

USING NANOTECHNOLOGY TO ADVANCE CANCER TREATMENT
GOLD NANOSHELLS AND PHOTOTHERMAL THERAPY

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ABSTRACT

The objective of nanotechnology is to gain atomic and molecular control over matter. In this article, the ideas of how gold nanoshells are used in photothermal therapy to cure cancer will be explored in detail. Gold nanoshell is a type of spherical nanoparticles which is made by a dielectric silica core coated with a thin layer of gold. They have diameters typically ranging in size from 10 to 200 nm. Gold nanoshells are used in photothermal therapy to destroy tumor cells by heating them to death when heated with near infrared light. This novel therapy seems to be a promising method to achieve tumour ablation in a non-invasive manner with minimal side effects. Using nanoshells has certain benefits over standard treatments today, such as its ability to specifically target cancer cells, its property of being non-toxic and the relatively simple application process involved. However, this technology of treating cancer is still in its infancy. A lot of research and clinical trials have to be done before the therapy can be widely used.

INTRODUCTION

Nanotechnology is the science and engineering of manipulating matter on an atomic and molecular scale to make devices with novel chemical, physical and biological properties. It is a rapidly growing field that has huge potential in transforming our world. More importantly, it has opened the door for medical applications of nanotechnology---- Nanomedicines, to work at the molecular level to diagnose, treat, and prevent disease. Today nanomedicines are being developed to have accurate, controllable, reliable, economic and rapid responsive diagnostic and treatment solutions for various kinds of diseases.

Nanotechnology deals with structures sized between 1 to 100 nanometre in at least one dimension, and involves developing materials or devices within that size. The reason why nanotechnology brings significant benefits to medicine is because biological processes, including events necessary for life and those that lead to cancer, also take place at the nanoscale. In fact, biological systems themselves contain various components which are essentially in the nanometer dimensions including proteins, nucleic acids and cell membranes. A typical protein such as haemoglobin, which carries oxygen through the bloodstream, is 5 nm in diameter.

Above all, nanotechnology has the potential to drastically improve screening, diagnosis, monitoring and treatment of cancer. Although the ability to manipulate technologies on this scale is still in its infancy, there has been huge progress in bringing nano-based cancer therapies into the clinic and many more are in development.

According to GLOBOCAN, an estimated 12.7 million new cancer cases and 7.6 million deaths occurred in 2008 worldwide. Meanwhile, breast cancer is one of the most commonly diagnosed cancers worldwide. As for UK, there were around 297,990 new cases of cancer diagnosed in 2007. Statistics have also shown that more than 1 in 3 people will develop some form of cancer during their lifetime. Hence, advances in cancer treatment are of great significance to all mankind. Traditional cancer treatment such as chemotherapy, which often employs drugs in high concentrations, and radiotherapy, are known to kill cancer cells effectively. However, these treatments may cause damage to healthy cells near a tumour in the process, leading to adverse side effects such as nausea, neuropathy, hair-loss, fatigue, and compromised immune function.

Researchers are exploring ways to physically destroy cancerous cells from within, instead of using chemotherapeutic agents to activate normal molecular mechanisms to induce cell death. Today gold nanoshells are being used in the laboratory to thermally destroy tumours from the inside which may potentially become a new means of fighting cancer. This method would require fewer drugs and mitigate the side effects of cancer chemotherapy drugs. In this article, the ideas of how gold nanoshells are used in photothermal therapy to cure cancer will be explored in detail.

Nanoshells are spherical particles with diameters typically ranging in size from 10 to 200 nm. In the case of a gold nanoshell, the dielectric core is a ball of silica and the shell is a thin layer of gold coated around the core. A variety of studies by numerous investigators are demonstrating that gold nanoshells have real promise as anticancer agents. They are being studied for uses in destroying cancerous cells by photothermal therapy, which is an experimental use of electromagnetic radiation to carry out hyperthermia. Hyperthermia is the application of heat to destroy solid tumours, which has been used as an adjuvant cancer treatment for some time but is not currently utilized as an independent treatment. Hyperthermia induces cell death through mechanisms such as rupture of cellular membranes and protein denaturation.

Nanoshells can be engineered to target cancerous cells and meanwhile designed to interact with specific wavelengths of light. Depending upon the wavelength of incident light, nanoshells can either scatter or absorb light. Several research groups have performed successful studies that prove nanoshells can be used as a precise treatment procedure that causes cell death in tumors.

As demonstrated by the work of Andre Gobin and a team of researchers from Rice University (2005), nanoshells and near infrared light (NIR) offer potent cancer-killing properties when used together. Laser-generated near infrared light has minimal interaction with components in body tissue, and therefore does not harm the body. When nanoshells were injected into a group of mice implanted with colon cancer, as the blood vessels that develop in fast-growing solid tumours were ill-formed and permeable, nanoshells travelling through blood ended up spilling out of these leaky vessels into tumour tissue. As a result, they accumulated in the tumour. The nanoshells were also hidden from the immune system because they were coated with poly-(ethylene glycol) or PEG as a protective polymer layer. This did not change the properties of the nanoshells but made them "invisible" to the body's natural defence mechanism. Subsequently, the addition of NIR laser light heated up the nanoshells, which were acting as exogenous energy absorbers to provide specific delivery of heat selectively to tumors, sparing normal surrounding tissue. At the end of the study, 82 percent of the mice in the experimental group survived with their tumours removed.

Similar findings were demonstrated by the work of Jennifer West, from Rice, and Susan Blaney, from Baylor (2010) five years later. In the first round of *in vivo* animal tests, they have successfully discovered a minimally invasive treatment for gliomas using near infrared-absorbing gold nanoshells that are thermally activated upon exposure to a near infrared laser, therefore causing irreversible damage to cancerous cells. Glioma is among the most aggressive and difficult-to-treat of all brain cancers because glioma tumours are often highly invasive and inoperable. The researchers injected the mice with gold nanoshells and waited 24 hours for the nanoshells to accumulate in the tumours. Laser-generated near-infrared light, which passed safely through biological tissues, was shined on the tumour for three minutes. The nanoshells converted the laser light into tumour-killing heat. Histology and inductively coupled plasma-mass spectrometry (ICP-MS) revealed that nanoshells delivered intravenously were selectively located in tumors and not adjacent muscle, which was highly desirable for minimizing the thermal damage to neighboring healthy tissue. All seven animals that received the nanoshell treatment responded, with four remained cancer-free 90 days after treatment while three got cancer returned in them. The results of these studies suggest that nanoshell-mediated photothermal therapy may one day become a viable option for glioma patients.

Another breakthrough was made by Rachel Atkinson, Dr. Jeffrey Rosen and Dr. Jenny C. Chang (2010). They found that by delivering a small amount of heat with a near-infrared laser to breast cancer cells that had been previously treated with radiation not only shrank the tumors but also boosted the effectiveness of the treatment and demonstrated a dramatically decreased population of stem cancer cells. Ms. Atkinson used both syngeneic mouse and human xenograft models of triple negative breast

cancer, one of the worst breast cancer types which lacks crucial receptors that can make it targetable with specific drugs. When she treated the tumours with ionizing radiation alone, the tumours would shrink, but a large percentage of the cells left behind were cancer stem cells, which were resistant to chemotherapy and radiation therapy and could regrow the tumour. However, subsequent introduction of gold nanoshells into the tumour and specific heating with a near-infrared laser for about 20 minutes, from 37°C to 42°C reduced the population of stem cells significantly. They concluded that the cancer stem cells were more sensitive to the combination treatment than the bulk of the tumour. It was the exact opposite response they saw with radiation only. Nanoshells were employed to deliver local hyperthermia and to sensitize tumours to radiation therapy. These original studies had demonstrated hyperthermia delivered through nanoshells increases perfusion of tumours with oxygen and also focally disrupts the blood supply to tumours, both of which enhance the effectiveness of radiation therapy. Ms. Atkinson also found that with the addition of hyperthermia, the cancer cells could not repair the damage done to their DNA and most of them died.

One of the merits of using nanoshells is that the whole body is not being heated. Studies have shown that whole-body hyperthermia can have serious side effects such as diarrhoea, nausea, vomiting, fatigue, and other symptoms of sunstroke. In this case, the gold nanoshells, which are 100-nanometer, invade the tumour through the leaky blood vessels that provide them nourishment. These findings have shown that local hyperthermia delivered by gold nanoshells plus radiation can eliminate radio resistant breast cancer stem cells as well as the bulk of the tumour, which may improve breast cancer treatment and survival rates.

Researchers cautioned that large ongoing efforts have to be made and follow-up work in the laboratory is needed before any human testing of the therapy can begin. Even so, human clinical trials of nanoshell photothermal therapy would probably be seen within the next five years.

DISCUSSION

Having reviewed the above three studies, we can point out that nanoshell photothermal therapy have several advantages over conventional cancer treatment. As shown in the studies, nanoshells have a distinctive optical property. They are able to interact strongly with electromagnetic waves such as infrared, radio waves and x-ray. When electromagnetic waves shine on a metallic nanoshell, it can start an interaction known as Surface Plasmon Resonance. By changing the relative sizes of the core and the shell, its surface plasmon resonance can be tuned in a broad spectrum of wavelength. Plasmon resonance is useful for fighting cancer because the increase in the magnitude of the oscillations successfully converts the incident light into heat and intensifies scattering effects. By far, gold displays very strong surface plasmon resonance effects.

Gold nanoshells have the benefit of being tunable to discrete wavelengths of light by varying the size of the core and the thickness of shell when human body can only allows certain wavelengths of light to pass through it. For cancer treatment, gold nanoshells are tuned to the wavelengths of near-infrared light so that properties of nanoshells will be triggered without operating. While current cancer treatments are rather nonspecific, one of the things that nanotechnology might offer, if you could target the nanoshells correctly, is the ability to target them to the specific cancer cells. Because of their size, nanoshells will preferentially concentrate in cancer lesion sites. This physical selectivity occurs through a phenomenon called Enhanced permeability and retention effect (EPR). The EPR effect helps to carry the nanoshells and spread inside the cancer tissue. Scientists can then externally apply near-infrared light that is absorbed by the nanoshells, which are thermally stable at therapeutic temperatures, creating an intense heat inside the tumor that selectively kills tumour cells without disturbing neighbouring healthy cells because they do not absorb the NIR light. Due to their tiny size, nanoshells have the ability to only heat up the attached cancer cell. This allows them to target and eliminate cancer cells while minimizing the amount of damage done to healthy cells. Also, as heat is generated specifically inside the tumour cells, side effects of traditional hyperthermia can be avoided. For instance, external application of heat may cause blisters, burns, fatigue, swelling, blood clots, or bleeding.

Furthermore, the inert gold surface of nanoshells provides several advantages, including noncytotoxicity, biocompatibility and it also facilitates conjugation to monoclonal antibodies or other biomolecules for both active tumor targeting and biosensing applications. The cytotoxicity of the nanoshells was checked by treating cancer cells with the nanoshells and taking the image without NIR radiation. It was found that there was no death of cells due to the nanoshells alone. Therefore, nanoshells are non-toxic and are likely to be excreted not causing any illness, unlike the chemotherapeutic drugs and radiation therapies which bring us unwanted side effects.

In addition, gold nanoshells are injected intravenously. This application method is relatively easy and safe, as demonstrated in animal models in the studies.

Besides, nanoshells provide a non-invasive access to the interior of a living cell, in contrast to the high morbidity and invasive nature associated with surgical resection. Once the nanoshells are injected into the blood stream and attach to the cancer cells, they are triggered by NIR light from outside the body without any cutting or harmful radiation. This novel treatment has the ability to treat small, poorly defined metastases or other deeply embedded tumors within vital regions where surgery is not feasible. Not having any operations, the time for recovery can be shortened.

Moreover, nanoshell photothermal therapy has a potential advantage to remove tumour in a single treatment. While, radiotherapy usually requires weeks of daily treatment causing much inconvenience and troubles to patients. This is because the total dose is divided into 'fractions' and patients usually have one treatment fraction each day. Likewise, chemotherapy treatments are given in cycles. When

cure is the treatment goal, Adjuvant chemotherapy may last for 4-6 months. Even if the cancer cells are not destroyed outright, they may become more sensitive to ionizing radiation therapy or to certain chemotherapy drugs, which may allow decrease in drug doses in such therapies. Consequently, treatment expenses are reduced resulting in a general societal benefit by reducing the costs to the public health system. Furthermore, thermal therapeutic procedures are fairly simple to perform and therefore they may improve recovery times, reduce complications and hospital stays.

Finally, heat-based treatments that cause cell death pose less risk to the development of cellular resistance when compared to drug treatments.

Clearly, nanoshells provide an opportunity to attack cancer cells physically at the cellular and molecular level. In the future, more research can be conducted on broader applications of nanoshells which can meanwhile assist the development of nanoshell photothermal therapy. For example, nanoshells can probably offer a more direct and selective means to target for cancerous cells, aim at getting straight to the source of the disease. Attempts have been made to coat nanoshell surfaces with antibodies or aptamers which are pieces of RNA that might be directed to a specific cell in the tumour. These antibodies will bind only to the specific antigens that are expressed on the cancer cells. This labeling method will greatly increase the specificity of nanoshells and create profound implications in cancer detection.

Furthermore, the combined use of nanoshells and imaging techniques highly deserves further investigations because early detection of cancer is often important for effective treatment. In addition to cancer treatment, nanoshells offer excellent potential for searching any possibility of developing a tumour in a patient. This is because gold nanoshells can be used as markers, which outline or cover the cancer cell, showing both its shape and size. They are suitable markers because gold nanoshells can be tuned to scatter near-infrared light in many different directions. Moreover, nanoshell can possibly be coated with magnetic or fluorescent particles which can also assist imaging of various kinds of cancer. As better imaging results facilitate diagnosis of cancer, the workload of pathologists and doctors can be reduced.

After all, whenever a new technology is being introduced into a community, the real challenge becomes public acceptance and how much risk society is willing to accept with the new technology before it is proven effective and 'safe'. There are always many ethical issues associated with it and nanomedicine is no exception.

Nanotechnology enable us manipulate matters at the atomic level. We will be able to develop things in molecular-sizes, which would give us unprecedented control over matter and the ability to shape the physical world. Some people argued that human beings should not be given such "god-like" power otherwise the laws of nature will be disrupted. With nanotechnology, others believed that there will be a risk of unwanted attack of biological organism at the molecular level. Furthermore, if nanoparticles were created to be self replicating and there were a problem with their limiting mechanism, they would multiply endlessly like viruses. To conclude, openness on technological issues is essential but regulation is also important. At the moment, there are no ethical issues concerning nanoshell photothermal therapy. Nevertheless, in general, nanomedicines should not be designed to be general purpose or self replicating. Furthermore, complex nanomachines should be tagged so as to allow them to be tracked in case they are lost. It would be difficult to deny the potential benefits of nanomedicines and stop development of research related to it since it has already begun to penetrate many different areas of research. However, it is important to investigate its ethical implications while it is still in its infancy. Potential ethical issues regarding different areas of nanomedicines should be examined and ethical guidelines and policies should be formulated in order to monitor and guide research and development in this field.

CONCLUSION

No doubt nanoshell photothermal therapy will become one of the major therapeutic treatments dealing with cancers in the future. However, before this novel treatment can be widely adopted, researchers must take the following pressing points into consideration. For example, what is the largest size tumor that nanoshells can effectively treat? How to precisely monitor the temperatures of both the tumor and the surrounding tissue? Is it possible to treat metastatic cancer by using large amount of nanoshells at the same time? How our body immune system would respond to nanoshells and the sudden elimination of the tumour in our body? Is it possible that nanoshells may interact with other medicines, cells, or tissues in harmful or unintended ways? How will they be removed from the body? Will cancer cells develop heat resistance and reduce the likelihood that they will die from direct cytotoxic effects of the heat? How can we effectively control the production of nanoshells in order to ensure their quality? Even though gold nanoshells are found to have successful applications in many biological fields, no one really knows what will happen to the material itself after treatment with the tumour cells. The fact that they are non-biodegradable and also catalytically active may create problems for the biological system. It is hoped that, in the near future, these questions will be addressed and the new properties of nanoshells will continue to be utilised in an increasing number of applications.

As many of the side effects and complications, as well as the other potential applications of nanoshells, are unknown, future research and clinical trials are the two most important areas to emphasize when talking about nanomedicine and cancer. Development of a better understanding of biological systems is also necessary. Although such nanotools still await construction, but they may become a reality in the near future. To achieve this goal, however, will require engineers and biologists using a step-by-step approach and work hand in hand to combine the best of both of their worlds in the fight against cancer.

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