



Tackling AMR – A Cross Council Initiative Theme 2: Accelerating therapeutic and diagnostics development

AMR Theme 2 Collaboration Grant Awards (announced in 2016) x3

The focus of the call was to drive forward innovative high quality multi-disciplinary collaborative research to address the broad challenges presented in AMR initiative - theme 2.

AMR Theme 1 Innovation Grant Awards (announced in 2015) x8

This call was for small, novel, high risk proposals to address the broad challenges presented in AMR initiative - theme 2. The focus of this call was on research that is potentially transformative, stimulating creative thinking across disciplines.

Links:

<http://www.mrc.ac.uk/research/initiatives/antimicrobial-resistance/tackling-amr-a-cross-council-initiative/>

<http://www.mrc.ac.uk/funding/browse/tackling-amr-theme-2-accelerating-therapeutic-and-diagnostics-development/>



Theme 2 Large Collaboration Grant

Grant Holder	Institution	Title of Award
Professor David Dockrell	University of Sheffield	Optimising Innate Host Defence to Combat Antimicrobial Resistance
Co-Investigators	Summary	
<p>University of Sheffield:</p> <p>Professor Stephen Renshaw Dr Helen Marriott Professor Simon Foster Professor Jamie Hobbs Dr Simon Jones Professor Alison Condliffe Professor Ian Sabroe</p> <p>University of Edinburgh:</p> <p>Professor Moira Whyte Dr Kev Dhaliwal Professor Mark Bradley Professor Ross Fitzgerald Professor David Hume Professor Christopher Haslett Dr John Baillie Dr Sarah Walmsley Dr Helen Brown Professor Adriano Rossi</p> <p>Newcastle University:</p> <p>Professor John Simpson Dr Muzlifah Haniffa</p> <p>University of Birmingham:</p> <p>Professor Timothy Mitchell</p>	<p>The treatment of bacterial infection is complicated by antibiotic resistance. The body's defence against bacteria relies on the immune system and requires blood cells, called macrophages and neutrophils that eat and kill bacteria. Despite being frequently exposed to bacteria that cause serious infections most people rarely become ill due to these bacteria. We can learn from how the immune system protects most people and develop medicines to re-engage this system if it fails. This approach is currently limited by incomplete understanding of the precise mechanisms that kill bacteria in immune cells but our consortium has made great strides to address this. We now wish to refine our understanding of mechanisms that we have already identified and supplement this with further experiments to identify the best approaches with which to modulate these responses in patients.</p> <p>In the body macrophages are the first line of defence against bacteria. We will use techniques that manipulate all the macrophage's genes individually and identify which are most important in regulating bacterial killing. We have also identified that when macrophages commit cell-suicide it helps clear bacteria and we will look for genes that regulate this process. When macrophages are overwhelmed by bacteria neutrophils are important to remove bacteria. For neutrophils we cannot manipulate the cell's genes but we will use an approach that uses antibodies to target all the proteins in the cell and will perform a similar screen to identify factors influencing bacterial killing. We also have some candidates we have already identified which regulate this process. We will then study how important the mechanisms we find are in models of infection where immune cells interact with other cell types. In particular we want to ensure we not only enhance bacterial killing but also minimize the capacity of neutrophil-derived immune factors to cause bystander damage to the body's tissues.</p> <p>Next we will screen panels of chemical structures to enhance the selected mechanisms of bacteria killing. We will work with industry partners to adapt these structures for medical use. In particular we will test how well these target the specific location in the cell where the killing factors are produced using new approaches, termed super-resolution microscopy (SRM), that allow us to measure their production and location in the cell with great precision. We will modify the chemical structures to ensure our medicines target the right mechanism and location in the macrophage or neutrophil. These compounds will then be tested in our models of bacterial infection, including models of bacteria resistant to multiple antibiotics.</p> <p>We will also test how the bacteria respond to attempts by the immune system to kill them. This will also inform understanding of how bacteria escape immune responses and spread between species to establish reservoirs of infection in animals that contribute to human disease with antibiotic resistant bacteria.</p> <p>To confirm our findings are relevant to patients and to test potential medicines that we develop we will study macrophages and neutrophils from healthy volunteers or patients at risk of bacterial infection. Our approach will be significantly enhanced by our ability to image the interaction of bacteria with macrophages and neutrophils, and specifically the factors that regulate or mediate bacterial killing, in the lung of patients. This involves new developments with unique chemical probes and fibre optical imaging. We can potentially translate our findings rapidly to patients because many of the agents we will use to manipulate the innate response are drugs licensed for other medical indications. Our approach will reduce reliance on antibiotics and provide an alternative approach based on modifying the body's immune response that will be active against a range of bacteria, irrespective of their sensitivity to antibiotics.</p>	

Theme 2 Large Collaboration Grant

Grant Holder	Institution	Title of Award
Dr Andrew Bailey	University of Bristol	Exploring Natures Silent Pharmacy

Co-Investigators

University of Bristol:

Dr Matthew Avison
Professor Gary Foster
Dr Colin Lazarus
Dr Paul Race
Dr James Spencer
Professor Christine Willis

Summary

Fungi have proven to be an important source of bioactive compounds in the past, with penicillins, cephalosporins and statins amongst the best examples. Recent developments in the ease with which we can sequence the genomes of fungi have revealed that fungi house a hitherto unexpectedly large number of gene clusters which appear to encode pathways for secondary metabolites, yet their chemical products are unknown and have not been evaluated in drug-discovery programmes. This suggests that there are many beneficial products yet to be discovered and exploited and these may include new classes of antibiotic which could be deployed to help combat the ongoing problems with antibiotic resistance.

Based on genome sequence data already available for selected target fungi, plus with generation of such data for other selected species of interest, we will develop a pipeline to quickly catalogue such gene clusters and to then design plasmid vectors to allow their expression in the fungus *Aspergillus oryzae*, a species which is very amenable to lab and industrial-scale cultivation. The use of a lab-friendly host fungus is necessary because our experience is that these gene clusters are usually cryptic; not usually expressed under laboratory conditions by the native fungus, and with products that cannot be predicted with any degree of confidence from genome data alone. The target fungi are each predicted to contain 40-60 such gene clusters based on what is typical for other fungi.

The plasmid vectors will be constructed in a series of expression cassettes we have already developed and tested, and will be made using a combination of yeast-based homologous recombination cloning, augmented by Gibson Assembly where necessary. This will be achieved using PCR products derived directly from genomic DNA, or where this is not readily achievable, by use of synthetic DNA designed from genome data. Such approaches should be readily scalable for high throughput use if they prove to be successful in our studies.

Our vector sets will allow coordinated expression of up to four genes per plasmid, with four different selectable markers available, meaning we can expect to readily express pathways comprising 16 genes, and could upgrade this system for additional genes should this prove necessary, which is ample capacity for the majority of pathways encountered in fungi.

Transformants of *A. oryzae* will then be analysed to determine if a new product is produced, and if so, this will be purified by reverse-phase HPLC with analysis by MS and by nmr to elucidate the structure.

Milligram quantities will be purified to allow antibacterial assays against a range of clinically-relevant pathogens to determine antibacterial efficacy for each compound. For compound displaying antibacterial properties, each compound will be evaluated against a range of bacteria displaying characterised resistance to antibiotics to quickly eliminate any compounds showing known modes of action or those where resistance is already prevalent.

For products passing this evaluation, we aim to fully characterise the biosynthetic pathway, including isolation of the intermediate stages in their biosynthesis and to identify products suited to further chemical modification to support studies into structure-activity relationships in this group of compounds.

Our aim is to design a production pipeline that will allow us to investigate every candidate gene cluster from an initial group of ten selected fungi. The isolates selected for this study have been chosen to span a range of differing lifestyles, including insect, fungal and plant pathogens, marine fungi and soil fungi. This would help to inform future choice of strains for a wider scale analysis in a second round of screening should there be time available.

Theme 2 Large Collaboration Grant

Grant Holder	Institution	Title of Award
Professor Christopher Walti	University of Leeds	Accelerating Development of Infection Diagnostics for Patient Management and Reduction of Antibiotic Misuse

Co-Investigators

University of Leeds:

Dr Lars Jeuken
Professor Mark Wilcox
Professor Michael McPherson
Dr Jonathan Sandoe
Dr Andrew
Professor Paul Miller
Professor Nikil Kapur
Professor Robert West
Dr Darren Tomlinson
Dr Michael Messsenger
Dr Bethany Shinkins

Summary

The discovery of antibiotics early in the 20th century revolutionised healthcare provision and antibiotics and other antimicrobials have become an integral part of modern healthcare. However, in recent decades, the use of antibiotics has increased massively, not only in healthcare provision but also in veterinary and agricultural (live stock) applications. This has led to an enormous rise in antimicrobial resistance (AMR), which is forming an ever-growing problem in modern healthcare, proving a serious threat to society. The number of instances where infections are resistant against common antibiotics is increasing rapidly, and bacterial infections with strains that are resistant to almost all known antibiotics (e.g. meticillin-resistant staphylococcus aureus, MRSA) have contributed to a significant number of death (almost 300 in 2012, source: Office for National Statistics) and caused significant problems for affected patients and healthcare providers.

The solution seems simple: drastically reduce the prescriptions of antimicrobials. However, where antimicrobials are required for medical treatment, withholding prescription is dangerous for the patient and unethical, and could furthermore negatively impact on the general public through increased spreading rates.

There are two major types of infections: viral and bacterial. Only bacterial infections can be treated with antibiotics, but certain symptoms are common to both types of infections. A typical example is throat pain, which could be caused by a bacterial infection (e.g. Streptococcus pneumonia) or viral (e.g. influenza), or in fact could be caused by non-infection causes such as heart failure. More critical examples include meningitis, which, when caused by a bacterial infection (meningococcal disease) needs immediate medical attention, while viral meningitis tends to take a milder course requiring rest and observation for encephalitis.

We argue that antimicrobial prescriptions can be reduced safely and ethically if better infection diagnosis is available. Many infections are viral in origin (and hence do not benefit from antibiotics), but often antibiotics are prescribed as a precaution as without suitable diagnostics the doctor cannot be sure what the origin of the infection is. Although some laboratory-based tests are currently available, these can take several days to give a clear answer, and hence precautionary antibiotic treatments are started before the test results are available.

In this research programme we will develop rapid diagnostic tests that can be performed by the doctor her/himself, i.e. a GP in a primary care clinic or a consultant in a hospital, which will give an answer in less than 15 minutes, quick enough to inform treatment before it is prescribed.

The first diagnostic test that this programme will develop will thus be to distinguish between viral and bacterial infections. Once a bacterial infection is diagnosed, or if symptoms are encountered which indicate bacterial infections, it is important to identify the bacterial strain that causes the infection, as different strains require different antibiotic treatments. The second diagnostic test that this project aims to develop is thus to test for pathogen that causes the infections and we have chosen the example of C. difficile infections, a common infection that causes severe diarrhoea. Finally, many bacteria are now resistant to common antibiotics and if the type of resistance is known, the antibiotic treatment can be tailored to be effective. The third diagnostic test that will be developed is thus to diagnose a common subtype of Carbapenem Resistant Enterobacteriaceae (CRE), which is common type of infection with antibiotic resistance. These quick and accurate tests will reduce the prescription of the wrong antibiotics, which will not only reduce to the total amount of antibiotics used (thus reducing AMR), but will also lead to a more effective patient management.

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Dr Matthew Avison	University of Bristol	Detecting Antibiotic Resistance Proteins in Clinical Samples Using Proteomics

Co-Investigators

University of Bristol:

Dr Kate Heesom
Dr Owen Martin Williams

North Bristol NHS Trust:

Professor Alasdair
MacGowan

Summary

Approximately 40,000 people die in the UK every year as a result of Sepsis, which is a medical condition usually triggered by the body's reaction to bacteria in the blood. When bacteria are present in the blood this is called bacteraemia. The bacteria can come from all sorts of places and can be of many different species. So a diagnosis of Sepsis doesn't tell a doctor what bacterium is responsible. Antibiotics kill bacteria, and so antibiotic therapy is absolutely critical to treating Sepsis. Without removing the underlying cause - the bacteraemia - treatment of Sepsis is unlikely to succeed. The dilemma that doctors face is that because they don't know the identity of the bacterium they want to kill, they are not certain what antibiotics to use. The rise of antibiotic resistance in bacteria makes this choice even more difficult. One way of dealing with this is to use "empiric therapy": to try a particular antibiotic, wait to see if the patient improves and if they don't, try another. But in the meantime, the patient may be getting more and more ill. The alternative approach is that the doctor may start treatment with the latest, most broad acting antibiotic they can find to give them the best chance of killing the bacteria. This means that this "last resort" drug might have been used when it wasn't really needed. Inappropriate use of a last resort drug is the primary driver for antibiotic resistance and will inevitably shorten its useful life.

What we really need is to give doctors information about the identity of the bacterium infecting a patient's blood and, more importantly, what antibiotics it is susceptible to. Then they can make informed antibiotic prescribing choices. At the moment, from the time a blood sample is taken from a patient where bacteraemia is suspected it can take 48 hours just to prove there are any bacteria present. Using new MALDI-TOF machines it is possible to identify the bacterium a few hours later, but that doesn't tell you anything about antibiotic susceptibility. It may take another 24 h to find out what antibiotics can be used. This means that patients can be on the wrong antibiotic for up to 72 hours. If that's a non-effective antibiotic, the patient's life is in danger, if it is an inappropriately used last resort antibiotic, the antibiotic's useful life is being shortened.

Everyone agrees that reducing the time it takes to get antibiotic susceptibility data to doctors is the key, not just for the treatment of patients, but also to better protect our dwindling supply of useful antibiotics. We feel that it may be possible to achieve this by identifying antibiotic resistance proteins - the tools bacteria employ to resist antibiotics - directly in bacteria isolated from patients' blood. If a particular resistance protein is present, the doctor would know not to use a particular drug. To test our hypothesis we want to test whether we can identify resistance proteins in bacteria in blood samples that have been cultured and processed exactly as they would be in hospital diagnostic labs. We will find out whether it is possible to use existing MALDI-TOF machines to identify at least some antibiotic resistance proteins 24 h earlier than is currently the case. We will also test whether it is possible to use more specialised LC-MS/MS machines to reduce the time to get antibiotic sensitivity data by up to 60 hours, giving a positive indication of antibiotic susceptibility about 12-15 h after sampling. It is not necessary to provide a diagnostic test that works minutes after sampling to have real clinical benefit. For severe Sepsis, each hour without working antibiotics gives a 6% increase in patient mortality, so even shaving tens of hours off the current minimum time it takes to predict antibiotic susceptibility would transform patient care.

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Dr Benjamin Raymond	University of Exeter	Rapid assessment of phage for combating antimicrobial resistance in <i>Enterobacter cloacae</i> using a novel insect model

Co-Investigators

University of Exeter:
Professor Angus Buckling

Summary

Antibiotics, drugs that can be used to treat and prevent bacterial infection, have revolutionized our ability to treat infectious disease and prevent infection during surgery. Unfortunately bacteria can become resistant to antibiotics by evolving. They can undergo genetic changes that enable them to tolerate or degrade antibiotics. We believe that there is a need to consider a whole raft of innovative solutions to resistance. One important possible solution is to increase our use of "biological" solutions to treat infections, such as the bacteria-killing viruses known as bacteriophage. While bacteriophage remedies have their limitations, they can be combined with antibiotics in a way that can improve treatment efficacy and also help slow the rate of the evolution of resistance. Evolution experiments require time and potentially many different hosts. While phage has much unexploited potential, currently it is difficult and expensive demonstrate the effectiveness of these tools by doing evolution of resistance experiments with laboratory mammals.

For this proposal, we have specifically developed an insect system to investigate the evolution of resistance to antibiotics in the bacterium *Enterobacter cloacae*. This species is particularly difficult to treat because of its naturally occurring resistance to many penicillin-based antibiotics. It is an important cause of bladder and kidney infections as well as infections associated with intensive care. Our insect model captures many of important aspects of infections in vertebrates but has the added benefits of being easy to manipulate, free of ethical oversight, and very cost effective. With this model we can vary antibiotic consumption, the presence of resistance plasmids and numerous important conditions that will allow us to mimic different real world scenarios with large numbers of individual hosts.

We will use experimental evolution to assess a range of ways of deploying bacteriophages to slow the evolution of resistance. This will include the use of virus to specifically kill those bacteria carrying genetic elements that confer resistance to antibiotics. We will investigate how to best to deploy bacteriophage in combination with phage, and how best to use phage to combat different forms of resistance. We will also look at important factors that might affect the value of phage in resistance management, such as the diversity of the bacteria in the gut.

With the insect experiments we can find out what happens in weeks or months, if we change a range of control measures. If we would do this in the real world, it would be harder, more expensive and potentially take years. Such an experimental system will never be perfect, but it will give us a good idea what will happen, cheaply and quickly.

While the insect models cannot entirely solve the problem of antibiotic resistance, we believe that they could provide an important new tool. With it we can rapidly look at the effectiveness of a large range of possible resistance management options on a population scale, and pick out the best ones, which can later be tried out in hospitals or in animal health.

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Professor Andrew Rycroft	Royal Veterinary College	Neutralization of Apx toxicity as an alternative to antibiotics for control of contagious porcine pleuropneumonia.

Co-Investigators	Summary
<p>Royal Veterinary College: Professor Brian Catchpole</p>	<p>Contagious pleuropneumonia is a severe acute disease that kills many growing pigs and causes lifelong damage to the lungs of those that survive. This impacts on the profitability of the production system. Pig farms regularly use antibiotics to control this disease because there is very little that can otherwise be used.</p> <p>Before the advising veterinary surgeon on a pig unit can reduce the use of antibiotics, we need alternatives for them to use. Apart from improving husbandry practices such as increasing ventilation and reducing the number of animals held together, there is little that can be offered. This is a problem throughout the world and is one of the primary reasons for using prescription antibiotics in pigs throughout Europe. In the UK, there is no effective vaccine because these have failed to protect pigs from disease, or the vaccine was itself toxic. Efforts to make on-farm vaccines (emergency vaccines) have not solved the problem because they are not efficacious and antibiotics, in feed, in water and by injection, are used in an attempt to avoid catastrophic losses.</p> <p>The disease is caused by a bacterium, <i>Actinobacillus pleuropneumoniae</i>, which produces two of three different protein toxins (ApxI, II and III). Production of these toxins by the pathogen is key to the disease process. Pigs that recover from disease have antibodies which neutralize the toxins and evidence suggests this is crucial in protecting pigs from the disease. It needs to be replicated in a successful vaccine. However, simply using the toxin(s) as a vaccine does not protect pigs. Despite stimulating production of antibodies these are not toxin-neutralizing antibodies. It appears that these bacteria have evolved to synthesise toxin molecules with irrelevant but highly immunogenic regions to distract the immune response to the wrong part of the toxin so that the antibody response is ineffective allowing the bacteria to spread and the disease continue.</p> <p>In this project we will eliminate those parts of the toxin that are distracting the immune response and which appear to be causing failure of the toxin molecules to generate a neutralizing response when used as a vaccine. These small fragments will be joined to a carrier protein, modified diphtheria toxin. This will enhance the immune response and make the antigen large enough to be recognised by the pigs' immune system as a vaccine antigen. We will immunize pigs with these modified toxins and measure the immune response and the neutralizing effect against the active toxins. To improve the method of testing the toxins and the effect of neutralizing antibody, we will develop and test a pig model of dermal oedema. This will be used to indicate the best vaccine antigens for use in the pig model of pleuropneumonia. We will then proceed to immunize pigs and test the efficacy of the vaccination by experimental challenge of the pigs with the virulent pathogen.</p> <p>If this hypothesis is correct, and the immune response to the toxin fragment is effective, this could be the step needed for production of an effective vaccination against pleuropneumonia and the opportunity, finally, to offer the pig industry an alternative to antibiotics which would markedly reduce the quantity of these drugs used in controlling pig respiratory disease.</p>

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Professor Laura Piddock	University of Birmingham	Applying New Tools to Identify Inhibitors of Antimicrobial Resistance Plasmid Transmission or Stability in Gram Negative Bacteria

Co-Investigators	Summary
<p>University of Birmingham:</p> <p>Dr Luke Alderwick</p>	<p>Antibiotics and antimicrobials underpin modern human and veterinary medicine. They are commonly used not only to treat infections, but also prior to surgery, and are extremely important for vulnerable patients with reduced immune function, including the young, elderly, transplant, cancer, and HIV/AIDS patients. However, the spread of multidrug resistant bacteria is rendering these treatments ineffective. The number of infections in people and animals caused by antimicrobial resistant bacteria are increasing to alarming proportions around the world, and new treatments are urgently needed. However, it has proven very difficult to find antibiotics that get inside bacteria such as E. coli, Salmonella and Pseudomonas aeruginosa (called Gram-negative bacteria). Furthermore, over the last few decades very few new antibiotics have made it to the market. Therefore, finding ways to make resistant bacteria susceptible to already existing antimicrobials is a very attractive strategy.</p> <p>One of the reasons antimicrobial resistance is such a growing problem is that bacteria are able to easily share their genetic information through a number of ways, including plasmid transmission. Plasmids are pieces of genetic material that can be moved from one bacterial cell to another. These plasmids often contain genes that allow bacteria to become resistant to antimicrobials (termed antimicrobial resistance genes). Therefore, bacteria are able to share antimicrobial resistance. This occurs on a global scale, with antimicrobial resistance plasmids rapidly traversing the globe, causing serious and difficult to treat infections worldwide.</p> <p>In this project, we will use a novel system we have developed to discover compounds that get rid of these antimicrobial resistance plasmids from bacterial populations. This could be used in a number of settings including animals, patients, farming, and waste water treatment. In animals, large quantities of antibiotics are used in a number of countries including high income countries such as the USA, which provides a platform for resistance to develop. This resistance can then spread to other nations. Our work would reduce the number of antimicrobial resistance genes in bacterial populations, therefore reducing the chances that these genes would get into human pathogens, where they could cause untreatable infections. Compounds identified in this study could also be used to clean surfaces, especially in hospitals, where antibiotic resistance is prevalent. They could also be used to eliminate antibiotic resistance genes from waste water, soil, compost, and farms. Our work could also be applied in hospitals where patients are routinely treated with antibiotics. Drugs developed from our work could be given to patients prior to antibiotic therapy, thus increasing bacteria susceptibility to antibiotics.</p> <p>In order to complete this work we have assembled a team of scientists with expertise in a wide range of different techniques. We will work together to provide new scientific information and knowledge crucial to combating antimicrobial resistance, by making bacteria sensitive to the antibiotics we already have available. Ultimately, this research will have a health benefit on the treatment of patients with life-threatening infections caused by antibiotic resistant bacteria.</p>

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Professor Robert Read	University of Southampton	A genetically modified nasopharyngeal commensal as a platform for human bacteriotherapy

Co-Investigators	Summary
<p>University of Southampton:</p> <p>Professor Ian Clarke Professor Saul Faust</p> <p>Public Health England:</p> <p>Professor Andrew Gorringe</p>	<p>Our long term objective is to invent a new type of medicine which consists of living bacteria which would be given as nose drops (akin to the Yacult drink that is commercially available and taken by mouth by people with bowel problems). We have recently published work in which we inoculated a small dose of a `friendly bacterium` - <i>Neisseria lactamica</i> - into the noses of participants and found that the bacterium was still present in their throats 6 months later, and caused no ill effects. Furthermore, the friendly bacterium stopped the participants from being infected with a related bacterium which can cause meningitis. This concept of `bacteriotherapy` is rapidly gaining credence as a way to treat bacterial infections - for example we now treat <i>Clostridium difficile</i> diarrhoea with bacteria derived from the stools of donors, and it works very well. We have discovered a way to genetically transform <i>Neisseria lactamica</i> with genes from a very wide range of living things, which means that we could potentially develop a range of bacterial medicines containing genes which exert specific desired effects in the recipients. For example, we could make a bacterial medicine which makes substances which kill harmful bacteria or viruses or which simply out-competes them. One of the problems with our idea is that when we inoculated students with the <i>Neisseria lactamica</i>, we found that 65% of them became colonised, but this was only 35% if we restricted the study to non-smokers. This would not be a very reliable bacteriotherapy and we would need to increase the likelihood of colonisation if this approach is to be of any use. So, in the proposed study, we will use our technology to make a strain of <i>Neisseria lactamica</i> which makes two proteins that are normally used by other bacteria to stick to cells. We will use for this purpose two proteins that are normally made by the related meningitis bacterium <i>Neisseria meningitidis</i>, to stick to the inner surface of the nose when it colonises humans. We will show that the new genetically modified strain has all of the characteristics we expect including the ability to stick better to cells in the laboratory, and that is safe to release into the community (because it is not more resistant to the immune system, or to antibiotics, and does not have increased capacity to gradually change into something more dangerous). We will then apply to the appropriate regulators for permission to repeat our studies with human volunteers to see if the genetically modified strain that we have generated manages to colonise better than the wild type bacterium from which it is derived. This would be the subject of a follow-on study - if that were to be successful this strategy that we have devised would be a future therapy of relevance to any disease process involving colonisation of the nasopharynx, eg pneumonia, Chronic Bronchitis, sinusitis, ear infection, meningitis or MRSA colonisation and disease.</p>

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Professor Bo Su	University of Bristol	Novel antimicrobial surfaces to combat AMR infections in medical implants and devices
Co-Investigators University of Bristol: Professor Howard Jenkinson Dr Angela Nobbs	Summary Despite tremendous improvements in surgical procedures, bacterial infection remains the dominant cause of medical device or implant failure, resulting in significant patient trauma and a huge burden on the NHS. Current solutions to combat such infections are largely based upon incorporation of chemicals (e.g. antibiotics) into the devices, but these approaches have a number of shortcomings. One of the biggest problems is the development of antimicrobial resistance amongst bacteria, which has been described by the government as a 'ticking time bomb' that poses an "apocalyptic" threat to public health. Thus a completely new way of killing antimicrobial-resistant (AMR) bacteria is urgently needed. This project explores a unique physical means to kill AMR bacteria by puncturing their cell walls with tiny spikes. Such structures are inspired by those found in nature on cicada wings and can be incorporated on the surface of implant biomaterials. This project aims to develop a range of innovative surfaces that are able to kill bacteria via nanospikes, including bacteria that are resistant to killing by antibiotics, and to determine exactly how the bacteria are being killed. With further commercial exploitation such novel antimicrobial surfaces have potential to be used for next-generation biomedical devices and implants, with improved performance compared to those devices in current use.	

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Dr Michael Hopkins	University of Sussex	Foresight Study on European Stakeholder Appraisal of Diagnostics to Manage Anti-Microbial Resistance

Co-Investigators	Summary
<p>The Office of Health and Economics:</p> <p>Dr Jorge Mestre-Ferrandiz Professor Adrian Towse</p> <p>University of Sussex:</p> <p>Dr Martin Llewelyn Professor Andy Stirling Dr Frederique Lang</p>	<p>It is well-documented that there is a desperate need for new antibiotics against established and emergent drug-resistant bacteria - the so called 'superbugs' - but we currently face a thin global pipeline of new agents in this area. Multiple factors drive the development and spread of antimicrobial resistance (AMR). A number of important on-going initiatives are underway to try to address this AMR challenge - but these are primarily focused on new antibiotics. There is a lack of an in-depth analysis in the peer-reviewed literature regarding diagnostics, even though development of bacterial infection diagnostics has been identified as a priority. For this reason, this proposal focuses on the development and use of diagnostics to address the AMR challenge. In theory, diagnostics have the potential to rapidly aid the management of antibiotic resistance as development times are shorter and so diagnostics can be brought into use more quickly in the battle against super bugs. Moreover, there is good evidence that the use of diagnostics can reduce unnecessary antibiotic use, but this has so far failed to translate into the development and use of appropriate technologies.</p> <p>This project provides a foresight study across seven EU nations to facilitate stakeholder appraisals of potential innovation pathways (covering development, validation, introduction and incentives) for a wide range of bacterial infection diagnostics - presented as scenarios that compete for public and/or private resourcing. The project's hypothesis is that some scenarios are attractive to a critical mass of stakeholders, while others will not be supported and are therefore unlikely to be viable in the short to medium term. The project's contribution will be to demonstrate clearly and transparently within and across stakeholder groups and countries, where there is consensus, divergence and uncertainties in relation to scenarios to support particular innovation pathways, as well as detailing the factors that underlie similarities, differences and uncertainties in appraisals. The project will be transformative for a range of stakeholders particularly, in the short term, research funders, researchers and small firms, who are often unable to undertake or access such analysis themselves. The project's impact aim is to drive higher resourcing and policy support towards particular viable pathways and therefore accelerate development of the needed diagnostics. In the short term this would occur through enhanced stakeholder co-ordination and by reducing missteps (investment in poorly supported approaches that do not meet stakeholder needs).</p> <p>SPRU and OHE are active in disseminating their research especially to policy and industry audiences, in addition to academia. Given the great policy and industry, as well as academic, interest in AMR solutions we plan to disseminate the outputs of this research very actively, via different means. The starting point will be the preparation of four academic articles for submission, and a policy brief. We will take advantage of running alongside key on-going initiatives via bilateral discussions, workshops and presentations. Our impact plan includes presentations to these and to policy makers, researchers/ industry/ clinicians, ensuring that UK and international research on AMR is better informed of downstream viewpoints allowing them to move beyond a "science push" approach.</p>

Theme 2 Innovation Grant

Grant Holder	Institution	Title of Award
Dr Justin O'Grady	University of East Anglia	Improving the management of sepsis through rapid pathogen and antibiotic resistance detection in blood

Summary

It is widely recognised that rapid diagnostics are crucial in the fight against antimicrobial resistance (AMR), allowing earlier and more precise targeting of pathogens with narrow-spectrum antibiotics, and for improving the management of life threatening infections such as sepsis. Current methods - blood culture and PCR based molecular tests - are not fit-for-purpose in this context. Blood culture methods have long turn-around times and offer poor clinical sensitivity; PCR based methods are not sufficiently comprehensive, detecting only selected pathogens and/or resistance markers. A paradigm shift in diagnostic microbiology is urgently required.

Next generation sequencing (NGS) based diagnosis has the potential to deliver this step change, being potentially as swift as PCR and as comprehensive as culture. However, sequencing-based pathogen identification in bloodstream infection diagnosis is very challenging owing to the vast amount of human DNA present compared with pathogen DNA (the ratio can be as high as $10^9:1$). Therefore, pathogen DNA enrichment is crucial and we are developing novel strategies to achieve this, removing the vast majority of the human DNA from blood (without any significant loss of pathogen DNA) and reducing the ratio of human:pathogen DNA from $10^9:1$ to $< 10:1$. We have proof-of-concept data to demonstrate that our approach, combined with MinION nanopore sequencing technology, can be used successfully to identify pathogens and their resistance genes in blood samples from patients with sepsis within 8h.

With this approach, if it can be introduced to the clinic, patients need receive only one dose of empirical broad-spectrum antibiotics before treatment can be tailored for the pathogen/patient - a true 'precision medicine' approach to antibiotic treatment. This dramatic improvement to the 'Start Smart - then Focus' approach to antimicrobial stewardship (Public Health England) will lead to a reduction in the use of broad-spectrum antibiotics, mitigating selection pressure for antibiotic resistance. It will also reduce the number of patients who receive inappropriate antibiotics for their infections, with contingent decreases in morbidity and mortality.

We propose to:

- Further develop and optimise our current pathogen DNA enrichment strategy and to test two new enrichment strategies
- Test a number of NGS technologies/platforms to determine the most suitable in terms of analysis time, flexibility, complexity of bioinformatics analysis, cost and comprehensiveness of sequencing results
- Run a clinical diagnostics evaluation, testing 50 well-phenotyped, biobanked human blood samples from sepsis patients and controls to validate the performance of the optimised NGS based method.

This project, combining our novel pathogen DNA enrichment strategies with NGS, represents the cutting edge of clinical microbiology and genomics, and will ensure the UK and the NHS are among the global leaders in genomics-based stratified and precision medicine.

The pathogen DNA enrichment and NGS workflows will be applicable to diagnostic samples from other life-threatening infections e.g. healthcare-associated pneumonia and complicated urinary tract infections. Comprehensive sequencing-based diagnostics will enable not only the wider use, but also the clinical development of narrow spectrum antibiotics. Lastly, they will identify bacterial strains and their variants, providing information that can be used for infection control and for both local and national epidemiology purposes. The preliminary work that I have performed, along with my expertise and that of my collaborators make me uniquely positioned to deliver this cutting edge, ambitious, high impact translational research project.