

## Impact Objectives

- Find new ways to treat conditions when current antibiotics stop working
- Tackle ineffective dosing and unrestrained prescribing of antibiotics
- Help to educate organisations and people to prevent antibiotic overuse, underuse and misuse

# A focus on resistance to antimicrobials

*Professor Jason Roberts is the Chief Investigator of a Centre for Research Excellence based at the University of Queensland in Australia. Below, he discusses his work on reducing antimicrobial use, the facilities at the Centre, and the importance of interdisciplinary collaboration to the success of the research*



**What were the driving forces behind the establishment of the Centre of Research Excellence in Redefining**

**Antimicrobial Use to Reduce Resistance (CRE REDUCE), and what are the key goals for the Centre?**

The genesis of the Centre is to be found in the clinical work of its chief investigators who observed that many antimicrobial treatments were failing, with a concomitant increase in the development of antimicrobial resistance. The main goals of the Centre, and the projects, are to better understand exposure-related antimicrobial resistance and formulation; clinical testing of newly established dosing regimens in order to optimise in vivo antimicrobial activity; and, ultimately, to improve patient outcomes.

**Could you describe some of the state-of-the-art facilities and equipment being used at the Centre?**

We have a bioanalysis laboratory run by a team of professional bioanalytical scientists, and a collection of analytical instruments to run a catalogue of assays, including instruments for chromatographic drug analysis techniques. We also have in vitro hollow-fibre infection model equipment that simulates pharmacokinetics in patients.

**How important is interdisciplinary collaboration to the success of this research?**

Interdisciplinary collaboration is integral to our work. CRE REDUCE attracts substantial external involvement and commitment from institutions nationally and internationally. We are coordinating an international team that includes intensive care, infectious diseases and transplant physicians, pharmacists, nurses, translational scientists, pharmacometricians, health service researchers, biostatisticians and clinical trial design experts. CRE REDUCE combines many of Australia's leading experts in infection, antimicrobial pharmacokinetics and dynamics, and antimicrobial resistance with other world leading collaborators in Australasia, Europe and the US.

**Can you talk about the training and development of young researchers through the Centre and why this is important?**

Each of the projects within the Centre is training researchers who will perpetuate related research. The Centre will train at least 15 PhD students, six research assistants and two postdoctoral fellows, as well as numerous interns, masters and undergraduate students. Antimicrobial resistance is a major global challenge and likely to remain so for some time. Training young researchers in this essential field of contemporary practice will build capacity for this type of work, create new knowledge for the benefit of Australia and the world,

and build research excellence that can meet future multi-resistant infection challenges.

**How is the Centre accelerating the translation of research findings into clinical practice and what tools are you using to share the new approaches with healthcare professionals?**

A major focus of our research is the translation of new knowledge into health policy and practice. Our research outcomes will be presented at local, national and international forums to advertise our new knowledge to relevant scientific communities. We will publish clinical results and clinical practice guidelines, and present to relevant Federal and State bodies and professional societies. We will build a greater and more relevant web presence through activity on our website, Twitter and other social media platforms.

**Finally, does the Centre have any outreach activities planned in the near future?**

CRE REDUCE plans to organise several Pharmacokinetic Modelling and Dose Optimisation Workshops. One of our most recent workshops, which took place in October 2016, focused on pharmacokinetic analysis using Pmetrics software and Bayesian forecasting using BestDose software. This course enabled participants to develop skills in population pharmacokinetic modelling and dose optimisation of antimicrobials in different clinical situations.

# Combating antimicrobial misuse

*The Australian Centre of Research Excellence in Redefining Antimicrobial Use to Reduce Resistance (CRE REDUCE) aims to redefine antimicrobial use and overcome resistance. As well as finding new ways to treat conditions, the Centre tackles ineffective dosing and helps educate organisations and people to prevent antimicrobial overuse, underuse and misuse*

While resistant microorganisms such as bacteria, fungi, viruses and parasites naturally evolve – often because they replicate themselves erroneously or resistant traits are exchanged between them – antimicrobial resistance (AMR) occurs when a microorganism becomes resistant to an antimicrobial drug that was originally effective at treating the infections caused by it. Furthermore, the use and misuse of antimicrobial drugs is accelerating the emergence of drug-resistant strains. It represents a significant global health challenge and has a negative impact on outcomes for patients, as well as on healthcare expenditure.

## PROLONGING THE EFFECTIVENESS OF ANTIMICROBIALS

With that in mind, the Centre of Research Excellence in Redefining Antimicrobial Use to Reduce Resistance (CRE REDUCE) has been established at the University of Queensland, Australia and is home to researchers intent on combating antimicrobial resistance and prolonging the clinical utility of antimicrobials.

Professor Jason Roberts is the Chief Investigator of CRE REDUCE and, along with some of Australia's most prominent experts, is leading attempts to focus on best practice for those patients most at risk of antimicrobial resistance. 'The current environment of high use of our limited range of antimicrobials and the associated escalation of resistance mandates a reassessment and an urgent optimisation of the way we utilise our existing antimicrobial agents,' he explains. 'Ensuring we use

existing antimicrobials in the correct doses across patient populations has been identified as a low-cost and high-impact measure to combat antimicrobial resistance.'

Sub-optimal dosing results from a lack of relevant pharmacokinetic and pharmacodynamic studies. A UK government-sponsored review on AMR identified that increasing this type of research would significantly contribute to the quest of making current antimicrobials last longer. CRE REDUCE is therefore conducting various investigations to stall the increase of AMR.

## A PLETHORA OF RESEARCH AREAS AT ANY ONE TIME

The CRE REDUCE team work on several different research areas at any one time, including the use of hollow fibre infection models (HFIM) to quantify how antimicrobial exposure leads to the emergence of AMR. Among other groups, critically ill adults, paediatric patients, individuals with pneumonia, and burns and obese patients, are all populations that are susceptible to AMR, and can have highly varied and suboptimal antimicrobial exposures. The HFIM area of research will determine the precise ways in which antimicrobial dosing leads to the increased emergence of resistance.

Ultimately, through the dynamic in vitro models the team use, they will be able to ascertain the specific doses of antimicrobials required to stop the emergence of resistance in so-called superbugs. In addition, the team's clinical pharmacokinetic studies will describe how drug concentrations in different

patient populations can lead to an increased risk of AMR.

'Our earlier clinical and pharmacokinetic studies have proposed and supported administration of beta-lactam antimicrobials by continuous infusion, in order to improve pharmacokinetic and pharmacodynamic attainment of these antimicrobials in patients with severe sepsis and septic shock,' says Roberts. 'We will now be moving on to a large, multinational, powered-to-mortality study of clinical outcomes of continuous versus intermittent beta-lactam antimicrobials administration in critically ill patients with severe sepsis.'

Another area of research will focus on the pharmacokinetics of antimicrobials in lung transplant, bone marrow transplant, and cystic fibrosis patients. Not only is AMR common in these patients, subtherapeutic concentrations represent a problem too and, as this patient population only has very limited pharmacokinetic data (but are still routinely treated with antimicrobial doses validated in healthy volunteers), improving knowledge will be of huge importance.

## THE IMPORTANCE OF TRANSLATING FINDINGS

The pharmacokinetics of antimicrobials in obese patients remains largely unknown, so the team at CRE REDUCE have established a specific area of research to fill in these knowledge gaps. Antimicrobial exposure in this group is difficult to predict, especially when coupled with the

pathophysiological changes caused by critical illness. Thus, through a multicentre, clinical pharmacokinetic study, the team will describe the pharmacokinetics of piperacillin, meropenem and fluconazole in critically ill obese patients.

The knowledge gained from the dynamic *in vitro* models and clinical pharmacokinetic studies will enable the team to describe new dosing regimens that are effective in treating patients, but suppress the emergence of resistance. Once these new dosing regimens have been described, Roberts and his team will test them in clinical outcome studies. Through a consultative process with relevant organisations and professional societies, the findings will be translated into novel treatment guidelines that will represent a huge step forward in meeting the global health challenge of AMR.

#### SOME INITIAL SUCCESS STORIES

Despite the fact the research taking place at CRE REDUCE is ongoing, some key success stories have already emerged. The increasing prevalence of obese patients in intensive care units represents a major challenge for prescribing clinicians, not least because of the difficulty in determining the appropriate and specific antimicrobial dosing in this group. Obesity causes significant alterations to the pharmacokinetics of antimicrobials, thus what might be the correct dosage for some patients is not necessarily translatable to others. However, the work of CRE REDUCE has helped inform the development of some guidelines.

'A retrospective study on the effects of obesity on the pharmacokinetics of two commonly used antimicrobials in ICU has been published in the *Journal of Antimicrobial Therapy*,' notes Roberts. 'This work is determining optimal dosing regimens for these patients and will guide recommendations for dosing guidelines to assist clinical practice.'

As well as their studies on obesity, the team have focused on sepsis – a major healthcare

issue for Australia's indigenous population. The rates of infection-related deaths are drastically higher in this population when compared to their non-indigenous counterparts. In response to this, researchers within CRE REDUCE have recognised the need to optimise antimicrobial treatment in the acute phases of active infection in this group of patients. 'The research we are conducting in the Central Australian and Top-End regions is addressing the many questions surrounding the pharmacokinetics and pharmacodynamics of antimicrobials in indigenous critically ill patients,' observes Roberts.

#### THE CURRENT AND FUTURE BATTLE IS BEING WAGED ON THREE FRONTS

While the research taking place at CRE REDUCE represents several steps forward in the quest to curb the development of AMR in various patient populations, there is still much to be done in this global battle. Accordingly, the Centre has established three fronts on which the fight will be won. To begin with, new ways of treating conditions when antimicrobials have stopped working will be found; ineffective dosing will be tackled, as well as the worrying practice of unrestrained prescribing of antimicrobials; and, importantly, the public and organisations will be educated on the dangers of AMR and how it is exacerbated through the overuse, underuse and misuse of antimicrobials.

In acknowledgement of the continuous battle against superbugs the global human population faces, CRE REDUCE is also committed to developing worldwide capacity to deal with AMR through fostering postgraduate and postdoctoral fellow research, and teaching undergraduate students and healthcare practitioners. Much like that being fought against, clinicians now and in the future must be resilient in the face of AMR and uphold the best practices that emerge from the research taking place at CRE REDUCE.

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## Project Insights

#### FUNDING

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The University of Queensland, Australia  
• Ghent University Hospital, Belgium •  
The Chinese University of Hong Kong  
• The Australian National University •  
The University of Melbourne, Australia  
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**Professor Jason Roberts** is a National Health and Medical Research Council Research Fellow at The University of Queensland, Consultant Clinical Pharmacist at the Royal Brisbane and Women's Hospital. His principal research theme is optimisation of antibiotic dosing in the critically ill. Professor Roberts has over 260 published papers and book chapters on this topic, has been awarded over \$20 million in grants and supervises 10 higher research degree students.

