Dr Stavros Selemidis discusses how his research into reactive oxygen species in biological processes is advancing understanding of mechanisms underpinning disease and novel pharmacological targets.

Can you first give a brief overview of your research background?

My PhD studies focused on identifying the cardiovascular actions of arguably one of the most important reactive oxygen (nitrogen) species: nitric oxide. This was the subject of the 1998 Nobel Prize in Medicine and at the time I found it fascinating that nitric oxide was a short-lived, endogenously produced gas that also acts as a signalling molecule in the body. From there, I became interested in other species of the reactive oxygen species (ROS) family, including superoxide anions and others, as they were identified as playing pathogenic roles in disease states such as atherosclerosis, cancer and neurodegenerative conditions. However, in 2010 I came to the realisation that nitric oxide was a short-lived, endogenously produced gas that also acts as a signalling molecule in the body. From there, I became interested in other species of the reactive oxygen species (ROS) family, including superoxide anions and others, as they were identified as playing pathogenic roles in disease states such as atherosclerosis, cancer and neurodegenerative conditions. However, in 2010 I came to the realisation that ROS are also likely to influence virus-induced pathologies; indeed, our preliminary work at the time demonstrated that influenza A virus infection resulted in bursts of ROS production and therefore a novel pharmacological target for the treatment of influenza. We showed that the inhibition of NADPH oxidase activity results in a marked reduction in airway inflammation and lung oxidative stress. Current anti-inflammatory drugs used to treat influenza have some efficacy in reducing inflammation but this comes at a cost of impaired virus clearance. Unexpectedly, this was not observed with the inhibition of NADPH oxidase activity. In fact, to our surprise, we observed a significant improvement in virus clearance.

You recently reported your latest findings at the Thoracic Society of Australia and New Zealand (TSANZ) conference, for which you were awarded the best scientific presentation. How important has this been in promoting your work to the wider scientific community?

I feel humbled to have won an award at the Cell Biology Division of TSANZ, the leading society for respiratory research in Australia and New Zealand. It signifies that my peers recognise the quality, innovation and standing of our work. The Society has a strong clinical presence, so any exposure and recognition helps to raise awareness among clinicians treating patients with respiratory disease at the bedside. Ultimately, I hope this will promote the clinical translation of our work.

What impact has a multidisciplinary approach had on your research?

Undoubtedly this approach has increased the impact of our work, as it has allowed us to address the problem with a broad spectrum of cutting-edge technologies and approaches. Consequently, we have published our work in several multidisciplinary journals. As a pharmacologist by trade with limited expertise in viruses and immunology, I drew on the expertise of a number of key collaborators from around Australia, most notably Associate Professor Ross Vlahos (respiratory science), Associate Professor Steven Bozinovski (innate immunity), Dr John Stambas (virology), Dr Paul King (respiratory clinician) and Associate Professor Grant Drummond (vascular biology). Collectively, this group of researchers strengthens our knowledge base and supports research from the basic level to the clinic.

Looking forwards, how do you see your research developing?

The progress of our work certainly rests on the outcomes of future funding. I envisage our research becoming more cross-disciplinary, with a broader use of sophisticated technologies. It is likely our work will move towards drug discovery in order to unravel more specific approaches for suppressing the key enzymes that we have identified as being major contributors to lung oxidative stress caused by flu.

Speaking broadly, what are your hopes for the future of oxidant and inflammation biology, and to what extent do you believe your work will help contribute to improving the outlook for patients?

We will continue to unravel key targets of virus-induced tissue injury that could be exploited by highly specific pharmacological inhibitors. Promisingly, new drugs that target host-dependent oxidative stress could be used in a polypharmaceutical approach with both antiviral drugs and vaccines, thereby tackling both host immunopathology and the virus.
INFLUENZA A VIRUS infections contribute substantially to morbidity and mortality rates across the world. Pandemic outbreaks of influenza have killed over 100 million people in the past century, while the seasonal burden of influenza places huge socioeconomic costs on healthcare systems and economies in developed and developing countries alike. Alarmingly, increased antiviral resistance and slow vaccine developments raise the likelihood of influenza A pandemics, emphasising the pressing demand for novel generic pharmacological strategies that improve existing therapies.

The introduction of new therapeutic drugs for influenza largely depends on attaining greater insight into the complex mechanisms that underpin the disease. Encouragingly, important strides have been recently achieved in this area. For example, reactive oxygen species (ROS) – the reactive and toxic oxygen-containing molecules produced by all mammalian cells – have been identified as significant contributors to many pathological processes when found in excess. In view of this, a growing body of research over the past decade has attempted to describe the behaviour of ROS in cell biology. This has resulted in a fuller scientific comprehension of ROS-induced processes – however further investigation is vital to uncover exactly how these molecules regulate the inflammation that is a common feature of many acute and chronic diseases, including influenza A.

COLLABORATION IS KEY
Dr Stavros Selemidis is one prominent researcher who has dedicated his research to understanding the role of ROS in the biological processes at the root cause of influenza A and cancer, specifically with reference to the identification of novel drug targets that could potentially treat these diseases. As a Future Fellow of the Australian Research Council (ARC), he heads the Oxidant and Inflammation Biology Group in the Department of Pharmacology at Monash University. Selemidis boasts an impressive track record with upwards of 30 scientific publications and over 10 invitations to speak at a range of national and international conferences.

With the aim of furthering his discoveries about ROS in disease mechanisms, Selemidis and his colleagues at Monash University have forged strong partnerships with numerous scientists. Most notably, the team are directing a multidisciplinary and collaborative programme involving researchers based at two other Australian universities – the University of Melbourne and Deakin University – with a threefold objective. Firstly, the programme seeks to establish a logical and unifying approach to identify cellular pathways that are influenced by ROS and relevant to influenza A virus infections. Secondly, it is pursuing the implementation of novel and selective tools to gain in-depth knowledge of these processes. Finally, the programme is endeavouring to validate these processes using appropriate cell and animal models. The aim is that these collaborative studies – which pool together multidisciplinary understanding and expertise – will inform modern drug discovery by identifying potential drug targets.

DRIVING DISCOVERIES
Importantly, Selemidis and his team have revealed innovative new insights into the function of ROS in pathological systems, the...
INTRODUCTION

UNDERSTANDING THE BIOLOGY OF REACTIVE OXYGEN SPECIES

OBJECTIVE

To utilise forefront technologies to identify and characterise fundamental biological and molecular processes influenced by toxic free radicals that are triggered by viruses such as the flu. The approach synergises with researchers with unique and complementary expertise across disciplines and universities to ultimately identify future drugs to treat flu infections.

KEY COLLABORATORS

Associate Professor Ross Vlahos; Associate Professor Steven Bozinovski, Department of Pharmacology, The University of Melbourne, Australia • Associate Professor Grant Drummond; Associate Professor Christopher Sobej, Department of Pharmacology, Monash University, Australia • Associate Professor Elizabeth Williams, Translational Research Institute and Princess Alexandra Hospital, Queensland, Australia • Dr John Stambas, Commonwealth Scientific and Industrial Research Organisation (CSIRO), Deakin University, Australia • Dr Paul King, Department of Medicine, Monash Medical Centre, Australia

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STAVROS SELEMIDIS is an Australian Research Council (ARC) Future Fellow and Head of the Oxidant and Inflammation Biology Group at the Department of Pharmacology, Monash University. Selemidis’ most recent research has provided key evidence that highly reactive and often toxic oxygen-containing molecules, i.e. reactive oxygen species, produced by the cells of the immune system, contribute to the pathophysiology of influenza A virus infections.

most notable of which is that the ROS produced by autoimmune cells are the key chemical mediators in the body’s response to the influenza A virus. As airborne environmental pathogens, influenza A viruses set a complex disease process in motion. On entering the lungs, they infect the epithelial cells – the cells lining the airways and forming the structure of the lungs – and the special sentinel inflammatory cells known as alveolar macrophages. In order to combat the rapid replication and spread of the pathogens, the host cell forces the virus into the endosome – a membrane-bound compartment within the cell – and releases a powerful range of chemical mediators in an attempt to eliminate it. However, while this response is necessary for fighting the invading virus, it also results in extensive inflammation and tissue damage in the host’s lungs: “Along with others, we have demonstrated that these inflammatory cells are major producers of ROS, contributing to lung tissue injury characterised by oedema and lung dysfunction,” Selemidis elucidates. “Therefore, the pathology initiated by the virus is not a direct effect of the virus per se, but rather an overambitious response by the innate immune system of the host.”

In another critical discovery, the researchers have pinpointed the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme as the key source of ROS. So far, NADPH oxides are the only family of enzymes that have been determined to have a primary function in the generation of ROS. This is significant because NADPH oxidase inhibitors could become a potential strategy for the control of influenza A virus pandemics in the future. Indeed, the suppression of NADPH oxidase activity – and, as a result, the reduction of oxidative stress – is currently a key area of investigation for Selemidis and his collaborators.

CLINICAL APPLICATIONS

Selemidis’ studies into the function of ROS in disease processes have important implications for the future control of infectious diseases. At present, his team is utilising preclinical animal models of disease in an attempt to make further inroads into the identification of novel drug targets. Excitingly, the targets that the researchers have already identified – such as Nox oxidases – are now the subject of clinical trials for the treatment of pulmonary fibrosis. It is anticipated that novel therapies will continue to be realised and developed: “Ultimately, detailed molecular, biochemical and pharmacological insights into the phenomena of influenza A viral and host interactions will lead to fundamental advancements in knowledge of cell function,” Selemidis enthuses. “These can then be used as foundations to more rationally develop novel therapeutics for treating influenza disease.”

Selemidis and his team have revealed the reactive oxygen species produced by autoimmune cells are the key chemical mediators in the body’s response to the influenza A virus

Looking ahead, the Oxidation and Inflammation Biology Group are eager to further their pursuit to fully understand immune system-induced ROS responses. Specifically, they intend to improve their methods for the detection of ROS and design more advanced tools for the manipulation of ROS levels in vivo, by using cell-specific knockout and transgenic mouse models. The team are also targeting the development of specific pharmacological inhibitor drugs. However, these innovations will only be made possible through the continuation and development of strong collaborative efforts between other scientists and the clinicians tackling respiratory disease on the frontline.