How has your academic and professional training prepared you for your most recent project?

I was trained initially as a molecular immunologist and have been working on the regulation of animal innate immunity since my PhD studies at Kansas State University. After spending two years of postdoctoral work at Yale University School of Medicine, I joined the faculty at Oklahoma State University in January 2002. I have been working on the identification and characterisation of novel host defence peptides and dietary modulation of animal innate immunity ever since.

At the heart of it, your work aims to reduce antibiotic resistance. Why is this a pressing issue?

Emergence of the pathogens that resist the actions of currently available antibiotics has become a major public health concern worldwide. According to the US Food and Drug Administration (FDA), 70 per cent of pathogens today are resistant to at least one antibiotic. Some pathogens, known as ‘superbugs’, can even tolerate multiple antimicrobials. Thus, there is now an urgent need to develop a new generation of antibiotics and antibiotic alternatives before infections once again become incurable.

Historically, there has been significant research on host defence peptides (HDPs). Why are they so attractive to the scientific community?

Since the initial discovery of cecropins in the Giant Silkmoth in the early 1980s, over 2,000 natural HDPs have been reported in virtually all species of life. Cecropins were originally isolated in an attempt to identify the innate immune factors in insects, which lack adaptive immunity and have to rely entirely on natural immunity for self defence.

Since then, HDPs have been revealed as critical components of animal innate immunity, capable of killing a variety of pathogens and even cancerous cells through electrostatic interactions with membranes, which is then followed by membrane lysis. Additionally, HDPs have a profound impact on the modulation of host response to infections.

Because of this, there is a growing interest in harnessing and improving their bactericidal and immunomodulatory properties for antimicrobial therapy, particularly against antibiotic-resistant bacteria.

Besides direct delivery of HDPs, you are pursuing an indirect antimicrobial approach by modulating the synthesis of endogenous HDPs. How can this indirect approach be utilised as a novel strategy to combat infectious diseases?

Due to the cost and short half-life associated with a typical peptide drug, it is more desirable and cost-effective to boost the synthesis of endogenous HDPs to help animals fight off infections.

Thus, it is conceivable that dietary supplementation of compounds that boost HDP production – individually or in combination – may augment animal innate immunity and disease resistance with zero reliance on antibiotics.

Has collaboration – academic or industrial – played a major role in your most recent work?

Collaboration is essential for our research because of the interdisciplinary and integrated nature of our programme. Having access to expertise in molecular biology, immunology, microbiology, pathology, statistics, genomics, metagenomics and bioinformatics is critical to the success of our research programme. Furthermore, for our laboratory discoveries to translate into practical applications in both human health clinics and livestock production sites, collaboration with

By boosting the innate immune system, Dr Glenn Zhang and his colleagues from Oklahoma State University, USA, hope to make antibiotic resistance a thing of the past.
IN 2006, AN infectious bacterium known as methicillin-resistant Staphylococcus aureus (MRSA) caused 1,652 deaths in the UK and thousands more around the world. In the UK this represented a fatality 30 times greater than the deaths caused by the same bacterium in 1993. Since then, the media has been awash with warnings of the so-called ‘superbugs’ and the dangers of antibiotic resistance.

Antibiotic resistance, the ability of a sub-population of a microorganism to evolve a resistance to one or – in the case of MRSA and other superbugs – multiple drugs used to eradicate them, is a growing phenomenon. With the threat of another outbreak or a new strain of superbugs, scientists are now searching for alternative strategies for treatment in both humans and animals.

Dr Glenn Zhang, Associate Professor in Oklahoma State University’s Department of Animal Science, USA, is one such scientist who, through altering synthesis of the peptides of the innate immune system, could soon be capable of effectively removing infection without the unwanted side-effect of resistance.

ANTIBIOTIC RESISTANCE

Whilst humans have been using specially selected mold and plant extracts to treat infections for over 2000 years, it wasn’t until the early 20th Century that antibiotics became testable and controllable clinical tools. Whilst these antibiotics – such as Fleming’s penicillin and Domagk’s Prontosil – have been invaluable in treating disease, the consequences of their overprescription and misuse are beginning to become apparent with the recent steep increase in antibiotic-resistant pathogens.

Typically, this kind of resistance occurs after a spontaneous or induced genetic mutation, or alternatively through the acquisition of resistance genes from other bacterial species. This results in the subsequent exposure to an antibiotic naturally selecting for the genes for resistance, which then, in turn, reproduce. As one would predict, the chance of developing resistance positively correlates to antibiotic prescription. Moreover, patients often fail to take the full course of their medication, thereby increasing the chances that resistant strains survive and reproduce.

Considering these factors, it is clear to see that the widespread use of antibiotics in livestock production – primarily for growth promotion and disease prevention – will result in similar concerns. In a bid to curb the potential damage antibiotic resistance may cause to this industry, legislation has been phased in over the past two decades. “The EU banned such practices

What major hurdles have you and your team faced thus far?

In translational research such as ours, it is not uncommon that some of the laboratory results may not be fully extrapolated to animal and human trials.

Although effective in vitro, some of our peptide analogues and HDP-promoting dietary compounds failed to work in live animals as effectively as in cells. With that said, it takes patience and persistence to bring the findings from bench to bedside.

Will you be disseminating your findings at any external events?

We have been sharing our research findings regularly at national and international meetings. The Conference of Research Workers in Animal Diseases is a great venue to keep updated with the latest in animal health research.

Serving as Treasurer and member on the Nominating Committee of the American Association of Veterinary Immunologists, I have had the pleasure of interacting with my fellow veterinary immunologists during the annual conference.

It is also my plan to attend livestock industry meetings more often in the future in order to raise the awareness and interest of various industry groups in our new technology.
in January 1996, with the US Food and Drug Administration (FDA) now following suit with a new policy to phase out the use of antibiotic growth promoters, which took effect in December 2013,” Explains Zhang.

For these reasons, there is now a need to develop alternative treatments that will attack these antibiotic-resistant pathogens, without the accompanying risks. One such way to do this is to change the treatment target altogether by boosting the host’s immune defences and thus increase the chances of pathogen clearance – albeit indirectly.

HOST DEFENCE PEPTIDES

Forming a major part of the innate immune system, host defence peptides (HDPs; also known as antimicrobial peptides) are found endogenously in all classes of life. Since they were first described in 1939, when antimicrobial substances – gramicidins – were isolated from Bacillus brevis, HDPs have been shown to be effective in killing both Gram-negative and Gram-positive bacteria, mycobacteria, enveloped viruses, fungi, parasites and even transformed cancerous cells.

Changing the treatment target altogether by boosting the host’s immune defences increases the chances of pathogen clearance – albeit indirectly.

This is achieved, in part, through direct mechanisms that often see HDPs attacking the membranes of pathogens. They have also been found to interfere with the synthesis of DNA, RNA, proteins and cell walls.

Additionally, HDPs have been shown to have a plethora of immunomodulatory functions on both the innate and adaptive immune systems, including the ability to alter host gene expression, act as chemoattractants and/or induce chemokine production.

As Zhang elaborates, it’s this ability of HDPs that makes them so attractive as alternatives to antibiotics: “Because they act on the host and not the pathogen, these compounds pose virtually no risk of inducing resistance”.

The peptides which modulate host immunity have remained elusive for quite some time. Zhang and his team’s first task was to, therefore, explore the immunomodulatory mechanisms of several specific HDPs before they could assess their efficacy and ability to prevent infection.

Previous studies have shown that HDPs are able to boost the immune response by inducing migration of neutrophils and macrophages (both phagocytes which fight infection) and activation of monocytes and dendritic cells. Boosting the synthesis of endogenous HDPs will undoubtedly enhance animal immunity and disease resistance, and Zhang’s group has found an exciting avenue to do this.

HDP STIMULATING COMPOUNDS

Defined as any compound which is made up from a carboxylic acid with a long aliphatic tail, fatty acids are categorised into either short-, medium-, long- or very long-chain fatty acids (SCFA, MCFA, LCFA and VLCFA, respectively). Intrigued by earlier studies that SCFAs are capable of inducing HDP synthesis and enhance bacterial clearance without triggering an inflammatory response, Zhang compared the relative efficacy of fatty acids in stimulating HDP expression.

His results indicated that, among all free saturated fatty acids of 1-18 carbons, 4-carbon butyrate is the most potent at up-regulating HDP gene expression in chicken and pig cells, whereas 6-carbon hexanoate and 7-carbon heptanoate are the strongest HDP inducers in human cells. In general, multiple HDPs are simultaneously induced by fatty acid treatment.

Additional studies by Zhang and his team found that SCFAs synergise with sugars and several plant extracts in promoting HDP synthesis in chicken cells. Cyclic adenosine monophosphate (cAMP), an important second messenger of many biological processes, also acts similarly in concert with SCFAs to augment HDP production in chicken cell culture. These outcomes clearly point out the potential for dietary supplementation of HDP-stimulating compounds as a novel antimicrobial strategy.

Whilst these early in vitro studies have produced promising results, there’s still a need for further assay before in vivo trials can begin to assess the efficacy of this alternative therapeutic avenue. The potential of HDP-inducing compounds could soon be realised in livestock production and translate for human application shortly after. A new drug to safeguard against infection and antibiotic resistance needs timely attention; attention which Zhang will uphold until such a tool can be brought to market.