Materials for Photo-Theranostic Applications

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The word theranostic is an amalgamation of "diagnostic" and "therapeutic" and can describe any materials, techniques, or ideas that can be used for either or both purposes. Light activatable, or photo-theranostics have garnered significant interest for cancer research in the past decade because of the safety, convenience, and low invasiveness of laser treatment compared to other treatments. The key advantage of photo-theranostics is the simplicity of locating and subsequently destroying cancerous cells in one procedure. This could lead to more precise removal of only the diseased tissue and have improved mortality rates compared to chemotherapy. Materials that would be useful for photo-theranostics are those which absorb strongly and then dissipate the energy through a desirable pathway. Two common examples of this energy dissipation are the photoacoustic effect[1], which converts the energy into mechanical pressure waves through expansion, and the photothermal effect[2] which converts the energy to a temperature rise.

The Photoacoustic effect, originally observed by Alexander Graham Bell in 1880[3], is a long known physical phenomenon that has recently for biomedical imaging and certain types of cancer therapy. Photoacoustic Tomography is the name given to the act of imaging by taking advantage of the photoacoustic conversion of an optically absorbant contrast agent. In photoacoustic tomography, a system is irradiated by a pulsed or modulated laser, the incident light from the laser is absorbed discriminately by the different materials that it interacts with, and certain materials will dissipate the absorbed energy and convert it to acoustic waves. These acoustic waves can be detected and interpreted by existing ultrasound technology. Figure 1 shows the process of photoacoustic tomography graphically.

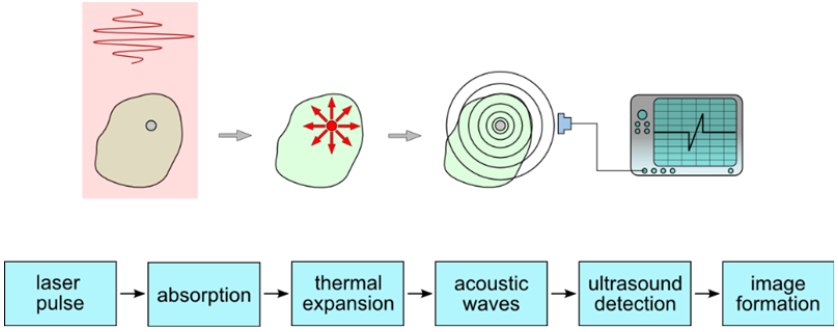

Figure 1: Schematic of the photoacoustic tomography workflow[4]

The images generated by the ultrasound detector show the location of the absorbing material as shown in Figure 2. The sharpness and intensity of the photoacoustic response will be dependent upon the extinction coefficient of the contrast agent relative to surrounding materials at the wavelength of the laser, and the relative concentration of the contrast agent being used. For simple tissue imaging there are many endogenous materials that can be viewed using photoacoustic imaging such as hemoglobin or melanin which can be seen in Figure 2.

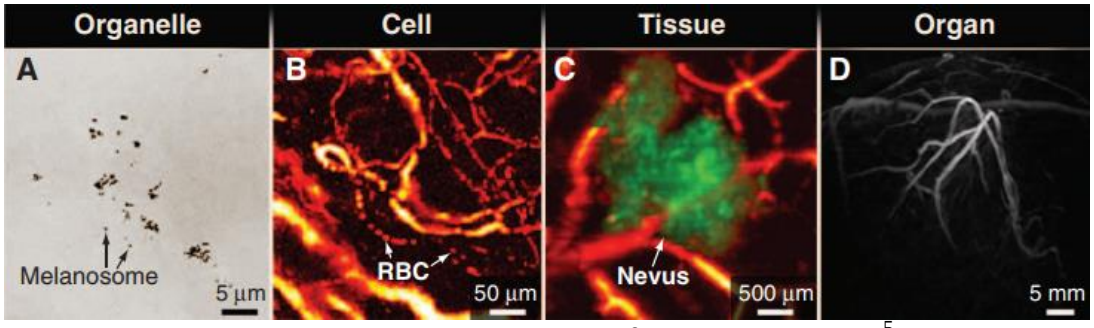

Figure 2: Photoacoustic images of biological systems[5]

In addition to being used for diagnostic purposes like photoacoustic tomography, the photoacoustic effect can also be used for therapeutic purposes. By varying the intensity and time of laser irradiation, the photoacoustic effect can also be used to cause localized cell death. In 2008, researchers discovered that Single-Walled carbon NanoTubes (SWNT), which have strong optical absorbance between 700 and 1100nm, can cause a particularly strong photoacoustic signal in response to a 1064nm, millisecond pulsed, Q-switched laser[6,7]. This acoustic response was so powerful it caused a nanoscale explosion. Using previously derived thermodynamic equations, the shockwave was estimated to create pressure in excess of 100MPa, which is about 1000 times atmospheric pressure[7]. By applying this same technique in tumor cells, the photo-induced acoustic shockwave can be used to obliterate diseased cells. SWNT are particularly useful tools for this study because they can be readily functionalized with other add-ons like targeting agents Bin Kang et al successfully conjugated a folate onto the same SWNT for this purpose[6]. The folate modification makes the material co-localize in tumor cells because the folate receptor protein is overexpressed in cancer cells[8].

In situations where the material does not undergo photoacoustic energy dissipation the material heats up in what is known as the photothermal effect, which was first published in 1933[9]. Studies have shown even tiny concentrations can result in localized heating in excess of 30°C[10,11]. Since 1990[12], the photothermal effect has been popularly employed to selectively kill tumor cells. One of the most popular photothermal agents is gold nanoparticles for several reasons. Importantly, Gold, like most nanomaterials, aggregate in tumor cells because the Enhanced Permeability and Retention (EPR) effect makes the addition of targeting agents unnecessary. is tunable absorbance properties colloidal gold which have been known for hundreds of years and thoroughly studied since the days of Faraday[14]. Because high absorbance relative to background is an important feature for selective heating for cell ablation, it is important to use materials that are strong absorbers at the wavelength of the laser. Because there are many good lasers available, it is most useful to tune the absorbance of the nanorods into the range of minimal biological tissue interference in the Near InfraRed (NIR) window as performed by M. Mackey et al in 2013[11].

The major determining factor in whether a material would undergo a photoacoustic or photothermal energy conversion is the type of laser[10,15]. A pulsed or modulated laser enhances the photoacoustic effect by forcing the materially to rapidly undergo pulsed thermal expansion, which encourages the acoustic wave formation[15]. A constant wave laser favors the photothermal conversion because it cannot induce the photoacoustic conversion unless varied[16,17]. There have been recent studies that explore the difference between the two phenomena and their potential application in cells both separate and together[10]. In the work by Du et al, multiple lasers (one pulsed and one continuous wave) were both used to irradiate an optically absorbing Zinc (II)

Phthalocyanine compound. After delivering the material into cancerous cells, the authors were able to use photoacoustic imaging, photoacoustic therapy, and photothermal therapy to map and kill tumor cells in vitro and in vivo[10].

Many materials are capable of undergoing a photoacoustic and/or photothermal energy conversion including gold nanoparticles, SWNT, semiconductive nanoparticles, organic dyes, and many more[18]. Most recent work in this area has been in applying new materials for photo-theranostic tumor identification and selective destruction, culminating in mouse-model studies, but not yet passing proof-of-concept studies[19]. The key barrier that must be overcome for widespread application and eventual human testing is tissue interference. While acoustic waves are not as easily scattered as light, some tissue, like bone, can adversely affect the response necessary for photoacoustic tomography. A major problem with using these photo-theranostic materials is that there are endogenous materials that could be unintentionally activated like melanin. Most current studies use nude mice, which are very pale and do not have comparable melanin levels to humans[19]. Because melanin can undergo both the photoacoustic and photothermal effect itself, it could cause significant damage to all tissue. Once this hurdle is overcome, these phototheranostics will be a very promising way of diagnosing and treating cancer.

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