Laser-Guided Magic Bullets – a Non-Antibiotic Answer to O'Neill

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In the United Kingdom, the recently-published O'Neill Report [1] provides recommendations for the continuance of the battle between mankind's antibiotics and our microbial foes. While there is also the mention of alternative – i.e. non-antibiotic – approaches to infection control, it appears that other biologicals such as bacteriophages and vaccines are those envisaged, rather than other chemical approaches.

The concept of the magic bullet, as proposed by Paul Ehrlich in the early 20th Century, was intended to describe a clean, efficient method of *in situ* infection control [2] – i.e. a drug molecule which would destroy the invading pathogen with no effect on the human host.

What was being described, of course, was the aspirational – and logical - development of Ehrlich's research concerning selective cell staining using aniline-derived dyes. He and his colleague Paul Gutmann had cured two patients of falciparum malaria in 1890/1 using the phenothiazinium dye methylene blue [3], and this resulted in its use as a lead structure in antimalarial drug development. However, although subsequent analogues indeed proved to be more active, they were still blue in nature [4] and this was considered to be undesirable due to tissue and waste-product staining.

The blue-staining phenomenon is, of course, merely a minor artefact if the intended medical outcome – e.g. antimalarial action - is successfully achieved. Managing the unusual side-effect is possible via effective counselling of the patient, relatives etc. This has been achieved in recent years during the conventional use of methylene blue in juvenile malaria in Burkina Faso [5].

Given the enormous potential of such dyes used photodynamically – i.e. with light activation – against conventional drug resistance, it is ironic that their clinical use should be inhibited by human alarm presented with, e.g., unusually-coloured urine. A non-coloured conventional drug having similar physicochemical properties and pharmacological profile will, of course, appear in similar concentrations without such negative psychological sequelae. It will be remembered that in the earliest days of penicillin therapy, the unchanged antibiotics were present in sufficient quantities to allow their recovery from the urine for re-use.

The fact is that, in order to interact correctly with its biological target, a systemically-administered drug must be given in sufficient concentration, and this will be far greater than its active concentration at the target site. In addition, the drug must be able to reach the target situation. Since most of the drug is thus wasted, our 21st Century definition of the magic bullet is considerably different to that of its inventor. Indeed, in the case of our dwindling supply of effective antimicrobial agents, it is overtly contradicted by the damage to the internal microbiota caused by oral administration.

In some infectious disease presentations, such damage is justified by the alternative outcome of non-administration (e.g. bacterial meningitis, septicaemia). However, there are many less serious presentations in which the target organisms are localised and alternative therapeutic approaches can be made, allowing the conservation of valuable conventional drugs. In addition, judicious use of such approaches would stop the spread of infection which leads to serious disease presentations such as those mentioned above. A good example of this is the decolonisation of pathogenic carrier status.

As noted, one such option arising from the dyes and staining alluded to is the photodynamic, or light-activated, approach, often referred to as photodynamic antimicrobial chemotherapy (PACT [6]).

Used against a microbial target, photosensitisers are normally termed, logically, 'photoantimicrobials'. On illumination with the correct wavelength of light – whether from a laser- or a light-emitting diode (LED) source - such molecules absorb the incident energy and become electronically excited. This excited state is sufficiently long-lived to allow reaction with, or energy transfer to, oxygen in the molecular environment and the production, *in situ*, of reactive oxygen species (ROS) such as the highly oxidising molecule singlet oxygen. Such is the labile nature of ROS that reaction with many different molecules is possible, but these are also very short-lived species (fractions of microseconds) and do not persist. This non-specific reactivity is highly effective in damaging microbial cell walls, membranes, organelles and enzymes and its multifactorial nature does not allow resistance selection, unlike conventional, single-mode-of-action drugs [7]. In addition, since the mode of action is chemical oxidation, chemicals produced by microbial cells, e.g. toxins and biofilm constituents, can also be damaged. The requirement for such activity is merely the conjunction of the photoantimicrobial, light of the correct wavelength and oxygen, with the directed nature of the illumination confining the photodynamic effect to the targeted area. Consequently, localised infection and colonisation (e.g. by MRSA [8]) constitute eminently suitable presentations for this approach, and would allow the conservation of conventional antimicrobials. Furthermore, such an approach would be equally suitable for veterinary application.

The clinical light-activation of a chemical product is an everyday event in dermatology, for example in the PUVA (psoralen-ultraviolet A) therapy of psoriasis and vitiligo (ironically, this combination is

itself photoantimicrobial). The use of red light and a photoantimicrobial agent such as methylene blue is little different to this, and is also similar in the fact that medical supervision may be required for its application, depending on the presentation. However, there is little reason to suggest that such supervision could not be achieved via GP and community clinics.

The O'Neill report makes considerable mention of the undoubted danger posed by carbapenemase-expressing Gram-negative bacteria, such as *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Carbapenemase expression means that there are few drugs currently available which are capable of dealing with these bacteria and, indeed, there are few in the pipeline. However, carbapenemases offer no defence at all against 'safe' photoantimicrobials such as methylene blue [9].

The rise of drug-resistant bacteria continues apace. There are very few new antibacterial agents being produced by the pharmaceutical industry, and this will not change in the short term, even if the O'Neill and similar recommendations are followed. Photoantimicrobials should be a part of the solution.

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