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Antimicrobial photodynamic therapy in the colon: delivering a light punch to the guts?

Mark Wainwright[1], **Tianhong Dai**[2,3], and **Michael R Hamblin**[2,3,4,*]

[1] School of Pharmacy & Biomolecular Science, Liverpool John Moores University, Liverpool, UK

[2] Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA

[3] Department of Dermatology, Harvard Medical School, Boston, MA

[4] Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA

Abstract

A paper in this issue of Photochemistry and Photobiology by Cassidy et al describes the use of a sophisticated drug delivery vehicle prepared by the hot melt extrusion process to deliver photosensitizers to the colon. The smart vehicle protects its cargo through the acidic environment of the stomach but releases the active photosensitizers in the higher pH and anaerobic environment of the colon. The goal is to use photodynamic therapy (PDT) to destroy pathogenic microorganisms that can cause disease when they grow out of control in the colon. Since the colon is an environment with a low oxygen concentration the investigators also used tetrachlorodecaoxide, an oxygen donor to boost the available oxygen concentration. The paper reports results with *Enterococcus faecalis* and *Bacteroides fragilis* but the real medical problem demanding to be solved is *Clostridium difficile* that can cause intractable drug-resistant infections after antibiotic use. There still remain barriers to implementing this strategy in vivo, including light delivery to the upper colon, oxygen availability and optimizing the selectivity of photosensitizers for bacteria over colon epithelial cells. Nevertheless this highly innovative paper lays the ground for the study of an entirely new and significant application for antimicrobial PDT.

Introduction

Photodynamic therapy (PDT) was discovered over one hundred years ago by the ability of certain dyes when combined with visible light in the presence of oxygen to kill various microorganisms. However PDT has not been much developed as a treatment approach for infections until recent times, but rather has been studied as a treatment for cancer, skin diseases and choroidal neovascularization. The recent alarming rise in drug resistance not only amongst bacteria but also involving fungi, parasites, viruses and almost all classes of pathogens has acted to change these priorities. The interest in antimicrobial PDT for infections is starting to rapidly increase although the actual clinical applications so far remain very limited. In most of these clinical applications the photosensitizer is topically applied to the infection as for instance rubbed on the skin for acne, injected into the dental pocket for periodontitis, or applied to the surface of a non-healing ulcer.

The application of photosensitizers to deeper-seated, semi-localized infections clearly requires more sophisticated drug delivery methods; such as a delivery vehicle that is engineered to only release its cargo at the target site.

*Corresponding author: HAMBLIN@HELIX.MGH.HARVARD.EDU (M. Hamblin).

Novel application for antimicrobial PDT

The current submission from Cassidy et al. [1] provides a model for the treatment of intestinal infection using several known photosensitizers and a methacrylate polymer delivery system to great effect against known colonic pathogens.

The alimentary tract relies on bacterial flora for efficient food breakdown, transit and elimination. A wide variety of bacteria – from Gram-positive aerobes to Gram-negative anaerobes is – present, normally in a synergistic relationship with the host. Thus when the microflora is damaged to any significant degree, for example under the action of oral antibiotics, gastric/enteric disorders usually ensue. Such disorders are due to the overgrowth of recalcitrant bacteria in areas of the GI tract previously colonized by antibiotic-susceptible species. Often in hospital patients, however, and particularly in the elderly or those being treated for multidrug-resistant bacterial infections, such is the damage to the microbial ecosystem that both morbidity and mortality rates increase. In such cases, the offending organism is usually the Gram-positive, microaerophilic bacterium *Clostridium difficile* [2], or the yeast *Candida albicans* [3].

It will be understood, of course, that there are antimicrobial agents available for both of these pathogens. For example, the glycopeptide antibiotic vancomycin and the nitroimidazole agent metronidazole are recommended for the treatment of *C. difficile* infection. However, as noted by Cassidy et al., the efficacy of these drugs is often variable [4]. In addition, other intestinal bacteria, such as *Enterococcus* spp. are a considerable cause for concern, and obviously more so where vancomycin resistance is involved.

The difficulty inherent in the application of conventional antimicrobial agents to colonic infection/superinfection surely constitutes a *prima facie* case for the application of the photodynamic approach. As Cassidy et al. [1] have shown, it is possible to realize high levels of bacterial kill against colonic bacteria using established photosensitizers/ALA. In addition, it is established that bacterial resistance to conventional chemotherapy does not affect susceptibility to photodynamic antimicrobial chemotherapy (PACT) – indeed, this has been reported for vancomycin-resistant *Enterococcus faecalis* [5].

It should also be remembered that PACT offers other advantages, particularly from the aspect of conventional drug conservation. While vancomycin is normally kept in reserve for the treatment of serious drug-resistant infection, typically with methicillin-resistant *Staphylococcus aureus* (MRSA), as noted it is currently a front-line treatment for *C. difficile* infection and this must surely impact on the wider development of resistance to vancomycin [6]. Indeed, infection with *C. difficile* has been correlated with vancomycin-resistant enterococcal (VRE) infection [7].

Obviously, hospital-acquired infection rates can only be decreased by breaking the infection chain, and significant falls will require increases in environmental hygiene control as well as more effective disease therapy. However, the photodynamic approach as described is antimicrobial, rather than specifically antibacterial or antifungal. Thus while specific conventional therapy of the colon using vancomycin etc. may be effective against *C. difficile*, by definition it would not affect VRE and could provide no check against nascent infection by *Candida* spp.

Smart Drug Delivery Vehicle

The approach taken by Cassidy et al [1] details a “smart” delivery vehicle for the potential aPDT of multi-drug resistant colon infections. It is an oral formulation prepared using the hot melt extrusion process. During the journey of the vehicle to its destination in the colon,

the vehicle can “smartly” protect its PS cargo when passing through the stomach. When it reaches the colon, the vehicle releases its cargo in a time dependent manner. In this procedure, the pH value of the environment serves as the “traffic signal” for the PS release. The pH value of 1, which is the value of an acid environment (stomach), is the “withholding signal”; while the pH value of >7, the value of the anaerobic environment in the gut is the “release signal”. With such a smart delivery vehicle that can recognize the “release signal”, PS would be released in a controlled manner. Recognizing the low availability of oxygen in the anaerobic environment in the colon these investigators incorporated an oxygen delivery vehicle in their formulation. Tetrachlorodecaoxide (TCDO) is a chlorite derivative that is used in wound dressings and can even be injected intravenously so it should not have unacceptable toxicity in the colon. Nonetheless, this study is so far still at the stage of *in vitro* testing and considerable further work would be needed to advance the concept to clinical application.

Caveats

There remain formidable potential obstacles to carrying out aPDT in the colon. How would the light be delivered? Although fiber optic devices with cylindrical diffusing tips exist that could in principle be advanced up the colon to the infected areas, it is not clear how much of the colon would need to be illuminated. Can the actual areas of infection be identified? Another serious potential problem concerns the availability of sufficient oxygen concentration in the colon. Although these investigators showed that the addition of TCDO was able to potentiate PACT-mediated bacterial killing (especially in the case of *Bacteroides fragilis*), oxygen limitation may still be problematic. In the clinical application it is possible that the light delivery fiber could be engineered to simultaneously deliver oxygen at the same time as the inactivating light. A third problem lies in the question of whether the photosensitizers would need to be specifically designed to bind to the bacteria rather than the colon tissue and cells, upon release from their smart vehicle. Numerous studies have reported sophisticated antimicrobial PS whose ability to selectively bind to bacteria rather than host mammalian cells has been optimized. Examples of these constructs are the polycationic conjugate between polyethylenimine and chlorin(e6) [8], specially constructed nanoparticles conjugated to PS [9] and a bacteriophage-Sn(ce6) conjugate that recognizes specific receptors on bacteria [10].

Conclusions

Even with all these caveats this innovative proposal to carry out colon-specific delivery of PS coupled with local illumination could destroy drug-resistant disease-causing bacteria and cause less damage to the commensal flora in other parts of the alimentary canal.

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References

1. Cassidy CM, Tunney MM, Caldwell DL, Andrews GP, Donnelly RF. Development of novel oral formulations prepared via hot melt extrusion for targeted delivery of photosensitizer to the colon. Photochem Photobiol. 201110.1111/j.1751-1097.2011.00915.x
2. Raza S, Baig MA, Russell H, Gourdet Y, Berger BJ. Clostridium difficile infection following chemotherapy. Recent Pat Antiinfect Drug Discov. 2010; 5:1–9. [PubMed: 19929843]

3. Kennedy MJ, Volz PA. Ecology of Candida albicans gutcolonization: inhibition of Candida adhesion, colonization, and dissemination from the gastrointestinal tract by bacterial antagonism. Infect Immun. 1985; 49:654–663. [PubMed: 3897061]

4. Kyne L. Clostridium difficile--beyond antibiotics. N Engl J Med. 2010; 362:264–265. [PubMed: 20089977]

5. Wainwright M, Phoenix DA, Gaskell M, Marshall B. Photobactericidal activity of methylene blue derivatives against vancomycin-resistant Enterococcus spp. J Antimicrob Chemother. 1999; 44:823–825. [PubMed: 10590285]

6. Nguyen GC, Patel H, Chong RY. Increased prevalence of and associated mortality with methicillin-resistant Staphylococcus aureus among hospitalized IBD patients. Am J Gastroenterol. 2010; 105:371–377. [PubMed: 19809406]

7. Rafferty ME, McCormick MI, Bopp LH, Baltch AL, George M, et al. Vancomycin-resistant enterococci in stool specimens submitted for Clostridium difficile cytotoxin assay. Infect Control Hosp Epidemiol. 1997; 18:342–344. [PubMed: 9154478]

8. Tegos GP, Anbe M, Yang C, Demidova TN, Satti M, et al. Protease-stable polycationic photosensitizer conjugates between polyethyleneimine and chlorin(e6) for broad-spectrum antimicrobial photoinactivation. Antimicrob Agents Chemother. 2006; 50:1402–1410. [PubMed: 16569858]

9. Pagonis TC, Chen J, Fontana CR, Devalapally H, Ruggiero K, et al. Nanoparticle-based endodontic antimicrobial photodynamic therapy. J Endod. 2010; 36:322–328. [PubMed: 20113801]

10. Embleton ML, Nair SP, Heywood W, Menon DC, Cookson BD, et al. Development of a novel targeting system for lethal photosensitization of antibiotic-resistant strains of Staphylococcus aureus. Antimicrob Agents Chemother. 2005; 49:3690–3696. [PubMed: 16127041]