Photoantimicrobials and PACT: What's in an Abbreviation?

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Abstract

The use of a separate nomenclature for the application of photosensitisers to the oncological and infectious disease fields represents a sensible approach. There is commonality, of course, in that both utilise light activation and act via the local generation of reactive oxygen species, but the difference in cellular targets is so great that different designs are required to achieve proper selectivity for a clinical end use, whether in human or veterinary medicine. The following represents a personal view, and perhaps a clarification of terms, in what might be considered a major etymological dichotomy existing within photodynamic research, on the 20th anniversary "PACT".

Introduction

A review with the title "Photodynamic antimicrobial chemotherapy (PACT)" appeared in the *Journal of Antimicrobial Chemotherap*y in 1998, 20 years ago.[1] I had several intentions in publishing this review.

Firstly, it was an attempt to gather together and consolidate as much of the light-activated antimicrobial research that had been reported in the recent past, as a "leading edge" piece. Secondly, and very importantly from my point of view, it was intended to provide an easily-recalled acronym which was distinct from the abbreviation PDT, used for the photodynamic therapy of cancer, which, at the time, massively overshadowed the nascent antimicrobial application.

The rationale behind the nomenclature was relatively straightforward: *photodynamic* due to light-activated production of reactive oxygen species; *antimicrobial* to specify action against microbial pathogens and emphasise utility in infection control, and *chemotherapy* because the main photosensitisers used also exhibited minor conventional ('dark') activity against microbes. This last part has been a problem for some, who prefer the purist idea that photodynamic therapy employs photosensitisers which are wholly non-toxic without light (never true, in my experience), and this has led to a number of alternative abbreviations – there have been no other *acronyms*.

'Chemotherapy' (Ger. *chemotherapie*) is a term coined by its inventor, Paul Ehrlich, in the early years of the last century. The word evolved from his discovery that certain dyes were able initially to kill

or inactivate microbial cells or cultures, and later to cure infectious disease in small animals, and then humans. The use of the word in conventional terms thus originally comes from clinical *antimicrobial* chemotherapy, rather than from the use of chemical agents against tumours, which began in the mid-20th Century.

Conventional anticancer chemotherapy is aimed at the killing of human tumour cells and, due to lower than desirable selectivity for tumour over healthy cells, significant side effects are often experienced. I would suggest that this is the main reason that the word *chemotherapy* is remembered and associated with cancer, rather than the much more widely-used – and milder - antimicrobial application.

Photoantimicrobial chemotherapy, as noted above, reflects the small, conventional, 'dark' toxicity associated with major photosensitisers such as methylene blue or toluidine blue, but this is toxicity against the target organisms, rather than host cells. It is up to those involved in the area to ensure that those governing the clinical transfer of the approach appreciate this, but the use of intentionally anticancer PDT agents as notional photoantimicrobials does nothing to support the argument.

While it is true that the killing agents involved in photodynamic processes are reactive oxygen species, these would not be produced without the photosensitiser. Indeed, the fact that methylene blue and toluidine blue may be effluxed from target cells and yet kill these cells on illumination[2] is testament to this. Such phenomena do not occur with conventional therapeutics.

The use of the compound word *photoantimicrobial* within my original review – i.e. a specific agent which is antimicrobial on illumination, as opposed to being a general photosensitiser - was a similar attempt to separate the active compounds used in the light-activated antimicrobial and anticancer fields and allow the proper distinction of those working with the former. While this may not seem important, I believe not only that it was in the late 1990s, but also that it remains so now – the anticancer and infection control applications should be well separated. One of the major problems with the use of photosensitiser preparations, such as haematoporphyrin derivative (HpD), in the mid-late 1990s (and later!) was a lack of selectivity between the target tumour and surrounding healthy tissue. Healthy host cell uptake in cancer treatment may be justified, but it is far less so in the therapy of infectious disease. Furthermore, the compounds which originally encouraged work in this field were small molecule, hydrophilic dyes such as the acridine proflavine, the triphenylmethane brilliant green and the phenothiazinium methylene blue. Each of these dyes has been used, clinically, in antisepsis, without the intentional use of light.

This is not to say that there should be no crossover at all between the two disciplines – obviously both require photosensitiser development and both need to understand and minimise toxic effects on the host – but my view has always been that they have quite different objectives and should thus be treated as separate entities.

It should be noted that PACT is often now shortened to the slightly less cumbersome *photoantimicrobial chemotherapy*.

Abbreviation and Chemotherapy

One of the big selling points in anticancer PDT was the idea that the photosensitisers used here were non-toxic in the absence of light. Given the dreadful side-effects often associated with conventional chemotherapy in this area – as noted above - a complete lack of toxicity is obviously highly appealing in an alternative approach. Since there has often been a branching-out from anticancer PDT groups into the antimicrobial arena, this definition has duly followed them, along with abbreviations used in research publications such as antimicrobial photodynamic therapy - APDT or, rather strangely, aPDT, which actually de-emphasises the antimicrobial focus of the operation! It is also very easy to confuse APDT (or, worse, aPDT), for example in a piece of manuscript text, with PDT itself, which was always my main problem with this abbreviation: a very slowly developing and hugely underfunded medical approach like ours requires as much clarity in communication as possible!

Perhaps a more important point against the use of the APDT abbreviation lies in the fact that the minor conventional toxicity of photoantimicrobials like methylene blue or toluidine blue is far less significant in mammalian cells than it is in microbes. Furthermore, the degree of this inherent or 'dark' microbial toxicity is not really of concern unless it is of a significance which would be detrimental to the approach as a whole, given eventual resistance. As an example, it must be incorrect to call the enhanced action of conventional fluoroquinolone antibacterials on illumination "APDT", since here the dark toxicity is considerable and is, indeed, the main route to cell killing, the photodynamic action being a fortunate extra. What is required from the photoantimicrobial approach is high activity against the microbial target with insignificant damage *to the host* in either light or dark conditions.

An earlier abbreviation concerning the anticancer application of photosensitisers was PCT, for *photochemotherapy*. This, again, was a realistic admission of its chemotherapeutic nature – the use of chemical agents which were activated by light. This has similarities to conventional radiosensitisation, but was also close to the phrase 'photochemical therapy', properly employed where the incoming radiation causes the formation of new covalent bonds between the therapeutic molecule and its target (typically a UV-activated furanocoumarin and DNA). There is, of course, considerable discussion as to whether, or where, the line should be drawn between this type of photochemistry and that leading to the generation of reactive oxygen species. However, photochemotherapy is also a fitting general description for either the anticancer or the antimicrobial approach, in the same way as there are both anticancer and antimicrobial chemotherapies in conventional healthcare.

Other abbreviations have appeared at various times: PDD for photodynamic *disinfection* and PDI for photodynamic *inactivation*. I have yet to encounter PDC, to cover photo*decolonisation*, but it will arrive, have no doubt! These are, again, not fully interchangeable terms, but are used with apparent abandon by various groups – typically in early publications.

As pointed out to me recently, the term *disinfection* has different meanings depending on the language used. Normally (in English) it is meant to describe the cleaning of pathogens from a surface, very often part of the physical environment – commercial disinfectants are usually surface cleaners. Also *photodisinfection* might mean the use of ionising radiation alone (typically ultraviolet) to kill microbes. However, since a wound can be disinfected, there is potential for confusion here.

Similarly, *inactivation* in terms of a pathogenic microbe might mean cell killing or the inhibition of cell replication, but is the correct term if viruses are the target, the conventional argument, of course, being that viruses are not living and thus cannot be killed.

Agents

There is also, in my opinion, a distinction to be made between *photosensitiser* (whether spelt –iser or -izer) and *photoantimicrobial*. Using these terms interchangeably does not help the antimicrobial cause and is, in many cases, incorrect. It should be remembered that effective, broad-spectrum activity is only possible with cationic photosensitisers – in other words, while many different photosensitisers can be used with suitable light to kill fungal, viral and protozoal cells, only cationic examples are generally effective against both Gram-positive and Gram-negative bacteria, whereas anionic and neutral photosensitisers are generally considerably less effective against Gram-negatives. Given the enormous and global danger currently posed by conventional drug-resistant Gram-negative bacteria, such as the *Enterobacteriaceae*, this is not an insignificant point. However, since the word *photoantimicrobial* is used as both a noun and an adjective (e.g. "a photoantimicrobial effect") it is difficult to associate it specifically with cationic photosensitisers. Haematoporphyrin derivative may not be a successful photoantimicrobial in terms of *Klebsiella pneumoniae*, but it usually is against Gram-positive bacteria. However, it would be helpful if anti-infective papers and applications talked about photoantimicrobials instead of photosensitisers.

Forwards?

Photoantimicrobials can make a significant difference in healthcare as the basis of non-conventional antimicrobial chemotherapy, and it is gratifying that there is such an active continuing literature concerning new compounds and applications. However, the move "from bench to bedside" in this area of infection control also continues to be a long one and, I would suggest, now requires a more organised/concerted approach. Consolidation of research via greater collaboration (and agreement) between research groups would allow the weight of impact required to interest and impress those bodies able to fund the pathway to the clinic. Importantly, the way in which we describe the research should be clear enough to those outside the research fraternity, if we wish them to provide such support. This means using established terms which properly describe the science contained in research documentation, whether this is a conference abstract, a research paper or a grant application. Employing new abbreviations - without strong rationale - only dilutes the impact of the prior art and will confuse new readers.

Conventional microbial toxicity is certainly present with the phenothiazinium photosensitisers mentioned here. If other photoantimicrobials are completely non-toxic, as is often claimed, this would clearly represent an improvement in molecular properties which should speed progress to the clinic, and should therefore be promoted. However, such claimants would do well to be completely certain of their data regarding dark toxicity before regulatory submission.

References

1 M. Wainwright, Photodynamic antimicrobial chemotherapy (PACT), *J. Antimicrob. Chemother.*, 1998, **42**, 13-28.

2 G.P. Tegos and M.R. Hamblin, Phenothiazinium antimicrobial photosensitizers are substrates of bacterial multidrug resistance pumps, *Antimicrob. Agents Chemother.*, 2006, **50**, 196-203.