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

around the same time that I spotted the Global Grants for Gut Health funding call.

What prompted you to apply for a Global Grant for Gut Health?
The application process was very straightforward, and I was pleased that the call was broad and flexible enough to allow us to put in a multi-disciplinary proposal. Essentially, it's a brilliant proof-of-concept grant programme, giving researchers the chance to get started on a large-scale project and achieve viable results. Winning the grant means we can quickly gain traction on this important topic, and we will hire a researcher for a year to focus on the project with me, and our cross-disciplinary team: Gerard Clarke, lecturer in psychiatry and neurobehavioural science; Timothy Dinan, professor of psychiatry; and Brendan Griffin, a senior lecturer in pharmaceutics. Another bonus of the grant programme is that there are no restrictions on intellectual property and publishing of follow-up research; this means it is significantly less complicated in the long term.

What does your project propose to do?
Our project proposal takes a step-by-step approach to verify how the microbiome affects the ability of individuals to respond to anti-depressants or anti-psychotics. First, we need to confirm that there is a clear difference in microbiome make-up between our patients with depression and our control group, which we and others have previously observed. To do this, we will take faecal samples from every individual in each group and analyse them to determine the bacterial communities and enzymes present. Ideally, none of the participants will have been given any drugs prior to the samples being collected. Once we have confirmed the microbial differences, we will then expose the enzyme fraction

The gut and the brain are separated anatomically but well-connected physiologically — with the microbiome mediating that connection.

of each sample — the so-called fecalase — to one of four commonly prescribed drugs, two anti-depressants and two anti-psychotics, in the lab. We will monitor how the bacterial enzymes in the samples metabolize the drugs. Our hypothesis is that microbiome-derived enzymatic activity in certain individuals could alter the structure or activity of the drugs, rendering them ineffective or resulting in potential side-effects or problems.

'BACTERIA, AND POSSIBLY PROBIOTICS, MAY AFFECT A PERSON'S ABILITY TO METABOLIZE DRUGS'

How will you examine drug metabolism in the body?
It has been shown that if you take a faecal sample from a person with depression and transplant that sample into a healthy rat, the rat will begin to show signs of depressive illness. We plan to build on this and will transplant our human faecal samples into rats. After a couple of weeks, once a unique humanized gut microbiome is established inside each animal, we will administer a single dose of one of the drugs to each rat and monitor what happens to the drug inside the body. This will generate pharmacokinetic data for the different drugs during depressive illness which we will analyse alongside the enzymatic activity and microbiome profile of each donor sample.

How might insights from these data eventually help patients?
We will use all these data to begin to build a predictive computer model. It would be brilliant if scientists could one day input data from a patient's faecal sample into a computer model, and it would predict how that patient might respond to specific drugs. Our initial model will incorporate details from people with depression, and look at anti-depressants, but could then be expanded to predict responses to other drugs for other conditions as well. This is an area I would be very keen to explore — presumably, if patients who are clinically depressed process anti-depressants differently from healthy people, then their ability to metabolize drugs for other conditions will also be affected. There is growing interest in this kind of research especially now as we begin to understand that particular bacteria, and possibly probiotics, may also inadvertently affect a person's ability to metabolize drugs and therefore their response to them. It is a potentially enormous area of research and future exploration.

What do you do when you're not in the lab?
When I'm not at work, you'd probably find me out running or taking part in adventure races. I find it so important to clear my head before or after a day at work. Many ideas spring to mind without other distractions. ■