Applications of Nanoparticles in Targeted Drug Delivery and Photothermal Therapy

A compendium of recently published peer-reviewed articles

The use of nanoparticles for targeted drug delivery, controlled release of therapeutic agents and photothermal therapy (PTT) is growing rapidly.[1] These particles offer multi-functional capabilities that include the ability to be tracked within the body, deliver a specific compound at a controlled rate, target a particular location, and remotely kill cells once in place. Biomolecules such as antibodies, oligonucleotides, or peptides can also be bound to the nanoparticle to direct it to a precise location while long circulation times can be achieved by coating particles with polyethylene glycol (PEG). In addition to drug delivery, these versatile particles can be engineered to include fluorescence, magnetic, and light scattering properties. Once at their intended destination, nanoparticles can act as a reporter, release a compound, or be remotely heated to damage nearby biological structures.

Nanoparticles can carry thousands of drug molecules embedded within or attached to their surface. For the sustained release of a therapeutic, the core of the particle can be filled with either a solid or high concentration liquid formulation of the drug; the shell layer controls the rate at which the drug diffuses out of the core. Silica shells that are porous with a well-defined thickness can provide precise control over the diffusion delivery rate. The silica shell layer can also be chemically modified to have an affinity for the drug itself. In this case, the large surface area of the porous shell can hold and then release the therapeutic compound. Alternatively, particles can be triggered to release their payload because of changes in the local environment or by external stimuli. The trigger can be pH, heat, light, or the presence of salts or other signaling molecules. Once the trigger is initiated, the drug is released from the particle providing further localization of the therapeutic treatment.

This compendium highlights recently published articles that describe the use of silica and metal-based nanoparticles to improve therapeutic delivery and enable novel photothermal treatments.

Drug Delivery

Zhao, et al., reported the development of mesoporous silica nanoparticles (MSNs) loaded with isoimperatorin, a traditional Chinese medicine, and encapsulated in lymphoma cancer cell membrane to construct a targeted drug delivery system.[2] Ca^{2+}-dependent proteins expressed on cancer cell membranes can mediate the adhesion and targeting of tumor cells. As shown using cell culture and animal models, the novel delivery platform had characteristics of immune escape, anti-phagocytosis, high drug loading rate, low pH value sensitivity, good biocompatibility, and active targeting of the tumor site, blocking the lymphoma cell cycle and promoting mitochondrial-mediated apoptosis.

In a subsequent study, Zhao, et al., constructed a similar anti-lymphoma drug delivery system using MSNs loaded with harmine, a type of beta-carboline alkaloid extracted from the seeds of Tribulus terrestris.[3] While harmine has demonstrated anti-tumor activity, it does not exhibit targeting behavior and is characterized by poor pharmacokinetics, which limits clinical application. In contrast, the MSN-harmine complex passively targeted the tumor tissue, showed pH-responsive drug release, was non-toxic and demonstrated efficient anti-lymphoma properties.

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MSNs have also been used to enable the combination of cancer immunotherapy and photodynamic therapy (PDT), a noninvasive therapeutic modality used against tumors accessible to a light source, to generate a systemic antitumor immune response against disseminated cancer.[4] This application used MSNs for theranostic positron emission tomography (PET)-guided PDT and neoantigen-based cancer vaccination. Multiple neoantigen peptides, a CpG oligodeoxynucleotide adjuvant, and photosensitizer chlorin e6 were loaded into the MSN nanoplatform; PET imaging revealed effective accumulation of the MSNs in tumors following intravenous administration. Subsequent PDT with laser irradiation recruited dendritic cells to PDT-treated tumor sites and elicited neoantigen-specific, tumor-infiltrating cytotoxic T-cell lymphocytes. Strong antitumor efficacy of PDT-immunotherapy against locally treated tumors and distant, untreated tumors was demonstrated in several mouse models. The authors suggest that MSNs offer a promising platform for combining imaging and PDT-enhanced personalized immunotherapy for the treatment of advanced cancer.

Silica nanoparticles are also being explored as physiochemical permeation enhancers that facilitate the oral delivery of protein therapeutics. Oral dosage forms of insulin and other protein drugs would markedly improve patient experience, compliance, and disease outcomes, but the physiology of the gastrointestinal tract prevents the use of this route of administration. Lamson et al., have described the use of anionic nanoparticles to bind intestinal surface receptors that mediate the opening of tight junctions, increasing intestinal permeability and enabling the oral delivery of proteins.[5] The authors report that the permeation-enhancing effect is a function of nanoparticle size and charge, with smaller (≤ 200 nm) and more negative particles such as silica conferring enhanced permeability.

Nanoparticles are also playing an important role in the development of theranostics which combine therapeutics and diagnostics for image-guided therapy. Mukerjee et al. recently described the synthesis and screening of antibody-conjugated silica-coated iron oxide nanoparticles for prostate-specific membrane antigen (PSMA)-specific cell targeting.[6] PMSA is a recognized target for the delivery of cancer therapeutics and imaging agents due to its high expression on the surface of prostate cancer cells. The authors generated an optimized PSMA-targeted magnetic iron oxide nanoparticle with silica applied to the nanoparticle surface. Silica was selected for nanoparticle shelling because it is inert, biocompatible, easily modified, thermally stable, and provides a rigid and stable coating that maintains nanoparticle solubility and stability after routine manipulations. These studies summarize a successful strategy for generating and evaluating a series of antibody-conjugated iron oxide nanoparticles that target PSMA and advance the potential of targeted theranostic agents for future treatment of prostate and other cancers.

While silica-coated nanoparticles are biocompatible and widely used in theranostics, imaging, and drug delivery, they can trigger a reaction of the innate immune system. Park et al., explored the use of noncovalent surface functionalization of silica nanoparticles with purified proteins to inhibit nanoparticle-induced complement activation and macrophage uptake, two innate immune reactions related to nanomedicines.[7] Silica nanoparticles were tested alone and after coating with bovine serum albumin, human serum albumin, fibrinogen, complement factor H, or immunoglobulin G proteins. All coatings except IgG protected against complement activation to varying extents; these coatings also blunted macrophage uptake. In addition to mitigating innate immune reactions, the authors note that these methods are scalable and might constitute a strategy for improving the immunological safety profile of silica and silica-coated nanoparticles as well as other types of inorganic nanoparticles.

In addition to silica-based nanoparticles, metal nanomaterials are being used extensively for drug delivery applications. Because nanoparticle-based drug delivery systems offer such a wide variety of functionalities, however, pre-clinical assessments can be challenging to compare to conventional formulations. Their size, charge, and surface functionalization can impact targeting and pharmacokinetic behavior. To address this challenge, Zazo, et al., used physiologically based pharmacokinetic (PBPK) modeling to provide a mechanistic approach for studying drug biodistribution in individual organs and tissues and predict human pharmacokinetics from preclinical studies.[8] The PBPK model was used to simulate stavudine biodistribution after the administration of a 40 nm gold nanoparticle-based drug delivery system in rats. The model confirmed that the stavudine-gold nanoparticle met important characteristics for a drug delivery system, including payload, sustained release, and increased in vitro and in vivo drug concentrations in cells and tissues.

Gold nanoparticles are being used for the precision delivery of powerful antibiotics. Fuller, et al., reported the use of a technique called electrospinning to immobilize different antibiotics on a fibrous mesh scaffold along with either cationic or anionic gold nanoparticles to target the delivery of the antibiotic.[9] Delivering the antibiotics directly to the infection site rather than via an oral dosage can be beneficial as oral dosages are distributed nonspecifically throughout the body, requiring a high dose to ensure

the proper concentration at the infection site. If an antibiotic can be delivered directly to the site of infection, the dosage can be lowered, reducing side effects and complications. The nanomesh structures had different antibiotic release profiles, with citrate-capped gold nanoparticles combined with colistin having the highest sustained release over 14 days. As a proof of concept, the authors believe these results describe an opportunity for fabricating meshes in which gold nanoparticles as a drug release mechanism for antibiotics.

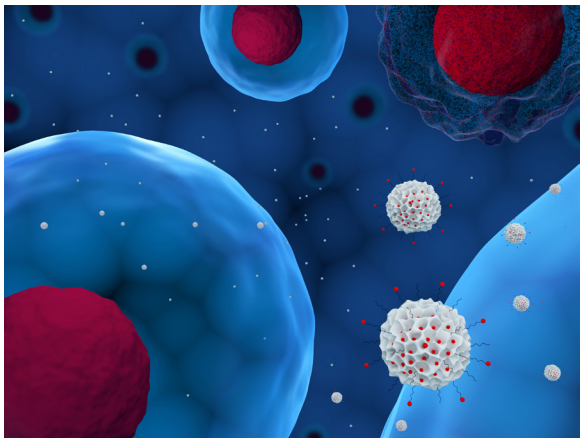

Figure 1: Mesoporous silica nanoparticles delivering drugs to cells

Ongoing work on the use of gold nanoparticles to deliver colistin considered a last line of defense in treating infections, is focused on enabling the same therapeutic effect but at a lower dosage to minimize dose-dependent side effects.[10] By delivering colistin coated on an anionic gold nanoparticle, the minimum inhibitory concentration of E. coli has been reduced sixfold compared to the antibiotic alone in studies conducted in nutrient broth. Given these results, the anionic colistin-coated gold nanoparticles show great promise for the delivery of this powerful antibiotic at a lower dosage with improved efficacy.

Goyal, et al., reported the use of layer-by-layer assembled silica core/gold shell nanoshells (LbL-NS) as vehicles for efficient intracellular delivery of microRNAs (miRNAs).[11] miRNAs are short non-coding RNAs whose ability to regulate the expression of multiple genes offers the potential to treat disease; unfortunately, miRNAs cannot passively enter cells due to their hydrophilicity and negative charge. LbL-NS were produced by coating negatively charged nanoshells with alternating layers of positive poly-L-lysine (PLL) and negative miRNA. The outer layer consisted of PLL to facilitate entry of the tumor suppressor miR-34a into triple-negative breast cancer (TNBC) cells and protect the miRNA. The authors reported that the LbL-NS efficiently delivered miR-34a to TNBC cells to suppress cancer cell growth, warranting their further investigation as tools for miRNA replacement therapy.

Advancements in engineering a compact near-infrared plasmonic nanostructure with image-enhancing agents for combined imaging and therapy have been reported by Henderson et al.[12] The authors developed a compact (sub-100 nm) multi-layer core-shell nanoparticle suitable for near-infrared (NIR) photothermal therapy that can provide simultaneous contrast enhancement for T1 magnetic resonance imaging (MRI) and fluorescence optical imaging (FOI). The structure encapsulates both types of contrast agents in the internal silica layer between the gold core and shell.

Photothermal Therapy

One of the most promising therapeutic applications of nanoparticles is the ability to locally generate heat. Plasmonic nanoparticles can be engineered to efficiently absorb light and convert the absorbed energy to heat, which is then released into the surrounding environment. By changing the size and shape of the plasmonic nanoparticle, the peak absorbance wavelength can be moved into the NIR region of the spectrum where skin and other biological tissues are relatively transparent. Magnetic nanoparticles can also be used for heating where instead of light, an oscillating electromagnetic field is used to generate heat-inducing eddy currents in the nanoparticles causing them to heat. While the equipment utilized to generate the magnetic field is complex, this treatment can be applied to areas in the body that are difficult to penetrate with light.

Among the many and varied applications of this nanoparticle-based approach is photothermal therapy (PTT) for cancer. PTT, which involves the application of plasmonic nanoparticles as light-triggered thermal transducers, has emerged as a promising cancer treatment strategy. A significant amount of research is underway to optimize PTT.

Jorgensen, et al., developed a single particle and PET-based platform to correlate the heat generation of plasmonic nanoparticles with their potential as cancer-killing agents.[13] Heat generation and absorption cross-section of single irradiated nanoparticles were quantified in vitro using a tempera-

ture-sensitive lipid-based assay and compared to their theoretically predicted photo-absorption. In vivo, heat generation of irradiated nanoparticles was evaluated in human tumor xenografts in mice using 2-deoxy-2-[F-18]fluoro-D-glucose (18F-FDG) PET imaging. To validate the platform, the authors quantified the photothermal efficiency of NIR resonant silica-gold nanoshells (AuNSs) and benchmarked the results against the heating of colloidal spherical, solid gold nanoparticles (AuNPs). Heat generation of the resonant AuNSs was superior compared to the non-resonant AuNPs both in vitro and in vivo. These results indicate that PET imaging can be used to reliably monitor early treatment response to PTT and offer a way to benchmark novel plasmonic nanoparticles for use in this novel treatment modality.

An ongoing challenge with plasmonic PTT is the need to minimize the damage to the surrounding tissue. Adjacent tissue can be damaged by absorption of laser light, thermal conductivity, nanoparticles diffusing from the tumor, or a combination of these factors.

He, et al, sought to better understand light–tissue interactions and thermal responses in porcine brain tissue samples including the brain stem, cerebrum, and cerebellum, under laser treatment.[14] The authors found that different tissues have differential optical and thermal properties and confirmed the enhancement of heating by adding plasmonic gold and silver nanoparticles. When the temperature under laser irradiation was measured, a significant difference between the heating of the brain stem and the other types of tissue was observed. The effect of plasmonic PTT on the tumor and the side effects on the healthy brain tissue are related in a non-trivial manner, depending on the tissue properties. As such, the authors conclude that a personalized analysis of the local brain tumor environment is needed to balance the effect and side effects prior to plasmonic PPT.

Heat distribution during PTT can be heterogeneous throughout the tumor volume, leading to the tumor only being partially treated. Simon, et al., have investigated whether giving the treatment repeatedly, referred to as fractionated PTT, increases efficacy in mice bearing subcutaneous tumors.[15] The study used silica-gold nanoshells in two fractionated protocols – either two or four laser treatments of a murine subcutaneous colorectal tumor model. Efficacy was evaluated by monitoring tumor growth and PET imaging of 18F-labeled glucose analog 18F-FDG. While the authors found no significant differences in tumor growth and survival in single-dose PTT or fractionated PTT, some animals showed inhibited tumor growth or complete tumor disappearance with fractionated PTT; these animals also showed a significant decrease in tumor uptake of 18F-FDG after therapy. Given these results, it is clear that many factors can affect the outcome of PTT and continued optimization is needed.

The potential of gold nanoshells and nanorods for tumor ablation in combination with NIR light is driving the development of superior nanomaterials and improved methods for optimizing irradiation regimens, which could improve PTT. Von Maltzahn et al, described the development of novel plasmonic nanomaterials to improve the specificity of cancer ablation by homing to tumors and acting as antennas for accepting externally applied energy.[16] The team synthesized PEG–protected gold nanorods that exhibit superior spectral bandwidth, photothermal heat generation per gram of gold, and circulation half-life compared with gold nanoshells, the prototypical tunable plasmonic particles. A single intravenous injection of PEG-nanorods enabled the destruction of all irradiated human xenograft tumors in mice. The authors believe that these results highlight the potential of integrating computational therapy design with nanotherapeutic development for precision tumor ablation.

Because the success of PTT treatment depends on many biological factors, routine use will necessitate robust patient monitoring and evaluation. The PET tracer 18F-FDG has been successfully used in cancer imaging; a decrease in 18F-FDG uptake in tumors following treatment could be interpreted as a loss of tumor viability. 18F-FDG evaluation can, however, be impaired by tumors that have a low baseline uptake or reside in or in the vicinity of tissues that have a naturally high glucose metabolism. To address this, Simon et al., evaluated diffusion-weighted imaging (DWI), an MR technique that characterizes the diffusion of water molecules within tissues, for early response monitoring of PTT in tumor-bearing mice using silica-gold nanoshells (NS).[17] NS-treated mice experienced inhibited tumor growth and significantly prolonged survival compared to control mice. Changes in 18F-FDG uptake and the apparent diffusion coefficient, the way DWI is quantified, correlated significantly with survival, demonstrating that both methods can be used for the early evaluation of PTT.

Conclusion

As demonstrated in the publications reviewed in this compendium, nanomaterials like gold nanospheres, gold nanoshells, gold nanorods, and iron oxide nanoparticles as well as silica and mesoporous silica nanoparticles can offer exceptional performance and unique capabilities in the applications of drug delivery and photothermal therapeutics

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