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Highlights

- In contrast to conventional optical fibers, which must be removed from the body soon after use, the biodegradable and biocompatible light sources may be used for long-term light delivery and need to be removed as they are gradually resorbed by the tissue. This letter aims to present two light sources which fulfill most of the requirements for iPDT and possibly for mPDT.

Introduction

Multiple clinical studies have shown that interstitial photodynamic therapy (iPDT) is a promising modality in the treatment of cancerous tumors in prostate, pancreas, head and neck cancer and brain. The laser fibers are into the target tissue inserted via needles, or placed in catheters [1]. However, the transport distance of light in biological tissues is limited by scattering and absorption. Practical therapeutic penetration depth is 0.1-1 mm for visible light in 400-600 nm and 2-3 mm for near infrared light in 700-1300 nm for most biological tissues. The fluence rate of therapeutic light must limited to prevent undesirable photothermal damage of tissues. The rate of oxygen consumption by the PDT process and the re-oxygenation rate of tissues may be also be an important consideration in deciding on fluence rate. Depending on photosensitiser and treatment site, lower fluence rates can also reduce pain problems. Consequently, when treating a large tumor, numerous lasers fibers must be inserted in the tumor. Moreover, except maybe for the brain, interstitial fibers cannot be left in tissue for a long period time. However, several studies have demonstrated

that metronomic PDT (mPDT) based on continuous low rate delivery of photosensitizer and light, induces an enhanced induction of cell apoptosis as compared with a conventional PDT regimen [2,3]. Thus, mPDT could benefit for light sources placed inside the tumor tissue and emitting for several hours or days.

Recently, several teams have elaborated innovative implantable and biodegradable light sources that can be used for iPDT and mPDT in particular. In contrast to conventional optical fibers, which must be removed from the body soon after use, the biodegradable and biocompatible light sources may be used for long-term light delivery and need not be removed as they are gradually resorbed by the tissue. This letter aims to present two light sources which fulfill most of the requirements for iPDT and possibly for mPDT.

Bioabsorbable polymer optical waveguide

The first innovative light emitting light source was developed by Nizamoglu et al.[4] .It is made of transparent and flexible poly(L-lactic acid) biopolymer. Polymers offer a wide range of biodegradation half-times, from 1 min to over a year [5]. The relative amount of GA (Glycolide acid) in PLA (poly(L-lactic acid)) increases the biodegradation rate in PLGA (poly (D,L-lactide-co-glycolide). Besides, lactide and glycolide-based copolymers are degraded by ester hydrolysis and break into monomers, which are further degraded and resorbed in the body with minimal systemic toxicity. Therefore, these polymers are chosen for making a resorbable light source. The solid waveguide is achieved by melt-pressing technique. Its dimensions are obtained by precise laser cutting. Consequently, this waveguide can be easily shaped. Nizamoglu et al designed a waveguide similar to a trident to perform photochemical tissue bonding. In this application, a standard multimode optical fiber (200 µm core, 0.48 NA) is bonded to the waveguide using an optical adhesive. This optical fiber is connected to a 532-nm laser. Tests performed at 1W and 15 minutes duration demonstrated the efficiency of this new device (see **figure 1**). Long term evaluation of this waveguide was not performed and biodegradability and toxicity were not evaluated. However, this new device is very promising due to relative ease of manufacture and ability to deliver substantial light intensities.
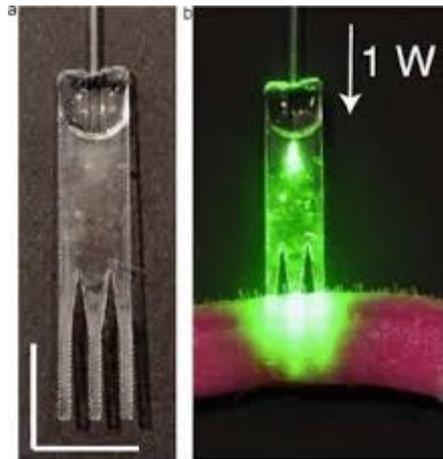
Figure 1: Hybrid biopolymer-based waveguide bundle engineered for optimal light delivery to the tissue. Scale bars, 10mm (from ref 4)

Near-infrared rechargeable "optical battery"

Another very innovative approach has been recently proposed by Hu et al [6]. This team has developed a near infrared (NIR) rechargeable "optical battery" implant for irradiation-free continuous PDT. By combining the $NaYF_4$:25%Yb,0.5%Tm upconversion materials with typical UV/blue upconversion emission (350/475 nm) and UV rechargeable $SrAl_2O_4$:2%Eu2þ,4%Dy3þ persistent phosphors (mass ratio, 1: 10), a green persistent luminescence at 520 nm can be activated by 980-nm NIR excitation due to the spectra overlapping between the upconversion emissions and absorption of persistent phosphors. The mixture was added into PDMS (biocompatible polydimethylsiloxane) and placed to special molds and degassed under vacuum for 30 min. The PDT optical battery can be obtained after solidify at 60 °C for 1 h and can be easily fabricated into any size and shape. Figure 2 shows several examples such as microneedles, wire, hollow tube or membrane (**figure 2**)
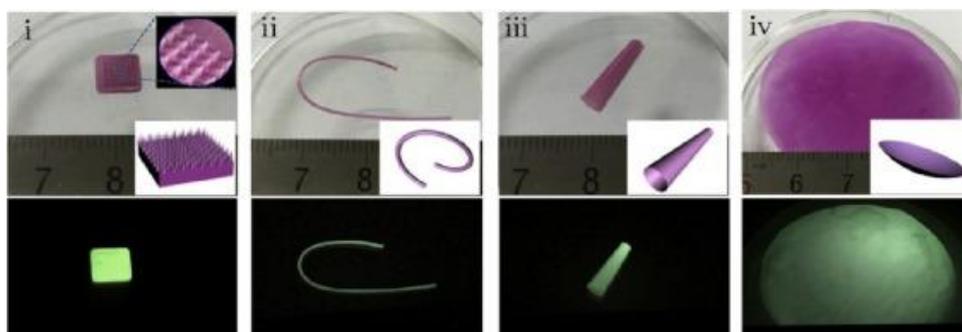

Figure 2: Photographs and 3D diagrams of the PDT implants with different shapes. i) PDT microneedles; *ii*) PDT wire *iii*) PDT hollow tube; *iv*) PDT membrane (from ref 6).

After short (5 s) charging process by 980-nm laser, the "optical battery" implant can generate green persistent luminescence for 30 minutes. 2W/cm² is enough to full charge the persistent materials without any overheating of the surrounding tissues. Furthermore, the PDT "optical battery" implant can still be charged to continuously generate singlet oxygen even in deep tissue as high as 4mm because of the deep tissue penetration of the NIR charging source. Due to the facile preparation, flexible and bio-stability of PDMS (biocompatible polydimethylsiloxane), the irradiation-free PDT implant can be easily optimized in size and shape aiming at different nidus sites

By adding the photosensitizer inside the battery, $^1O_2$ can be continuously generated under persistent luminescence. Hu et al evaluated Rose Bengal which is known to be a potent photosensitizer [7]. An experiment was performed on HT29 tumor implanted subcutaneously into mice (**figure 3**). Results clearly demonstrate that this implantable O2-generating PDT device greatly decreased the tumor volume of the mice after two NIR irradiation per day for 15 days.

Upconversion materials such NaYF4 have potential toxicity problems. However compared to upconversion nanoparticles, there is no IV injection [8]. At last, the degradation of this optical battery should be studied carefully.
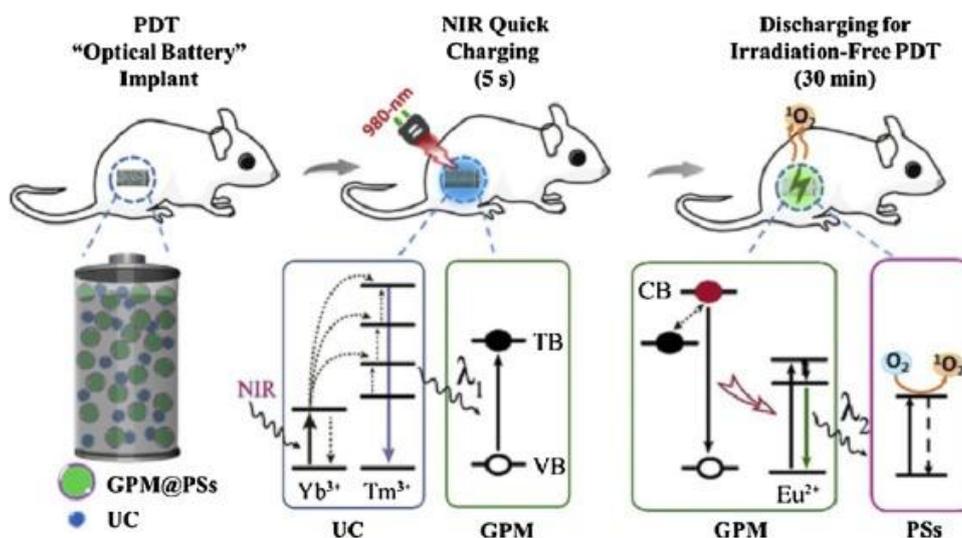

Figure 3: *Schematic illustration of the NIR light rechargeable persistent luminescence activated PDT "optical battery" implant for tumor inhibition (GPM: green persistent luminescence materials; PSs: photosensitizers; UC: upconversion materials; TB: trapping band; VB: valence band). (from ref 6)*

Conclusion

These innovative bioabsorbable waveguides and optical batteries may initiate a new paradigm and find widespread use in medicine. The use of polymers such as polydimethylsiloxane, PLA or PLGA,.. give a great adaptability of size and shape to specifically target a nidus site. Further studies should evaluate the safety of the biodegradation process which will be required in order to approve these light sources on humans.

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