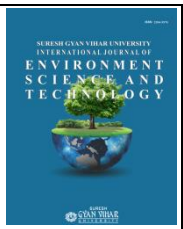

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Review article

Plasmonic Nanogold for Effective Photothermal Cancer Therapy

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Keywords

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Abstract

The recently emerged cancer treatment modality, photothermal therapy (PTT) has garnered significant attention as non invasive biomedical technique for localized treatment of solid tumors. The therapeutic effects in terms of destroying tumor cells are derived from the local hyperthermia due to heat generated by the photo-sensitizers. In this regard, the gold nanoparticles (GNPs) have emerged as powerful photoactive agents to perform PTT owing to their biocompatibility and unique tunable optical properties. The localized surface plasmon resonance (LSPR) effect in GNPs enable them to efficiently convert near-infrared (NIR) light into heat to ablate cancer cells while causing no significant harm to the surrounding healthy tissues. The efficiency of PTT can be optimized by modifying the shape and size dependent LSPR of GNPs. This review provides a comprehensive overview of the advancements in GNP-based PTT, highlighting the diverse types of GNPs, and their application in photothermal cancer treatment.

Introduction

Cancer is the second leading cause of mortality worldwide, causing millions of deaths every year. The emergence of significantly high number of new cancer cases is seriously alarming. (Adeel et al., 2020; Bao et al., 2016). There is no considerable decrease in the risk of death from cancer, despite improvements in diagnosis, treatment, and preventative measures (Cole & Holland, 2015). The traditional approaches towards cancer therapy involve surgery,

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chemotherapy and radiotherapy (Beik et al., 2019). The surgical method is an invasive approach and involves the resection of malignant solid tumors from the body. This method is often unable to eliminate all tumor cells, particularly in cases where metastasis has already occurred (Chen et al., 2015). On the other hand, the chemotherapy procedure involves the use of anticancer therapeutic agents such as doxorubicin, vinblastine, cisplatin and vincristine that inhibit mitosis by damaging or altering DNA, hampering DNA repair and inhibiting macromolecular biosynthesis. This method suffers from non-specific targeting and often fails to distinguish between tumor cells and healthy cells and thereby posing risk to the latter. Furthermore, this method is also subjected to the issue of inefficacy due to poor pharmacokinetic features of anticancer drugs that are often associated with low solubility, stability, and metabolism. The radiation therapy depends upon the use of high-energy photons or charged particles for cancer cell ablation. This approach relies on damaging the DNA strands in cancer cells, however the radiations affecting surrounding healthy tissue, may lead to risk of secondary cancer (Navya et al., 2019; LeBrun & Zhu, 2018). To overcome the limitations associated with conventional methods, a significant amount of research have been devoted for the development of new efficient treatment methods that can either replace or supplement the existing modalities by lowering unwanted side effects while increasing the efficacy. The tumor immunotherapy is a relatively safe and effective method which is based on the ability of immune cells to identify and kill tumor cells. It has been proven highly successful, especially in case of hematological tumors (Deng et al., 2021; Wu et al., 2019). Gene therapy is another promising strategy to treat cancer and has led to many hundreds of clinical trials in recent years. The general strategies involve expression of pro-apoptotic and wild type tumor suppressor genes as well as targeted silencing of oncogenes (Pucci et al., 2019). In this regard, RNA interference (RNAi) has been regarded as significant technological advancement for targeted gene silencing using small interfering RNAs (siRNAs). Besides these methods, there is photodynamic therapy (PDT) which is based upon administration of a photo-sensitizer (PS) into the body and subsequent activation by light to derive therapeutic effects. The therapeutic benefits are derived from generation of cytotoxic reactive oxygen species (ROS) upon activation of PS. The ROS can oxidize crucial cellular biomolecules which ultimately leads o the destruction of tumor cells (Lucky et al., 2015). On the other hand, the clinically practised hyperthermia based cancer therapy has also been recognized as a powerful procedure to damage and kill cancer cells. Hyperthermia treatments can be performed on small areas of the body or the entire body. These treatments are often used as an adjuvant therapy to make cancer cells susceptible to other treatment modalities.

The size, location, and type of the tumors are taken into consideration while choosing the right energy sources for hyperthermia cancer therapy (HT). The photothermal therapy (PTT), magnetic nano hyperthermia (MNH), radiofrequency (RF), and ultrasound nano hyperthermia (UNH) are four main types of HT based on energy sources (Kang et al., 2020). Amongst these methods, the PTT has emerged as a non-invasive and minimally toxic therapeutic modality that relies on generation of localized heat owing to photo-excitation of photothermal agents after irradiation with appropriate near-infrared (NIR) light (650-1700nm). The high temporal-spatial resolution with no adverse effects has made PTT an attractive method for treatment of nearly all types of cancers (Sun et al., 2021). In this context, different metal, carbon and semiconductor based nanomaterials have already gained significant attention to facilitate PTT because of their strong photothermal conversion efficiency (Fernandes et al., 2020). The biocompatible GNPs with plasmonic properties have been of great interest to perform PTT. This article discusses the application of differently shaped gold nanoparticles in PTT application.

Hyperthermia: An Approach to Cancer Treatment

Hyperthermia (HT) has been extensively explored by scientists as a therapeutic approach to combat cancer. Originally the observation was made by William Coley in 1891 when he noticed a correlation between erysipelas, a streptococcal skin infection and tumor regression. In an attempt to recreate this phenomenon he intentionally induced HT in cancer patients with bacterial extracts named Coley's toxins and observed an antitumor response (Chatterjee et al., 2011). Since then, HT has been employed by investigators as either an alternative to surgery or in combination with radiation and/or chemotherapy to induce antitumor effects (Toraya-Brown & Fiering, 2014). HT involves treatment of oncogenic cells with the temperature ranging from 40-48 °C, obtained from external heat sources, for a period of one hour or more (Chicheł et al., 2007). This range of temperature degrades the enzymatic cell protein and induces cell apoptosis. Even slightly higher temperatures are known to significantly enhance the effects of chemotherapy and radiation therapy (Moroz et al., 2001). Integrating HT with chemotherapy serves the dual purpose of heat ablation of cancer cells as well as triggering the release of chemotherapeutic drug from thermosensitive drug carriers, directly at the desired site. Furthermore, heat increases the internalization of drugs and the drug carriers as the permeability of cell membrane increases at relatively high temperature (Phung et al., 2019). HT has been known to enhance the effects of radiotherapy specifically in the temperature range of 41-43 °C. The modification of different molecular parameters by HT is known to be

involved in sensitizing tumor cells to radiation and thereby enhancing the potential of targeted radiotherapy. The enhanced benefits have been reported to be derived from increased sensitivity of hypoxic and nutritionally deficient cells in low pH, inhibition of radiation-induced DNA damage repair, sensitization of the "S" phase cells and increased intrinsic sensitivity to hyperthermia of sarcomas and melanomas as described by N.R. Datta et al. (Datta et al., 2015). The conventional HT approaches applied in clinical practices are not tumor specific and are very challenging to perform. For an example, whole body HT can cause thermal lesions due to superficial overheating and regional HT has limited specific absorption rate distribution (Kaur et al., 2016; Mortezaee et al., 2021). In contrast, PTT has emerged as an advantageous cancer treatment modality for targeted and localized effects and is currently being explored in number of clinical trials. The PTT requires photo-active or plasmonic nanomaterials that can absorb light in both near-infrared (NIR) windows namely, NIR-I (750-1000 nm) and NIR-II (1000-1350 nm). The application of NIR light for PTT based cancer treatment has been gaining tremendous attention as it can penetrate relatively deeper into living tissue when compared to ultraviolet and visible light and exhibits reduced absorption and scattering leading to non-significant photodamage to biological tissues. The plasmonic nanomaterials can harvest energy from the external adjustable laser irradiation and efficiently concert it to heat which leads to increase in the temperature at the tumor site while causing no harm to the surrounding healthy cells. However, ineffective ablation of deep seated tumors and overexpression of heat shock proteins during PTT need to be addressed to realize the full potential of this method. (Liu et al., 2019).

Role of Nanoparticles in Hyperthermia and Limitations

Nanoparticle (NP) mediated HT has revolutionized the current diagnostic and treatment procedures for advanced biomedical applications. They mediate localized thermal ablation of tumor cells by playing the role of the primary source of heat while harnessing the energy from the external source (Beik et al., 2016). A large number of NIR responsive nanoparticles such as magnetic nanoparticles, carbon nanotubes, polymeric nanoparticles and gold nanoparticles have been developed and investigated for their performance in cancer PTT. The magnetic nanoparticles develop heat when exposed to alternating magnetic fields (AMF) and thus act as nanoheaters. These nanoheaters mediate an irreversible physiological damage in the tumor cells which leads to effective therapeutic outcomes (Bañobre-López et al., 2013; Kumar et al., 2021). A few examples of magnetic nanoparticles include ferromagnetic nanoparticles such as iron oxide (Sun et al., 2013; Ebrahimisadr et al., 2018), super-

paramagnetic iron oxide nanoparticles (SPION) (Reyes-Ortega et al., 2021; Kaushik et al., 2020) and doped iron-oxide nanoparticles (Drake et al., 2007). During the application of these nanoparticles, care is taken to determine the thermal dose rate, because uncontrolled application of large field amplitude can lead to overheating issues (Vines et al., 2019). On the other hands, carbon nanotubes exhibit a combination of remarkable attributes for the development of the next generation photothermal agents. The CNTs correspond to a very wide range of optical absorption and fluorescence properties. The photophysical properties of CNTs can be effectively tuned by modifying the wall number, diameter, and length (Singh & Torti, 2013). In an interesting study, the dispersion of single walled carbon nanotubes (SWCNTs) using Evans Blue (EB) facilitated combined chemo-photothermal therapy. The method was proved to show improved effects over individual treatment procedures for the treatments performed in MDA-MB-435 cell line (Zhang et al., 2015). In this context, the multiwalled CNTs (MWCNTs) are relatively advantageous over SWCNTs for chemo-photothermal therapy. Alongside strong optical absorption properties, MWCNTs allow relatively high loading of chemotherapeutic drugs because of large surface area and thus suitable for different anticancer therapy applications. Effective integration of chemotherapy and photothermal therapy was achieved by MWCNTs functionalized with TAT-chitosan. This system showed sustained release of doxorubicin alon with significant photothermal ablation of tumor cells upon NIR irradiation (Dong et al., 2017). The clinical use of CNTs is limited due to the long-term safety, and excretion which first need to be adequately addressed. The scope of improvement also lies in improving the uniformity in size of particles, standard optimization of drugs and their controlled release (Son et al., 2016). The other system, polymeric nanoparticles (PNPs) can be designed to incorporate various drugs and absorb near-infrared (NIR) light for chemophotothermal treatment of cancer cells. The self-assembled polymeric nanoparticles based on poly (heptamethine) in the presence of PEG-PLA were developed for bimodal bioimaging and photothermal therapy. This multifunctional nanomedicine formulation facilitated biodistribution study and inhibited growth of cervical carcinoma cells upon laser irradiation. However, PNPs possesses several drawbacks in terms of poor drug loading efficiency, stability and uncontrolled drug release (Lin et al., 2016). A biodegradable semiconducting polymer nanoparticles, having vinylene bond in structural backbone unit, was reported for its enhanced photoacoustic and PTT efficiencies. The vinylene bonds facilitated the breakdown of nanoparticles into smaller fragments under the influence of oxidative stress. This significantly increased the mass absorption coefficient by 1.3 folds and PTT efficiency by 2.4 folds when compared to the

counterpart system without vinylene bond (Lyu et al., 2018). In this line, gold nanoparticles have gathered significant attention in biomedical applications, due to their unique biocompatibility and surface functionalization properties. The nanogold-based structures have been reported to act as highly efficient theranostic agents (Bardhan et al., 2011).

Nanogold in Medicine and Hyperthermia based Cancer Therapy

The biological application of gold (Au) was first discovered in 1890 by Robert Koch when he determined that gold cyanide was toxic for the tuberculosis bacillus in vitro. Further, ionic gold was proved to relive from joint pains in patients suffering from rheumatoid arthritis. The application of gold has evolved from the application of gold salts to gold nanoparticles for potential biomedical use as imaging probes, drug delivery systems, and therapeutic agents (Balfourier et al., 2020). The application of plasmonic GNPs has the potential to tremendously impact the efficacy of PTT. The unique properties of GNPs such as ease of surface functionalization, passive accumulation of GNPs within tumors via the enhanced permeability and retention (EPR) effect, and high biocompatibility, makes them an ideal candidate for PTT. The plasmonic GNPs exhibit strong thermal stability, excellent pre-clinical tolerance, and minimal adverse effects **(**Norouzi et al., 2018; Riley & Day, 2017). The optical properties of GNPs are dependent on plasmons which refer to the collective oscillation of conduction electrons present on a noble metal when stimulated with light. An absorption band known as the plasmon resonance (PR) is created when the incident photon frequency resonates with the collective oscillation of conduction electrons. Since the disturbance of the incident electromagnetic wave on the metal decreases rapidly with depth, the resonance occurs frequently on the metal surface, which is known as surface plasmon resonance (SPR). The local SPR (LSPR) occurs when the SPR is limited to small volumes of nanoparticles that are similar in size to the wavelength of the incident light (Bai et al., 2020). The LSPR is dependent on the shape and size of GNPs and can be easily tuned towards NIR region which is suitable for PTT application. More complex shapes exhibit more enhanced LSPR when compared with spherical GNPs (Hussein et al., 2018). To modulate the LSPR, several different shapes of GNPs have been examined such as nanorods, nanocubes, nanowires and nanoprisms. Similarly, triangular, pentagonal and hexagonal shaped gold particles have been fabricated in nano-dimensions (Alex & Tiwari, 2015) (Figure 1).

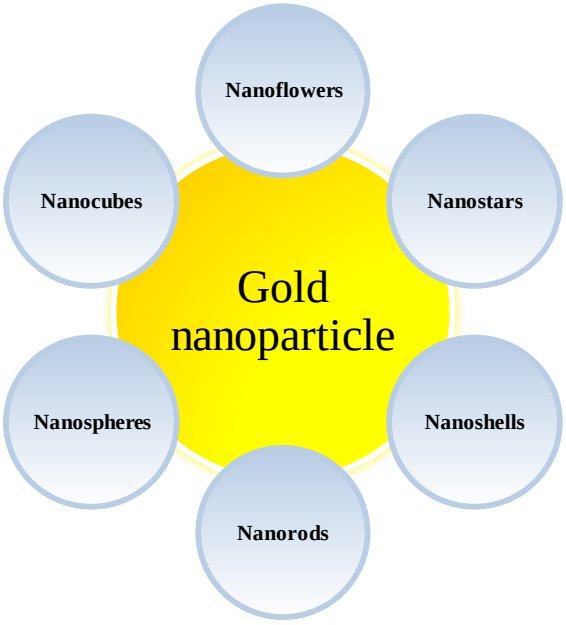

Figure 1. Differently shaped gold nanoparticles reported for potential photothermal therapy (PTT) against cancer.

Commonly used GNPs for PTT

Gold Nanostars

The anisotropic structure of gold nanostars (GNSs) endows them with unique optical properties that are relevant for photothermal therapy. The GNSs are represented as nanostructures having a central core and a number of protruding tips. Due to ease of tailoring the said structural features of gold nanostars (GNS), it is possible to tune optical absorption in desirable light spectrum which therefore allows them to be used as PTT agents. The multiple sharp tips and spikes of GNS play an extraordinary role of magnifying the local electromagnetic field by many folds and hence providing concentrated heat to the cancer cells (Liebig et al., 2019; Liu et al., 2018). The multifunctional hybrid nanomaterials based on GNS have also been reported to give rise to superior photothermal effects. A study reported the synthesis of stable and biocompatible graphene oxide and GNS (GO-AuNS) hybrid nanomaterial with excellent PTT efficacy. The developed hybrid nanopatches showed strong absorption in the near-infrared therapeutic window (650–900 nm) and were internalized intact by SKBR-3 epithelial breast cancer cells. The enhanced PTT effects were reported by this hybrid system in terms of higher increase in temperature when compared with nanostars and graphene oxide alone at low laser power (0.75 W cm^{-2}) (Nergiz et al., 2014). In another study the fabrication of polydopamine-modified GNS was reported for PTT of cancer. The GNS was stabilized by poly (ethylene glycol) (AuNSs@PDA-PEG) which showed excellent

biocompatibility and photostability. In vitro studies in HeLa cell line reported 10.02% decrease in cell viability when exposed to 808 nm laser irradiation after incubation with AuNSs@PDA-PEG. The effect of PTT was attributed to mitochondrial dysfunction, enhanced lysosomal membrane permeability and autophagy (Li et al., 2019). The GNS has also been developed as multimodal nanoconstruct demonstrating to function as drug delivery systems, PTT and/or photoacoustic imaging agents (Figure 2). The silica coated plasmonic gold nanostars demonstrated effective PTT after heating under laser illumination, with temperatures reaching 45 °C in 10 minutes and the silica shells enhanced the photoacoustic (PA) signal of dual plasmonic gold nanostars by improving thermal transfer and reducing thermal resistance at the gold-water interface. Tumors treated with nanostars showed a significant temperature rise resulting in enhanced tumor destruction after photothermal treatment (Raghavan et al., 2017). Another multimodal therapeutic strategy combining drug delivery and photothermal therapy was developed based on gold nanostar liposome-entrapped mesoporous silica core–shell nanostructure. This system encapsulated both hydrophilic (doxorubicin) and hydrophobic (docetaxel) drugs wherein thermosensitive liposomes acted as gatekeepers. Upon NIR laser exposure, the nanostars exhibited temperature dependent release of drug due to rupture of liposome. The combined chemo-photothermal therapy enhanced cytotoxicity against MDA-MB-231 and MCF-7 cancer cells, effectively inhibiting tumor growth after intratumoral injection and NIR laser treatment, offering a promising platform for multimodal tumor therapies (Cai et al., 2020).

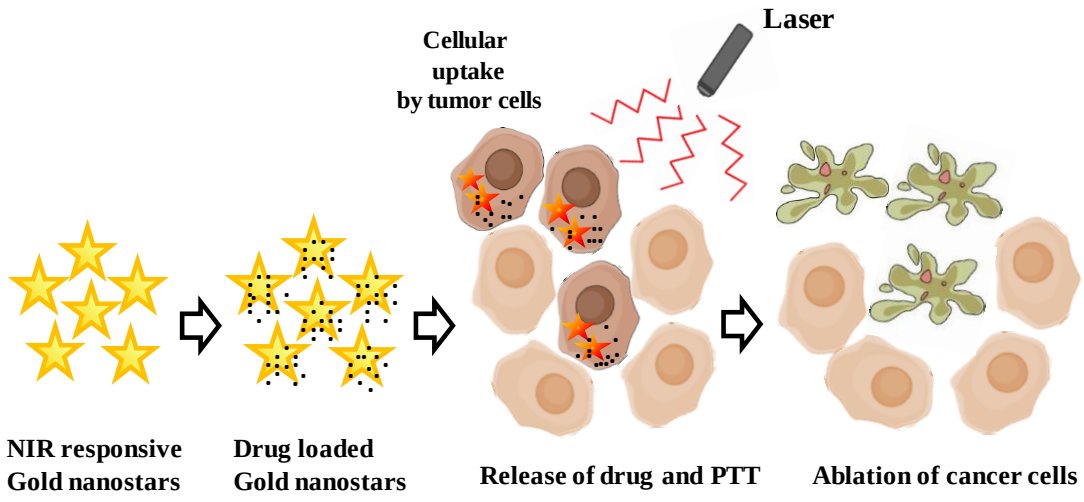

Figure 2. Representative schematic for chemo-photothermal therapy using gold nanostars.

Gold Nanoshells

The gold nanoshells have also drawn a significant attention due to their easily tunable surface plasmon resonance and are represented as a spherical layer of gold around a solid or hollow core. The shell thickness can be adjusted through synthetic optimizations for size dependent desirable absorption to find application in cancer PTT (Wang et al., 2018; Lal et al., 2008). For one such example, the gold nanoshells were grown on oleanolic acid containing chitosan coated liposomes (GNOLs) for chemo-photothermal therapy. The gold nanoshells provided photothermal effect and lipid bilayers showed thermal-sensitive behaviour which resulted in the substantial disruption of lipid coating after NIR light irradiation for boosted drug release that was also aided by pH responsive behaviour of chitosan to achieve enhanced tumor inhibition rates. The system easily accumulated in the tumor cells through EPR effect and responded to hyperthermia and low pH to yield excellent antitumor effect In Vitro and In Vivo (Luo et al., 2016). Similarly, a nanoplatform was developed that consisted of a polymeric {poly(lactic-co-glycolic acid); (PLGA)} core containing anticancer drug, doxorubicin and a porous gold shell. The gold shell provided the nanoplatform with ability to absorb NIR light and subsequently release for photothermal treatment and accelerated drug release. The gold shell was further functionalized with human serum albumin, fluorescent dye indocyanine green and folic acid to endow the nanoplatform with multifunctional characteristics to derive maximum benefits of the combinatorial therapy. Enhanced in vitro cell cytotoxicity effect was observed in MDA-MB-231 and HeLa cancer cell lines. In Vivo imaging and biodistribution studies were performed to track the nanoplatform in immunodeficient BALB/c nude mice (Topete et al., 2016). In a study reported P. Tuersun et al. the importance of the optimal core radii and shell thicknesses of silica-gold and hollow gold nanoshells based on Mie theory was highlighted to achieve maximum effects in photothermal therapy. It was emphasized that smaller gold nanoshells of high aspect ratios can prove to be excellent PTT agents. The analysis of numerical studies revealed that hollow gold nanoshells can offer little superior light absorption characteristics at smaller particle size in comparison to silica-gold nanoparticles (Tuersun & Han, 2018).

Gold Nanorods

The gold nanorods are rod shaped gold nanoparticles and have been extensively investigated for photothermal therapy application due to their remarkable optical properties, adjustable aspect ratio, and easy surface modification. The AuNRs exhibit unique LSPR and tunable optical absorption possible by just changing the aspect ratio (Meng et al., 2019; Taylor et al., 2022). The surface functionalization of gold nanorods allows it to be used for multimodal

therapy applications. The solid gold nanorods (GNRs) conjugated with antiepidermal growth factor receptor (anti-EGFR) antibodies were used as in vitro contrast agents for molecular imaging and PTT. The target ligands functionalized gold nanorods could easily differentiate between nonmalignant epithelial cell line (HaCat) and two malignant oral epithelial cell lines HOC 313 clone 8 and HSC 3. This was possible to achieve because of overexpression of EGFR on malignant cells. Only laboratory microscope was sufficed to visualize the malignant cells in dark field owing to scattered red light from gold nanorods. Interestingly, laser treatment studies revealed that the cancer cells needed relatively low laser energy to be photothermally ablated than nonmalignant cells, lading to selective inhibition of cancer cells (Huang et al., 2006). Multifunctional GNR probes coated with MUA (11-mercaptoundecanoic acid) and linked with low-molecular-weight chitosan oligosaccharide (Mw ~5000) via carbodiimide (EDC) coupling agent and a tumor targeting monoclonal antibody against EGFR, was reported for noninvasive imaging, specific targeting and effective photothermal therapy. Initial in vitro and then in vivo toxicity assessments indicated biocompatibility of the developed nanorods (Charan et al., 2012). Another study reported the development of gold nanorods of three different sizes (38 × 11, 28 × 8, and 17 × 5 nm) for checking the photothermal therapy efficacy based on different sizes. The research aimed at identifying the optimal AuNR size for effective heat generation during PTT. Theoretical studies and in vitro experiments were considered to determine the plasmonic properties and therapeutic efficacy. The optimal size provided the best balance between light absorption and heat conversion. Additionally, the electric field extension from surface facilitated efficient heat generation through inter-particle interaction (Mackey et al., 2014). In an interesting study, intranuclear photothermal therapy was performed at ultralow laser irradiation power (0.2 W/cm^2) using gold nanorods conjugated with nuclear location signal peptides (GNRs-NLS). The study demonstrated that GNRs-NLS effectively accumulated in cell nuclei and caused mild temperature increases upon laser irradiation that led to cancer cell death through apoptosis by damaging DNA and inhibiting DNA repair. Conversely, negligible antitumor effects were shown by GNRs without nuclear targeting ligands under the same experimental conditions. This approach was unique in terms of therapeutic benefits resulting from apoptosis rather than necrosis which is usually observed in most of the PTT based treatments. Additionally, tumor treatment with GNRs-NLS led to gradual but significant regression which was again different from most of the reported procedures that mentioned harsh burning-up of tumors. The findings suggested that GNRs-NLS could potentially be translated into clinical applications for cancer treatment (Pan et al., 2017).

Other Shapes of GNPs

Other than the three gold nanostructures discussed above, there are few others that have been reported to have potential application in PTT. One such example is the developed gold nanoflowers which showed significant NIR light absorption and very strong photothermal cytotoxicity. The nanoflowers were developed using vesicle template produced by amine based surfactants and subsequent deposition of nanogold on the surface. The LSPR of these nanoflowers was easily modulated by controlling their size. Also NIR light irradiation was reported to facilitate the entry of relatively large nanoflowers under hyperthermia conditions. The nanoflowers were reported to be biocompatible and have toxic effects only upon NIR light exposure (Han et al., 2014). Another example includes the development of popcorn-like gold nanostructures using extracellular vesicles as templates. The gold nanoparticles assembly was grown on the surface of anticancer drug containing extracellular vesicles which when exposed to near-infrared irradiation, led to hyperthermia induced tumor ablation and triggered drug release, enabling a combined chemo-photothermal therapy (Zhang et al., 2019).

Table 1: Representative examples for synthetic methods of commonly used differently shaped GNPs

S.No.	Shape of GNPs	Synthesis method	Reference
1.	Gold nanostars	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) as a reducing and shape directing agent	(Nergiz et al., 2014)
		Citrate-stabilized seed solution mixed with gold salt, silver salt and ascorbic acid	(Li et al., 2019)
		Mixture of gold and silver salt treated with ascorbic acid	(Raghavan et al., 2017)
2.	Gold nanoshells	Seed solution mixed with chitosan/lipids and $NaBH_4$ as reducing agent	(Luo et al., 2016)
		Citrate stabilized seed solution, PLGA nanoparticles, gold salt in potassium carbonate and ascorbic acid as reducing agent	(Topete et al., 2014)
3.	Gold nanorods	Seed solution, gold salt, CTAB, BDAC (Benzyldimethylhexadecyl-ammonium chloride), silver salt and ascorbic acid	(Huang et al., 2006)
		Seed solution, gold salt, CTAB, silver salt,	(Charan et al.,

		ascorbic acid, sodium sulphide	2012)
		Seed solution, gold salt, CTAB, silver salt, ascorbic acid	(Mackey et al., 2014)

Conclusion

The GNP-mediated PTT has provided significant hope for cancer treatment and has been extensively exercised in the last decade either alone or in combination with different therapeutic procedures already available in clinics. This cancer treatment method has become a relevant choice lately due to the facts that it is a non-invasive procedure and poses non-significant damage to normal surrounding tissues. The importance of this method lies in application of biologically relevant NIR light for generation of heat directly ablate tumor cells. Also, a significant advantage in cancer cell killing can be derived by controlling the temperature to choose between cell apoptosis and necrosis. Amongst the plethora of different types of nanoparticles, the GNPs are excellent photoactive agents to facilitate PTT due to their unique and tunable optical properties. Different PTT relevant attributes have been imparted to gold nanoparticles while modulating their shapes and sizes for effective cancer therapy. In this context, differently shaped gold nanoparticles such as nanostars, nanoshells and nanorods have emerged potent PTT agents that are able to give desirable outcomes in combination based cancer therapy. These PTT agents works well in combination with chemotherapy drugs to increases the therapeutic efficacy for instance, by providing temperature mediated substantial release of the drug at the tumor site. Such GNP based intervention can also sensitize cancer cells for radiotherapy by increasing cell permeability. The combination with immunotherapy is gaining significant attention in this regard and different scientific groups are already engaged in putting down its roots in biomedical application. As of now, not many GNP-based systems have actually been approved by health agencies and therefore designing new multimodal therapy formulations has become essential.

References

Adeel, M., Duzagac, F., Canzonieri, V., & Rizzolio, F. (2020). Self-therapeutic nanomaterials for cancer therapy: a review. *ACS Applied Nano Materials*, 3(6), 4962-4971.

Alex, S., & Tiwari, A. (2015). Functionalized gold nanoparticles: synthesis, properties and applications—a review. *Journal of Nanoscience and Nanotechnology*, *15*(3), 1869-1894.

Bai, X., Wang, Y., Song, Z., Feng, Y., Chen, Y., Zhang, D., & Feng, L. (2020). The basic properties of gold nanoparticles and their applications in tumor diagnosis and treatment. *International Journal of Molecular Sciences*, *21*(7), 2480.

Balfourier, A., Kolosnjaj-Tabi, J., Luciani, N., Carn, F., & Gazeau, F. (2020). Gold-based therapy: From past to present. *Proceedings of the National Academy of Sciences*, 117(37), 22639-22648.

Bañobre-López, M., Teijeiro, A., & Rivas, J. (2013). Magnetic nanoparticle-based hyperthermia for cancer treatment. *Reports of Practical Oncology & Radiotherapy*, 18(6), 397-400.

Bao, Z., Liu, X., Liu, Y., Liu, H., & Zhao, K. (2016). Near-infrared light-responsive inorganic nanomaterials for photothermal therapy. A*sian Journal of Pharmaceutical Sciences*, 11(3), 349-364.

Bardhan, R., Lal, S., Joshi, A., & Halas, N. J. (2011). Theranostic nanoshells: from probe design to imaging and treatment of cancer. *Accounts of Chemical Research*, *44*(10), 936-946.

Beik, J., Abed, Z., Ghoreishi, F. S., Hosseini-Nami, S., Mehrzadi, S., Shakeri-Zadeh, A., & Kamrava, S. K. (2016). Nanotechnology in hyperthermia cancer therapy: From fundamental principles to advanced applications. *Journal of Controlled Release*, 235, 205-221.

Beik, J., Khateri, M., Khosravi, Z., Kamrava, S. K., Kooranifar, S., Ghaznavi, H., & Shakeri-Zadeh, A. (2019). Gold nanoparticles in combinatorial cancer therapy strategies. *Coordination Chemistry Reviews*, 387, 299-324.

Cai, Z., Zhang, Y., He, Z., Jiang, L. P., & Zhu, J. J. (2020). NIR-triggered chemo-photothermal therapy by thermosensitive gold nanostar@ mesoporous silica@ liposome-composited drug delivery systems. *ACS Applied Bio Materials*, 3(8), 5322-5330.

Charan, S., Sanjiv, K., Singh, N., Chien, F. C., Chen, Y. F., Nergui, N. N., Huang, S.H., Kuo, C. W., Lee, T. C., & Chen, P. (2012). Development of chitosan oligosaccharide-modified gold nanorods for in vivo targeted delivery and noninvasive imaging by NIR irradiation. *Bioconjugate Chemistry*, 23(11), 2173-2182.

Chatterjee, D. K., Diagaradjane, P., & Krishnan, S. (2011). Nanoparticle-mediated hyperthermia in cancer therapy. *Therapeutic Delivery*, 2(8), 1001-1014.

Chen, Q., Ke, H., Dai, Z., & Liu, Z. (2015). Nanoscale theranostics for physical stimulus-responsive cancer therapies. *Biomaterials*, 73, 214-230.

Chicheł, A., Skowronek, J., Kubaszewska, M., & Kanikowski, M. (2007). Hyperthermia–description of a method and a review of clinical applications. *Reports of Practical Oncology & Radiotherapy*, 12(5), 267-275.

Cole, J. T., & Holland, N. B. (2015). Multifunctional nanoparticles for use in theranostic applications. *Drug Delivery and Translational Research*, 5, 295-309.

Datta, N. R., Ordóñez, S. G., Gaipl, U. S., Paulides, M. M., Crezee, H., Gellermann, J., Marder, D., Puric, E., & Bodis, S. (2015). Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future. *Cancer Treatment Reviews*, 41(9), 742-753.

Deng, X., Shao, Z., & Zhao, Y. (2021). Solutions to the drawbacks of photothermal and photodynamic cancer therapy. *Advanced Science*, 8(3), 2002504.

Dong, X., Sun, Z., Wang, X., & Leng, X. (2017). An innovative MWCNTs/DOX/TC nanosystem for chemo-photothermal combination therapy of cancer. *Nanomedicine: Nanotechnology, Biology and Medicine*, 13(7), 2271-2280.

Drake, P., Cho, H. J., Shih, P. S., Kao, C. H., Lee, K. F., Kuo, C. H., Lin, X.Z., & Lin, Y. J. (2007). Gd-doped iron-oxide nanoparticles for tumour therapy via magnetic field hyperthermia. *Journal of Materials Chemistry*, 17(46), 4914-4918.

Ebrahimisadr, S., Aslibeiki, B., & Asadi, R. (2018). Magnetic hyperthermia properties of iron oxide nanoparticles: The effect of concentration. *Physica C: Superconductivity and its applications*, 549, 119-121.

Fernandes, N., Rodrigues, C. F., Moreira, A. F., & Correia, I. J. (2020). Overview of the application of inorganic nanomaterials in cancer photothermal therapy. *Biomaterials Science*, 8(11), 2990-3020.

Han, J., Li, J., Jia, W., Yao, L., Li, X., Jiang, L., & Tian, Y. (2014). Photothermal therapy of cancer cells using novel hollow gold nanoflowers. *International Journal of Nanomedicine*, 517-526.

Huang, X., El-Sayed, I. H., Qian, W., & El-Sayed, M. A. (2006). Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. *Journal of the American Chemical Society*, 128(6), 2115-2120.

Hussein, E. A., Zagho, M. M., Nasrallah, G. K., & Elzatahry, A. A. (2018). Recent advances in functional nanostructures as cancer photothermal therapy. *International Journal of Nanomedicine*, 2897-2906.

Kang, J. K., Kim, J. C., Shin, Y., Han, S. M., Won, W. R., Her, J., Park, J. Y., & Oh, K. T. (2020). Principles and applications of nanomaterial-based hyperthermia in cancer therapy. *Archives of Pharmacal Research*, 43, 46-57.

Kaur, P., Aliru, M. L., Chadha, A. S., Asea, A., & Krishnan, S. (2016). Hyperthermia using nanoparticles–promises and pitfalls. *International Journal of Hyperthermia*, 32(1), 76-88.

Kaushik, S., Thomas, J., Panwar, V., Ali, H., Chopra, V., Sharma, A., Tomar, R., & Ghosh, D. (2020). In situ biosynthesized superparamagnetic iron oxide nanoparticles (SPIONS) induce efficient hyperthermia in cancer cells. *ACS Applied Bio Materials*, *3*(2), 779-788.

Kumar, A. V. P., Dubey, S. K., Tiwari, S., Puri, A., Hejmady, S., Gorain, B., & Kesharwani, P. (2021). Recent advances in nanoparticles mediated photothermal therapy induced tumor regression. *International Journal of Pharmaceutics*, *606*, 120848.

Lal, S., Clare, S. E., & Halas, N. J. (2008). Nanoshell-enabled photothermal cancer therapy: impending clinical impact. *Accounts of Chemical Research*, 41(12), 1842-1851.

LeBrun, A., & Zhu, L. (2018). Magnetic nanoparticle hyperthermia in cancer treatment: History, mechanism, imaging assisted protocol design, and challenges. *Theory and Applications of Heat Transfer in Humans*, 2, 631-667.

Li, Y., Wang, X., Yang, D., Hu, P., Gao, L., Chen, D., Qiao, Y., Wu, Y., Jiang, X., & Li, G. (2019). Polydopamine-coated gold nanostars for near-infrared cancer photothermal therapy by multiple pathways. *Journal of Materials Science*, 54(18), 12036-12048.

Liebig, F., Henning, R., Sarhan, R. M., Prietzel, C., Schmitt, C. N., Bargheer, M., & Koetz, J. (2019). A simple one-step procedure to synthesise gold nanostars in concentrated aqueous surfactant solutions. *RSC Advances*, 9(41), 23633-23641.

Lin, W., Li, Y., Zhang, W., Liu, S., Xie, Z., & Jing, X. (2016). Near-infrared polymeric nanoparticles with high content of cyanine for bimodal imaging and photothermal therapy. *ACS Applied Materials & Interfaces*, 8(37), 24426-24432.

Liu, Y., Bhattarai, P., Dai, Z., & Chen, X. (2019). Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer. *Chemical Society Reviews*, 48(7), 2053-2108.

Liu, Y., Crawford, B. M., & Vo-Dinh, T. (2018). Gold nanoparticles-mediated photothermal therapy and immunotherapy. *Immunotherapy*, 10(13), 1175-1188.

Lucky, S. S., Soo, K. C., & Zhang, Y. (2015). Nanoparticles in photodynamic therapy. *Chemical Reviews*, 115(4), 1990-2042.

Luo, L., Bian, Y., Liu, Y., Zhang, X., Wang, M., Xing, S., Li, L., & Gao, D. (2016). Combined near infrared photothermal therapy and chemotherapy using gold nanoshells coated liposomes to enhance antitumor effect. *Small*, 12(30), 4103-4112.

Lyu, Y., Zeng, J., Jiang, Y., Zhen, X., Wang, T., Qiu, S., Lou, X., Gao, M., & Pu, K. (2018). Enhancing both biodegradability and efficacy of semiconducting polymer nanoparticles for photoacoustic imaging and photothermal therapy. *ACS Nano*, *12*(2), 1801-1810.

Mackey, M. A., Ali, M. R., Austin, L. A., Near, R. D., & El-Sayed, M. A. (2014). The most effective gold nanorod size for plasmonic photothermal therapy: theory and in vitro experiments. *The Journal of Physical Chemistry B*, *118*(5), 1319-1326.

Meng, L., Zhang, J., Li, H., Zhao, W., & Zhao, T. (2019). Preparation and progress in application of gold nanorods. *Journal of Nanomaterials*, 2019(1), 4925702.

Moroz, P., Jones, S. K., & Gray, B. N. (2001). Status of hyperthermia in the treatment of advanced liver cancer. *Journal of Surgical Oncology*, 77(4), 259-269.

Mortezaee, K., Narmani, A., Salehi, M., Bagheri, H., Farhood, B., Haghi-Aminjan, H., & Najafi, M. (2021). Synergic effects of nanoparticles-mediated hyperthermia in radiotherapy/chemotherapy of cancer. *Life Sciences*, 269, 119020.

Navya, P. N., Kaphle, A., Srinivas, S. P., Bhargava, S. K., Rotello, V. M., & Daima, H. K. (2019). Current trends and challenges in cancer management and therapy using designer nanomaterials. *Nano Convergence*, 6(1), 23.

Nergiz, S. Z., Gandra, N., Tadepalli, S., & Singamaneni, S. (2014). Multifunctional hybrid nanopatches of graphene oxide and gold nanostars for ultraefficient photothermal cancer therapy. *ACS Applied Materials & Interfaces*, 6(18), 16395-16402.

Norouzi, H., Khoshgard, K., & Akbarzadeh, F. (2018). In vitro outlook of gold nanoparticles in photo-thermal therapy: a literature review. *Lasers in Medical Science*, *33*, 917-926.

Pan, L., Liu, J., & Shi, J. (2017). Nuclear-targeting gold nanorods for extremely low NIR activated photothermal therapy. *ACS Applied Materials & Interfaces*, *9*(19), 15952-15961.

Phung, D. C., Nguyen, H. T., Phuong Tran, T. T., Jin, S. G., Yong, C. S., Truong, D. H., Tran, T. H., & Kim, J. O. (2019). Combined hyperthermia and chemotherapy as a synergistic anticancer treatment. *Journal of Pharmaceutical Investigation*, 49, 519-526.

Pucci, C., Martinelli, C., & Ciofani, G. (2019). Innovative approaches for cancer treatment: Current perspectives and new challenges. *ecancermedicalscience*, 13.

Raghavan, V., O'Flatharta, C., Dwyer, R., Breathnach, A., Zafar, H., Dockery, P., Wheatley, A., Keogh, I., Leahy, M., & Olivo, M. (2017). Dual plasmonic gold nanostars for photoacoustic imaging and photothermal therapy. *Nanomedicine*, 12(5), 457-471.

Reyes-Ortega, F., Delgado, Á. V., & Iglesias, G. R. (2021). Modulation of the magnetic hyperthermia response using different superparamagnetic iron oxide nanoparticle morphologies. *Nanomaterials*, *11*(3), 627.

Riley, R. S., & Day, E. S. (2017). Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *9*(4), e1449.

Singh, R., & Torti, S. V. (2013). Carbon nanotubes in hyperthermia therapy. *Advanced Drug Delivery Reviews*, 65(15), 2045-2060.

Son, K. H., Hong, J. H., & Lee, J. W. (2016). Carbon nanotubes as cancer therapeutic carriers and mediators. *International Journal of Nanomedicine*, 5163-5185.

Sun, H., Xu, L., Fan, T., Zhan, H., Wang, X., Zhou, Y., & Yang, R. J. (2013). Targeted hyperthermia after selective embolization with ferromagnetic nanoparticles in a VX2 rabbit liver tumor model. *International Journal of Nanomedicine*, 3795-3804.

Sun, H., Zhang, Q., Li, J., Peng, S., Wang, X., & Cai, R. (2021). Near-infrared photoactivated nanomedicines for photothermal synergistic cancer therapy. *Nano Today*, 37, 101073.

Taylor, M. L., Wilson Jr, R. E., Amrhein, K. D., & Huang, X. (2022). Gold nanorod-assisted photothermal therapy and improvement strategies. *Bioengineering*, 9(5), 200.

Topete, A., Alatorre-Meda, M., Iglesias, P., Villar-Alvarez, E. M., Barbosa, S., Costoya, J. A., Taboada, P., & Mosquera, V. (2014). Fluorescent drug-loaded, polymeric-based, branched gold nanoshells for localized multimodal therapy and imaging of tumoral cells. *ACS Nano*, 8(3), 2725-2738.

Toraya-Brown, S., & Fiering, S. (2014). Local tumor hyperthermia as immunotherapy for metastatic cancer. *International Journal of Hyperthermia*, 30(8), 531-539.

Tuersun, P., & Han, X. E. (2014). Optimal design of gold nanoshells for optical imaging and photothermal therapy. *Optik*, 125(14), 3702-3706.

Vines, J. B., Yoon, J. H., Ryu, N. E., Lim, D. J., & Park, H. (2019). Gold nanoparticles for photothermal cancer therapy. *Frontiers in Chemistry*, 7, 167.

Wang, Y. C., Rhéaume, É., Lesage, F., & Kakkar, A. (2018). Synthetic methodologies to gold nanoshells: an overview. *Molecules*, 23(11), 2851.

Wu, D., Yu, Y., Zhao, C., Shou, X., Piao, Y., Zhao, X., Zhao, Y., & Wang, S. (2019). NK-cell-encapsulated porous microspheres via microfluidic electrospray for tumor immunotherapy. *ACS Applied Materials & Interfaces*, 11(37), 33716-33724.

Zhang, D., Qin, X., Wu, T., Qiao, Q., Song, Q., & Zhang, Z. (2019). Extracellular vesicles based self-grown gold nanopopcorn for combinatorial chemo-photothermal therapy. *Biomaterials*, *197*, 220-228.

Zhang, L., Rong, P., Chen, M., Gao, S., & Zhu, L. (2015). A novel single walled carbon nanotube (SWCNT) functionalization agent facilitating in vivo combined chemo/thermo therapy. *Nanoscale*, 7(39), 16204-16213.