Current Clinical and Medical Education

Received 28 May 2024 | Revised 30 May 2024 | Accepted 30 Jun 2024 | Published Online 01Jul 2024

Published By: Vision Publisher

ISSN 2942-0792

CCME 02 (7), 29-41

Hyperthermia in Cancer Therapy with Gold Nanoparticles: New Approaches to the Treatment

Mohammed Talib Nayel Al-Sultani[1], Fatima Saad Wahid Al-Araji[2], Hayder Hameed Mohammed AL-Saadi[3], Ali Saad Abbas Al-Khafaji[4], Ali Basim Idan AL-Mamoori[5], Ameer Raad Saad[6]

[1]Al-Hilla University College, Department of Medical Physics, Iraq.
[2]University of Kufa, College of Science, Department of Physics, Iraq.
[3]Al-Hilla University College, Department of Medical Physics, Iraq.
[4]Al-Hilla University College, Department of Medical Physics, Iraq.
[5]Al-Hilla University College, Department of Medical Physics, Iraq.
[6]Al-Mustaqabal University College, Department of Medical Physics, Iraq.

Abstract: Hyperthermia, a little increase in tumour temperature, increases the sensitivity of cancer cells to radiation and chemotherapy. Getting there isn't easy, and the tried-and-true ways have their limitations. To get around some of the problems and produce tumour hyperthermia, it is possible to load tumours with energy-transducing nanoparticles that are systematically administered. However, there are distinct obstacles that nanoparticles must overcome before they can be used in clinical settings. Nanorods and gold nanoshells, superparamagnetic iron oxide particles, and carbon nanotubes are the three main nanoparticle formulations discussed in this article, which also provides a brief overview of the present technological state of the art. Nevertheless, hyperthermia's clinical potential remains unfulfilled, despite its promise in cancer management. This is so for a number of reasons. Traditional approaches to attaining global hyperthermia lacked standardisation, specificity, and were inherently laborious. Even newer ways of producing hyperthermia can be intrusive and cause uneven heating inside tumours and, in rare cases, hot areas in healthy tissues around them. Thanks to injectable nanoparticles like SPIONs, GNSs, and CNTs, ablative temperatures may now be achieved inside highly localised regions of the body while other sections remain at normal or near-normal temperatures. This is a major breakthrough. As an alternative to the more conventional methods of tumour hyperthermia, nanoparticles show great promise. The use of nanoparticles in tumour hyperthermia is not without its obstacles, though. The consistency and sufficiency of nanoparticle buildup at the tumour site is a big concern. It is still challenging to achieve homogeneous temperature across the tumor's core and mantle, even with incredibly tiny nanoparticles. The centre of a tumour that is little vascularized is not an ideal place for nanoparticles to enter consistently. Finding ways to uniformly raise temperature in the core requires investigating other possibilities. The problem of quality control is a further obstacle to the clinical translation of nanoparticles. Size and compositional differences within and between batches of laboratory-made nanoparticles are common. The likelihood of variance grows in direct proportion to the increasing complexity of nanoparticle compositions. Usually, the zetasizer or another dynamic light scattering device is used to determine the nanoparticle size distribution, but this method only gives an approximation of the hydrodynamic radius and not the nanoparticles' true diameter.

Keywords: Gold Nanoparticle, Cancer, Techniques, Hyperthermia Techniques

Corresponding Author: Mohammed Talib Nayel Al-Sultani †, Al-Hilla University College, Department of Medical Physics, Iraq.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material,which is available to authorized users.

Introduction

The subject of whether heat may promote healing has long captivated doctors, who study the effects of heat on the human body in both healthy and unhealthy states. Experience over many centuries has tentatively concluded that heat can actually play a role in the treatment of numerous diseases, including cancer, given optimal conditions. The use of heat can be compared to surgical removal of tumours in that it kills tumour cells directly. It can cause a wide variety of responses, from a protective mechanism mediated by heat shock proteins to cellular death caused by necrosis mediated by irreversible protein and macromolecule coagulation. On the other hand, normal tissues are vulnerable to deadly quantities of untargeted heat [1,2], which is a risk with any treatment. On the other hand, a less severe temperature increase, which is not fatal on its own, can supplement and enhance the efficacy of other treatment methods. So, let's start by defining some terminology so we can clearly identify the type of heat we're talking about. Hyperthermia is commonly defined in medical literature as an increase in core body temperature, either systemically or locally, and occasionally intentionally caused for therapeutic purposes. We call a therapy modality thermoablation when its main purpose is to destroy malignant tissue using heat.

As indicated earlier, however, heat can also be applied at levels below what is necessary for ablation. The goal is to make the malignant tissue more receptive to other treatments, like chemotherapy and ionising radiation. This type of subablative heating is commonly referred to as hyperthermia and is typically seen as separate from thermoablation in this particular situation. Both thermoablation and hyperthermia are used interchangeably in this review; nevertheless, they are distinct in meaning according to the treatment's goal rather than a specific temperature. Time of exposure is one of several variables that determine the ablation threshold temperature [3-5]. Nevertheless, in reality, it is usually thought of as ablative to reach temperatures above 45°C, though considerably greater temperatures (>50°C) are usually achieved locally to cause tumour necrosis. The goal of hyperthermia treatment is to keep body temperatures between 41 and 45 degrees Celsius.

Lower temperatures of approximately 41-42°C (mild temperature hyperthermia) are effective as adjuncts to radiation therapy and chemotherapy, while ablative temperatures burning off tumours is an appealing choice. The main reasons behind this are an increase in blood flow and oxygen delivery, which lasts for about a day or two, and a decrease in oxygen demand, which leads to a shift towards anaerobic metabolism and cell death caused by hyperthermia. These factors work together to increase the oxygenation of tumour tissue. The immune system can be stimulated by hyperthermia as well. We have a better grasp of the subcellular processes that make cells vulnerable to different types of harm, and the molecular mechanisms of these hyperthermia effects are being uncovered [6, 7]. The fact that normal cells, tumour vascular endothelial cells, and tumour cells are all fundamentally susceptible to heat-induced cytotoxicity is now well-established.

The acidotic and nutrient-deprived environment inside the tumour renders them more thermosensitive, nevertheless, due to poor blood flow and oxygen transfer through disordered tumour neovasculature. Hypoperfused locations within the tumour core are less sensitive to radiation-induced cytotoxicity, which relies on the formation of oxygen free radicals within well perfused regions. Therefore, heat therapy can work in tandem with radiation therapy to increase the sensitivity of hypoxic areas. Chemotherapeutic medications are better delivered to the tumour cores, which are weakly vascularized [8], when perfusion is increased. Combining hyperthermia with chemotherapy or radiation therapy has been shown to significantly improve outcomes in several clinical and preclinical investigations. These studies have focused on various tumour types, including those of the brain, cervix, prostate, breast, bladder, oesophagus, rectum, cervix,

head and neck, and lungs. In most cases, this combination therapy plan enhances local control, cure, and palliation without increasing treatment toxicity.

All of these things suggest that hyperthermia is a great addition to the cancer caregiver's toolbox of treatment options. Hyperthermia has been known to have a therapeutic effect on cancer for over a century, but this information has led to virtually little clinical use of the treatment. The problem is not with hyperthermia itself, but with the difficulty of applying it in a controlled and precise way. This is not a little task for clinicians, and if this problem is solved, this efficient cure might be used by everyone. Fortuitous findings about the impact of fever on tumours led to the first approaches to induce hyperthermia in cancer [8, 9]. For more than a hundred years, people had noticed that erysipelas, a streptococcal skin infection, and tumour regression went hand in hand. However, it wasn't until 1891 that Dr. William Coley recorded proof of this link in sarcoma patients. In an effort to mimic this effect for cancer treatment, he eventually developed bacterial cocktail (Coley's toxin) that purposefully caused a fever to trigger an antitumor reaction. Not only was this among the earliest proofs of immunotherapy's effectiveness, but it also most likely constitutes the first clinical use of hyperthermia for cancer treatment. Since then, numerous researchers have utilised hyperthermia in cancer treatment, either alone or in conjunction with conventional therapy, in ways that are more targeted and comparatively safer.

Hyperthermia methods that are more up-to-date

Ideal hyperthermia induction methods would employ a clinically robust approach to produce targeted, regulated, and uniform hyperthermia. Sometimes, satisfying both of these requirements is possible. In therapeutic practice, three forms of hyperthermia have long been utilised: whole body, regional, and local. As its name suggests, whole body hyperthermia involves an increase in core body temperature. One early use of this technique is in Dr. Foley's efforts to induce fever for therapeutic purposes. At now, thermal chambers and hot water blankets are the tools used to do this. Despite the fact that this approach puts healthy tissues through the stress of a higher temperature [11, 12], it can be useful in cases of metastatic cancer when focal hyperthermia fails to control the disease. However, clinical practice rarely employs whole body hyperthermia procedures. Nevertheless, new, unpublished evidence suggests that tumor-bearing mice housed in warmer environments appear to have a noticeably longer tumour doubling time compared to control animals housed in conventional air-conditioned rooms.

While further studies are required to confirm these results and apply them to real-world situations, they seem to lend credence to the idea that modest temperature hyperthermia can improve the immune system's reaction to cancer. The standard method of administering regional hyperthermia involves injecting hot liquids into the area of the body where the cancer is located. A portion of the patient's blood, which has been heated outside of the body, is infused into an artery that supplies the leg where the tumour is located. Another common method involves injecting a heated solution of anticancer medications into the peritoneum to treat malignancies like mesothelioma [12, 13]. While whole-body and regional hyper-thermia treatments do not produce heat that is particularly targeted to tumours, they do not cause significant toxicity either. Although major cardiovascular adverse effects including myocardial ischemia, thrombosis, and cardiac failure are extremely rare, patients treated with whole body hyperthermia do occasionally have gastrointestinal symptoms such nausea, vomiting, and diarrhoea. When considering regional hyperthermia, it is important to consider both its benefits and the risks connected with the invasive operation. The process necessitates a dedicated facility, which presents non-trivial hurdles in terms of setup cost and professional labour.

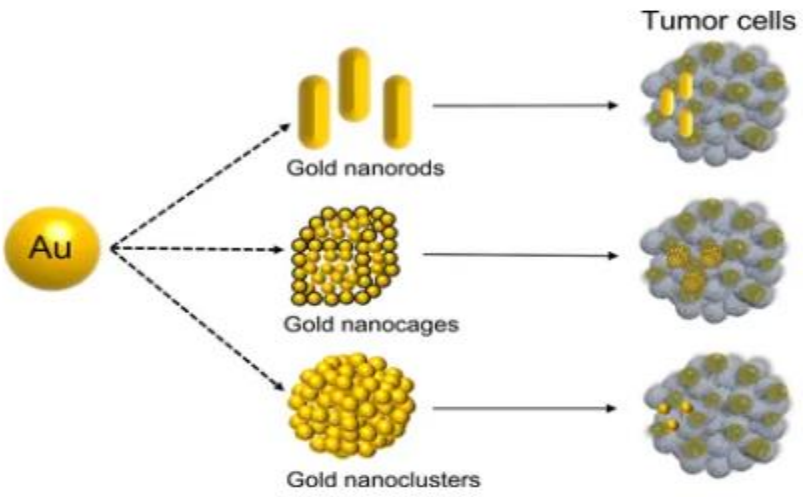

Figure 1. Different shapes of GNPs.

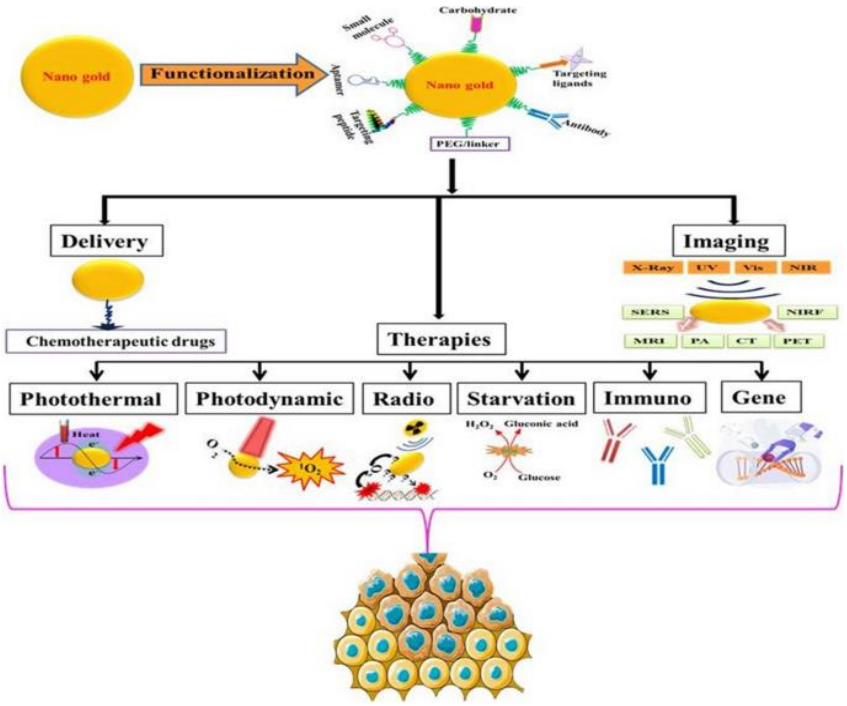

Figure 2. Illustrates the use of functionalized AuNPs for combinational multimodal theranostics

Conversely, local hyperthermia has the benefit of targeting only tumours. From least invasive to most invasive, external, luminal, and interstitial techniques are used to generate local hyperthermia. For tumours of the vagina and cervical region, a technique called luminal hyperthermia involves inserting specialised metallic probes as near to the tumour as feasible; for a more uniform heating of the tumour, interstitial hyperthermia employs an array of probes implanted within the tumour parenchyma. You can either install heat sources into the probes themselves or use external heating sources to heat them.

The thermal dosimetric profile that results from these procedures is often diverse, with the highest intensity along the probe and a steep decline in intensity as one proceeds away from it. These methods are typically somewhat intrusive. By bringing several interstitial probes closer together, this nonuniformity can be partially mitigated; nevertheless, this method becomes more invasive [14-16]. Substituting tiny metal antennas ("seeds") in the tumour parenchyma for the probe array can further lessen the invasiveness of this type of interstitial hyperthermia. The seeds are then noninvasively activated by exposure to an external energy source. Ferromagnetic seeds, like as iron, are heated in an alternating magnetic field to produce hyperthermia, which is heat that rises from within the tumour instead of outside it. For tumours that are deeply embedded, the process of implanting seeds inside the tumour can be quite invasive and difficult. But the procedure is noninvasive and completely adjustable by adjusting the magnetic field strength, and the hyperthermia session is spaced out in time from the invasive treatment. In order to comply with federal requirements and build special rooms that are electromagnetically protected, administering this treatment requires a significant financial expenditure.

Both high-intensity focused ultrasound and electro-magnetic radiation (e.g., microwave, laser, and radiofrequency) are capable of delivering heat from outside the tumour, a process known as external hyperthermia. Most of the time, image guidance and energy focus on the tumour as shown by imaging allow for tumour specificity. Like heating tumours by pressing a warm object (such as a hot water bottle) against the skin above the tumour [17, 18], these methods have the ability to deposit energy into normal tissues along the beam's path. In the second scenario, higher surface temperatures are required to reach target tumour temperatures due to the insulating effects of the subcutaneous fat layer and plexus of blood vessels. This creates a temperature gradient from the skin to the tumour, and as the surface temperatures rise, the likelihood of skin erythema and desquamation increases.

All of this boils down to the benefits and risks of using old-fashioned ways to induce hyperthermia. Although hyperthermia shows great potential as a therapy modality, there are numerous shortcomings in the methods used to achieve, sustain, monitor, and model it. So, there's still a need for more modern ways to induce hyperthermia. It would be ideal if technology could target specific tumours with less disruption to surrounding tissue and more consistent heat. As a result of this need, researchers have been looking into using nanoparticles, which are extremely small pieces of matter composed of thousands of atoms, to induce hyperthermia. Materials with a longest dimension less than 100 nm are considered nanoparticles, as described in earlier chapters. However, particles as small as 1 μm are also commonly included in this definition. Structure, signalling, relationships, and control are all provided by parts of the cellular machinery that work at this molecular or nano-scale. Reducing interventions to this level is typically necessary for controlling and managing these processes. As a result, nanoparticles are intriguing because, unlike other materials, they may be able to regulate and manipulate interactions at the molecular or supramolecular level that occur on the nanoscale [20-23]. Furthermore, nanoscale matter frequently exhibits unexpected therapeutically useful features.

Many different kinds of gold nanoparticles, SPIONs (superparamagnetic iron oxide nanoparticles), and CNTs are among the most studied nanoparticles for hyperthermia. These "nanotransducers" work in various ways, but they all rely on quantum phenomena to absorb light from the outside and store it in tissues. There have been rumblings of additional nanoparticles that may have hyperthermia applications beyond the three main ones. Hyperthermic agents have been investigated using various materials, such as fluorescent quantum dots, nanoparticles of silver and zinc, and lanthanum manganite particles that have been loaded with silver ions. When compared to more traditional forms of hyperthermia induction, the use of nanoparticles has a number of distinct benefits.

Extreme heat to make use of gold nanoparticles

The optical resonances of the surface plasmons give metallic nanoparticles their distinctive properties compared to the bulk form of the same metal. When exposed to light with a specific wavelength, the nanoparticles absorb and scatter the light intensely, converting the resonant energy into heat. The rapid loss of electrons from the outer shell of metal atoms causes this phenomena. An electron cloud contains the dispersed electrons that cause electrical conductivity and other metallic properties. A plasmon, like a photon for light waves, is a quantum of a "electron wave" that occurs when free electrons oscillate. Like photons, plasmons can be thought of as quasiparticles, which is a level below elementary particles. The interaction between two wave particles [24, 25], photons and plasmons, can couple to create a new quasiparticle known as a polariton. This is analogous to a resonant effect, which occurs when two waves contact with one another. The ultraviolet spectrum is home to the resonance frequencies of the vast majority of bulk metals. As a result, metals appear shiny because visible light hits them without causing resonance and instead is reflected back. Metals with visible-light-resonance frequencies, like gold and copper, are responsible for their lustre. Metal surfaces exposed to a positively dielectric medium, such as air, also contain plasmons. This is because metals have a negative dielectric constant. Surface plasmons (SP) are lower-energy versions of the electron oscillations that happen in the metal's bulk. The SP waves also travel perpendicular to the surface, which is different from the bulk plasmons. Surface plasmon resonance (SPR) is the process by which a photon interacts with a surface plasmon (SP) at its resonant frequency, giving rise to a surface plasmon polariton (SPP). The SPP travels across the surface until it is either absorbed by the metal (primary) or dispersed by surface imperfections (minor), in which case it loses some of its energy as radiation. A short pulse pulse (SPP) rapidly releases its energy into a metal because the rate of energy decay is exponentially proportional to the distance travelled.

The modest surface dimensions of spherical metal nanoparticles allow them to be made resonant to light at specific wavelengths. When considering a specific metal-medium pair, the size of the nanoparticle positively correlates with the SPR frequency. This is because larger particles and aggregation of particles cause the resonant frequency to shift from the yellow to the red portions of the electromagnetic spectrum [26-29]. For instance, SPR at visible wavelengths (about 520 nm) is observed in solid spherical gold nanoparticles, and this effect becomes marginally stronger with increasing particle diameter. Because native tissue chromophores absorb light at such a low rate in the near-infrared (NIR) spectrum, these gold plasmon resonances can be tailored to reach the depths of human tissues when made in specific geometries.

The resonance frequency becomes divided into two absorption bands when the nanoparticles' shape is altered from spherical to more oblong rodlike (GNRs). A transverse mode, corresponding to the nanorods' shorter dimension, and a longitudinal mode, corresponding to the nanorods' longer axis, are two distinct bands. Typically seen in the red to near-infrared (NIR) spectrum, the lower-energy longitudinal mode has a longer wave-length than the transverse mode, which resonates at approximately 520 nm. An inverse relationship between the nanorods' aspect ratio and the resonance frequencies and relative intensities of the two peaks is seen.

In contrast to solid gold nanospheres, which have an optical absorption maximum at 540 nm and can only be slightly tuned to different wavelengths, GNRs composed of solid gold with different diameters can be optically tuned. Therefore, the spherical formulation has little clinical utility; on the other hand, GNRs, which have high length/diameter aspect ratios, can be adjusted to the near-infrared (NIR) region and may find use in certain therapeutic settings. In the longer dimension, typical GNR sizes are around 45 nm, and they typically have an aspect ratio of about 3. During seed-mediated chemical synthesis, the anisotropic

elongation of a sphere to a cylindrical shape is facilitated by the inclusion of a strongly charged surfactant, such as cetyl trimethylammonium bromide (CTAB), in the most popular synthetic method for GNRs. Despite the fact that CTAB inhibits GNR aggregation in solution as well, it is cytotoxic and is thus frequently eliminated through costly and time-consuming repeated centrifugation or dialysis [30-35], which in turn reduces the GNR yield. Another common method for making GNRs more biocompatible besides removing CTAB is coating the GNR surface with polysaccharides, block copolymers, or PEG.

The gold nanoshell (GNS) is a variant of this controllable plasmonic nanoparticle that features a silica dielectric core with a thin layer of colloidal gold applied to its surface. The resonance frequency can be changed to the near-infrared (NIR) region by either increasing the diameter of the silica core or decreasing the thickness of the gold layer, or both, even though this particle is spherical like the gold nanoparticle. The correct size of silica core and the correct thickness of gold layers on top make this task easy to accomplish. Luckily, silica nanoparticles can be easily sourced as uniformly sized particles that are extremely monodisperse and range from nanometers to larger than a micrometre. To make the gold epilayer, the amine groups on the surface of the silica core are adsorbed with gold colloid. Chloroauric acid treatment decreases the amount of gold adsorbed onto the colloid, creating a nucleation site that facilitates the growth and coalescence of the gold colloid with nearby gold colloids to produce a full shell. You can adjust this reaction, and it determines how thick the shell is. Reducing the amount of gold required and the potential cost of therapy, the thin gold shell improves the SP response by efficiently capturing incident photons and producing heat. Typically, GNSs have a diameter of 50–150 nm and exhibit considerable solubility in water, particularly when kept at low temperatures. 176 Cancer Nanotechnology Typically, silica-GNSs that may be activated by near-infrared light have a silica core that is 120 nm in diameter and a diameter of around 150 nm.

Research on the biocompatibility and safety of GNSs has cleared the path for their use in human clinical trials under the experimental device exemption. Clinical trials for GNSs utilising interstitial illumination with near-infrared lasers for thermoablation applications are now underway for head and neck cancer and prostate cancer.

One variation of the core/shell gold nanostructure involves dissolving the core, resulting in a hollow GNS that is filled with salts and water. These unique gold nanoparticles exhibit excellent photothermal heating and a robust, tuneable plasmon resonance that reaches well into the near-infrared spectrum (~950 nm). It is very conceivable to create extremely monodisperse uniform hollow GNSs with diameters ranging from 30 to 50 nm, as the capacity to produce uniform hollow nanoshells is similarly dependent on the core's homogeneity. Hollow GNSs, in contrast to GNRs, can be solution-stabilized without the need of a cytotoxic surfactant. A latex bead was used as the sacrificial core in earlier studies of hollow GNSs. The majority of recent studies have focused on cobalt nanoparticles. The cobalt core is entirely oxidised, leaving only dissolved salts in the core, after the gold shell has grown and the core/shell structure has been exposed to air. It is uncertain if the entire amount of cobalt can be extracted from the hollow centre of these particles, similar to the situation with CTAB on GNRs [36, 37]. Whatever form it takes, surface plasmon resonance (SPR) helps to "trap" incident resonant photons on gold nanostructures.

Gold nanoparticles often have an absorption cross section that is four to five orders of magnitude larger than the strongest absorbing Rhodamine 6G dye molecules. Infrared light can excite gold nanoparticles, which have absorption cross sections that are up to a thousand times larger than indocyanine green, a dye that has been approved by the FDA. Femtosecond transient absorption spectroscopy revealed a very fast

(picosecond-scale) photon energy transfer to the metal nanoparticle. Over the next hundred picoseconds, the metal's energy dissipates into the medium.

Cancer treatment using gold nanoparticle-mediated hyperthermia

Thermal ablation of tumours has been made possible by utilising the photothermal activation of gold nanoparticles and their accumulation within tumours through the EPR effect. Clotting cell death, according to in vitro research, requires local temperatures higher than 50°C. Also, between 40 and 47 degrees Celsius, in particular, it is possible to foretell when cultivated cells will sustain irreparable damage by using a combination of temperature and time (Roti Roti 2008). There is a lot of room for error when trying to pin down an in vivo thermal cytotoxicity threshold due to factors like tissue type, temperature rise duration and uniformity, tissue vascular perfusion (the heat sink effect), and heat delivery method. However, when heating is limited to a few minutes, a temperature in the 45-50°C range is typically considered the absolute minimum that must be crossed for ablation to be successful. Using a thin layer of AlGaN embedded with Er3+ ions as a photoluminescence surrogate for temperature [38- 41], the experimental determination of the effect of laser power on local temperature rise surrounding a 40-nm gold nanoparticle was carried out. When a 532-nm laser is excited at 3.8×10^4 W/m², the average temperature change surrounding a heated nanoparticle is around 90 K, and the temperature distribution around it follows a normal distribution.

In contrast to systems that rely on water for heat dissipation, this one uses air and, to a lesser extent, the film. Reduced heat dissipation from the nanoparticle to the surrounding matrix is caused by the predicted thermal interface conductance, which is only 10 MW/m2 K. Depending on the surface's hydrophilicity, which can range from 50 for hydrophobic surfaces to 200 for hydrophilic ones, the thermal interface conductance of gold nanoparticles in water-based solutions can be 100−130 MW/m2 K. Laser illumination of tissue loaded with a sufficient quantity of gold nanoparticles can quickly result in ablative temperatures, as shown in these research.

Temperature increases within this expected range have been observed in living organisms. We found that 24 hours after injecting 8×10^1 nanoshells/g intravenously into nude mice, laser illumination of subcutaneous human colorectal tumours causes a rapid increase in temperature, which levels out after approximately 5 minutes. A temperature increase of around 14°C over base-line (about 31°C) was seen with a 0.8-W laser output, compared to increases of approximately 10°C and 5°C, respectively, with 0.6- and 0.4-W laser outputs. Thermocouples implanted into the tumour [42, 43]or noninvasive magnetic resonance thermal imaging, which records the change in proton resonance frequency with increasing temperature, are two ways to monitor these temperature spikes.

Reports of this kind of thing with different gold nanoparticles are not uncommon. A study found that mice with sarcomas could benefit from intravenous injections of pegylated GNRs (9.6 mg/kg, optical density = 120). After twenty-four hours, 808 nm lasers operating at 1.2 and 1.6 W/cm2 were applied to the tumours for ten minutes. A needle thermocouple inserted into the tumour was used to measure the temperature, and the results showed that the average tumour equilibrium temperature is 46.3°C and 43.6°C, respectively. In a related study, mice with human glioblastoma tumours were given 2.5×10^41 hollow GNSs (either targeted or untargeted). After 24 hours, the mice in the targeted group showed a higher maximum temperature of 57.75 ± 0.46°C compared to the untargeted group, when exposed to NIR laser illumination (16 W/cm2, 3 min, 808 nm).

In an influential article that ushered in the era of gold nanoparticles used for cancer thermal treatments. Afterwards, a study was conducted on mice with subcutaneous CT26/wt murine colorectal cancers. The

mice were divided into three groups for the treatment: a control group that did not receive any intravenous injections or laser treatment, a sham group that received an intravenous injection of 0.9% sterile saline followed by laser treatment at a later time (6 hours later) using an 808 nm diode laser at 800 mW and 4 W/cm2 for 3 minutes, and a treatment group that received 2.4 × 1010 nanoshells injected intravenously and then underwent the same type of laser treatment. The GNS group had a far longer survival rate (over 90%) than the sham and control groups (all mice died within 3 weeks). Research has since shown that greater treatment outcomes can be achieved [44] by actively targeting tumours with gold nanoparticles instead of letting them accumulate within tumours. Some of the possible applications of gold nanoparticles in cancer treatment are highlighted by these important early experiences.

However, there is a rising interest in combining nanoparticles for hyperthermia (i.e., non-ablative temperatures) with other modalities like radiation therapy, as opposed to employing them alone for tumour thermoablation with gold. In theory, at these temperatures, the neighbouring tissues to the tumour, which could potentially be ablated, are less likely to suffer collateral harm. We have studied the possibility of improving radiation therapy's effectiveness by means of GNS-mediated mild thermal hyperthermia (about 41°C for 20 minutes). The time it took for the tumour volume to double was nearly double when heat was followed by radiation therapy (a single dose of 10 Gy). The improvement in radiation response in vivo was explained by an initial rise in tumour vascular perfusion after hyperthermia, as shown by dynamic contrast-enhanced MRI with more contrast enhancement in the tumor's core, and then by an increase in vascular disruption, as shown by decreased vascular density and more hypoxic and necrotic zones inside the tumour. Due to their incapacity to penetrate deep into the tumour parenchyma, relatively large GNSs were thought to get trapped in the perivascular region, leading to vascular collapse and subsequent downstream necrosis. Another study showed that GNS-mediated hyperthermia also makes cancer stem cells more sensitive to radiation therapy. These cells are thought to be the main culprits behind treatment failure and metastasis spread.

The volume of the remaining tumour has a higher proportion of stem cells, even though radiation of breast cancer xenografts reduces the tumour. Radiation with GNS-mediated hyperthermia, on the other hand, decreases the proportion of stem cells in the residual tumour and further reduces tumour volume. The necessity to transplant more cells into mice in the combination therapy group in order to regenerate tumours was validated by further examination into these intriguing findings using limiting dilution transplantation of cancer cells from residual tumours. This was in comparison to the radiation group and the control group.

Conclusion

Hyperthermia improves the efficacy of radiation and chemotherapy by increasing tumour vascular perfusion, which in turn reduces hypoxia within tumour cores. On the other hand, nanoparticle-mediated hyperthermia has other significant functions in cancer, such as making resistant cancer stem cells more sensitive to radiation and disrupting microvasculature. This is partially due to the fact that this method of producing heat inside tumours is unusual in that it focuses on the blood vessels from the inside out, causing hyperthermia. The fact that it is possible to attain hyperthermia in this way without invasive procedures and to regulate its conformality by means of tumor-specific nanoparticle accumulation and laser beam collimation to exact tumour outlines makes it an attractive kind of hyperthermia. The motivation for potentially bringing this method into clinical practice comes from these characteristics of nanoparticle-mediated hyperthermia.

Nanoparticles like SPIONs, GNSs, and CNTs have just entered the field of cancer hyperthermia, which shows great promise for improving the effectiveness of conventional treatments like chemotherapy and radiation. Photothermally activatable gold nanoparticles offer a number of benefits over other activatable

nanoparticles when it comes to medical use. For starters, gold is a noble metal, which means it is unlikely to cause any harm because it is chemically and physiologically inert as well as thermally and molecularly stable. Indeed, gold has a long history of safety when given in tiny doses, and there is much clinical evidence with its usage in the treatment of diseases like rheumatoid arthritis. Second, NIR-activatable GNSs measuring approximately 150 nm and GNRs measuring about 45 nm are well within the size regimes that allow tumor-specific accumulation via the EPR effect. This is in line with the average size of vascular fenestrations within tumours, which ranges from 60 to 400 nm. Lastly, the EPR phenomenon allows for passive accumulation in tumours, but the gold surface can also be easily attached to biomolecules like PEG or peptides/antibodies via thiol linkages, allowing them to evade the reticulo-endothelial system or specifically target tumours or tumour vasculature. Last but not least, gold nanoparticles may be able to skip the costly and time-consuming drug classification process and go straight to clinical translation by being classed as devices instead. Still, there are a few problems with clinical translation that have plagued conventional hyperthermia for decades. Problems in appropriately reporting temperature dose-time properties, real-time monitoring of hyperthermia, and modelling of tumor-specific thermal dose distributions are among them. We may soon be able to detect hyperthermia noninvasively thanks to advancements like magnetic resonance thermal imaging. Similar to radiation dosimetry, newly discovered methods and tools for forecasting thermal dose based on concentrations of gold nanoparticles within tumours should enable a priori treatment planning using thermal dosimetry. Compared to radiation dosimetry, which just requires physical factors to be considered, thermal dosimetry presents a more difficult problem since it is a reflection of both physiological and physical heat creation and dissipation. Creating hyperthermia noninvasively and without costly equipment is the main benefit of nanoparticle-mediated hyperthermia. The additional need to determine the nanoparticle formulation's safety and acceptability is the distinctive translational challenge with this type of hyperthermia. It is also necessary to assess the specific treatment circumstances in order to ascertain the appropriateness and consistency of nanoparticle accumulation at the tumour site. Because nanoparticles cannot penetrate sufficiently into tumour cores that are minimally vascularized, it is still difficult to achieve a consistent temperature throughout the tumor's core and periphery, even when using extremely tiny nanoparticles.

Light, even near-infrared light, has a limited ability to penetrate tissues, which limits the applications of photothermal therapy to superficial targets (such as skin, the chest wall, intraoperative tumour beds, etc.), those that can be reached with an endoscope, or those that can be implanted with interstitial catheters (which reduces the noninvasiveness of the treatment somewhat). Last but not least, hyperthermia, like radiation and chemotherapy, works best when applied locally to the tumour. Concurrent accumulation occurs in various different tissues, the liver being the most notable, even though the EPR effect permits passive accumulation within tumours. Because of this, this method is not as effective for treating liver tumours and those in the vicinity. Even though it's not as noticeable, accumulation in other sites nevertheless warrants careful study of the biodistribution and pharmacokinetics of every particle that could be used in therapy.

References

1. Kennedy, L. C., L. R. Bickford, N. A. Lewinski et al. 2011. A new era for cancer treatment: Gold-nanoparticle-mediated thermal therapies. Small 7:169–183.
2. Choi, W. I., J. Y. Kim, C. Kang, C. C. Byeon, Y. H. Kim, and G. Tae. 2011. Tumor regression in vivo by photothermal therapy based on gold-nanorod-loaded, functional nanocarriers. ACS Nano 5:1995–2003.

3. Maeda, H. 2001. The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting. Advances in Enzyme Regulation 41:189–207.
4. Coley, W. B. 1891. II. Contribution to the knowledge of sarcoma. Annals of Surgery 14:199–220. Day, E. S., J. G. Morton, and J. L. West. 2009. Nanoparticles for thermal cancer therapy. Journal of Biomechanical Engineering 131:074001.
5. DeNardo, G. L., and S. J. DeNardo. 2008. Update: Turning the heat on cancer. Cancer Biotherapy & Radiopharmaceuticals 23:671–680.
6. Kim, J. H., E. W. Hahn, and S. A. Ahmed. 1982. Combination hyperthermia and radiation therapy for malignant melanoma. Cancer 50:478–482.
7. Diagaradjane, P., A. Shetty, J. C. Wang et al. 2008. Modulation of in vivo tumor radiation response via gold nanoshell-mediated vascular-focused hyperthermia: Characterizing an integrated antihypoxic and localized vascular disrupting targeting strategy. Nano Letters 8:1492–1500.
8. Dickerson, E. B., E. C. Dreaden, X. Huang et al. 2008. Gold nano- rod assisted near-infrared plasmonic photothermal therapy (PPTT) of squamous cell carcinoma in mice. Cancer Letters 269:57–66.
9. Doss, J. D., and C. W. McCabe. 1976. A technique for localized heating in tissue: An adjunct to tumor therapy. Medical Instrumentation 10:16–21.
10. El-Sayed, I. H., X. Huang, and M. A. El-Sayed. 2006. Selective laser photo-thermal therapy of epithelial carcinoma using anti-EGFR antibody conjugated gold nanoparticles. Cancer Letters 239:129–135.
11. Everts, M. 2007. Thermal scalpel to target cancer. Expert Review of Medical Devices 4:131–136. Feldman, A. L., S. K. Libutti, J. F. Pingpank et al. 2003. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. Journal of Clinical Oncology 21:4560–4567.
12. Franckena, M., and J. van der Zee. 2010. Use of combined radiation and hyperthermia for gynecological cancer. Current Opinion in Obstetrics & Gynecology 22:9–14.
13. Fuller, K. J., R. D. Issels, D. O. Slosman, J. G. Guillet, T. Soussi, and B. S. Polla. 1994. Cancer and the heat shock response. European Journal of Cancer 30A:1884–1891.
14. Ge, Z. B., D. G. Cahill, and P. V. Braun. 2006. Thermal conductance of hydrophilic and hydrophobic interfaces. Physical Review Letters 96:186101.
15. Harmon, B. V., Y. S. Takano, C. M. Winterford, and G. C. Gobe. 1991. The role of apoptosis in the response of cells and tumours to mild hyperthermia. International Journal of Radiation Biology 59:489–501.
16. Hirsch, L. R., R. J. Stafford, J. A. Bankson et al. 2003. Nanoshell- mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. Proceedings of the National Academy of Sciences of the United States of America 100:13549–13554.

17. Friedenthal, E., J. Mendecki, C. Botstein, F. Sterzer, M. Nowogrodzki, and R. Paglione. 1981. Some practical considerations for the use of localized hyperthermia in the treatment of cancer. Journal of Microwave Power 16:199–204.

18. Hirsch, L. R., A. M. Gobin, A. R. Lowery et al. 2006. Metal nanoshells. Annals of Biomedical Engineering 34:15–22.

19. Maeda, H., J. Wu, T. Sawa, Y. Matsumura, and K. Hori. 2000. Tumor vascular permeability and the EPR effect in macro-molecular therapeutics: A review. Journal of Controlled Release 65:271–284.

20. Hosta-Rigau, L., I. Olmedo, J. Arbiol, L. J. Cruz, M. J. Kogan, and F. Albericio. 2010. Multifunctionalized gold nanoparticles with peptides targeted to gastrin-releasing peptide receptor of a tumor cell line. Bioconjugate Chemistry 21: 1070–1078.

21. Glazer, E. S., and S. A. Curley. 2010. Radiofrequency field-induced thermal cytotoxicity in cancer cells treated with fluorescent nanoparticles. Cancer 116:3285–3293.

22. Goldberg, S. N., G. S. Gazelle, E. F. Halpern, W. J. Rittman, P. R. Mueller, and D. I. Rosenthal. 1996. Radiofrequency tissue ablation: Importance of local temperature along the electrode tip exposure in determining lesion shape and size. Academic Radiology 3:212–218.

23. Huang, X., X. Peng, Y. Wang, D. M. Shin, M. A. El-Sayed, and S. Nie. 2010. A reexamination of active and passive tumor targeting by using rod-shaped gold nanocrystals and covalently conjugated peptide ligands. ACS Nano 4: 5887–5896.

24. Huilgol, N. G., S. Gupta, and R. Dixit. 2010a. Chemoradiation with hyperthermia in the treatment of head and neck cancer. International Journal of Hyperthermia 26:21–25.

25. Irish, C. E., J. Brown, W. P. Galen et al. 1986. Thermoradiotherapy for persistent cancer in previously irradiated fields. Cancer 57:2275–2279.

26. Kah, J. C., K. Y. Wong, K. G. Neoh et al. 2009. Critical parameters in the pegylation of gold nanoshells for biomedical applications: An in vitro macrophage study. Journal of Drug Targeting 17:181–193.

27. Krishnan, S., P. Diagaradjane, and S. H. Cho. 2010. Nanoparticle-mediated thermal therapy: Evolving strategies for prostate cancer therapy. International Journal of Hyperthermia 26:775–789

28. Luk, K. H., M. E. Francis, C. A. Perez, and R. J. Johnson. 1984. Combined radiation and hyperthermia: Comparison of two treatment schedules based on data from a registry established by the Radiation Therapy Oncology Group (RTOG). International Journal of Radiation Oncology, Biology, Physics.10:801–809.

29. Magin, R. L., and R. K. Johnson. 1979. Effects of local tumor hyperthermia on the growth of solid mouse tumors. Cancer Research 39:4534–4539.

30. Melnikov, O. V., O. Y. Gorbenko, M. N. Markelova et al. 2009. Ag-doped manganite nanoparticles: New materials for temperature-controlled medical hyperthermia. Journal of Biomedical Materials Research A 91:1048–1055.

31. Huilgol, N. G., S. Gupta, and C. R. Sridhar. 2010b. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial. Journal of Cancer Research and Therapeutics 6:492–496.

32. Hurwitz, M. D., J. L. Hansen, S. Prokopios-Davos et al. 2011. Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer: Long-term results from Dana–Farber Cancer Institute study 94–153. Cancer 117:510–516.

33. Moros, E. G., J. Penagaricano, P. Novak, W. L. Straube, and R. J. Myerson. 2010. Present and future technology for simultaneous superficial thermoradiotherapy of breast cancer. International Journal of Hyperthermia 26:699–709.

34. O'Neal, D. P., L. R. Hirsch, N. J. Halas, J. D. Payne, and J. L. West. 2004. Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles. Cancer Letters 209:171–176.

35. Patra, C. R., R. Bhattacharya, D. Mukhopadhyay, and P. Mukherjee. 2010. Fabrication of gold nanoparticles for targeted therapy in pancreatic cancer. Advanced Drug Delivery Reviews 62:346–361.

36. Rao, W., Z. S. Deng, and J. Liu. 2010. A review of hyperthermia combined with radiotherapy/chemotherapy on malignant tumors. Critical Reviews in Biomedical Engineering 38:101–116.

37. Roti Roti, J. L. 2008. Cellular responses to hyperthermia (40–46 degrees C): Cell killing and molecular events. International Journal of Hyperthermia 24:3–15.

38. Schwartzberg, A. M., T. Y. Olson, C. E. Talley, and J. Z. Zhang. 2006. Synthesis, characterization, and tunable optical properties of hollow gold nanospheres. Journal of Physical Chemistry B 110:19935–19944.

39. Seegenschmiedt, M. H., R. Sauer, C. Miyamoto, J. A. Chalal, and L. W. Brady. 1993. Clinical experience with interstitial thermoradiotherapy for localized implantable pelvic tumors. American Journal of Clinical Oncology 16:210–222.

40. Skrabalak, S. E., L. Au, X. Lu, X. Li, and Y. Xia. 2007. Gold nano-cages for cancer detection and treatment. Nanomedicine (London) 2:657–668.

41. Stewart, J. R., and F. A. Gibbs, Jr. 1984. Hyperthermia in the treatment of cancer. Perspectives on its promise and its problems. Cancer 54:2823–2830.

42. Thrall, D. E. 1980. Clinical requirements for localized hyperthermia in the patient. Radiation and Environmental Biophysics 17:229–232.

43. Van den Berg, C. A., J. B. Van de Kamer, A. A. De Leeuw et al. 2006. Towards patient specific thermal modelling of the prostate. Physics in Medicine & Biology 51:809–825.

44. Waldman, S. A., P. Fortina, S. Surrey, T. Hyslop, L. J. Kricka, and D. J. Graves. 2006. Opportunities for near-infrared thermal ablation of colorectal metastases by guanylyl cyclase C-targeted gold nanoshells. Future Oncology 2:705–716.