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Editorial

# Special section: Focus on anti-microbial photodynamic therapy (PDT)

In the face of widespread and increasing resistance of fungal, bacterial and viral pathogens to common antibiotics, therapeutics and therapies, the need for alternative efficient and affordable treatment of infections and illnesses caused by those pathogens has become imperative. That applies not only to human infections but extends to veterinary medicine and plant pathology. High population density, high mobility of people, goods and non-human vectors between very different ecological niches, where an equilibrium between living organisms has developed over generations – leading to a quasi "resistance" of the endemic population towards endemic microbes – exacerbate the problem. When suddenly transferred to different environments, people and microbes are confronted with new challenges that they may answer in unexpected and possibly fatal ways. Highly specific approaches like antibiotic therapy, which usually targets a very specific metabolic step typical for the pathogen, fail when the microbe circumvents that very step for whatever reason. A transfer from dry/cold to hot/wet climate may suffice.

Alternatives need to address these shortcomings of present therapeutic approaches. Photodynamic therapy seems to offer a promising alternative. As with many similar apparently "new" developments, the idea itself – and even the application of PDT against microbial infections – is not new (for examples, see Wainwright et al. later in this section, or refer to early descriptions in Pharaonic burial sites of the use of berberine and other photoactive compounds in combination with light for cosmetic use and, apparently, treatment of skin diseases).

The main advantages of anti-microbial PDT are high target specificity (by design and choice of compound and protocol), few undesired side effects and almost no development of resistance mechanisms in known pathogens (due to the mode of action and type of (bio)chemical target). The reason for the latter is the generalised action of the light-activated drug on vital cell structures once the drug has accumulated inside the target cell.

As with all treatments involving chemical compounds, the first crucial step is to get the drug fast, efficiently and exclusively accumulated in the target location. The advantage of PDT is that the drug is inactive in the dark and only becomes active when exposed to light of a specific wavelength. This means that during the distribution phase, the drug – if properly designed and kept out of reach of activating radiation – will not induce any side effect. Visible (day-) light only poses a problem when the drug used absorbs in that region. Systemic application of the drug may be more affected by this aspect compared to topical application (examples: Donnelly et al., Prates et al., this section). As with other pharmaceuticals, besides physico-chemical properties of the drug itself, galenics and application protocol are of major importance for this step.

Many "traditional" anti-microbial drugs need to enter and accumulate inside the cell. As this process often requires transport mechanisms, it is the first point at which a target cell may develop resistance by modifying the transport system required by the drug. Of course, that also applies to photoactivateable drugs that need to accumulate inside a cell.

Here we find another advantage of several PDT drugs over many traditional anti-microbials. Cell wall structures and membranes are the main target of PDT drugs, and so the drugs do not necessarily need to enter the cell. Specific and proper adhesion to these structures suffices for light-activated destruction of the target cell. Thus target cells have no chance to develop resistance by stopping uptake, increasing metabolic detoxification or increasing export of the drug.

Another way to circumvent cellular resistance is to exploit the fact that several essential compounds for an organism are chromophores/fluorophores and – important for PDT type I (oxygen-dependent photodynamic effect) – are part of or located in close vicinity to oxidative metabolism (mitochondria). In other words, the compounds themselves are vital for the cell, and must be either imported or generated by internal processes, which might be inducible. Examples are now well established heme-based photoactivateable drugs and 5-aminoleavulinic acid (ALA) derivatives as metabolic precursors for internal cellular production of heme drugs in competent cells.

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When a cell depends on the existence of this specific compound, it will die if the internal production or import is disabled – an effect desirable for a pathogen. If the cell does not cease import or production, one can activate the drug with specific irradiation and the cell will die that way. Either way, the goal (killing the pathogen) can be achieved.

To exploit this possibility one needs to determine if, and to what extent, pathogens offer a specific composition of internal photoactivateable compounds – distinctively different from the host. Dietel et al., in this special section, address that question. They determined the fluorescent compounds of intestinal microbes. They show that different species exhibit distinct and well distinguishable patterns and spectra of fluorescent compounds. This information can be used for diagnostic purposes (using low intensity irradiation with wavelengths specific for a certain organism), (photo-)therapy (using high intensities) and treatment efficiency determination. If a highly specific chromophore is sufficiently abundant in the target organism, one only needs to activate it by irradiation with the right wavelength and dose. These metabolic peculiarities can also be exploited for specific enrichment of photoactivateable drugs in a specific target organism by supplying the right metabolic precursor before irradiation or up-regulation of the internal production.

Because they are well separated from the genetic material during action on external structures or, when inside a cell, act preferentially on membranes and other general cell structures, the risk of PDT drugs inducing surviving mutants of the target species or accidentally affecting surrounding cells is very low compared with traditional anti-microbials.

Besides the advantages that anti-microbial PDT offers, it has some limitations.

(1) PDT drugs require external energy from a specific radiation source to become active.
(2) PDT type I requires sufficient oxygenation of the target in addition to sufficient concentration of the activator drug.
(3) Target cells must be accessible for the activating radiation energy. Penetration depth of the activating radiation is a limiting factor. Thus, surfaces can easily be treated. Deeper layers need longer wavelengths or special light delivery systems. This may be important for treatments of deeply infiltrating fungal or bacterial infections where only the upper layers can be eliminated and a reservoir of vital pathogens remains below the penetration depth.
(4) Absorption (= loss of useable energy for treatment) by surrounding tissue needs to be considered and compensated for.
(5) Activating wavelengths must be sufficiently different from absorption characteristics of surrounding tissues to avoid energy loss and possible side-effects from high intensity irradiation.

Despite these limitations, we can conclude that PDT offers a number of advantages over traditional anti-microbial therapies. Safety margins (desired effect/undesired side-effect) for PDT drugs in use are usually high compared to traditional anti-microbials. Complete replacement of all other established anti-microbial therapies with PDT will not be possible, but PDT offers a potent alternative and/or supporting therapeutic means to existing approaches, and at very reasonable costs.

Expansion of anti-microbial PDT for treatment of parasitic diseases is underway, with promising initial results. These diseases are a major health factor in developing countries. They can be a problem for the developed world too under conditions of overpopulation, decreasing hygienic standards and rising average temperatures that allow expansion of the distribution of many parasites presently still confined to tropical regions.

This introduction has aimed to outline the still rather unknown field of anti-microbial PDT to a wider audience. The following presentation of selected papers highlights actual research topics. The field is developing fast, with interesting research challenges and many positive developments. It is of high actual and future value, given the problem of the ever-increasing number of Multi-Drug-Resistance (MDR) pathogens.

If readers are inspired to join anti-microbial PDT research with new ideas and from new perspectives, a major goal of this special section will have been achieved.

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