Institution: University College London

Unit of Assessment: 3A - Allied Health Professions, Dentistry, Nursing and Pharmacy: Dentistry

Title of case study: The use of light-activated antimicrobial agents for the treatment of periodontitis, caries and other infectious diseases

1. Summary of the impact

Periodontitis is a significant public health concern affecting more than half of those over 30 years of age. Our research on light-activated antimicrobial agents (LAAAs) has resulted in the development of a novel, non-invasive therapy that quickly and safely treats periodontitis, thereby reducing antibiotic usage. This technology was developed for commercial use through a licence agreement with Ondine Biomedical and their subsidiary company PDT Inc., as a system called Periowave. Periowave is available in Canada, Mexico and South East Asia, has been granted CE marking and FDA approval is currently being sought. To date an estimated 92,000 treatment kits have been sold and 313,000 patients treated. The system has now also been adapted for use in hospitals to eradicate MRSA from the anterior nares thereby preventing post-surgical infections.

2. Underpinning research

Since 1993, a research programme on the use of light-activated antimicrobial agents (LAAAs) to treat periodontitis, caries and other infectious diseases has been undertaken at the UCL Eastman Dental Institute (EDI), led by Professor Michael Wilson. LAAAs are drugs that have no antimicrobial activity in the dark but are activated by light of an appropriate wavelength – they are intended to supplement or replace the use of traditional antibiotics and antiseptics and have the advantage that microbes are very unlikely to become resistant to them as the active moieties are singlet oxygen and free radicals. Furthermore, unlike antibiotics, LAAAs can also inactivate a wide range of bacterial virulence factors e.g. enzymes and lipopolysaccharides.

Initial work in 1995 focused on the potential of the technology to prevent and/or treat oral infections. A variety of potential LAAAs were screened for their ability to kill the wide range of bacteria involved in the aetiology of caries, gingivitis and periodontitis. Potential LAAAs included phenothiaziniums, cyanines, porphyrins, chlorins and phthalocyanines – each of these had to be matched with a laser emitting light with a wavelength corresponding to the absorbance maximum of the LAAA. Target organisms included *Streptococcus mutans*, lactobacilli, *Porphyromonas gingivalis* and *Prevotella intermedia*. The most promising compounds were then investigated for their effectiveness at killing the target organisms under environmental conditions similar to those that exist in the oral cavity. Hence, the organisms were grown as biofilms (which resemble dental plaques) and the effects of the presence of saliva and gingival crevicular fluid on the effectiveness of the LAAAs was studied. Optimum parameters (LAAA concentration, light dose, light energy density) needed for killing under these conditions were established **[1, 2]**.

Following licensing of our patent to Ondine Biopharma in 1998, EDI embarked on a collaborative research programme with the company to develop a technology specifically aimed at treating periodontitis – this was named “Periowave”. Methylene blue was chosen as the LAAA because of its antimicrobial effectiveness and safety profile and this required a laser emitting light with a wavelength of 670 nm. Extensive studies were carried out to determine the optimal and clinically acceptable parameters (concentration of methylene blue, light dose, light energy density) required to kill a range of periodontitis-associated organisms grown as biofilms in the presence of gingival crevicular fluid. Studies involving tissue culture and animals were also carried out to ascertain if the optimal parameters for achieving a bactericidal effect would induce damage to mammalian tissues. We also demonstrated that LAAAs, unlike antibiotics, can inactivate bacterial virulence factors and can down-regulate inflammatory processes. This ground-breaking finding means that LAAAs have a major advantage over antibiotics in the treatment of infectious diseases **[3, 4]**.

Ondine Biopharma used these findings to develop an appropriate LAAA-containing formulation and to design a hand-held light delivery system suitable for use by dentists. Laboratory and studies were undertaken at EDI to confirm the effectiveness of the device for clinical application, and this has been confirmed in further trials in the US, Canada and China **[5]**. Work is now underway to extend the use of LAAAs in other clinical areas, for example for use in hospitals to reduce the environmental load of pathogens thereby helping to prevent hospital-acquired infections **[6]**.

3. References to the research

[1] Wilson M, Dobson J, Sarkar S. Sensitization of periodontopathogenic bacteria to killing by light from a low-power laser. Oral Microbiol Immunol. 1993 Jun;8(3):182-7. http://dx.doi.org/10.1111/j.1399-302X.1993.tb00663.x

[2] Bhatti M, MacRobert A, Meghji S, Henderson B, Wilson M. Effect of dosimetric and physiological factors on the lethal photosensitization of Porphyromonas gingivalis in vitro. Photochem Photobiol. 1997 Jun;65(6):1026-31. http://dx.doi.org/10.1111/j.1751-1097.1997.tb07964.x

[3] Packer S, Wilson M. Inactivation of proteolytic enzymes from *Porphyromonas gingivalis* using light-activated agents. Las Med Sci 2000;15:24-30 http://dx.doi.org/10.1007/s101030050043

[4] Kömerik N, Wilson M, Poole S. The effect of photodynamic action on two virulence factors of gram-negative bacteria. Photochem Photobiol. 2000 Nov;72(5):676-80. http://dx.doi.org/10.1562/0031-8655(2000)072<0676:TEOPAO>2.0.CO;2

[5] Andersen R, Loebel N, Hammond D, Wilson M. Treatment of periodontal disease by photodisinfection compared to scaling and root planing. J Clin Dent. 2007;18(2):34-8. http://www.oraldent.co.uk/dloads/PDD%20Clinical%20Data.pdf

[6] Efficacy of a novel light-activated antimicrobial coating for disinfecting hospital surfaces. Ismail S, Perni S, Pratten J, Parkin I, Wilson M. Infect Control Hosp Epidemiol 2010; 32: 1130–1132. http://dx.doi.org/10.1086/662377

Peer-reviewed funding

Evaluation of photodynamic therapy for the treatment of biofilm-related infections. Ondine Biopharma. 2000-5. £300,000

Light-activated antimicrobials in the prevention/treatment of methicillin-resistant *Staphylococcus aureus* infections (with Nair S and Cookson B). Medical Research Council. 2001-4. £152,904

Control of microbial contamination of surfaces in hospitals using light-activated antimicrobial agents. Charles Wolfson Charitable Trust. 2003-6. £119,950

Improving the delivery of 5-aminolaevulinic acid in photodynamic therapy: synthesis and biological studies of novel peptide prodrugs (with I. Eggleston and A. MacRobert). BBSRC. 2006-9. £440,097

Light-activated antimicrobial agents. (with S. Nair, I. Parkin, Q. Pankhurst, M. Singer). Ondine Biopharma Inc. 2005-8. £456,000

Chemical vapour deposition for the generation of visible light-activated antimicrobial coatings (with Ivan Parkin, Jon Pratten). EPSRC. 2007-10. £505,486

Light-activated antimicrobial polymers for the prevention of catheter-associated infections (with Ivan Parkin, Jon Pratten). BBSRC. 2007-10. £543,680

The use of light-activated antimicrobials to prevent catheter-related infections. (with Parkin I, Pratten J, MacRobert AJ, Mosse S, Kay C). Medical Research Council. 2011-3. £1,100,327

4. Details of the impact

Our research has resulted in a new treatment for periodontitis, Periowave, that provides significant benefits over existing antibiotic (and potentially invasive surgical) treatments. The technology we developed was licensed to Ondine Biomedical in 1998 for periodontal treatment. Over the following eight years, the company undertook a number of collaborative projects with the EDI, including sponsoring a clinical trial. UCL has received more than £1m in research investment from Ondine to develop and evaluate this technology. Licensing income received by UCL from the commercialisation of the patents is approximately £0.4m. Further income is also anticipated as a consequence of the technology being licensed to Ondine for the treatment of caries **[a]**.

Through this collaboration, Ondine developed the Periowave system. This consists of a hand-held light-emitting device and a syringe containing the LAAA. A solution of the LAAA is applied to the disease site by a dentist, who then irradiates it with light from the athermal laser for 60 seconds. The treatment takes only a few minutes overall and is painless and stress-free, compared to a long course of antibiotics (up to seven days) or repeated scaling of teeth. This reduces concerns of limited patient compliance and the risk of adverse side effects of antibiotics and/or conventional periodontal treatment **[b]**.

Periowave has been available commercially in Canada since 2006, and has since been licensed in Japan, Hong Kong, Singapore and Mexico. The system is currently under review by the Korea Food & Drug Administration. It has also been given CE marking by the EC. Six core staff are employed by Periowave Dental Technologies in sales and marketing, along with a network of distributors in various countries. To date approximately 92,000 Periowave treatment kits have been bought and used on an estimated 313,000 patients. Aside from trial data indicating clinical benefit, clinicians and patients have attested to its benefits. Comments include:

> "*Periowave photodisinfection is a rapid, painless approach to removal of the harmful bacteria*."
>
> "*Periowave is a painless and stress- free way to control the health of my gums*."
>
> "*My first Periowave treatment was just great. It was completely painless, and it was interesting to hear scientifically what was going on. There was absolutely no discomfort. If somebody gave me a choice between Periowave and an antibiotic, I would take Periowave™ in a flash. No antibiotics!"* **[c]**.

The principles of LAAAs and Periowave have wider impacts on public health than periodontitis. One of the main problems confronting medicine in the 21st century is the increasing prevalence of antibiotic-resistant bacteria. This, combined with a shortage of new antibiotics under development, means that the ability to treat infectious diseases is diminishing. A further impact of our work on LAAAs has thus been their adaption for the prevention and/or treatment of other infections. Based directly upon the principles of Periowave (see company website **[d]**) Ondine have now developed a system (MRSAid^{TM}) for eradication of methicillin-resistant *Staphylococcus aureus* from the nose **[e]**. A recent study conducted by Vancouver General Hospital of 5,000 patients revealed that use of this nasal photodisinfection system reduced post-surgical infection by almost 40 per cent and saved the hospital $1.3m in costs relating to post-surgical infections and re-admissions. The hospital was awarded a prize for innovation by the International Consortium for Prevention and Infection Control (ICPIC) in Geneva for this work, and have now adopted the system into routine clinical practice **[f]**.

Further applications of the principles of LAAAs are presently being investigated for: (i) preventing catheter-associated infections (by fabricating catheters from LAAA-containing polymers), (ii) reducing the microbial load on hospital surfaces (by coating surfaces with LAAA-containing polymers) and (iii) preventing wound infections (using dressings containing LAAAs).

5. Sources to corroborate the impact

[a] Details of licensing and commercial benefits to Ondine (including sales data provided by the company) can be verified by UCL Business. Contact details provided.

[b] http://www.periowave.com/what-is-periowave/how-periowave-works.aspx

[c] http://www.periowave.com/testimonials.aspx

[d] http://www.mrsaid.com/technology/photodisinfection/

[e] http://www.mrsaid.ca/

[f] http://www.huffingtonpost.ca/2013/07/04/vgh-wins-prize-for-light-_n_3547544.html