METALLIC NANOPARTICLES FOR PHOTOTHERMAL THERAPY

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***Abstract*- Photothermal therapy (PTT) is a promising novel treatment for head and neck cancers. In PTT, metallic nanoparticles (NPs) are used to convert light energy of a laser to heat, which causes cell death in the surrounding tumour tissue. The composition, morphology, and size of these NPs influences the safety and efficacy of PTT. This review concludes that the optimal NPs for PTT have a bimetallic composition with a silver core and golden shell, a star-shaped morphology, and a size between 5 and 150 nm. Depending on size, these nanoparticles have properties required for PTT, such as an optimal photothermal conversion efficiency in the near infrared region (NIR), efficient tumour uptake, low accumulation in other organs, and prevention of immediate clearance. Before metallic NPs can be applied in PTT, a suitable method of synthesis must be developed, next to tumour targeting strategies and coatings. The efficacy and safety should be determined using animal models, organoids, and clinical trials.**

***Index Terms*-** Head and neck cancer, netallic nanoparticles, near infrared light, photothermal therapy

I. INTRODUCTION

Yearly, over 3000 patients in the Netherlands get the diagnosis of head and neck cancer (HNC) (Nederlandse Kankerregistratie, 2022). The treatment of HNC is very dependent upon the type and stage of the cancer, but it often includes a combination of radiotherapy, surgery and systemic therapy (Mody et al., 2021). This can come with severe consequences, such as toxic side-effects or (partial) loss of speech.

A promising new treatment for HNC is photothermal therapy (PTT). PTT is based on the conversion of light energy of a near infrared light (NIR) laser to heat, which causes cell death in the surrounding tissue (Chen et al., 2019). Multiple photothermal agents can be used to achieve this effect, and important traits for these agents are a specificity for tumour cells and high photothermal conversion efficiency (PCE). (Han & Choi, 2021).

Metallic nanoparticles (NPs) can be used as a photothermal agent for PTT due to surface plasmon resonance (SPR). This describes the oscillation of free electrons at the surface of a metal in resonance with an electromagnetic field applied to its particles. The oscillation of electrons is converted to localised heat (Lv et al., 2021). The use of NPs makes it possible to utilise the SPR effect by targeting tumour cells specifically.

Several clinical trials have been conducted with nanomaterial-mediated PTT by the company AuroLase®, using silica-gold nanoshells (Han & Choi, 2021). A trial for prostate cancer showed promising results in tumour reduction (NCT02680535), which indicates the effectiveness of PTT as a treatment for cancer. A trial on refractory and/or recurrent HNC tumours was not completed as patients showed side-effects (NCT00848042). These clinical trials show that PTT is a promising new therapy, where optimization of the treatment is needed to increase the efficacy and decrease the side effects.

By optimising the NPs in PTT treatment, a more successful cancer therapy could be found for this group. The composition, morphology and size of the NPs influence the light to heat conversion due to a change in the SPR effect. The composition of the NPs also influences their toxicity and stability. The aim of this literature review is therefore to discuss the optimal morphology, size and composition of metallic NPs for the use in PTT.

II. METHODS

The Google Scholar search engine is used, with the following key words in varying combinations: bimetallic, nanoparticles, photothermal therapy, surface plasmon resonance, synthesis, gold, silver, head and neck cancer, morphology, shape, composition, size. Included studies must have been published in the past 15 years and be peer-reviewed. They can be experimental studies or reviews. Studies published before 2007 and non-English publications are excluded from this review.

III. RESULTS AND FINDINGS

A. Composition

Metallic NPs can be used in PTT due to the SPR effect which describes the conversion of light into heat by oscillation of electrons. Noble metals have a strong SPR effect, which makes them effective in producing heat and therefore a good candidate for use in PTT (Lv et al., 2021).

Gold is the most explored noble metal for PTT because the metal requires low radiation energies due to its optical-thermal conversion efficiency. The low radiation energies make PTT less invasive (Jabeen et al., 2014). In addition, gold nanoparticles have an excellent photostability, low cytotoxicity and are biocompatible, which is beneficial for their use as a medical treatment (Hwang et al., 2014). Silver materials have also gained attention recently for the use in PTT due to low toxicity and a better heat conductivity than other metals (Boca et al., 2011). Combining silver and gold into bimetallic NPs offers unique optical properties, which cannot be found in monometallic NPs. The SPR effect of these bimetallic NPs is stronger and the absorption spectra are broader (Boote et al., 2014). To obtain NPs which have the advantages of silver and gold, without the drawbacks of both metals, the core of the particle should be silver and the so-called shell should be gold

(Calderon et al., 2021). These properties make bimetallic NPs preferred for the application of PTT.

B. Morphology

The morphology of metallic NPs significantly influences their physical properties and therefore affects the possible application in photothermal therapy. The optimal absorption of the NPs is in the near infrared region (NIR) between 750 and 900 nm, due to the maximal penetration depth in the tissue and the minimal absorption by biomolecules in the skin and the blood (Hwang et al., 2014). Next to this, NPs with an optimal absorption in the NIR region can be activated with an infrared laser, which makes it possible to apply the treatment at a specific place in the body (Lv et al, 2021). A great diversity of NP shapes is possible, varying from spheres to cubes, rods, wires, and cages (Xie et al., 2010).

Spherical NPs made of only gold have a characteristic absorption at 500-600 nm, which is in the visible spectrum. However, changing the shape to a non-spherical one can shift the absorption to the NIR region between 750 and 900 nm (Xie et al., 2010). The most common morphology of pure gold NPs with absorption in the NIR region are nanorods. These NPs exhibit two wavelength bands, caused by longitudinal and transverse oscillation of electrons, of which the stronger longitudinal wavelength band is in the NIR region (Huang et al., 2007). Gold nanorods have been shown to be effective *in vivo* in ablating ovarian tumour cells (Jang et al., 2012).

Gold nanocages are cubes with hollow interiors and porous walls. NPs of this shape have a variable SPR effect depending on the amount of added metal precursor and can therefore be tuned to exhibit absorbance in the NIR region (Skrabalak et al., 2018). The use of golden nanocages in PTT has been shown to be promising with an *in vivo* study. In this study, golden nanocages of 45 nm were used with an LSPR of 810 nm. They were coupled to an antibody targeting the epidermal growth factor (EGFR) that is overexpressed on breast cancer cells. This caused cellular death of breast cancer cells after irradiation with a laser (Chen et al., 2007).

Another morphology of gold NPs showing absorption in the NIR region are so-called nanostars, or branched NPs. They consist of a core with sharp tips, where the size of the tips influences the optical properties (Hao et al., 2007). Applied electrical fields can be enhanced near the tips of the stars, leading to heat generation. Therefore, a nanostar with long tips, called a nano-urchin, can cause effective photothermal ablation (Liu et al., 2013). Next to this, nanohexapods (nanostars with 6 spikes) have shown greater tumour uptake and photothermal conversion efficiency than gold nanorods and nanocages (Vines et al., 2019).

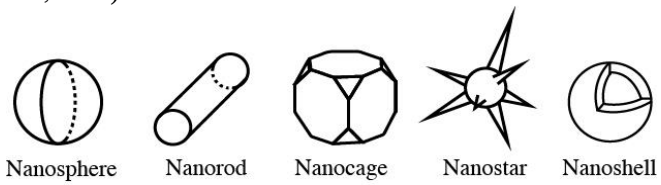

FIGURE 1.
Schematic representation of possible shapes of nanoparticles. The shapes are based on the review of De Berardis et al. (2020).

Besides gold NPs, the shift of absorbance from the visual spectrum to the NIR region also occurs in bimetallic NPs, such as those with an iron oxide core and a gold nanoshell. These particles in solution have been irradiated with NIR light with a centre wavelength of 808±10 nm leading to an increase of the temperature of the solution (Ji et al, 2007). Nanostars made of silver and gold also exhibit absorption in the NIR region as these show an absorbance peak at 949 nm (Joseph et al., 2019).

To conclude, the absorbance of gold and bimetallic NPs can be shifted from the visual spectrum to the NIR region by changing the shape from spherical to a nanorod, nanoshell, nanocage, or nanostar, where nanohexapods are the most optimal morphology for PTT due to their great tumour uptake and photothermal conversion efficiency (Vines et al., 2019).

C. Size

Nanoparticle size influences several properties that affect how suitable the particles are for photothermal therapy. Firstly, the nanoparticle distribution in the body after intravenous injection is influenced by the size of the NPs. NPs larger than 200 nm get removed by the reticuloendothelial system, which causes direct clearance and thereby an ineffective therapy (de Barros, 2012). Research by Moghimi et al. (2012) suggested that filtration by the reticuloendothelial system can be avoided by using NPs smaller than 150 nm. However, NPs of a size under 10 nm, are also unsuitable for photothermal therapy, since they quickly get filtered out of the body by the renal system due to their small size (Zuckerman, 2012).

Additionally, accumulation of NPs at sites outside of tumour tissue is undesirable, since this can have cytotoxic effects. The largest accumulation of NPs occurs in the heart, the liver, and the spleen (Dreaden, 2012). Several studies have been conducted to discover at what size NPs accumulate least. In the research of Jong et al. (2008) mice were intravenously injected with gold NPs of size 10, 50, 100 and 250 nm. After 24 hours, the amount of gold NPs in the blood, heart, lung, thymus, liver, spleen, kidney and brain was measured and it was observed that most NPs accumulated in the liver and spleen. The particles with a size of 10 nm accumulated in almost every organ, while the larger particles were only found in the blood, liver, and spleen. Interestingly, the particles with size of 50 nm showed the lowest accumulation in the liver and spleen compared to all other sizes. Research of Sonavane et al. (2008) found similar results after injecting mice with 15, 50, 100, and 200 nm NPs. 15 nm NPs accumulated most throughout the tissues, while the 50 nm NPs had the lowest accumulation in the liver and spleen.

Another factor that influences the efficiency of PTT is how well the particles are able to reach the tumour cells. Due to the leaky vasculature and the poor lymphatic drainage around tumours, the interstitial fluid pressure in tumours is high (Hoffman, 2006). This pressure is higher at the core of the tumour, making it harder for NPs to reach the centre. A model of tumour tissue has shown that NPs of 12 nm are better at penetrating the tumour than larger particles (Chauhan, 2012). An *in vivo* study by Natarajan et al. (2008) confirmed these results, in which tumour targeting was compared for NPs of size 20, 30, and 100 nm. They found that the 20 nm particles were more efficient at targeting the tumour than their bigger-sized counterparts.

However, the NPs of 20 nm did have a lower heating capacity than their bigger-counterparts, which is another aspect that needs to be considered.

Hence, the range for NPs suitable for PTT lies between 10 and 150 nm and within this range certain sizes are more favourable for certain aspects. While NPs of 50 nm show lower accumulation in the liver and spleen, NPs around 20 nm are best at reaching tumour tissue. Therefore, it is not agreed upon what the 'ideal' size for NPs is.

IV. DISCUSSION

In order to realise NPs with optimal composition, shape and size, a suitable method of synthesis must be developed. With current techniques this is hard to accomplish chemically, for the reason that golden spikes will be reduced quicker than silver, which leads to the formation of NPs with a golden core and silver spikes. These NPs are less preferred for PTT as explained earlier (Calderon et al., 2021). Moreover, the preparations of NPs are usually carried out by various physical and chemical methods like laser ablation, pyrolysis, lithography, chemical vapour deposition, sol-gel technique, and electrodeposition which are very expensive and hazardous. Using these methods also leads to the presence of some toxic chemicals absorbed on the surface that may have adverse effects in applications (Roopan et al., 2014).

After completing synthesis of the NPs, several aspects need to be further researched and taken into account. Firstly, different methods for the administration of the NPs need to be explored. Some known strategies are intra-tumour injection, active targeting, biometric targeting and programmed targeting (Zhao et al., 2021). In addition, different coatings should be tested. Polyethylene glycol is a coating with high potential to use successfully and safely on golden NPs for drug purposes (Zamora-Justo et al., 2019). Over and above that, the distribution through the body and the natural clearance of the NPs should be checked in animal models. Additionally, the cytotoxicity could be tested on organoids before entering the clinical trials (Angela L Caipa Garcia, 2021). After finalising the preclinical experiments, the newly developed therapy for PTT should be tested in the clinical trials, including additionally needed devices, e.g. NIR lasers. In the course of these trials efficacy and adverse effects will be tested on test patients.

V. CONCLUSION

To conclude, the optimal NPs for PTT have a bimetallic composition with a silver core and golden shell, combining the best of both worlds.The optimal morphology is likely to be a nanohexapod due to their good tumour uptake and photothermal conversion efficiency. NPs of a size between 10 and 150 nm are optimal, where NPs of 50 nm show lower accumulation in organs, and NPs under 30 nm are best at reaching the tumour tissue. More research is needed on the synthesis of the optimal NPs. Before the NPs can be utilized in PTT, the options for administration and coatings should be explored, and research is needed on the distribution through the body and the cytotoxicity.

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