Dr Marnie Peterson shares an insight into her hunt for new weapons to fight bacterial infections by exploring the mechanisms behind exotoxins in the pathogenesis of infections such as *Staphylococcus aureus*.

First, could you offer a brief overview of your research objectives and goals?

The goal of our research is to develop therapeutics to treat and prevent infections with a focus on *Staphylococcus aureus*. We are particularly interested in microbicides with anti-microbial and anti-inflammatory properties as well as new vaccination strategies. Our primary objectives are to determine the mechanisms of action of secreted toxins (exotoxins) on mucosal surfaces in the pathogenesis of *S. aureus* infections. Exotoxins (including superantigens and cytolyisins) induce pro-inflammatory signals from epithelial cells by undescribed mechanisms, which contribute to superantigen penetration of multi-layered epithelial tissue and systemic disease, including toxic shock syndrome.

We have developed *in vitro* cell culture, *ex vivo* infection mucosal models and *in vivo* animal models of toxic shock syndrome to characterise these mechanisms of action, to identify biomarkers predictive of disease and virulence, and to determine the efficacy and toxicity of experimental therapeutics.

In what ways does your present research build on existing knowledge?

Superantigen interactions with immune cells have been well characterised. Our approach differs as we focus on the interplay between *S. aureus* exotoxins and the host mucosa, which acts as a barrier to systemic disease. We hypothesise that the penetration and systemic effects of superantigens (eg. TSST-1) secreted from bacteria growing on mucosa depends on the direct, receptor-mediated interactions of superantigens with mucosal epithelial cells and synergistic actions of other *S. aureus* exotoxins.

Our research builds upon existing studies by our research group and others that have described superantigen-induced changes in epithelial cellular morphology and secretion of proinflammatory cytokines from vaginal, bronchial, nasal, and intestinal epithelial cells. We specifically seek to understand the mechanism of action of superantigen-induced cytokines and changes in cellular morphologies to develop improved therapeutics and preventative approaches for *S. aureus* infections. These approaches include inhibiting the production of exoproteins, developing host cell receptor antagonists or small molecule inhibitors of pro-inflammatory signalling pathways to prevent microbial/superantigen-induced local tissue damage, inflammation and shock described in various forms of *S. aureus* infections including skin and soft tissue infections, pneumonia, and toxic shock syndrome.

In 2007 you formed a collaboration with 3M. Could you tell us more about them and how your work has benefited from their resources?

Ultimately, for research to be translated and have an impact on society, the science needs to be developed commercially. My research programme has been enhanced significantly by a collaboration formed with 3M Medical Division in 2007. My laboratory developed several mucosal/infection models that are used to determine and predict the clinical efficacy, toxicity and mechanisms of action of 3M proprietary technologies including antisepsics and wound healing agents. My laboratory has become an integral component of research and development for 3M Infection Prevention and Skin and Wound Care Divisions. These studies have expanded over four years to include a clinical randomised placebo controlled study. Our collaborative research has resulted in presentation of data at international research conferences, several manuscripts and licensing of new technologies and innovations.

How key has NIH funding been to your work? How difficult do you find it to secure sufficient funding?

There is certainly both a high degree of prestige and responsibility that comes with an
Since the advent of the antibiotic age with the discovery of penicillin in 1928, bacterial infection is a diminished threat to human health. With this diminution has come a decline in the public concern in the developed world. However, as antibiotic resistance develops, the spectre of bacteria has returned to loom large in the public consciousness. No longer is it the ravages of tuberculosis or cholera but the so-called ‘superbug’ Methicillin-resistant Staphylococcus aureus (MRSA). Outbreaks of MRSA or Clostridium difficile have made people cognisant of the perils of bacterial infection once more. However, at times the truth is lost behind the headlines.

Journalists can tend to concentrate on the tales of filthy hospitals and the ‘superbug’ threat. However, regardless of antibiotic resistant traits, S. aureus is an important human pathogen, which colonises vaginal mucosa and the nostrils, with rates of up to 30 per cent of the population. “It is a transient member of the normal human microbial flora,” outlines Dr Marnie Peterson of the University of Minnesota, who is conducting research in this area. “Colonisation by S. aureus is a risk factor for disease, as the person’s own flora is often the source of infection. It is one of the leading causes of serious infections in the U.S. including pneumonia, bone and joint infections, endocarditis, sepsis, atopic dermatitis and severe life-threatening toxic shock syndrome (TSS).” An additional effect of colonisation can include the life-threatening skin and soft-tissue infection, necrotising fasciitis; all of which constitute the infection as a very real threat to a wide range of people.

Toxic shock syndrome

TSS is a rare but extremely serious potential consequence of S. aureus infection. It is caused by the secretion of toxins called superantigens by the bacteria. This causes the syndrome through the dramatic stimulation of a non-specific immune response. The superantigen binds to a receptor on the surfaces of immune cells called macrophages. The bound S. aureus toxin forces a binding between this receptor, called MHC-II or major histocompatibility complex II, and its counterpart on the surface of another immune cell class, T-cells. This linkage makes the T-cells produce and release a type of cell-signalling chemical called cytokines in massive numbers. This ‘cytokine storm’ causes a potentially catastrophic inflammatory response which means the patient must suffer a high fever, malaise, low blood pressure, and potentially coma and multiple organ failure.

Burgeoning antibiotic resistance is a global problem; against this context, innovative work led by the University of Minnesota and in collaboration with private companies to translate basic research directly into product development, aims to lead us to novel treatments.
STAPHYLOCOCCAL SUPERANTIGEN INTERACTIONS WITH VAGINAL EPITHELIUM

OBJECTIVES
Severe manifestations of *Staphylococcus aureus* -induced pathology are caused by exotoxins (superantigens and cytolsins). Dr Peterson’s objectives are to determine the mechanisms of *S. aureus* exotoxins’ induction of epithelial inflammatory signals, which contribute to toxin penetration through tissue and ultimately disease, in order to aid the development of improved therapeutics to treat and prevent these infections.

KEY COLLABORATORS
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**MATERIALIZED DEPENDENCIES**

**PUBLIC FINANCE AND PRIVATE INVESTMENT**

“The development of new microbicides is a logical progression from the identification of critical microbial pathogenicity determinants,” says Peterson. “This linked approach has allowed me to obtain funding for basic and translational/ drug-development research from governmental institutes, including the National Institutes of Health (NIH), as well as industrial entities such as 3M Infection Prevention and Skin and Wound Care Divisions.”

Incorporating both public and private funding into the same research group has been cited recently by the *Lancet* among others as important for driving forward the discovery of novel antibacterial therapeutics. This is because for research to have an impact on society the science needs to be developed commercially. The reciprocal relationship between Peterson and 3M, started in 2007, has led to development of mucosal models of infection. These are essential for the work of Peterson’s lab. Furthermore, such models can be used to predict the efficacy, toxicity and mechanisms of 3M technologies like antiseptics and wound healing agents. Peterson is also halfway through a four year NIH grant for studying the interaction of Staphylococcal superantigens and haemolysins (staphylococcal exoproteins) with the female reproductive tract mucosa.

**FUTURE PROSPECTS**

Glycerol monolaurate (GML) looks particularly promising, of the potential novel microbicides Peterson and her team are working on. A naturally derived compound used in the food and cosmetics industries, it has been shown to be both effective at inhibiting the growth of *S. aureus* and delaying the production of exoproteins. Importantly GML has also been shown to have immunomodulatory effects on epithelial cells. This means it prevents the production of the proinflammatory cytokines that can snowball into the eruptive immune response which causes TSS.

“We sought to explore the dual anti-microbial/ anti-inflammatory activity of GML as a vaginal microbicide,” recalls Dr Peterson. The ensuing study found that GML-containing gels could be the first agents that allow simultaneous management of candidiasis and vaginal bacterial infections. "GML gels killed both Candida and Gardnerella while maintaining normal vaginal microflora," she adds. This clinical study was a small pilot study of GML’s effects, involving less than 40 women; however it shows good evidence of the effectiveness of GML as a microbicide in the context of the vaginal mucosa.

To move this forward to full clinical trials, Peterson is clear that partnerships with small drug development companies are vital. To that end, GML technologies were licensed by the University of Minnesota to a small start-up company (Hennepin Life Sciences). Moreover, the identification and validation of biomarkers predictive of *S. aureus* disease and virulence will be necessary if scientists are going to develop experimental therapeutics.