Antimicrobial Photodisinfection Therapy: Essential Technology for Infection Control

Nicolas G. Loebel, PhD[1]
Carolyn M. Cross, M.S.C., MBA, CFA[1]
David M. Meller, PhD[1]
Jason Hickok, RN, MBA[2]
Roger Andersen, MD, MPH, RAC[2]

[1] Ondine Research Laboratories, Inc., Bothell, WA
[2] Ondine Biomedical, Inc., Vancouver BC

Abstract

Antimicrobial photodynamic therapy (APDT, photodisinfection) is a treatment modality that involves the administration of a light-sensitive compound, known as a photosensitizer (PS), followed by light irradiation at a specific wavelength that electrodynamically pumps the PS into an excited and cytotoxic state. APDT is minimally invasive and already used clinically to treat a wide range of microbial infections. APDT has been shown to eradicate pathogenic microorganisms including Gram-positive and Gram-negative bacteria, viruses, protozoa, and fungi and, unlike traditional antibiotics, does not induce resistance following repeated exposures to the therapy (Pedigo et al, 2009; Tavares et al, 2010; Costa et al, 2011; Cabiscol et al, 2000; Lauro et al, 2002; Jori & Coppellotti, 2007; Cassidy et al, 2010; Giuliani et al, 2010; Martins et al, 2018; Al-Mutairi et al, 2018).

For these reasons, we believe APDT will evolve into an essential tool for infection control and become a vital part of the solution to the global antimicrobial resistance (AMR) crisis. This report will explain the fundamental principles of APDT and illustrate the ways in which APDT can be used to directly decolonize human epithelial surfaces, reduce the risk of hospital-acquired infections, improve viral prophylaxis, and improve patient outcomes.

History of Antimicrobial Photodisinfection Therapy (APDT)

The first accounts of using light for the treatment of physical illness appeared in Egyptian, Indian, and Chinese writing more than 30 centuries ago (Deniell & Jill, 1991). The first detailed evidence for the antimicrobial activity of certain photosensitizers combined with light was documented in Munich by Oscar Raab, who noticed that the toxic effect of acridine dye on paramecia was greater on sunny days (Raab, 1900). Overshadowed by the development of antibiotics, another 80 years would pass before seminal work in APDT began to appear in the literature (Bertoloni et al, 1985; Malik et al, 1990). The discovery and subsequent development of hematoporphyrin in 1841 (Diels & Arissian, 2011) led to development of first-generation sensitizers such as Photofrin™ for oncotherapy, and ultimately to second and third-generation porphyrins, porphyrin derivatives, and benzoporphyrins that have improved the therapeutic window in multiple indications (Abdel-Kader, 2016).

Research in APDT is being actively pursued in a number of countries including the USA, Canada, Brazil, China, Germany, France, Austria, Russia and Italy among others, with more than 700 papers published over the last 5 years. A large number of presentations are regularly made on this topic at international conferences including those organized by the American Society for Microbiology, Society for General Microbiology, International Photodynamic Association, International Association for Dental Research, British Society for the Study of Infection and the International Congress of Chemotherapy. APDT research has been supported by several well-known grant-awarding bodies including MRC, BBSRC, EPSRC, the Wellcome Trust, NIH, Wolfson Foundation, Leverhulme Trust and the Charles Wolfson Charitable Trust.

Fundamentals of Antimicrobial Photodisinfection Therapy (APDT)

The basic electrodynamics of photosensitized reactions (Figure 1) involves the absorption of photons by the ground-state PS, causing electrons to be pumped to an excited singlet state. The excited-state PS can then engage in several different reactions that are destructive to microbes, such as electron transfer reactions and the formation of radicals, including the potent hydroxyl radical (Type I, redox reactions). A second activation pathway (Type II, peroxidation reactions) also exists, by which energy transfers via forbidden transition from the PS singlet state to an intermediate triplet state, a feature of only certain dyes like methylene blue (MB). Because surrounding oxygen molecules are one of the few biological molecules that exist in a naturally occurring triplet ground-state, the oxygen can absorb, or “quench” the PS triplet state energy in a non-radiative exchange process. The oxygen molecules then pump to their own singlet state forming highly reactive singlet oxygen.

Singlet oxygen is one of most powerful oxidative species known, and when generated in close proximity to bacterial membranes, rapidly results in membrane perforation, protein cross-linking, and consequent cell death. It has been demonstrated that singlet oxygen can exert potent cytotoxic effects on microbes without being internalized (Dahl et al, 1987). The singlet oxygen lifetime in biological media is short – less than 0.05 µs – due to quenching by water, and therefore the mean diffusion distance of the molecule is less than 0.02 µm before returning to ground state (Moan & Berg, 1991). This short active lifetime localizes the kill to the immediate vicinity of the activated molecule.

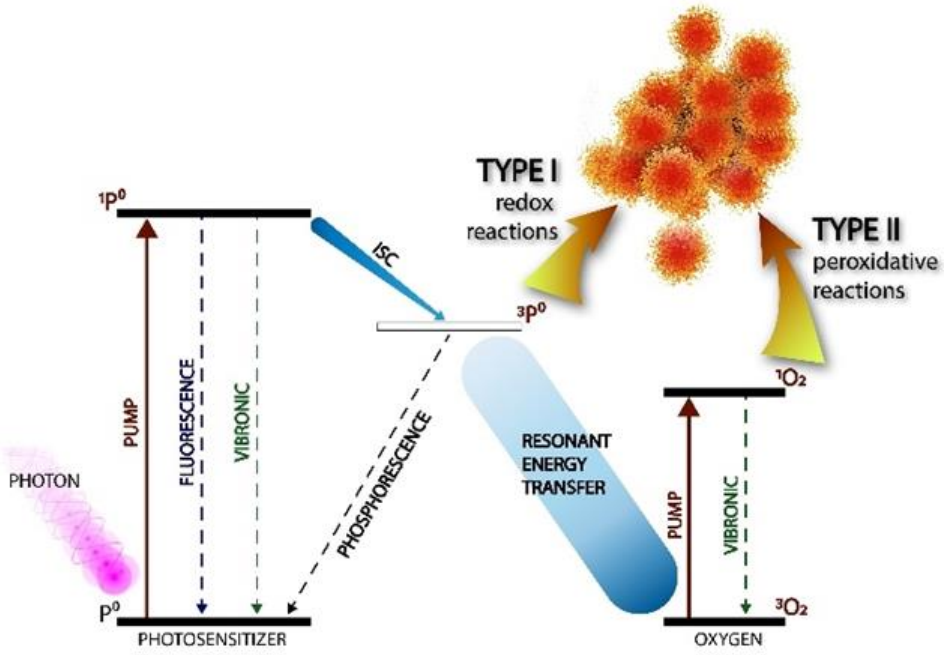

Figure 1: The electrodynamics of photodisinfection therapy. Source: Ondine Biomedical, Inc.

The most effective antimicrobial photosensitizers are positively charged (cationic) which permits them to preferentially bind to negatively-charged (anionic) microbial cell membranes. These cationic PS's bind poorly to zwitterionic (net neutral) human cells which are therefore protected from damage (Loebel et al, 2016). The destructive reactions caused by singlet oxygen are relatively selective for the organisms to which the PS adheres. The destructive effect is further amplified by the PDT "bystander" effect (Alexandre et al, 2007), a cooperative inactivation process between cells in a given microcolony, most likely mediated by microbicidal photoproducts or the transfer of lysosomal enzymes from nearby cells. Broad-spectrum activity against viruses is rapid and potent; here the active cidal mechanism involves diffusion-limited penetration across the envelope or capsid, followed by covalent cross-linking and destruction of side chains and backbone sites at multiple positions on viral proteins; downstream chain reactions causing aggregation, altered conformation and directly oxidized guanosine residues; and cross-linking, scission and irreversible oxidation of DNA and RNA with high second-order rate constant.

Clinical Use of APDT

The treatment of oral infections by APDT has been extensively studied for many years and has become a well-established therapeutic option in dentistry. Several recent reviews have demonstrated efficacy in treatment of periodontitis (Joseph et al, 2017; Azaripour et al, 2018; Meimandi et al, 2017), caries (Cieplik et al, 2017), endodontic infections (Mohammadi et al, 2017), and peri-implantitis (Ghanem et al, 2016). APDT has also been found to be effective in the treatment of a variety of other infectious diseases caused by bacteria, fungi and

protozoa including brain abscesses (Lombard et al, 1985), acne (Hongcharu et al, 2000; Wiegell et al, 2006; Tuchin et al, 2003; Seo et al, 2016; Tao et al, 2015; Serini et al, 2018), folliculitis (Lee et al, 2010), *H. pylori* (Wilder-Smith et al, 2002), diabetic and skin ulcers (Carrinho et al, 2018; Aspiroz et al, 2017; Lei et al, 2015; Morley et al, 2013; Mannucci et al, 2014), interdigital mycosis (Calzavara-Pinton et al, 2004), keratitis (Amescua et al, 2017), onychomycosis (Morgado et al, 2017), candidiasis (Scwingel et al, 2012), cutaneous leishmaniasis (Asilian & Davami, 2006), oral paracoccidiodomycosis (Dos Santos et al, 2017), and refractory chronic rhinosinusitis (Desrosiers et al, 2013).

Treatment of viral infections with APDT also has a long clinical history. In the 1970s, a series of clinical studies demonstrated efficacy in treating infections due to the herpes simplex virus (Wainwright, 2003; Kharkwal et al, 2011). The most widely investigated viral infections have been those associated with human papilloma virus (HPV), a group of more than 150 types of virus that affect the skin and mucous membranes. In addition to causing diseases such as respiratory papillomatosis, genital warts, and skin warts (Ohtsuki et al, 2009; Hu et al, 2018), certain HPV types are carcinogenic and can result in cervical, vulvar, penile, and anal intraepithelial neoplasia (Grce & Mravak-Stipetić, 2014; Tommasino, 2014). APDT using a variety of photosensitizers has been shown to be successful in the treatment of a range of HPV-associated infections including respiratory papillomatosis (Shikowitz et al, 1998; Shikowitz et al, 2005), plantar warts (Schroeter et al, 2005), condylomata acuminate (Wang et al, 2007; Shi et al, 2013), cervical intraepithelial neoplasia (Soergel et al, 2010; Hillemanns et al, 2014), and penile intraepithelial neoplasia (Paoli et al, 2006).

APDT Is More Than a Skin-Surface Microbicide

The damage inflicted by pathogenic microbes on their host, as well as their ability to avoid host defense systems, is mediated by a variety of virulence factors such as exotoxins, endotoxins, capsules, adhesins, invasins, and proteases (Casadevall & Pirofski, 2001). While antibiotics can kill microbes and thereby prevent *further* production of host-damaging virulence factors, few have any effect on *pre-existing* virulence factors or those which are released *during* the cidal process. These factors can continue to produce damaging effects even after the offending microbes have been killed (Lepper et al, 2002).

In contrast to most antibiotics, light-activated PS's are generally able to neutralize microbial virulence factors or reduce their effectiveness or decrease their expression. The ability to modify the biological activities of lipopolysaccharides (LPS's, endotoxin) is of particular interest because LPS's are potent immuno-modulators that can induce secretion of several pro-inflammatory cytokines by host cells (Packer & Wilson, 2000; Pourhajibagher et al, 2018; Pourhajibagher et al, 2017; Shrestha et al, 2015; Giannelli et al, 2017; Tubby et al, 2009; Tseng et al, 2015; Bartolomeu et al, 2016; Calvino-Fernández et al, 2013; Pourhajibagher et al, 2016; Kato et al, 2013; Pereira et al, 2015; Cavaillon, 2018). Activated photosensitizers have been shown to be potently effective at reducing the activity of LPS's, proteases, and a variety of exotoxins. The bimodal ability to eliminate microbes responsible for an infection and to simultaneously inactivate or decrease the expression of many of the molecules responsible for host tissue destruction constitutes an important advantage over most antibiotics, as this combines both antimicrobial and anti-inflammatory approaches into a single treatment.

APDT is Safe for Human Use

Numerous pre-clinical and clinical studies have demonstrated that APDT is safe for use in treating human tissue colonization and infection. For all the energetic reactivity of the ROS produced, several factors including the extremely short radical lifetime and small active distance scale, selectivity for anionic microbes, and the inherent resistance to oxidative stress of mammalian cells result in minimal damage to neighboring host tissues (Moan & Berg, 1991; Soukos et al, 1996; Millson et al, 1997; Soergel et al, 2010; Wang et al, 2007). Soukos *et al*. (1996) found that the viability of oral fibroblasts and keratinocytes was unaffected by the PS Toluidine Blue O (TBO) and associated light dose needed to kill *Streptococcus sanguinis*.

A number of photosensitizers, including MB and TBO, have been shown to have no deleterious effects on the gastric mucosa of rats at bactericidal concentrations and light doses (Millson et al, 1997). In a clinical study aimed at detecting tissue damage associated with APDT, two cycles of APDT employing aminolevulinic acid esters as the PS were found to exert no damage to the cervix of the test patients (Soergel et al, 2010). The absence of tissue damage following the successful treatment of urethral condylomata acuminata (due to HPV) by APDT using aminolevulinic acid has also been reported (Wang et al, 2007).

After clinical studies in several thousand patients (Bryce et al, 2014), Ondine has commercially deployed APDT at tertiary care facilities in Canada over the past 5 years, treating the anterior nares of > 50,000 patients in order to eliminate microbes causing surgical-site infections (the MRSAid™ and Steriwave-ND™ system). Surgical-site infection rates at one of the largest acute care hospitals in Canada have fallen >50% since deployment of the system, with <0.1% adverse event rate and no serious adverse events whatsoever. Deployments in the oral cavity, the nasopharynx, presurgical skin surface preps and in mechanically ventilated patients have demonstrated that APDT is safe when used on tissues ranging from fully keratinized to stratified squamous non-keratinized and pseudostratified ciliated columnar epithelia. The system is Health Canada approved for reduction of potentially pathogenic microorganisms in the anterior nares, and has gained a CE Mark for the same indication. The system is not yet approved for sale in the US, but has been awarded Qualified Infectious Disease Product status as well as Fast Track approval, and is available in the US only under the terms of Ondine's Expanded Access (Compassionate Use) program.

APDT Does Not Induce Microbial Resistance

The generation of ROS in neutrophils, monocytes, and eosinophils is one of the primary means by which the human immune system combats infecting microbes. These pathogens have evolved protection strategies against oxidative stress by up-regulating antioxidant enzymes when exposed to ROS (Cabiscol et al, 2000), suggesting one method by which microbes could develop increased resistance to APDT. However, these biochemical responses are minute compared to the overwhelming oxidative stress placed on the microbe by APDT.

Numerous studies involving repeated exposure of microbes to APDT and then re-testing the susceptibility of survivors have provided no evidence that resistance development occurs (Pedigo et al, 2009; Tavares et al, 2010; Costa et al, 2011; Cabiscol et al, 2000; Lauro et al, 2002; Jori & Coppellotti, 2007; Cassidy, C.M., Donnelly, R.F. et al, 2010; Giuliani et al, 2010; Martins et al, 2018; Al-Mutairi et al, 2018). In particular, the speed of kill and the external peroxidative mechanism of ROS appear to limit the ability to develop resistance to APDT (Maisch, 2015), in part because the genome is never exposed to the cidal mechanism.

In one example utilizing the PS Methylene Blue against MRSA, re-culturing experiments carried out over several consecutive years demonstrated no decrease in susceptibility to APDT (Figure 2), whereas high-level resistance to oxacillin was established after less than a dozen cycles (Pedigo et al, 2009). This finding has been duplicated in studies with more complex sensitizers (Tavares et al, 2010) and also in viruses, where no increase in resistance was demonstrated after numerous cycles of APDT (Costa et al, 2011).

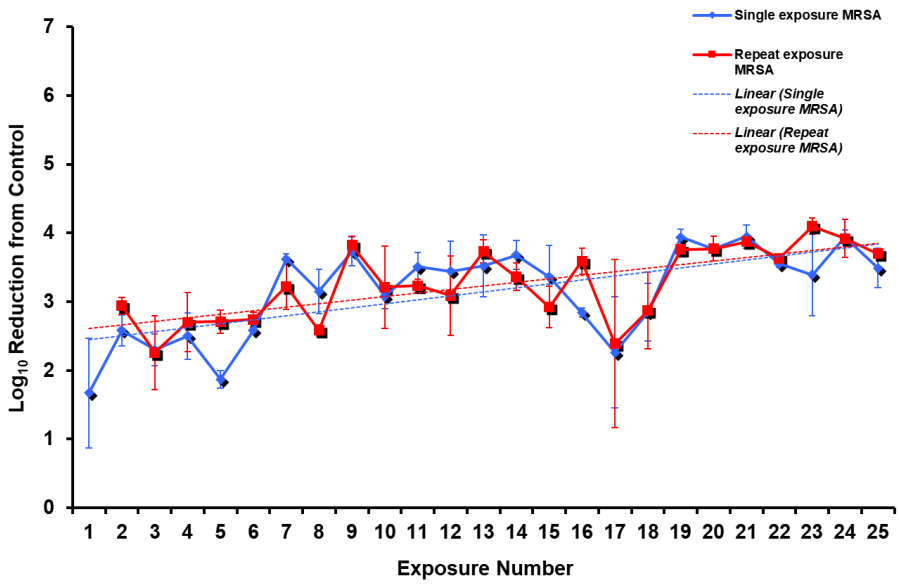

Figure 2: Repeated applications of APDT to MRSA utilizing Methylene Blue does not promote microbial resistance (Pedigo et al, 2009).

Antiviral Applications of APDT

Methylene-blue mediated photodisinfection has been used for decades to inactivate viral (and other) pathogens in blood products in Europe (Theraflex®, Macopharma, Lille, France). As early as 2011, our group investigated the possibility of inhibiting mother-to-child transmission of HIV, using a phage surrogate, and found that we could inactivate 100% of the virions as expected (Bhagwandin et al, 2011).

The ongoing transmission and geographic expansion of SARS-CoV-2 in human populations has spurred Ondine to consider how best to further deploy APDT as an antiviral application targeting the anterior nares staging site, as well as the tracheobronchial ecological niche of this virus within the human host. In the last 20 years, three coronaviruses have crossed the species barrier causing disease in humans - SARS-CoV in 2002, MERS-CoV in 2012 and SARS-CoV-2 in 2019. HCoV case fatality ratios range from 2 – 20% with disproportionate impact on immunocompromised and elderly populations. Infection is known to occur from the luminal side of the airway, and progeny viruses are released from the same side facilitating spread through coughing and sneezing. The virus targets columnar and pseudostratified tracheobronchial cells residing on the basement membrane, employing multiple different strategies to evade the innate immune response during the first phase of infection. Once epithelial infection progresses, double-membrane vesicle formation occurs in a similar fashion to other positive-strand RNA virus pathogenesis, followed by autophagy and release of the progeny payload. No general therapy exists to treat coronavirus-induced disease in humans; treatment with steroids, interferon and antiviral drugs such as Ribavirin is not especially effective. Limited data suggests that anti-HIV protease inhibitors, nucleoside analogs and chloroquine may be of some use, but resistance mechanisms such as mutated nsp-12 and -14 polymerases and MRP-1 have already been identified. No commercial vaccine is currently available.

Recent research (Zou et al, 2020) has shown high nasal titer of SARS-CoV-2 is present for the first 12 – 14 days of colonization, prior to widespread pulmonary dissemination. An early, simple and relatively inexpensive intervention opportunity may therefore exist to reduce viral titer in the anterior nares by

deployment of APDT. Target populations include patient-facing healthcare workers; port staff; military and inmate populations; and of course, patients themselves, whether symptomatic or otherwise. Treatment could reasonably be expected to delay onset of COVID-19, reduce severity of symptoms, reduce human-to-human transmission rates, permit more time for innate immunity responses to develop and, because of the broad spectrum of APDT, reduce opportunistic infection rates from a variety of viral, bacterial and fungal pathogens.

A second, pulmonary deployment route also may exist, where a nebulized photosensitizer may be inhaled followed by intrapulmonary light activation. Respiratory drugs that are specifically designed for inhalational deployment offer significant advantages over systemic administration routes, including direct delivery to the disease site, rapid onset of action, high pulmonary efficacy, increased half-life and reduced risk of systemic side effects. We propose to use this inhalational route to place the nebulized, photodynamically-activated drug (aqueous methylene blue USP 0.01% compounded with various excipients and adjuvants) directly to the tracheobronchial epithelium in order to eliminate all superficial viral, bacterial and fungal microorganisms including HCoV's. In other Health Canada-approved otolaryngological applications including decolonization of the anterior nares and paranasal sinuses, this photodynamic disinfection approach has been proven both safe and effective in tens of thousands of patients presenting to tertiary care centers over the past five years (Bryce et al, 2014). Efficacy is maintained in biofilm and in the presence of human serum exudates. The low-molecular weight drug is capable of penetrating the epithelium to within a few cell layers, and therefore activity against superficial intracellular pathogens is expected. This matches the biodistribution of HCoV's in the thin, pseudostratified, tracheobronchiolar environment. Light distribution in lung tissue at the methylene blue-required wavelength of 670 nm is excellent (Cassidy, C.M., Tunney, M.M. et al, 2010).

We have previously deployed APDT within endotracheal tubes of mechanically ventilated patients and understand how to deliver transbronchial therapy. Other groups (Geralde et al, 2017) have demonstrated reduction of pneumonia in animal models using similar techniques, with transcutaneous light sources that are easy to apply. Our supply chains are in place for both drug API, drug product, and devices to deliver drug and light. The company maintains an audited quality management system under ISO13485:2016, MDSAP and the new EU-MDR and is capable of responding to product demand should trials prove successful. If so, we would expect this well-understood, proven drug-device combination (already the subject of compassionate use exemption in the US), to require a far shorter and far less expensive development schedule than that required by novel vaccines or systemic antivirals.

Pharmacoeconomic Impact

With growing demands for cost containment across all sectors of the healthcare system, there is an increasing emphasis being placed on the importance of cost savings in addition to superior patient outcomes. APDT has been shown to demonstrate significant pharmacoeconomic benefit in clinical settings, especially when deployed in lengthy procedures coupled with high propensity for surgical site infection such as spine surgery (Banaszek et al, 2019). Recent publications from the CDC (2019) and the Council of Canadian Academies (2019) detail the growing economic impact resulting from increasing antimicrobial resistance to global economies, confirming the enormously expensive predictions made in the O'Neill Report (O'Neill, 2016). By 2050, 10 million people are predicted to die annually from resistant infections, more than the combined predicted deaths from cancer, diabetes and cholera combined. By this time, antimicrobial resistance is projected to have cost US$100 trillion, primarily from a 2 - 3.5% reduction in Global Gross Domestic Product. We expect cost-effective infection-prevention therapies, such as antimicrobial Photodynamic Therapy, that do not promote antimicrobial resistance and reduce reliance on existing antibiotics, to become critically important components of the clinical armamentarium into the 21st Century and beyond.

Conclusion

Photodisinfection Therapy is based on well-known electrodynamic principles and has become an established therapeutic option for a wide range of medical conditions from microbial infections to cancer. Ondine Biomedical has successfully pioneered several applications of antimicrobial PDT into the clinic, including nasal decolonization for eradication of pathogenic microflora associated with nosocomial infection; treatment of chronic periodontal disease (often refractory to local and systemic antibiotics as well as metalloprotease inhibitors); treatment of chronic sinus disease refractory to surgery, systemic antibiotics and/or steroids; and eradication of biofilms in ventilator tubes which cause ventilator-associated pneumonia. Other pipeline products include treatment of burns and wounds (both to eradicate pathogens, and to separately enhance wound healing); treatment of long-term catheter ports, locks and hubs such as those involved in dialysis; treatment of antibiotic-resistant otitis externa; and treatment of viral conditions including peri-oral herpes virus lesions and oral lichen planus, neither of which are susceptible to antibiotic prophylaxis.

The company is now turning its attention to antiviral applications in the pulmonary system, driven by the CDC declaration of the US public health emergency regarding SARS-CoV-2. Recent research (Zou et al, 2020) has shown high nasal titer of SARS-CoV-2 is present for the first 12 – 14 days of colonization, prior to widespread pulmonary dissemination. **An early, simple and relatively inexpensive intervention opportunity may therefore exist to reduce viral titer in the anterior nares by deployment of APDT.** Target populations include patient-facing healthcare workers; port staff; military and inmate populations; and of course, patients themselves, whether symptomatic or otherwise. Treatment could reasonably be expected to delay onset of COVID-19, reduce severity of symptoms, reduce human-to-human transmission rates, permit more time for innate immunity responses to develop and, because of the broad spectrum of APDT, reduce opportunistic infection rates from a variety of viral, bacterial and fungal pathogens.

A second, pulmonary deployment route also may exist, where a nebulized photosensitizer may be inhaled followed by intrapulmonary light activation targeting all superficial viral, bacterial and fungal microorganisms including HCoV's.

Antimicrobial resistance (AMR) brought about by the misuse and overuse of antibiotics and other antimicrobials represents one of the world's most pressing public health problems and has been listed by the World Health Organization as one of mankind's top health threats. After demonstrating the therapeutic and pharmacoeconomic benefits of antimicrobial PDT in major Canadian tertiary care centers over many years, we believe that broader dissemination of the technology is both prudent and warranted. Antimicrobial PDT holds significant potential to combat the current global antimicrobial resistance crisis due to its demonstrated clinical efficacy and lack of resistance formation, while promoting stewardship of existing antibiotics, antivirals and antiseptic agents that are increasingly challenging and expensive to develop.

About Ondine Biomedical

Ondine Biomedical Inc. (Ondine) is a Canadian company headquartered in Vancouver, BC, Canada with Research & Development facilities in Bothell, Washington, USA and a commercial team located in Chicago, Il. Founded in 1997, Ondine is dedicated to the development of non-antibiotic, anti-infective photodisinfection therapies for a broad spectrum of bacterial, viral, and fungal infections.

Ondine is the recognized global leader in APDT technology and has won numerous awards for its work advancing patient safety alongside better surgical outcomes. Ondine has developed products targeting the top three nosocomial vectors – intra-nares decolonization to reduce surgical site infections (SSIs), in-situ disinfection of endotracheal tubes to reduce the incidence of ventilator-associated pneumonia (VAP), and disinfection of catheter hubs, locks and ports to reduce the incidence of catheter-associated infections (CAIs). The Company has also developed balloon-catheter based therapies for chronic infections such as Chronic Refractory Sinusitis (CRS). Most recently the company introduced the SurgENT™ sinus irrigation catheter in the United States and Canada intended for hydrodynamic debridement of the sinus. Next-generation products including pulmonary antiviral applications, mobile point-of-care photodynamic wound dressings and photodynamic treatment of burn wounds prior to grafting are under development.

References

Abdel-Kader, M. H. (2016). Antimicrobial Photodynamic Therapy: A Decade Of Development and Clinical Study. In *Photodynamic Medicine, From Bench to Clinic*. Ed. Kostron, H. and Hasan T., Royal Society of Chemistry, 1-21.

Alexandre, J., Hu, Y., Lu, W., Pelicano, H., & Huang, P. (2007). Novel action of paclitaxel against cancer cells: bystander effect mediated by reactive oxygen species. *Cancer Research*, 67:3512–3517.

Allison, R. R., Sibata, C., & Gay, H. (2009). PDT for cancers of the head and neck. *Photodiagnosis and Photodynamic Therapy*, 6(1), 1-2.

Al-Mutairi, R., Tovmasyan, A., Batinic-Haberle, I., & Benov, L. (2018). Sublethal photodynamic treatment does not lead to development of resistance. *Frontiers in Microbiology*, Jul 31;9:1699.

Amescua. G., Arboleda, A., Nikpoor, N., Durkee, H., Relhan, N., Aguilar, M. C., Flynn, H. W., Miller, D., Parel, J. M. (2017). Rose bengal photodynamic antimicrobial therapy: A novel treatment for resistant fusarium keratitis. *Cornea*, Sep;36(9):1141-1144.

Asilian, A., & Davami, M. (2006). Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. *Clinical and Experimental Dermatology*, Sep,31(5):634-7.

Aspiroz, C., Sevil, M., Toyas, C., & Gilaberte, Y. (2017). Photodynamic Therapy With Methylene Blue for Skin Ulcers Infected With *Pseudomonas aeruginosa* and Fusarium spp. *Actas Dermo-Sifiliográficas*, Jul-Aug;108(6):e45-e48.

Azaripour, A., Dittrich, S., Van Noorden, C. J. F., Willershausen, B. (2018). Efficacy of photodynamic therapy as adjunct treatment of chronic periodontitis: a systematic review and meta-analysis. *Lasers in Medical Science*, Feb;33(2):407-423.

Bader, M. J., Stepp, H., Beyer, W., Pongratz, T., Sroka, R., Kriegmair, M., Zaak, D., Welschof, M., Tilki, D., Stief, C. G., & Waidelich, R. (2013). Photodynamic therapy of bladder cancer – a phase I study using hexaminolevulinate (HAL). *Urologic Oncology*, Oct;31(7):1178-83.

Banaszek, D., Inglis, T., Ailon, T., Charest-Morin, R., Dea, N., Fisher, C.G., Kwon, B.K., Paquette, S.J., Street, J., (2019), The efficacy and cost-effectiveness of photodynamic therapy in prevention of surgical site infection, *The Spine Journal*, September, (19) : 9, S138

Bartolomeu, M., Rocha, S., Cunha, Â., Neves, M. G., Faustino, M. A., & Almeida, A. (2016). Effect of photodynamic therapy on the virulence factors of *Staphylococcus aureus*. *Frontiers in Microbiology*, Mar 7;7:267.

Berthiaume, F., Reiken, S. R., Toner, M., Tompkins, R. G., & Yarmush, M.L. (1994). Antibody-targeted photolysis of bacteria in vivo. *Biotechnology (N Y)*, Jul;12(7):703-6.

Bertoloni, G., Viel, A., Grossato, A., & Jori, G. (1985). The photosensitizing activity of haematoporphyrin on mollicutes. *Journal of General Microbiology*, Sep;131(9):2217-23.

Bhagwandin, B., Loebel, N., Baskaran, S., Thomas, J., Andersen, R. (2011). Use of antimicrobial photodynamic therapy for prevention of HIV transmission from Mother to Child: a novel approach. IAS 2011, A-361-0132-01094.

Bhatti, M., MacRobert, A., Henderson., B, Shepherd, P., Cridland, J., & Wilson, M. (2000). Antibody-targeted lethal photosensitization of *Porphyromonas gingivalis*. *Antimicrobial Agents in Chemotherapy*, Oct;44(10):2615-8.

Bryce, E., Wong, T., Forrester, L., Masri, B., Jeske, D., Barr, K., Errico, S., Roscoe, D. (2014), Nasal photodisinfection and chlorhexidine wipes decrease surgical site infections: a historical control study and propensity analysis. *Journal of Hospital Infection* 88 (2), 88-95.

Cabiscol, E., Tamarit, J., & Ros, J. (2000). Oxidative stress in bacteria and protein damage by reactive oxygen species. *International Microbiology*, Mar;3(1):3-8.

Calvino-Fernández, M., García-Fresnadillo, D., Benito-Martínez, S., McNicholl, A. G., Calvet, X., Gisbert, J. P., & Parra-Cid, T. (2013). *Helicobacter pylori* inactivation and virulence gene damage using a supported sensitiser for photodynamic therapy. *European Journal of Medicinal Chemistry*, Oct;68:284-90.

Calzavara-Pinton, P. G., Venturini, M., Capezzera, R., Sala, R., &Zane, C. (2004). Photodynamic therapy of interdigital mycoses of the feet with topical application of 5-aminolevulinic acid. *Photodermatology, Photoimmunology & Photomedicine*, Jun;20(3):144-7.

Carrinho, P. M., Andreani, D. I. K., Morete, V. A., Iseri, S., Navarro, R. S., Villaverde, A. B. (2018). A study on the macroscopic morphometry of the lesion area on diabetic ulcers in humans treated with photodynamic therapy using two methods of measurement. *Photomedicine and Laser Surgery*, Jan;36(1):44-50.

Casadevall, A., & Pirofski, L. (2001). Host-pathogen interactions: the attributes of virulence. *Journal of Infectious Diseases*, Aug 1;184(3):337-44.

Cassidy, C. M., Donnelly, R. F., & Tunney, M. M. (2010). Effect of sub-lethal challenge with Photodynamic Antimicrobial Chemotherapy (PACT) on the antibiotic susceptibility of clinical bacterial isolates. *Journal of Photochemistry and Photobiology B: Biology*, Apr 2;99(1):62-6.

Cassidy, C.M., Tunney, M.M., Mageeb, N.D., Elborn, J.S., Bell, S., Singha, T.R.R., Donnelly, R.F., (2010), Drug and light delivery strategies for photodynamic antimicrobial chemotherapy (PACT) of pulmonary pathogens: A pilot study, *Photodiagnosis and Photodynamic Therapy* (2011) 8, 1—6.

Cavaillon, J. M. (2018). Exotoxins and endotoxins: Inducers of inflammatory cytokines. *Toxicon*, Jul;149:45-53.

CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

Cieplik, F., Buchalla, W., Hellwig, E., Al-Ahmad, A., Hiller, K. A., Maisch, T., & Karygianni, L. (2017). Antimicrobial photodynamic therapy as an adjunct for treatment of deep carious lesions-A systematic review. *Photodiagnosis and Photodynamic Therapy*, Jun;18:54-62.

Costa, L., Tomé, J. P., Neves, M. G., Tomé, A. C., Cavaleiro, J. A., Faustino, M. A., Cunha, Â., Gomes, N. C., & Almeida, A. (2011). Evaluation of resistance development and viability recovery by a non-enveloped virus after repeated cycles of APDT. *Antiviral Research*, Sep;91(3):278-82.

Council of Canadian Academies, 2019. When Antibiotics Fail. Ottawa (ON): *The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada*, Council of Canadian Academies.

Dahl, T. A., Midden, W. R., & Hartman, P. E. (1987). Pure singlet oxygen cytotoxicity for bacteria. *Photochemistry and Photobiology*, Sep;46(3):345-52.

de Oliveira, R. R., Schwartz-Filhom H. O., Novaes, A. B. Jr, & Taba, M. Jr. (2007). Antimicrobial photodynamic therapy in the non-surgical treatment of aggressive periodontitis: a preliminary randomized controlled clinical study. *Journal of Periodontology*, Jun;78(6):965-73.

Daniell, M. D., & Hill, J. S. (1991). A history of photodynamic therapy. *ANZ Journal of Surgery*, May;61(5):340-8.

Desrosiers, M. Y. et al. (2013) Sinuwave photodisinfection for the treatment of refractory chronic rhinosinusitis: a case series. Poster presented at: *American Rhinologic Society at American Academy of Otolaryngology 59th Annual Meeting*, Vancouver BC, 2013.

Diels, J. & Arissian, L. (2011). Laser, The Power and Precision of Light, John Wiley & Sons, Inc., New Jersey, USA, 2011, vol. 1, *The Lasers in Medicine*, p. 93.

Dos Santos, L. F. M., Melo, N. B., de Carli, M. L., Mendes, A. C. S. C., Bani, G. M. A. C, Verinaud, L. M., Burger, E., de Oliveira, I., Moraes, G., Pereira, A. A. C., Brigagão, M. R. L., Hanemann, J. A. C., & Sperandio, F. F. (2017). Photodynamic inactivation of *Paracoccidioides brasiliensis* helps the outcome of oral paracoccidiodomycosis. *Lasers in Medical Science*, May;32(4):921-930.

Eljamel, S. (2010). Photodynamic applications in brain tumors: a comprehensive review of the literature. *Photodiagnosis and Photodynamic Therapy*, Jun;7(2):76-85.

Embleton, M. L., Nair, S. P., Heywood, W., Menon, D. C., Cookson, B. D., & Wilson, M. (2005). Development of a novel targeting system for lethal photosensitization of antibiotic-resistant strains of *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, Sep;49(9):3690-6.

Furukawa, K., Kato, Y., Usuda, J., & Kato, H. (2016). Antimicrobial Photodynamic Therapy: A Decade of Development and Clinical Study. In *Photodynamic Medicine, From Bench to Clinic*, Ed. Kostron, H., & Hasan, T., Royal Society of Chemistry, pp. 405-420.

Geralde, M.C., Ilaiali S.L, Inada, N.M., Salina, A.C.G., Medeiros, A.I., Kuebler, W.M., Kurachi, C., Bagnato, V.S., Pneumonia treatment by photodynamic therapy with extracorporeal illumination – an experimental model, *Physiol Rep*, 5(5), 2017, e13190, doi: 10.14814/phy2.13190.

Ghanem, A., Pasumarthy, S., Ranna, V., Kellesarian, S. V., Abduljabbar, T., Vohra, F., Malmstrom, H. (2016). Is mechanical curettage with adjunct photodynamic therapy more effective in the treatment of peri-implantitis than mechanical curettage alone? *Photodiagnosis and Photodynamic Therapy*, Sep;15:191-6.

Giannelli, M., Landini, G., Materassi, F., Chellini, F., Antonelli, A., Tani, A., Nosi, D., Zecchi-Orlandini, S., Rossolini, G.M., & Bani, D. (2017). Effects of photodynamic laser and violet-blue led irradiation on *Staphylococcus aureus* biofilm and *Escherichia coli* lipopolysaccharide attached to moderately rough titanium surface: in vitro study. *Lasers in Medical Science*, May;32(4):857-864.

Giuliani, F., Martinelli, M., Cocchi, A., Arbia, D., Fantetti, L., & Roncucci, G. (2010). In vitro resistance selection studies of RLP068/Cl, a new Zn(II) phthalocyanine suitable for antimicrobial photodynamic therapy. *Antimicrobial Agents in Chemotherapy*, Feb;54(2):637-42.

Grce, M., & Mravak-Stipetić, M. (2014). Human papillomavirus-associated diseases. *Clinical Dermatology*, Mar-Apr;32(2):253-8.

Hillemanns, P., Petry, K. U., Soergel, P., Collinet, P., Ardaens, K., Gallwas, J., Luyten, A., & Dannecker, C. (2014). Efficacy and safety of hexaminolevulinate photodynamic therapy in patients with low-grade cervical intraepithelial neoplasia. *Lasers in Surgery and Medicine*, Aug;46(6):456-61.

Hongcharu, W., Taylor, C. R., Chang, Y., Aghassi, D., Suthamjariya, K., & Anderson, R. R. (2000). Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *Journal of Investigative Dermatology*, Aug;115(2):183-92.

Hopper, C. (2000). Photodynamic therapy: a clinical reality in the treatment of cancer. *Lancet Oncology*, 1, 212-219.

Hu, Z., Li, J., Liu, H., Liu, L., Jiang, L., & Zeng, K. (2018). Treatment of latent or subclinical Genital HPV Infection with 5-aminolevulinic acid-based photodynamic therapy. *Photodiagnosis and Photodynamic Therapy*, Sep;23:362-364.

Jocham, D., from Wietersheim, J., Pflüger, H., Steiner, H., Doehn, C., Büttner, H., Böhle, A., & Kausch, I. (2009). [BCG versus photodynamic therapy (PDT) for nonmuscle invasive bladder cancer-a multicentre clinical phase III study]. *Current Urology*, Mar; 40 (2): 91-9.

Jori, G. & Coppellotti, O. (2007). Inactivation of pathogenic microorganisms by photodynamic techniques: Mechanistic aspects and perspective applications. *Anti-Infective Agents in Medicinal Chemistry* (Formerly *Current Medicinal Chemistry - Anti-Infective Agents*), 6. 119-131.

Joseph, B., Janam, P., Narayanan, S., & Anil, S. (2017). Is antimicrobial photodynamic therapy effective as an adjunct to scaling and root planing in patients with chronic periodontitis? A systematic review. *Biomolecules*, Nov 24;7(4).

Kato, I. T., Prates, R. A., Sabino, C. P., Fuchs, B. B., Tegos, G. P., Mylonakis, E., Hamblin, M. R., Ribeiro, M. S. (2013). Antimicrobial photodynamic inactivation inhibits *Candida albicans* virulence factors and reduces in vivo pathogenicity. *Antimicrobial Agents in Chemotherapy*, Jan;57(1):445-51.

Kharkwal, G.B., Sharma, S.K., Huang, Y.Y., Dai, T., & Hamblin, M.R. (2011). Photodynamic therapy for infections: clinical applications. *Lasers in Surgery and Medicine*, Sep;43(7):755-67.

Kostron, H. (2010). Photodynamic diagnosis and therapy and the brain. *Methods in Molecular Biology*, 635:261-80.

Lauro, F. M., Pretto, P., Covolo, L., Jori, G., & Bertoloni, G. (2002). Photoinactivation of bacterial strains involved in periodontal diseases sensitized by porphycene-polylysine conjugates. *Photochemical and Photobiological Sciences*, Jul;1(7):468-70.

Lee, J.W., Kim, B.J., & Kim, M.N. (2010). Photodynamic therapy: new treatment for recalcitrant *Malassezia* folliculitis. *Lasers in Surgery Medicine*, Feb;42(2):192-6.

Lei, X., Liu, B., Huang, Z., & Wu, J. (2015). A clinical study of photodynamic therapy for chronic skin ulcers in lower limbs infected with *Pseudomonas aeruginosa*. *Archives of Dermatological Research*, Jan;307(1):49-55.

Lepper, P.M., Held, T.K., Schneider, E.M., Bölke, E., Gerlach, H., & Trautmann, M. (2002). Clinical implications of antibiotic-induced endotoxin release in septic shock. *Intensive Care Medicine*, Jul;28(7):824-33.

Loebel, N., Andersen, R., Dawson, T., & Cross, C. (2016) Antimicrobial photodynamic therapy: a decade of development and clinical study. In *Photodynamic Medicine, from Bench to Clinic*. Ed. Kostron, H. & Hasan, T., Royal Society of Chemistry, pp. 519-548.

Lombard, G. F., Tealdi, S., & Lanotte, M. M. (1985). The treatment of neurosurgical infections by lasers and porphyrins. In *Photodynamic Therapy of Tumors and other Diseases*, Jori, G., & Perria, C., Eds., Libreria Progetto, Padova, pp. 363-366.

Maisch, T. (2015). Resistance in antimicrobial photodynamic inactivation of bacteria. *Photochemical and Photobiological Sciences*, 14, 1518.

Malik, Z., Hanania, J., & Nitzan, Y. (1990). Bactericidal effects of photoactivated porphyrins--an alternative approach to antimicrobial drugs. *Journal of Photochemistry and Photobiology B: Biology*, May;5(3-4):281-93.

Mannucci, E., Genovese, S., Monami, M., Navalesi, G., Dotta, F., Anichini, R., Romagnoli, F., & Gensini, G. (2014). Photodynamic topical antimicrobial therapy for infected foot ulcers in patients with diabetes: a randomized, double-blind, placebo-controlled study--the D.A.N.T.E (Diabetic ulcer Antimicrobial New Topical treatment Evaluation) study. *Acta Diabetologica*, 51(3):435-40.

Manoury, V., & Mordon, S. (2016). Antimicrobial photodynamic therapy: a decade of development and clinical study. In *Photodynamic Medicine, from Bench to Clinic*. Ed. Kostron, H. & Hasan, T., Royal Society of Chemistry, pp. 441-447.

Martins, D., Mesquita, M. Q., Neves, M. G. P. M. S., Faustino, M. A. F., Reis, L., Figueira, E., & Almeida, A. (2018). Photoinactivation of *Pseudomonas syringae* pv. actinidiae in kiwifruit plants by cationic porphyrins. *Planta*, Aug;248(2):409-421.

Meimandi, M., Talebi Ardakani, M. R., Esmaeil Nejad, A., Yousefnejad, P., Saebi, K., & Tayeed, M. H. (2017). The effect of photodynamic therapy in the treatment of chronic periodontitis: A review of literature. *Journal of Lasers in Medical Sciences*, Summer;8(Suppl 1):S7-S11.

Millson, C. E., Thurrell, W., Buonaccorsi, G., Wilson, M., Macrobert, A. J., & Bown, S. G. (1997). The effect of low-power laser light at different doses on gastric mucosa sensitised with methylene blue, haematoporphyrin derivative or toluidine blue. *Lasers in Medical Science*, 12:145-150.

Moan, J., & Berg, K. (1991). The photodegradation of porphyrins in cells can be used to estimate the lifetime of singlet oxygen. *Photochemistry and Photobiology*, Apr;53(4):549-53.

Mohammadi, Z., Jafarzadeh, H., Shalavi, S., & Kinoshita, J.I. (2017). Photodynamic Therapy in Endodontics. *The Journal of Contemporary Dental Practice*, Jun 1;18(6):534-538.

Morgado, L. F., Trávolo, A. R .F., Muehlmann, L. A., Narcizo, P. S., Nunes, R. B., Pereira, P. A. G., Py-Daniel, K. R., Jiang, C. S., Gu, J., Azevedo, R. B., Longo, J. P. F. (2017). Photodynamic therapy treatment of onychomycosis with aluminium-phthalocyanine chloride nanoemulsions: A proof of concept clinical trial. *Journal of Photochemistry and Photobiology B: Biology*, Aug;173:266-270.

Morley, S., Griffiths, J., Philips, G., Moseley, H., O'Grady, C., Mellish, K., Lankester, C. L., Faris, B., Young, R. J., Brown, S. B., & Rhodes, L. E. (2013). Phase IIa randomized, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonized, chronic leg ulcers and diabetic foot ulcers: a new approach to antimicrobial therapy. *British Journal of Dermatology*, Mar;168(3):617-24.

Morton, C. A., McKenna, K. E., & Rhodes, L. E. (2008). British association of dermatologists therapy guidelines and audit subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *British Journal of Dermatology*, Dec;159(6):1245-66.

Muragaki, Y., Akimoto, J., Maruyama, T., Iseki, H., Ikuta, S., Nitta, M., Maebayashi, K., Saito, T., Okada, Y., Kaneko, S., Matsumura, A., Kuroiwa, T., Karasawa, K., Nakazato, Y., & Kayama, T. (2013). Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors. *Journal of Neurosurgery*, ct;119(4):845-52.

O'Neill, J., Tackling drug-resistant infections globally: final report and recommendations (2016). *The Review on Antimicrobial Resistance*, Wellcome Trust, HM Government.

Ohtsuki, A., Hasegawa, T., Hirasawa, Y., Tsuchihashi, H., & Ikeda, S. (2009). Photodynamic therapy using light-emitting diodes for the treatment of viral warts. *Journal of Dermatology*, Oct;36(10):525-8.

Paoli, J., Ternesten Bratel, A., Löwhagen, G. B., Stenquist, B., Forslund, O., & Wennberg, A. M. (2006). Penile intraepithelial neoplasia: results of photodynamic therapy. *Acta Dermato-Venereologica*, 86(5):418-21.

Pedigo, L. A., Gibbs, A. J., Scott, R. J., & Street, C. N. (2009). Absence of bacterial resistance following repeat exposure to photodynamic therapy. *Proc. SPIE 7380, Photodynamic Therapy: Back to the Future*, 73803H, 13 July.

Pereira, C.A., Domingues, N., Silva, M.P., Costa, A.C., Junqueira, J.C., & Jorge, A.O. (2015). Photodynamic inactivation of virulence factors of *Candida* strains isolated from patients with denture stomatitis. *Journal of Photochemistry and Photobiology B: Biology*, Dec;153:82-9.

Pourhajibagher, M., Ghorbanzadeh, R., & Bahador, A. (2018). Investigation of arginine A-specific cysteine proteinase gene expression profiling in clinical *Porphyromonas gingivalis* isolates against photokilling action of the photo-activated disinfection. *Lasers in Medical Science*, Feb;33(2):337-341.

Pourhajibagher, M., Boluki, E., Chiniforush, N., Pourakbari, B., Farshadzadeh, Z., Ghorbanzadeh, R., Aziemzadeh, M., & Bahador, A. (2016). Modulation of virulence in *Acinetobacter baumannii* cells surviving photodynamic treatment with toluidine blue. *Photodiagnosis and Photodynamic Therapy*, Sep;15:202-12.

Pourhajibagher, M., Chiniforush, N., Shahabi, S., Sobhani, S., Monzavi, M. M., Monzavi, A., & Bahador, A. (2017). Monitoring gene expression of rcpA from *Aggregatibacter actinomycetemcomitans* versus antimicrobial photodynamic therapy by relative quantitative real-time PCR. *Photodiagnosis and Photodynamic Therapy*, Sep;19:51-55.

Raab, O. (1900). Uber die Wirkung fluoreszierender Stoffe auf Infusorien. *Z Biol*, 39:524-526.

Rühling, A., Fanghänel, J., Houshmand, M., Kuhr, A., Meisel, P., Schwahn, C., & Kocher, T. (2010). Photodynamic therapy of persistent pockets in maintenance patients-a clinical study. *Clinical Oral Investigations*, Dec;14(6):637-44.

Sayanagi, K., Hara, C., Fukushima, Y., Sato, S., Sakaguchi, H., & Nishida, K. (2019). Time course of swept-source optical coherence tomography angiography findings after photodynamic therapy and aflibercept in eyes with age-related macular degeneration. *American Journal of Ophthalmology Case Reports*, Jun 1;15:100485.

Scherz, A., Salomon, Y., Linder, U., & Coleman, J. (2016). Antimicrobial photodynamic therapy: a decade of development and clinical study. In *Photodynamic Medicine, from Bench to Clinic*. Ed. Kostron, H. & Hasan, T., Royal Society of Chemistry. 2016, pp. 461-480.

Schroeter, C. A., Pleunis, J., van Nispen tot Pannerden, C., Reineke, T., & Neumann, H. A. (2005). Photodynamic therapy: new treatment for therapy-resistant plantar warts. *Dermatologic Surgery*, Jan;31(1):71-5.

Scwingel, A. R., Barcessat, A. R., Núñez, S. C., & Ribeiro, M. S. (2012). Antimicrobial photodynamic therapy in the treatment of oral candidiasis in HIV-infected patients. *Photomedicine and Laser Surgery*, Aug;30(8):429-32.

Seo, H.M., Min, H.G., Kim, H.J., Shin, J.H., Nam, S.H., Han, K.S., Ryu, J.H., Oh, J.J., Kim, J.Y., Lee, K.J., Lee, S.J., Kim, H.S., Kim, J.I., Song, M.K., & Kim, W.S. (2016). Effects of repetitive photodynamic therapy using indocyanine green for acne vulgaris. *International Journal of Dermatology*, Oct;55(10):1157-63.

Serini, S. M., Cannizzaro, M. V., Dattola, A., Garofalo, V., Del Duca, E., Ventura, A., Milani, M., Campione, E., & Bianchi L. (2019). The efficacy and tolerability of 5-aminolevulinic acid 5% thermosetting gel photodynamic therapy (PDT) in the treatment of mild-to-moderate acne vulgaris. A two-center, prospective assessor-blinded, proof-of-concept study. *Journal of Cosmetic Dermatology*, Feb;18(1):156-162.

Shi, H., Zhang, X., Ma, C., Yu, N., Wang, J., Xia, L., Ge, X., Liu, M., & Duan, A. (2013). Clinical analysis of five methods used to treat condylomata acuminata. *Dermatology*, 227(4):338-45.

Shikowitz, M. J., Abramson, A.L., Freeman, K., Steinberg, B. M., & Nouri, M. (1998).Efficacy of DHE photodynamic therapy for respiratory papillomatosis: immediate and long-term results. *Laryngoscope*, Jul;108(7):962-7.

Shikowitz, M. J., Abramson, A.L., Steinberg, B. M., DeVoti, J., Bonagura, V.R., Mullooly, V., Nouri, M., Ronn, A. M., Inglis, A., McClay, J., & Freeman, K. (2005). Clinical trial of photodynamic therapy with meso-tetra (hydroxyphenyl) chlorin for respiratory papillomatosis. *Archives of Otolaryngology - Head and Neck Surgery*, Feb;131(2):99-105.

Shrestha, A., Cordova, M., & Kishen, A. (2015). Photoactivated polycationic bioactive chitosan nanoparticles inactivate

bacterial endotoxins. *Journal of Endodontics*, May;41(5):686-91.

Soergel, P., Loehr-Schulz, R., Hillemanns, M., Landwehr, S., Makowski, L., & Hillemanns, P. (2010). Effects of photodynamic therapy using topical applied hexylaminolevulinate and methylaminolevulinate upon the integrity of cervical epithelium. *Lasers in Surgery and Medicine*, Nov;42(9):624-30.

Soukos, N. S., Wilson, M., Burns, T., & Speight, P. M. (1996). Photodynamic effects of toluidine blue on human oral keratinocytes and fibroblasts and *Streptococcus sanguis* evaluated in vitro. *Lasers in Surgery and Medicine*, 18(3):253-9.

Tao, S. Q., Li, F., Cao, L., Xia, R. S., Fan, H., Fan, Y., Sun, H., Jing, C., & Yang, L. J. (2015). Low-Dose Topical 5-Aminolevulinic Acid Photodynamic Therapy in the Treatment of Different Severity of Acne Vulgaris. *Cell Biochemistry and Biophysics*, 73(3):701-6.

Tavares, A., Carvalho, C. M., Faustino, M. A., Neves, M. G., Tomé, J. P., Tomé, A. C., Cavaleiro, J. A., Cunha, A., Gomes, N. C., Alves, E., & Almeida, A. (2010). Antimicrobial photodynamic therapy: study of bacterial recovery viability and potential development of resistance after treatment. *Marine Drugs*, Jan 20;8(1):91-105.

Tommasino, M. (2014). The human papillomavirus family and its role in carcinogenesis. *Seminars in Cancer Biology*, Jun;26:13-21.

Tseng, S. P., Hung, W. C., Chen, H. J., Lin, Y. T., Jiang, H. S., Chiu, H. C., Hsueh, P. R., Teng, L. J., & Tsai, J. C. (2017). Effects of Toluidine blue O (TBO)-photodynamic inactivation on community-associated methicillin-resistant *Staphylococcus aureus* isolates. *Journal of Microbiology, Immunology and Infection*, Feb;50(1):46-54.

Tubby, S., Wilson, M., & Nair, S. P. (2009). Inactivation of staphylococcal virulence factors using a light-activated antimicrobial agent. *BMC Microbiology*, Oct 5;9:211.

Tuchin, V. V., Genina, E. A., Bashkatov, A. N., Simonenko, G. V., Odoevskaya, O. D., & Altshuler, G. B. (2003). A pilot study of ICG laser therapy of acne vulgaris: photodynamic and photothermolysis treatment. *Lasers in Surgery and Medicine*, 33(5):296-310.

Tvenning, A. O., Hedels, C., Krohn, J., & Austeng, D. (2019). Treatment of large avascular retinal pigment epithelium detachments in age-related macular degeneration with aflibercept, photodynamic therapy, and triamcinolone acetonide. *Clinical Ophthalmology*, Feb 1;13:233-241.

Valduga, G., Bertoloni, G., Reddi, E., & Jori, G. (1993). Effect of extracellularly generated singlet oxygen on Gram-positive and Gram-negative bacteria. *Journal of Photochemistry and Photobiology B: Biology*, Nov;21(1):81-6.

Vince, R. V., Madden, L. A., Alonso, C. M., Savoie, H., Boyle, R. W., Todman, M., Paget, T., & Greenman, J. (2011). Identification of methicillin-resistant *Staphylococcus aureus*-specific peptides for targeted photoantimicrobial chemotherapy. *Photochemical and Photobiological Sciences*, Apr;10(4):515-22.

Wainwright, M. (2003). Local treatment of viral disease using photodynamic therapy. *International Journal of Antimicrobial Agents*, Jun;21(6):510-20.

Wang, X. L., Wang, H. W., Huang, Z., Stepp, H., Baumgartner, R., Dannecker, C., & Hillemanns, P. (2007). Study of protoporphyrin IX (PpIX) pharmacokinetics after topical application of 5-aminolevulinic acid in urethral condylomata acuminata. *Photochemistry and Photobiology*, Sep-Oct;83(5):1069-73.

Wiegell, S. R., & Wulf, H. C. (2006). Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *British Journal of Dermatology*, May;154(5):969-76.

Wilder-Smith, C. H., Wilder-Smith, P., Grosjean, P., van den Bergh, H., Woodtli, A., Monnier, P., Dorta, G., Meister, F., & Wagnières, G. (2002). Photoeradication of *Helicobacter pylori* using 5-aminolevulinic acid: preliminary human studies. *Lasers in Surgery and Medicine*, 31(1):18-22.

Zhang, P., & Wu, M.X. (2018). A clinical review of phototherapy for psoriasis. *Lasers in Medical Science*, Jan;33(1):173-180.

Zou, L., Ruan, F., Huang, M., Liang, L., Huang, H., Hong, Z., Yu, J., Kang, M., Song, Y., Xia, J., Guo, Q., Song, T., He, J., Yen, H-L., Peiris, P., Wu, J., (2020). SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *New England Journal of Medicine*, DOI: 10.1056/NEJMc2001737.