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Nanomedicine for Targeted Photothermal Cancer Therapy: Where Are We Now?

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Thermal treatment (or hyperthermia) of tumors has a long history, dating back to the 19th century when a partial tumor regression was observed in patients with a fever. Through great efforts in developing technology for controlled and localized heating, as well as better understanding of the mechanisms behind temperature-induced cell killing, modern thermal treatment has proven to be effective alone or when combined with other cancer treatments such as radiation therapy and chemotherapy [1].

Although still in the early stages of development, ideal photothermal therapy (PTT) refers to treating cancer by targeted delivery of biocompatible photothermal nanoparticles and heat to the site of interest without damaging the surrounding healthy tissue. Well-designed nanoparticles will generate heat after the absorption of non-toxic light, which is usually in the near-infrared range (NIR, 650–900 nm), for the killing of cancer cells. Considering the limited penetration depth (a few centimeters) of NIR light as well as the varied locations of tumors in humans, the delivery of localized light may be either invasive or non-invasive. The efficiency of in vivo PTT depends greatly on the accumulation of light-responsive nanoparticles, the light-to-heat conversion efficiency, and the light dose (i.e. light power density and light exciting time).

Many nanomaterials of interest are currently being investigated for PTT, such as: noble-metal nanostructures like gold [Au] nanoshells, Au nanorods, Au nanocages, and palladium [Pd] nanosheets [2, 3]; carbon-based nanostructures such as single- or multi-walled carbon nanotubes [4], graphenes and their derivatives [5, 6]; copper-based nanocrystals, for example copper sulfide and copper selenide [7, 8]; and porphyrin-based nanoassemblies like porphysomes and nanoporphyrin [9, 10]. Although encouraging photothermal ablation of

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tumors in small animals has been reported using these nanoparticles since last decade [11], clinical translation is extremely slow, as very few of them are now under clinical trials.

Translational Research of Au Nanoshells

Initially invented by Naomi Halas and Jennifer West from Rice University in the mid-1990s, PEGylated silica-cored Au nanoshells are the first photothermal nanoparticles that have advanced into clinical trials, appearing as AuroShell® Particles in 2008 [12]. Preclinical studies confirmed the accumulation of nanoshells in tumors based on the enhanced permeability and retention (EPR) effect after intravenous (i.v.) injection in mice [13]. Thermal ablation could then be achieved by the illumination of the tumor using NIR (808 nm) laser light delivered via fiber optics. Because nanoshells do not accumulate in healthy tissue, this *AuroLase Therapy* allowed the precise thermal ablation of the tumor along its irregular boundaries while preserving the surrounding healthy tissue. A biomedical company named Nanospectra Biosciences was founded to promote this technology.

Before clinical trials, systematic toxicity studies in mice, rats, and dogs were also carried out based on the International Organization for Standardization (ISO)-10993 guidance standards for the Biological Evaluation of a Medical Device to fully investigate the biodistribution, clearance, and acute toxicity of Au nanoshells [14]. Although long-term retention of the nanoshells in the reticuloendothelial system (the liver and spleen) was observed, no obvious toxicity was indicated in any of these studies. Similar issues are also seen in other nanoparticles of similar size, making this an unsurprising result.

An efficacy study of *AuroLase Therapy* in patients with primary and/or metastatic lung tumors is anongoing clinical trial (ClinicalTrials.gov ***Identifier: NCT01679470***) in the United States. Patients are given a systemic i.v. infusion of Au naoshells and a subsequent escalating dose of laser radiation delivered by optical fiber via bronchoscopy. A second clinical trial is aiming to focus on treating patients with refractory and/or recurrent tumors of the head and neck (ClinicalTrials.gov ***Identifier: NCT00848042***). Although the addition of targeting ligands to the surface of Au nanoshells could potentially improve their accumulation in tumors as evidenced by the successful vascular-targeted PTT of glioma in mice [15], so far Au nanoshells are expected to accumulate in patients purely based on the EPR effect in these two clinical trials.

New Photothermal Nanoparticles

Despite the long and costly process (10 to 15 years and millions of dollars) of the first case of translating Au nanoshells to the clinic, preclinical studies with many newly-discovered photothermal agents in labs globally have shown encouraging results. For example, freestanding hexagonal Pd nanosheets with a thickness of less than 10 atomic layers were synthesized using carbon monoxide as a surface confining agent. As-prepared nanosheets exhibited a well-defined but tunable surface plasmon resonance peak in the NIR region and enhanced photothermal stability when compared to conventional gold or silver nanostructures [3]. Copper selenide ($Cu_{2-x}Se$) nanocrystals are another new type of photothermal agent with strong NIR optical absorption and a high molar extinction coefficient (7.7×10^7 $cm^{-1}M^{-1}$ @ 980 nm) [8]. Through doping with copper-64 (^{64}Cu, a

radioisotope with a 12.7 h half-life), researchers also succeeded in integrating intrinsic positron emission tomography (PET) imaging with PTT by developing [^{64}Cu]CuS nanoparticles [7]. Although preliminary toxicity studies showed negative results in all these newly developed nanoparticles, more systematic and long-term in vivo studies in different species are needed before clinical translation.

In addition to the above-mentioned inorganic-based photothermal agents, biodegradable porphyrin-based nanoassemblies are attractive organic nanomedicine agents, which hold greater potential for clinical translation due to their simplicity and high biocompatibility [9, 10]. In one study, porphysomes with unique photothermal and photoacoustic properties were synthesized from self-assembled phospholipid-porphyrin bilayers [9]. As-synthesized porphysomes were enzymatically biodegradable and induced only minimal acute toxicity in mice with an extremely high intravenous dose (1000 mg/kg). The potential of porphysomes as nanocarriers for loading ^{64}Cu (or Mn^{3+} ions) to form an intrinsic PET (or magnetic resonance imaging) agent has also been demonstrated recently [16, 17], highlighting their great potential as a novel biodegradable theranostic nanomedicine.

Future Perspective

Preclinical research of PTT will continue to grow quite quickly in the next decade. Although adding targeting ligands to the surface of photothermal nanoparticles could mean additional synthetic steps, costs, and greater regulatory hurdles during good manufacturing practice (GMP) [18], the engineering of tumor actively-targeted photothermal nanoparticles holds a greater chance for higher accumulation efficacy of nanoparticles in the tumor site, and will become one of the important directions for research in the next few years. Image-guided PTT and the combination of thermal therapy with conventional chemotherapy will be other promising research areas, considering that most photothermal nanoparticles are also photoacoustic imaging agents [19], and the already-demonstrated synergistic effects of thermo-chemotherapy (or thermo-radiotherapy) [20].

Great challenges still exist in pushing photothermal nanoparticles from bench to bedside. Caution needs to be taken when selecting the best nanoplatform. Nanoparticles that contain heavy metal elements or that can not be degraded in vivo may find it difficult to be approved by the Food and Drug Administration (FDA) due to their long-term toxicity concerns. Thus, liposome-like and biodegradable porphysomes with a strong NIR absorption capability might become the next promising nanomedicine for entering clinical trials. Also, most nanoparticles are known to lose their uniformity and reproducibility when production is scaled up. Therefore, great efforts are needed to ensure high quality control (e.g. good laboratory practice [GLP] and GMP) of nanoparticles that are to be translated. Finally, closer partnership among academic researchers, clinicians, pharmaceutical industries, the National Cancer Institute, and the FDA are necessary to promote the translational research of promising photothermal nanoparticles.

Conclusion

The last decade has demonstrated that nanomedicine-based PTT is a highly promising cancer management technique. Although the photothermal nanoparticles reported so far have been focused on proof-of-concept PTT demonstrations in small animals, we believe that more clinical trials of photothermal nanoparticles will be approved by the FDA, and the currently-ongoing clinical trials of Au nanoshells will bring us one step closer to curing cancer by targeted PTT.

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Weibo Cai is currently an Associate Professor of Radiology and Medical Physics at the University of Wisconsin – Madison. He received a PhD degree in Chemistry from UCSD in 2004. After post-doctoral training at Stanford University, he launched his career at UW – Madison in early 2008 and was recently promoted to Associate Professor with Tenure. His research at UW - Madison is primarily focused on molecular imaging and nanotechnology (http://mi.wisc.edu/), investigating the biomedical applications of various agents developed in his laboratory for imaging and therapy of cancer and cardiovascular diseases.

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