Antimicrobial contact lenses

Professor Mark Willcox provides an insight into his microbial adhesion prevention efforts and discusses the possibilities presented by the antimicrobial peptide melimine, particularly in relation to contact lens manufacturing.

Can you briefly outline your research background?

I conducted my PhD at the University of Manchester, UK, in the area of medical microbiology, focusing on the role of bacterial adhesion in dental plaque formation and the subsequent development of decay. This introduced me to the concept of microbes adhering to surfaces as a preferred mode of growth and the ability of these communities to produce pathological effects. After finishing my PhD and spending a year as a postdoctoral scientist, in 1988 I migrated to Australia to take up a position at the Institute of Dental Research in Sydney. There, I carried on my work on microbial adhesion and broadened my interests to examine the ability of oral bacteria to bind to blood components and cause disease.

After five years at the Institute of Dental Research I started to look around for other positions. I saw an advert for a role within the School of Optometry and Vision Science at the University of New South Wales, specifically in its Cornea and Contact Lens Research Unit. The Unit was looking for a scientist to set up a research programme studying how microbes adhere to contact lenses and produce ocular disease. It sounded interesting and an area in which I could contribute, so I applied and got the job! The School had recently received funding for seven years from the Australian Government’s Cooperative Research Centre scheme to develop new contact lens materials and part of my role was to understand how bacteria might interact with these materials.

What are the key aims of your current research?

My overarching goal is to develop surfaces that reduce the ability of microbes to adhere, thus reducing many of the pathologies associated with microbial adhesion. I have a National Health and Medical Research Council grant to run a large-scale clinical trial to assess the safety and efficacy of two antimicrobial contact lenses compared to a normal lens. The hope is that at least one of these will show a significant reduction in microbial adhesion and the associated inflammation of the ocular surface.

In addition, I am working on developing an antimicrobial coating for cochlear implants. This research is funded by an Australian Research Council linkage grant and it has now moved into preclinical testing. I have also recently been looking at applying antimicrobial surfaces to catheters.

In what ways can microbes in biofilms adhering to contact lenses cause harm to wearers?

While contact lens wear is a generally safe and effective way of correcting refractive errors, it can lead to ocular infection. The most severe and acute problem is infection of the cornea (keratitis). If not treated aggressively, promptly and with the right antibiotics, the eye can scar, negatively impacting vision. Biofilms are also associated with non-infectious corneal inflammation – in other words an acute inflammatory response produced by the eye because of the colonisation of contact lenses, but without the bacteria penetrating and replicating in the tissue. As there is no infection, there is little risk of any loss of vision. However, the inflammation is associated with redness of the eye and pain.

Your research has identified a novel peptide called melimine as a potential antimicrobial coating for contact lenses. Can you reveal any findings you have made so far with this peptide?

Melimine has many properties that make it an ideal candidate as an antimicrobial coating for medical devices. It is effective against many different bacteria, fungi and protozoa. It is not toxic to mammalian cells at active concentrations; indeed, its therapeutic index (antimicrobial concentration versus toxic concentration) is 150:1. Importantly, when cultured 30 times in sub-inhibitory concentrations, bacteria do not gain resistance to it. Melimine is resistant to the action of proteases such as trypsin, and is readily heat sterilisable. Additionally, when bound to a contact lens it results in >99.99 per cent reduction in adhesion of bacteria.

Does melimine have the potential to be applied to other medical devices in the future?

Yes. As mentioned, we are looking at using melimine to coat cochlear devices and catheters. Indeed, as it appears to be very safe, we envision using melimine for a variety of applications such as on orthopaedic devices, replacement organs and pacemakers.
Combating microbial adhesion

Within the University of New South Wales, a group of researchers is conducting groundbreaking research aimed at preventing microbial adhesion to surfaces through the development of novel antimicrobial coatings.

**The Adhesion of** harmful microbes to synthetic and organic surfaces within the body poses a significant threat to human health. Generally, these microbes live in communities known as biofilms, encased in polymers that protect them from microbicides, protozoa and the immune system. Indeed, previous research indicates that microbial cells within biofilms are 1,000 times more resistant to these threats than those existing outside of biofilms. Furthermore, it is estimated that microbes contained within biofilms are responsible for at least 60 per cent of all human infections. Therefore, if scientists can determine a way to prevent the adhesion of microbes and the formation of biofilms, human health would benefit considerably.

**How Biofilms Affect Human Health?**

Biofilms are a problem for humans in many ways - they reside on water pipes, contaminating the water supply and causing the pipes to corrode, as well as being associated with many human diseases such as cystic fibrosis.

This condition is the result of mutations in one of the genes that regulates water and ion transport and results in, among other problems, thick mucous secretions in the lungs that are difficult to remove by coughing. Bacteria colonise the thick stagnant lung secretions. In particular, the bacterium *Pseudomonas aeruginosa* colonises the lung and is associated with progressive, severe disease. The median age of survival is still only 30-40 years, and pulmonary disease remains the principal cause of morbidity and mortality.

**An Antimicrobial Answer**

At present, few antimicrobial medical devices are available on the international market and there are no antimicrobial contact lenses at all. The antimicrobial devices that do exist generally contain silver or adsorbed antibiotics. However, the clinical efficacy of such devices has, overall, been limited; silver is not the most potent antimicrobial material and the antimicrobial effect of adsorbed antibiotics can be reduced when they are released too rapidly or when microbes have developed resistance. For this reason, scientists are now searching for more effective strategies to prevent microbial adhesion, and thus, the harmful colonisation of medical devices.

This is exactly the aim of the research group led by Professor Mark Willcox at the School of Optometry and Vision Science within the University of New South Wales. For decades, the Willcox team has been working to devise effective ways to prevent microbial adhesion and biofilm formation, as well as develop...
INTRODUCTION

PREVENTION OF MICROBIAL ADHESION

OBJECTIVES

• To demonstrate the efficacy and safety of melimine-coated contact lenses in large-scale clinical trials

• To understand the mechanism of action of bound melimine against bacteria

• To demonstrate the effectiveness of bound melimine to prevent bacterial adhesion, but facilitate mammalian cell adhesion

KEY COLLABORATORS

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MARK WILLCOX received his BSc from the University of the West of England, UK, in 1983. Willcox then went on to conduct his PhD under the supervision of Dr David Drucker at the University of Manchester. In 1988 he moved to Australia for a postdoctoral position at the Institute for Dental Research, Sydney, and in 1993 started at the School of Optometry and Vision Science, UNSW. Willcox became Professor at the School of Optometry and Vision Science in 2004 and has recently been appointed Associate Dean of Research Training in the Faculty of Science.

ANTIMICROBIAL SURFACE AGENTS

Antimicrobial surface agents suitable for use in the manufacture of contact lenses and internal medical devices. So far they have demonstrated the significant promise of antimicrobial peptides (AMPs), as these can be both potent and non-toxic.

MELIMINE

There is one AMP in particular that has caught the attention of Willcox and his team: melimine. Produced by combining the most potent components of the melittin and protamine proteins, studies conducted by the Willcox group have already shown this novel AMP to have substantial potential as an antimicrobial coating. It is effective against numerous types of bacteria, including those that are highly resistant to conventional antibiotics, as well as fungi and protozoa. Overall it resulted in a reduction in microbial adhesion of over 99.9 per cent. Furthermore, lab studies indicate that bacteria do not develop resistance to melimine even when cultured repeatedly in the AMP. Combined with the findings that melimine is non-toxic to mammalian cells at active concentrations, it should remain relatively stable in the body and is readily heat sterilisable, it is little wonder that the researchers are excited about melimine’s potential.

Melimine’s safety has already been confirmed in a human phase I clinical trial. This was the first such trial of a cationic antimicrobial coating in the world – a fact that goes to highlight the cutting-edge nature of this research. To date, the safety and efficacy of melimine as a contact lens coating has been tested in humans, while positive results have been shown in animal models of infection and inflammation associated with contact lenses, catheters and cochlear devices.

IMPROVING HEALTH

Large-scale phase II/III trials are scheduled to take place later this year to further test melimine’s ability to reduce the inflammation associated with contact lens wear. It is the Willcox team’s hope that positive results at this stage will act as a stimulus for contact lens manufacturers to invest in further antimicrobial contact lens research. This will provide a significant boost for the New South Wales lab, which has relied significantly on industry funding for more than two decades of research. “Convincing funding bodies and grant reviewers of the importance of conducting contact lens research has proven a great challenge,” reveals Willcox. “Without the manufacturers’ willingness to fund both basic and applied research, we would not have discovered melimine in the first place.”

In addition to their work on melimine’s applications in contact lens manufacturing, Willcox is planning to extend its use to catheters and cochlear devices in animal models. Their aim is to bring these applications to clinical trials in due course.

Finally, the team still needs to elucidate some of the mechanisms through which melimine’s impressive efficacy as an anti-adhesive is achieved. With this in mind, efforts are currently underway to determine exactly how melimine binds to a bacterial surface and precisely why this reduces microbial adhesion. Once these questions have been answered, activities aimed at designing even more effective coatings, which can bind to surfaces in different ways and are suitable for a wider range of applications, can commence. The research group is particularly excited by recent findings in this area that suggest that human cells can bind to and grow more effectively on melimine-coated surfaces than on non-coated surfaces. These findings could pave the way to the production of surfaces for medical devices designed for long-term implantation that can prevent microbial adhesion while facilitating cell growth and so better sealing the device within the body.

THE DANGERS OF CONTACT LENS MICROBIAL COLONISATION

For every 10,000 contact lens wearers:

• >5 individuals will experience an eye infection

• 500 individuals will be affected by eye inflammation

• 1 in 2,500 people who wear contact lenses and remove them at night will contract keratitis

• 1 in 500 people who wear contact lenses and sleep in them at night will contract keratitis

Contact lens wear is the most common risk factor for corneal infection (keratitis) in developed countries.