Dr Peter A Burke discusses his work improving decontamination methods for prions and their associated diseases, and the unlikely discovery that propelled his team into the field of malaria research.

Can you begin by explaining what prions are and why prion decontamination is so important?

Prions are proteinaceous infectious agents that are transmissible – they can have different structures and infect different animals but they are all proteins. Prions are in all our bodies and the normal forms have some function – although we don’t know exactly what this is yet. The problems arise when these proteins become ‘rogue’. When this happens, their quaternary structure changes and they begin to accumulate in the brain and cause neurological damage. It’s now a well-established fact that prion diseases can be transmitted between people and there have certainly been instances of iatrogenic transference – that is, they have been spread via medical practice or treatment. As such, understanding how to decontaminate medical instruments against prions is crucial.

Why have surgical decontamination classifications not been adjusted to mitigate the threat of prion disease transfer?

The reason classification has not been changed to account for prions is largely due to their relative rate of infection. Creutzfeldt-Jakob disease (CJD) – a prion disease – affects around one person per million; in the US that’s between 300 and 450 cases per year. So you can see why the effort has not been made, but the problem is that these diseases are devastating and always terminal. CJD is usually only identified shortly before or after death, and at that point it’s likely that a patient will already have undergone surgery and thus facilitated disease transmission. Prions stick to surgical instruments very well, as they are typically found in brain tissue, which is lipophilic and doesn’t wash away easily. If you’re the next person that gets the same set of equipment, and it’s only been steam sterilised – well, that’s a scary thought.

Can you now explain the leap into antimalarial medication and how this technique has been applied to target malarial parasites?

We collaborated with the University of Lisbon Medical Centre and specifically Professor Thomas Hänscheid, who had read some of our published work and was intrigued by the haemazoid structure of IFDOs. He was interested in using the methodologies that we had developed to screen antimalarial products. We began to work together on this, and although these studies are not as advanced as our research into prions, the results so far have been very promising.

Following on from this, why has progress in the identification of target treatment drugs and disinfection methods for prion diseases been so slow?

It’s been slow because the US Food and Drug Administration decided through an advisory panel several years ago (which I actually testified in front of, alongside several other experts) that at that point in time they would not do anything about this issue. There hasn’t been as big an outcry in the US as there was in the UK and France, as these countries were afflicted with variant CJD in the 1990s which struck young people in relatively high concentrations within a very short period of time. The European community therefore took a more progressive approach, and pledged to protect the public from these diseases.

What makes the IFDO model useful for malarial researchers?

Its facility lies in the fact that it’s a simple test that only takes a couple of days, and which you can run in your lab without any real sophistication. If you can do microbiology, you can do this test. There are of course simple tests in the area of antimalarial research already, but I’ve been told by experts in the field that this is simpler and easier than those currently used – so we’re hopeful that this will speed up the clinical trials process.
Accidental antimalarial advancement

A team of researchers at the Ohio-based medical solutions company STERIS has made significant headway in preventing the iatrogenic transfer of prions using a novel model. They are now applying that model to screen antimalarial drugs.

First isolated in 1984, the misfolded proteins known as prions are still relatively new to science. They are suspected of being responsible for the group of diseases referred to as the transmissible spongiform encephalopathies (TSEs), although this hypothesis is still the subject of some debate, as it would make prions the only known form of infectious agent to contain no nucleic acid. The question of what causes prions, which exist in our bodies in a harmless form, to change their morphology and become neurologically damaging, is still open. An increasing wealth of data indicate that it occurs when prions are in their oligomeric phase rather than their β-amyloid plaque form, suggesting to many researchers that only the latter is cytotoxic.

The TSEs caused by prions are universally fatal, but human forms like Creutzfeldt-Jakob disease (CJD) affect a relatively low number of people, and are rarely transmitted through contaminated medical equipment. This balance of low risk versus high mortality has meant that attitudes towards TSEs vary considerably worldwide. In some parts of Europe, such as France and the UK, where TSE health scares in recent decades remain fresh in the minds of citizens and legislators, these pathogens are considered a potent danger. In order to mitigate the threat of iatrogenic transfer, surgeons routinely use advanced decontamination procedures to remove all trace of prions from their utensils. Conversely, in the US, the government has taken no stand on the issue – and this means that not only do such sterilisation methods go unused, but the companies that provide them are prevented by federal law from pitching directly to hospitals.

Neutralising the threat

Dr Peter A Burke is Senior Vice President and Chief Technology Officer at STERIS, a company based in Ohio and concerned with providing effective solutions for the prevention of infection and contamination. His team has developed a significant amount of time to prion research. The World Health Organization (WHO) recommends that contaminated tools be subjected to extremely strong alkaline treatment before undergoing autoclave sterilisation, but this process contributes to significant wear on surgical utensils and is therefore expensive and unappealing to clinicians. The STERIS team has developed alternative solutions – now available in the EU – and is working on further tools to prevent the accidental transmission of these deadly proteins.

One of the problems the group encountered in the study of prions is that the experimental methods used are generally costly and time-consuming – partly because of the risks and subsequent safety precautions necessary when handling them. To make their processes more efficient, the STERIS team therefore began using a new model to test their hypotheses – and one based on an interesting finding. In 1989, Dr D W Burdon of Birmingham General Hospital, UK, described a strange phenomenon that he called the ilium fluid-dependent organism (IFDO). Even at that time, Burdon was able to identify the marked similarities between this strange new replicating agent and what he called the ‘unconventional agents’ behind CJD – which included resistance to proteinase K and various decontamination methods.

The IFDO caught the attention of Burke's group, which initially found it so similar to a prion that they assumed it was one. After careful analysis, the team found that the...
INTRODUCTION

A NOVEL WAY TO GROW HEMOZOIN-LIKE CRYSTALS IN VITRO AND ITS USE TO SCREEN FOR HEMOZOIN-INHIBITING ANTIMALARIAL COMPOUNDS

OBJECTIVES

• To develop the ilium fluid-dependent organism (IFDO) model for modelling prions and testing new methods of prion decontamination for use in medicine
• Using the haemazoid structure of IFDOs to screen novel antimalarial drugs

KEY COLLABORATORS

Dr Gerald McDonnell, STERIS Corporation, Mentor, Ohio, USA
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DR PETER A BURKE: serves as Senior Vice President and Chief Technology Officer for STERIS Corporation. He is responsible for STERIS’s research, innovation, technology development and regulatory functions, and works closely with the company’s marketing, sales, manufacturing and support functions to facilitate new applications of current technologies. This leads the development of new technologies from conception to commercialisation. Burke holds PhDs in Microbiology and Biochemistry from St John’s University, and has authored over 25 patents, as well as 30 scientific/business publications.

IFDO was something much more useful: an agent similar in all functional aspects to a prion, but non-infectious. This made it an ideal tool for their continued efforts to create new decontamination agents. Using the IFDO model, Burke’s team was able to identify and optimise a number of compounds for the disinfection of surfaces and devices contaminated with prions. In fact, its use has facilitated the discovery of some unlikely solutions to this problem. Decontaminating agents they had previously thought to be ineffective against prions were shown to act against them in unexpected ways, and the IFDO is the only model capable of uncovering these mechanisms.

MOVING TO MALARIA

As it turned out, the development of effective disinfectants would not be the only outcome of the team’s work. When they published some of their work making use of the IFDO, they caught the attention of an unlikely would-be collaborator: a malaria researcher in Lisbon, Portugal. Professor Thomas Hanscheid was intrigued by the IFDO, not because of its resemblance to prions, but because of its resemblance to haemoglobin. The Plasmodium falciparum parasite feeds on haemoglobin and excretes free haem – a metabolite that is toxic to the red blood cells that the protozoan inhabits. A vital part of P. falciparum’s parasitisation, therefore, is to convert this free haem into non-reactive haemoglobin. Disruption to this metabolic process creates an environment that is toxic and deadly to the parasite; it therefore presents a popular research target for scientists hoping to develop effective malaria therapies, and those trying to understand the underlying mechanisms for current antimalarial drugs.

The STERIS group’s methodologies for cultivating the IFDO in vitro for prion research created a unique – and serendipitous – opportunity to quickly and easily validate antimalarial agents. Pursuing this potential application, the team tested a number of well-established drugs which are known to be effective, including quinines – hypothesised to target the parasite’s ability to crystallise haem into haemozoin. Interestingly, the results of this assay found that not only quinines, but also artemisinins and tetracyclines, inhibited the formation of haemozoin-like crystals, suggesting that their mysterious mechanisms may be fundamental to this process as well.

A FIGHT FOR THE FUTURE

Looking ahead, the team plans to apply their prion assay to a range of additional effective and ineffective antimalarial agents, to determine whether the system can reliably screen them to determine their potential use as malaria therapies. By using a spectrum of agents with varying potencies, they hope to get differential results – confirming that their system has the potential to become an effective method for screening drug candidates quickly and efficiently, an asset that would significantly benefit the fight against malaria.

Time for change?

The Spaulding classification was devised by Dr Earle Spaulding of Temple University, Philadelphia, in 1957. Spaulding created this simple three-tier system to indicate what level of treatment a surgical tool would require based on its usage:

1. Contact with intact barriers such as the skin necessitates a low level of disinfection
2. Contact with mucosal membranes necessitates a high level of disinfection
3. Contact with blood barriers and sterile areas of the body necessitates sterilisation

This system has been the mainstay of decontamination practice in surgery for decades – but after almost 60 years, it may be time to update the system. Not only have new threats such as prions been identified in that time, but biocide-resistant microorganisms have now been shown through clinical evidence to be responsible for infection outbreaks following unexpected disinfection failure. To Spaulding’s credit, for the most part his system remains as useful now as it was when he developed it – but the few exceptions are dangerous enough to call for change in the future.