant for Gut Health to explore **THE EVOLUTIONARY PATH OF ONE COMMON GUT BACTERIUM**, *Escherichia coli*, inside living animals.

Isabel Gordo is an evolutionary biologist with a keen interest in bacterial evolutionary genetics. Since 2004, she has been an independent principal investigator and leads the evolutionary biology lab at Instituto Gulbenkian de Ciência near Lisbon, Portugal. Her team studies bacterial adaptation processes in ecologically relevant environments, which led them to develop their mouse model of the mammalian gut microbiota ecosystem. Gordo is fascinated by the interactions, within and between bacterial species, that shape and modulate antibiotic resistance. She aims to design new strategies to limit antimicrobial resistance.

What is the background to your research?

We understand a lot about the diversity of microbial species in the gut microbiome. However, we still know very little about the genetic diversity within individual species. This information could provide us with valuable insights into evolution and the tactics that species use to evade antibiotic treatments, for example, or how a species might become pathogenic and trigger disease. The exploration of evolution in a single bacterial species has been pioneered by the brilliant evolutionary biologist Richard Lenski. It was his research that first inspired me to work in this field. His now-famous flask-based experiment monitoring the evolution of thousands of generations of the common gut bacteria *E. coli* over the past 30 years in his Michigan laboratory is extraordinary. There is so much to learn from his ground-breaking work.

The evolution of *E. coli* team are (from left) Ricardo Ramiro, Daniela Güleresi, Nelson Frazão, Paulo Durão and Isabel Gordo.

What will your new grant-funded project add to this field?

We still don't know how individual species evolve, or how quickly they evolve, in vivo — inside the gut of a living creature. We will use our novel mouse model for this purpose. We want to quantify as precisely as possible how quickly *E. coli* evolves, and we will study this process in real time. This will allow us to build a more accurate picture of the evolutionary dynamics and population diversity of a single gut species. It is rare to zoom in on one species in the microbiome, and the foundations we have laid in the past few years will help us achieve this.

How will mice help you discover more about *E. coli*'s evolution?

We recently developed a mouse model for the sole purpose of examining the microbiome. We know that the model is viable because it has already provided us with good data during previous research projects. The genetic make-up of the model animal is fully controlled — every mouse is genetically identical. They are fed the same diet, and will be colonized, simultaneously, with the same coloured fluorescent *E. coli* bacterial strain from a human. The fluorescence will allow us to easily trace the *E. coli* population within the gut. The mice already have an *E. coli* strain naturally present in their gut. We will focus on these two strains, the resident and the colonizer, and monitor how they compete and evolve over the lifetime of each mouse.

Why have you chosen to focus on *E. coli*?

The *E. coli* bacterium is great to work with because we know so much about it, including its genetic make-up and

metabolism. This means we can identify and follow any new mutations or alterations as they appear. *E. coli* is also a rapid reproducer, capable of producing a new generation every 1 to 2 hours in the mouse gut. This means that, over the space of a few months, we can hopefully get a clear picture of thousands of generations of the *E. coli* strains as they evolve to live alongside each other.

'IT IS RARE TO ZOOM IN ON ONE SPECIES IN THE MICROBIOME'

What do you hope to find?
There are two key pressures on a bacterium when it enters a new environment: how it will adapt to live alongside the cells already present, and how it will evolve to evade challenges to its survival, such as antibiotics. We will monitor the bacteria for adaptations and determine what benefits these evolutionary shifts confer to new generations.

It is reasonable to expect that the colonizers will evolve more quickly than the resident bacteria, because they must adjust to the new environment that the resident bacteria are already acclimatized to. We'll explore the speed at which the colonizers accumulate adaptations, and whether this is constant over the mouse lifetime, or if adaptive responses slow as time goes on. We are particularly interested in horizontal gene transfer – that is, the potential sharing of genetic material between the resident strain and the colonizing strain. We're also interested in identifying clones that can evolve more rapidly than others, and what knock-on effects they have on the resilience of the *E. coli* populations. These details will provide valuable insights into the mechanisms inherent in disease progression, and how microbes build resistance to drugs.

Why did you apply for a Global Grant for Gut Health?
I was already familiar with the excellent research funded by Yakult because I spoke at a conference they hosted in Brazil a few years ago. When we saw the funding call on social media, my team and I thought 'Ah! This is just what we've been waiting for!' It felt serendipitous. I worked very closely with my team on the application — biochemist Paulo Jorge Rêgo Durão, evolutionary biologist Ricardo Ramiro, and microbial geneticist Nelson Frazão. We drafted ideas, wrote together, and collaborated on the final edits with input from respected fellow researchers. I believe this played a large part in our success – we had a fully formed concept and provided evidence of our prior work in the same field to demonstrate that, as a team, we are capable of achieving the goals we have set ourselves in this project. It means a lot to us to have been awarded this grant, and we strongly believe our mouse model will be an invaluable asset to this emerging area of microbiome research.

And finally, how do you like to spend your free time?
I love to spend time with my family, particularly with my teenage daughter. My favourite sport is tennis – I really enjoy playing regularly and I also like to watch the international matches. This time of the year [June] is wonderful, with the big tennis tournaments across Europe, like the French Open and Wimbledon. It's a welcome distraction from monitoring mice in a lab! ■

GUT FEELING ABOUT DRUG METABOLISM DURING DEPRESSION

After many years studying the gastrointestinal tract, pharmacologist and senior physiology lecturer Niall Hyland will use his Global Grant for Gut Health to examine how the microbiome influences the ability to **METABOLISE ANTI-DEPRESSANT OR ANTI-PSYCHOTIC DRUGS**.

Niall Hyland is a senior lecturer in the Department of Physiology, and a faculty member in APC Microbiome Ireland, at University College Cork. In his early career he took a PhD in pharmacology, spent time in Louisiana, and as a post-doc in Calgary before returning to Ireland in 2007 to join APC Microbiome Ireland. On returning to Cork, his primary research focus was on the gut-brain disorder Irritable Bowel Syndrome (IBS), providing him with a strong basis from which to study the influence of the gut microbiome on drug metabolism in psychiatric illnesses.

What inspired you to get involved in microbiome research?
It is only in the last 20 years or so that our gut microbiome has become the focus of many physiological studies. Scientists became aware that these microbes were likely both benefitting and adversely affecting our health in various ways. More recently, experts have begun to explore the microbiome's interaction with medications. Individuals respond to drugs in different ways, and it appears that each person's microbiome may play a significant role in how drugs are absorbed and metabolized by the body. I have followed new research in this area with great interest because of my background as a pharmacologist. These insights prompted my team to ask the question 'If depression has a knock-on effect on the microbiome and can generate gut-related disorders, how might depression affect the ability to process anti-depressant or anti-psychotic drugs?' It was