PDT: light at the end of the tunnel?

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It is effective, selective and rather ingenious but photodynamic therapy (PDT) has not yet fulfilled its potential. A new non-release strategy that cages the drug should enable it to do its job without causing the problems that have thus far dogged PDT [1].

An exciting technology

PDT uses the energy of light to destroy tumours [2]. First, a photosensitive drug is targeted to tumour tissue, preferably a solid tumour not too deep within the patient's body. The drug is then excited by focusing a light source on the surrounding tissue. Lasers are normally used at 650–800 nm, but light-emitting diodes and fluorescent light sources can also be effective.

The drug transfers its excess energy to oxygen molecules in the surrounding milieu. The resulting reactive oxygen species, such as singlet oxygen, can cause serious damage to macromolecules and cellular components in surrounding tumour cells. Because the drug requires radiation for its effect, and the radiation is concentrated on the tumour area, there is little oxidative damage in normal tissues. However, where there is light, you will always find shadows.

PDT problems

Drug delivery is one of the main difficulties with PDT. Typically, PDT drugs are porphyrin-based and therefore have an extensive system of conjugated double bonds. This property makes them ideal for absorbing light, but normally renders the molecule somewhat hydrophobic. Such species are difficult to formulate into an effective drug, so various encapsulation strategies have been studied to protect the molecule from the aqueous environment. Encapsulation has the added benefit of increasing the size of the agent. This confers on the drug some selectivity for tumours; these tissues have a greater propensity to engulf and retain macromolecules because of their characteristically 'leaky' vasculature.

Numerous studies have used liposomes, oils and polymeric micelles as encapsulation methods, with some success. However, all of these techniques suffer from one unpleasant side effect: after controlled release and photosensitization, the drug is free to circulate the body, accumulating in the eyes and skin. This leads to phototoxic side effects, rendering the patient highly sensitive to light. A further disadvantage is that liposomes can be engulfed and destroyed by cells of the reticuloendothelial system (RES). Such problems have limited the emerging field of PDT, but an ingenious solution could be at hand.

Dynamic ceramics

A new development that addresses the various problems of previous PDT applications has been described [1] by a team from the State University of New York's Institute for Lasers, Photonics and Biophotonics (http://www.photonics.buffalo.edu/), in collaboration with members of Roswell Park Cancer Institute (http://www.roswellpark.org/), which is the birthplace of PDT. For the drug, they chose 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH), which is undergoing Phase I/II clinical trials for esophageal cancer at Roswell Park [3].

The drug is encapsulated within a ceramic-based nanoparticle, the physical properties of which make it ideal for the job. The spherical particles of ~35 nm diameter are made from silica, or similar materials, and are readily prepared at ambient temperature using a simple procedure. They are stable to fluctuations in temperature and pH and small enough to evade the RES. The shape, size and porosity can all be tailored, and the exterior of each particle can be functionalized to improve targeting. The success of the technique relies upon the tiny pores in the ceramic particle, which range from 0.5–1.0 nm. This is too small to allow the drug to escape its encapsulation but small enough to enable oxygen to diffuse back and forth. Thus, HPPH can exert tumour-killing effects without being released into the blood stream.

So far, the technique has only been demonstrated *in vitro*. The HPPH-containing nanoparticles were actively taken up by cultured UCI-107 and HeLa tumour cells. Irradiation at 650 nm with a laser caused significant tumour cell death, leaving fewer than 10% of HeLa cells viable (Figure 1). Preliminary *in vivo* tests have now begun. According to Paras Prasad, one of the researchers from the State University of New York, the ceramic nanoparticles seem to accumulate exclusively in the tumour tissue without the need for active targeting. After phototherapy, the ceramic spheres should retain the drug, and are unlikely to cause the side-effects that were seen with earlier encapsulation methods. 'Even if the particles do not degrade,' said Prasad, 'since they are very small – less than 50 nm – they are expected to be excreted from the body through the kidney.' Animal trials should take about six months, but it is too early to say when human trials might begin.

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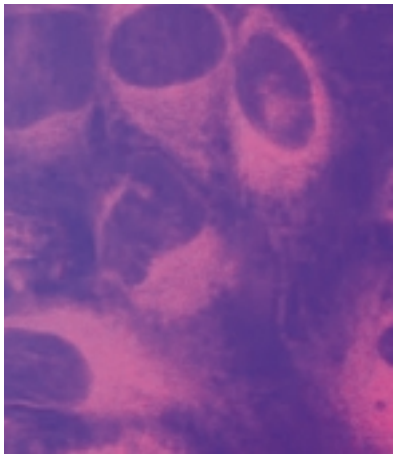

Figure 1. Confocal fluorescence image of severely damaged tumour cells treated with HPPH-doped nanoparticles. Image provided by Paras Prasad of the State University of New York, Buffalo (http://www.photonics.buffalo.edu/).

Prasad also elaborated on an extension of the technique, whereby a magnetic core is encapsulated within a silica nanoparticle and targeted to tumour tissue. The magnetically impregnated tumour cells could then be killed by exposing the tissue to a DC magnetic field. This is a potentially complementary technique to PDT, as Prasad explained, 'If photodynamic drugs can be encapsulated within such nanoparticles, they can work as dual-killers, by the magnetic as well as photodynamic action.'

Promise and potential

So, will PDT finally be associated with words such as 'routine' and 'successful', rather than 'promising' and 'potential'? Stan Brown of the University of Leeds, UK (http://www.leeds.ac.uk/), a PDT expert not connected with the study, has mixed feelings. 'The two fundamental problems to be overcome in developing PDT are to achieve good selectivity and lack of generalized skin photosensitivity,' he said. 'If this approach can achieve either of these then that would represent significant progress.' However, he cautioned that without *in vivo* data, it is not quite clear whether the nanoparticle approach will do everything the authors expect.

References

1 Roy, I. *et al.* (2003) Ceramic-based nanoparticles entrapping water-insoluble photosensitizing anticancer drugs: a novel drug-carrier system for photodynamic therapy. *J. Am. Cham. Soc.* 125, 7860–7865

2 Sharman, W.M. *et al.* (1999) Photodynamic therapeutics: basic principles and clinical applications. *Drug Discov. Today*, 4, 507–517

3 Henderson, B.W. *et al.* (1997) An *in vivo* quantitative structure-activity relationship for a congeneric series of pyropheophorbide derivatives as photosensitizers for photodynamic therapy. *Cancer Res.* 57, 4000–4007

Fgl2: link between hepatitis B and SARS?

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A new clotting factor protein, Fgl2/fibroleukin prothrombinase, has been found to be important in viral infection, including hepatitis B [1], by researchers at the University of Toronto, Canada (http://www.utoronto.ca/).

A greater understanding

Chronic hepatitis B virus affects ~300 million people worldwide [2,3] and a greater understanding of the pathogenesis of viral-induced hepatocellular injury is required. The Fgl2/fibroleukin protein is also triggered by corona virus in mice, which suggests a possible link to the human corona virus that causes SARS.

Almost 80,000 people become infected with hepatitis B virus each year in the USA, despite the fact that it is a vaccine-preventable disease [4]. There are >1 million chronically infected individuals within the USA and these patients are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. Chronic hepatitis B virus can often lead to severe complications and death after decades of infection.

Fgl2/fibroleukin

Fgl2/fibroleukin is an immune coagulant, which can directly cleave prothrombin into thrombin and has the characteristics of a serine protease. Expression is markedly upregulated by interferon-γ (IFN-γ), which is also important in viral-induced liver disease in humans and model systems. It was initially cloned from CD8+ cytotoxic T cells and shares homology of its carboxyl terminus with fibrinogen β and γ chains.

The viral pathogens that cause liver disease are not all directly cytopathic for the hepatocyte. For example, an immune response to the virus causes the hepatocellular injury that is associated with hepatitis B virus, rather than direct hepatocellular necrosis induced by the virus. Fibrin deposition and thrombosis within the microvasculature of the liver is also important in the immune response to viral infection of the liver. Importantly, the pathways by which vascular

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