

## APC Microbiome Ireland Postgraduate Programme

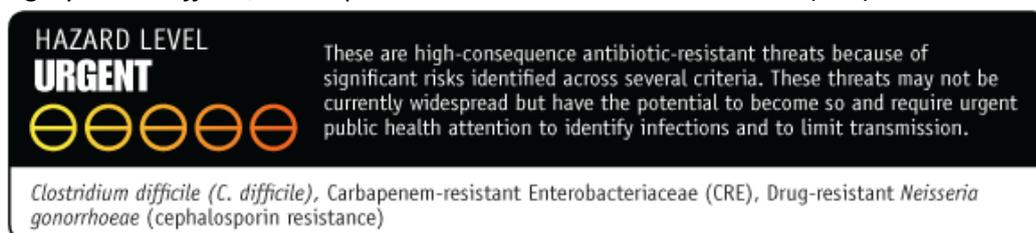
### Exploiting the microbiota for potential solutions to the antimicrobial resistance crisis



“Antimicrobial resistance (AMR) poses a fundamental threat to human health, development, and security. We are running out of time,” said Dr Margaret Chan, Director-General of WHO. Microbes are evolutionarily well equipped to evolve to overcome barriers to their ongoing survival. This includes the ability of microbes, such as bacteria, viruses, fungi and some parasites, to develop resistance to antimicrobials (i.e. antibiotics, antivirals, antimalarials) and to become antimicrobial resistant. As a consequence, standard therapeutics can become ineffective against these pathogens, and the infections persist and disseminate. Infections with resistant organisms are difficult to treat, often requiring costly and sometimes toxic alternatives. A Wellcome Trust and UK Department of Health report<sup>1</sup> released in 2016 estimated that each year at least 700,000 people across the world die from infections that are resistant to current antibiotics, and by 2050, drug-resistant infections will take an estimated 10 million lives per year. The report further predicts that the economic cost of lost global production caused by antimicrobial resistance will amount to approximately \$100 trillion between now and 2050 if it is not tackled. Ireland has a relatively high rate of antimicrobial resistance in human health compared to most European countries, and ranks above the EU average for consumption of antibiotics in the community<sup>2</sup>.

The first antibiotic was penicillin, discovered by Alexander Fleming in 1928, and while it wasn't distributed among the general public until 1945, it was used during World War II for surgical and wound infections. By 1940 the first bacterium resistant to penicillin was isolated, penicillin-resistant *Staphylococcus*. In his Nobel acceptance lecture on December 11, 1945, Fleming warned of the misuse of antibiotics and the ability of bacteria to develop resistance. Today bacterial pathogens such as *Shigella*, *Pneumococcus*, *Streptococcus*, *Enterococcus*, *Mycobacterium tuberculosis*, *Pseudomonas*, *Neisseria gonorrhoeae*, *Enterobacteriaceae* and *Clostridium* spp. have all developed resistance to antibiotics. The emergence of these “superbugs”, which have become the scourge of hospitals and nursing homes, is particularly worrying. The CDC published a report in 2013 outlining the top 18 drug-resistant threats in the US, and categorised them as urgent, serious or concerning threats. Three bacteria (Figure 1) were listed in the URGENT category – *C. difficile*, Carbapenem-resistant *Enterobacteriaceae* (CRE) and *Neisseria gonorrhoeae*.

Figure 1: Three bacterial species listed at the hazard level URGENT by the Centres for Disease Control.



Antibiotic resistance is rising to dangerously high levels in all parts of the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases. Infections like pneumonia, gonorrhoea and post-operative infections, as well as HIV, tuberculosis and malaria are increasingly becoming untreatable because of AMR. Left unchecked, AMR is predicted to have significant social, health security, and economic repercussions that will seriously undermine the development of countries. The high levels of AMR already seen in the world today result from overuse and misuse of antibiotics and other antimicrobials in humans, animals (including farmed fish), and crops, as well as the spread of residues of these medicines in soil, and water. Within the broader context of AMR, resistance to antibiotics is considered the greatest and most urgent global risk requiring international and national attention.

#### About APC Microbiome Ireland:

APC Microbiome Ireland (<http://apc.ucc.ie>) is an internationally renowned SFI-funded research institute, which explores the role of the microbiome (microbiological community) in health and disease. The scale and scope of microbiome research has become one of the fastest moving areas of biology, of relevance to all branches of human medicine and veterinary science, and is of growing importance to the economic welfare of society. The APC has created a trans-disciplinary environment conducive to innovation with a mission to link Irish science with industry and society through excellence in research, education and outreach. Our institute is a partnership between University College Cork (<https://www.ucc.ie/en/>), Teagasc Food Research Centre (<https://www.teagasc.ie/contact/offices/moorepark-teagasc-food-research-centre/>) and the Cork and Mercy University Hospitals, and is home to a team of over 300 researchers and clinicians. The APC collaborates with over 25 national and international industry partners from the food, agriculture, pharmaceutical, biotechnology and diagnostic

sectors. APC research focuses on mining the microbiota to identify products (probiotic strains, metabolites, phage, prebiotics, anti-microbials etc) that can promote health and help prevent disease. This is of relevance to many populations, such as infants, athletes and elderly, and very relevant to disorders such as obesity, cardiovascular health, inflammation and colon cancer. APC Microbiome Ireland operates in the functional food and pharmaceutical sectors, developing food and pharma solutions targeting the gut microbiota for health promotion throughout life.

#### **How the PhD Programme will support the strategic research goals of APC Microbiome Ireland:**

APC Microbiome Ireland has taken a strategic decision to develop a postgraduate programme in antimicrobial resistance, in order to address this important global challenge. The APC already has ongoing research in the area of antimicrobial resistance, with a large programme on developing new antimicrobials against bacterial pathogens. But given the significance of this societal challenge, we will develop an anti-microbial resistance research theme, to address additional aspects of how human and animal microbiomes can be exploited and targeted to develop potential solutions to AMR. AMR is a very broad societal issue, and the APC will not be able to address all the areas of concern, but will instead focus specifically on how the microbiome relates to AMR. APC/SFI will fund up to 6 postgraduate positions (PhD, MEd or MSc) to help address topics involving AMR, all of whom **must start their research projects in 2018 (usually October 2018)**. Each student will have at least one secondment to an international lab to develop new skills.

**PhD studentships will be for up to 4 years duration. MSc or MEd studentships will be for 2 years duration.** Some project laboratories may be located in Teagasc Moorepark, but all students will be registered in UCC. The students will be part of UCC's structured PhD programme and will be expected to carry out a number of postgraduate training modules to develop transferable and complementary research skills, as part of their Professional Development Plan, <https://www.ucc.ie/en/graduatestudies/structured/>.

The student bursaries will cover

1. Student stipend (€18,500 per annum)
2. University fees (EU level fees)
3. The host laboratory will receive research, training & network funding for purchase of consumables, travel budget for the student to attend international conferences, and for secondments to international labs.

#### **Student Applications:**

We welcome applications from highly qualified students of all nationalities as follows: Applicants must hold, or anticipate receiving before October 2018, a university degree that qualifies them to enter a PhD in the country where the degree was obtained (in Ireland a minimum of a 2.1H). All applications need to be supported by a minimum of two academic reference letters, and are evaluated solely on the basis of qualification and scientific potential. Please see UCC's requirements for English language proficiency for postgraduate students at <https://www.ucc.ie/en/study/comparison/english/>

Students must send **pdf versions** of the following

1. Student CV that includes all University subjects/results achieved to date. Evidence of English proficiency should be provided for non-native speakers. Max 3 pages; Filename: Surname\_CV
2. Motivational letter, stating why the student wants to join the APC's AMR PhD programme, and indicating their top 3 projects of choice (in order of preference) from the list below. Max 1 page; Filename: Surname\_Letter
3. Two Academic reference letters on institutional headed paper, signed and dated. (Filename: Student Surname\_Referee Surname\_Ref). It is the applicant's responsibility to ensure that references reach us on time.

**All documents must be e-mailed to [APC.administrator@ucc.ie](mailto:APC.administrator@ucc.ie) with AMR Postgraduate Application in the e-mail subject by **Friday 23.59 GMT on March 2<sup>nd</sup> 2018**.**

Students will be informed if they have been shortlisted on March 16<sup>th</sup> 2018 by e-mail. Shortlisted students will be invited for interview, either in person or by Skype, on Monday April 9<sup>th</sup> 2018. **Successful students MUST start their projects in 2018**. A maximum of 5 PhD projects, or 4 PhDs and 2 MSc projects, will be funded.

For general queries on the postgraduate programme please e-mail [s.cudmore@ucc.ie](mailto:s.cudmore@ucc.ie). For queries on specific projects please contact the Project Leader in the list below.

APC PIs	Collaborating PIs	Title	Abstract	Potential Secondment	Contact
<b>Available PhD Projects</b>					
Colin Hill, Paul Ross	Leslie Hoyles, Imperial College London.	Phage Therapy to treat Listeria monocytogenes using novel bacteriophages and their lysins	Listeriosis caused by L. monocytogenes is one of the most deadly bacterial infections currently known - with a mean mortality rate in humans of 20 to 30% or higher despite early antibiotic treatment. Several recent studies have revealed that L. monocytogenes persistent forms could in fact be tolerant to antibiotics, and metabolic alterations correlate with antibiotic resistance. We are now in a post-antibiotic era, and bacteriophages therapies are the subject of this project. These ubiquitous viruses selectively and specifically target and kill their host bacteria, leaving the surrounding commensals untouched. In fact, bacteriophages targeting L. monocytogenes are readily used in the food industry and a means of biocontrol. Surprisingly, however there are no anti-listerial therapies available to treat the human disease.	Imperial College London	<a href="mailto:c.hill@ucc.ie">c.hill@ucc.ie</a>
Colin Hill, Paul Ross	George Salmond, Cambridge University.	Bacteriophage and antimicrobial resistance.	There are several issues facing the use of phage therapy in clinical practice. 1) the target must be identified for effective phage therapy to be deployed. Modern rapid diagnostics alleviates this issue, but we will focus on chronic diseases, where the pathogen identification is not an issue. Targets will include Clostridium difficile and Staphylococcus aureus. 2) regulatory issues must be overcome if phage are to be used in the clinic. Issues such as safety and the potential for transfer of antibiotic resistance genes will be addressed.	Cambridge Uni	<a href="mailto:c.hill@ucc.ie">c.hill@ucc.ie</a>
Pauline Scanlan, Silvia Melgar, Marcus Claesson, Paul Cotter	Villie Friman (York), Alex Hall (ETH Zurich), Julian Marchesi (ICL & Cardiff)	Elucidating the impact of clinical and subclinical levels of different antibiotics on gut microbiota ecology and functionality	Humanity is facing a global public health crisis relating to infectious and non-infectious disease control arising from the widespread use and misuse of antibiotics. This project will use a novel, multidisciplinary approach to investigate how exposure to clinical and subclinical levels of different antibiotic classes 1) drive resistance evolution to antibiotics for a broad range of ecologically and clinically relevant gut microbes in a community context, 2) alter the composition and potential functionality of a model community of gut microbes, and 3) how antibiotic mediated changes in the gut microbiota impact host physiology with respect to markers for chronic diseases such as obesity and diabetes.	University of York, Imperial College London	<a href="mailto:p.scanlan@ucc.ie">p.scanlan@ucc.ie</a>
Paul Cotter	Alain Filloux (Imperial College London); Avelino Alvarez-Ordóñez (University of Leon, Spain)	Antimicrobial sensitization through quorum quencing	Biofilms are densely packed communities of microbial cells that grow on living or inert surfaces and surround themselves with secreted polymers, which provide considerable levels of protection from antibiotics and other antimicrobials. The formation of biofilms is facilitated by communication (quorum sensing) between microorganisms and, thus, inhibition of this communication can make a major contribution to preventing biofilm formation/ facilitating biofilm destruction through enhanced antimicrobial sensitivity. This PhD project focusses on newly identified producers of compounds that can cause such inhibition of communication (quorum quencing), their characterisation and application to enhance pathogen susceptibility to antimicrobials.	Imperial College London, University of Leon	<a href="mailto:paul.cotter@teagasc.ie">paul.cotter@teagasc.ie</a>
Catherine Stanton, Paul Ross, Tony Ryan	Julian Marchesi, Imperial College London	Early human life exposure to antibiotics and the consequent resistome	The infant gut undergoes colonisation during delivery and rapidly evolves in early life, influenced by mode of delivery, maternal microbiota, environmental factors and exposure to antibiotics. The aim of this study is to assess the impact of antibiotic exposure in early life on the development of the infant gut resistome. We will use human milk and gut microbial DNA already available from mother and infant cohorts (recruited via INFAMILK, INFANTMET and MYNEWGUT studies, and will recruit new subjects, as necessary), i.e. human milk microbiota from lactating women exposed and not exposed to antibiotics, infant gut microbiota of preterm infants; vaginally delivered full term infants with no antibiotic exposure; caesarean delivered infants receiving antibiotics at delivery and infants being treated with antibiotics for infections in the early weeks of life. We will investigate the antibiotic resistance profile of these infants' gut microbiota and its presence in human milk, and correlate the results with maternal and infant antibiotic history. We will conduct quantitative PCR on the DNA extracts to determine the prevalence of resistance genes from different antibiotic families.	Imperial College London	<a href="mailto:catherine.stanton@teagasc.ie">catherine.stanton@teagasc.ie</a>

Paul Ross, Catherine Stanton, Colin Hill	Julian Marchesi, Imperial College London	Characterising the antibiotic resistance profile of the cow rumen and milk	The majority of cows worldwide are fed indoors and see little of the pastures used in Ireland. While manure is widely used as a natural fertilizer to promote grass growth, land spreading of sewage sludge on agricultural land not only poses risks to terrestrial ecosystems, but may also be associated with microbiological and chemical hazards to food safety, including the spreading of antimicrobial resistance among herbivores and their food produce. The bovine rumen is home to novel and diverse microorganisms and their associated genes. In this proposal we aim to investigate the antibiotic resistance among the rumen microbiota from Irish dairy cows on grass fed vs indoor feeding systems.	Imperial College London	<a href="mailto:p.ross@ucc.ie">p.ross@ucc.ie</a>
Cormac Gahan, Paul Cotter	Tim O'Sullivan, Pharmacy UCC	Development of selective drugs for the treatment of cryptosporidiosis	Cryptosporidium parvum is an intestinal parasite that is a common cause of diarrhea (cryptosporidiosis) in Ireland and worldwide and causes chronic, often fatal disease in up to 50% of patients with AIDS. The protozoan is resistant to anti-infective therapies which are limited to a single drug (Nitazoxanide) that has limited efficacy. This project proposes an interdisciplinary approach to this problem through a dual strategy which will (1) identify novel lead compounds with anti-protozoal activity from the human gut metagenome and (2) chemically repurpose a known lead compound to enhance anti-Cryptosporidium activity.	GSK	<a href="mailto:c.gahan@ucc.ie">c.gahan@ucc.ie</a>
Michael Prentice, Barry Plant, Paul O'Toole	Trevor Lawley, Sanger, UK; Alan McNally, Birmingham University	The airborne microbiome and resistome of hospitals	Fluorescent particle detection suggests many more viable cocci or spore-shaped objects are present in hospital air than are grown by culture. Selective culture readily finds antimicrobial resistant bacteria in hospital air and it is likely that the hospital air resistome and underlying airborne microbiome is poorly characterised by culture-based methods. This project will characterise the hospital air microbiome and resistome and compare it with the gut microbiome to establish a source relationship which could be influenced by manipulation of gut commensals. Effects of interventions on air quality and the need hospitals and air handling redesign will be assessed.	Sanger, Birmingham Uni	<a href="mailto:m.prentice@ucc.ie">m.prentice@ucc.ie</a>
Paul Ross, Colin Hill	Elaine Holmes, Imperial College London	Use of bacteriocins as an alternative to antibiotics for improved growth and health in livestock	Antibiotics are routinely used in livestock to prevent and treat infections and to enhance growth. However, such usage has been linked to antibiotic resistant microorganisms in humans and animals and deemed a leading cause of antibiotic resistance escalation. Bacteriocins, microbially-produced antimicrobial peptides, offer a potential alternative. The aim of this proposal is to investigate the effects of 3 bacteriocins, nisin, lacticin 3147 and bactofencin on porcine growth and health with emphasis on the fecal microbiome and metabolome. The project will also investigate if protection from intestinal proteases enhances bacteriocin efficacy through the use of protease-resistant nisin derivatives and encapsulated nisin.	Imperial College London	<a href="mailto:p.ross@ucc.ie">p.ross@ucc.ie</a>
<b>Available MSc Projects</b>					
Catherine Stanton, Paul Ross, Colin Hill	Diana Di Gioia, Department of Agricultural Sciences, University of Bologna, (UNIBO), Italy.	Antimicrobial resistance in the bee gut microbiota and in honey	Tackling the issue of antibiotic resistance requires a one health approach, including increasing our understanding of the transfer of antibiotic resistance from environmental sources to the human via the food chain. This study will investigate gut microbiota and antibiotic resistance profile of the bee gut, sampling bees from Ireland and other European sites (accessible through recently funded H2020-MSCA-RISE-2017 project NO PROBLEMS). Additionally, we will track the transfer of antibiotic resistance genes from bee gut to the honey produced by these bees. Moreover we will investigate if bees from the same hive transfer antibiotic resistance genes to others in the hive.	University of Bologna	<a href="mailto:catherine.stanton@teagasc.ie">catherine.stanton@teagasc.ie</a>
Stephen Byrne, Paula O'Leary	Teresa Barbosa, Aoife Fleming, UCC, Esmita Charani, Imperial College London	antimicrobial prescribing: A mixed methods study. Evaluating the feasibility of an academic detailing intervention with General Practitioners in primary care to optimise	The overuse and inappropriate use of antibiotics both in primary and secondary care has been documented extensively in the literature. Techniques such as behavioural change e.g. educational out research is one means by which prescribing practices have been optimised. One such method of educational out research is known as Academic Detailing (AD). AD is a form of continuing medical education (CME) in which a trained health professional visits prescribers in their practice to provide them with evidence-based, non-commercial information. While AD has been adopted in Australia and the United States, this strategy is not routinely used in Ireland. The aim of this study is to raise awareness amongst GPs pertaining to the effect of antimicrobial prescribing on the microbiome of their patients.	Imperial College London	<a href="mailto:stephen.byrne@ucc.ie">stephen.byrne@ucc.ie</a>