FUTURE DEVELOPMENTS OF NANOTECHNOLOGY FOR THE DETECTION AND TREATMENT OF CANCER

BY

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PASS WITH MERIT

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Abstract

Many years and billions of pounds have been funnelled into research to expand upon our understanding of cancer and ascertain new ways of treating it. Despite the treatments becoming more targeted, the current methods of treatment are often extremely invasive to the diagnosed individual and cannot always guarantee complete removal of the tumour.

Nanotechnology is a truly multidisciplinary field, calling on both medicine and engineering to form new machinery. This paper will propose a nanotechnology based, real-time alerting system to prevent the damage of cells during tumour removal using altered nanoshells. As a medical tool, it would be an invaluable breakthrough in diagnosis and enable precise targeting of the tumour. Through existing knowledge of nanotechnology, it may soon be possible to develop 'smart' nanoparticles that are capable of *in vivo* detection of tumour cells, enhance the contrasts for MRI scans and finally denature the cells – all within a single nanoparticle.

Introduction

In England, around 254,800 people are diagnosed with a malignant cancerous tumour every year. Statistically 1 in 4 patients will die within 5 years of a definitive diagnosis. Cancer primarily occurs in the elderly, with only 25.5% of cases being found in people under 65 years of age. [1] In the UK alone, around £6.3 billion is spent on treatments for patients with cancer by the NHS.[2] Although cancer is such a devastating disease, there has yet to be a fully cogent treatment developed.

However, within the last 10-15 years, the applications of nanotechnology in medicine have become increasingly apparent. Scientists hope that with further research it will not only play a part in the removal of tumours, but also the identification of malignant and displaisic tissue before it has formed into a visible mass. This would provide an invaluable resource to be utilized by the medical profession.

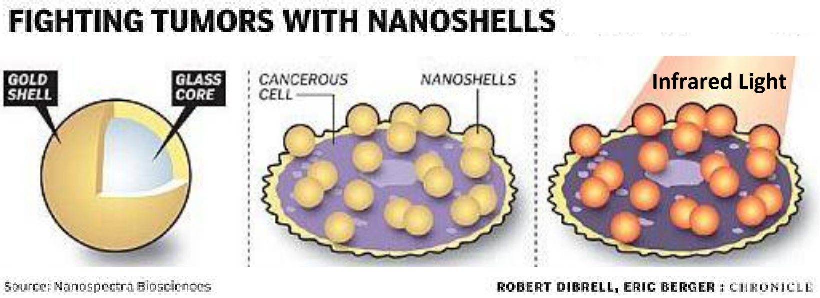
Nanotechnology is focused on the control and knowledge of atoms and molecules in the range of 1 – 1,000 nanometres, that are usually man-made.[3] A single nanometre is a billionth, or 1×10^{-9}, of a meter. In comparison, a sheet of paper is 100,000 nanometres (nm) thick, whilst a DNA double helix is only 2nm.

The idea of 'nano-technology' was originally conceived in 1959 by the physicist Richard Feynman in his speech "There's Plenty of Room at the Bottom". Feynman described it as a way to manipulate and alter individual atoms and molecules in order to create working structures at a minute level. The word nanotechnology only became the official term after it was defined in 1974 in a paper by Professor Norio Taniguchi as "Nano-technology mainly consists of the processing of, separation, consolidation, and deformation of materials by one atom or by one molecule". [3]

Nanotechnology is used frequently in our lives in the form of passive nanostructures, such as aerosols and polymers, yet has the potential to become of much greater use, epecially in medicine. Currently, tools such as the quantum dots (Q-dots) and the nanoshell (Naomi Halas, 2004) are in futher development for the early detection of illness. Shimon Weiss demonstrated that Q-dots are nano-crystals that embed themselves inside of a diseased structure and allow scientists to monitor abnormal cell activity.

Often the treatment of a tumour is very unpleasant and can cause further damage to cells in the body. This is especially clear in chemotheraphy, where healthy cells as well as cancerous tumors are killed. Additional complications can also occur, such as posioning in some cases owing to its high toxicity and low accuracy. In fact, only 1 and 10 parts per 100,000 of intravenously administered monoclonal antibodies reach a tumour *in vivo*.[4]

The targeted drug delivery of nanoparticles means that much smaller quantities of a specific drug are needed to be injected and that the damage is limited to the cancerous cells only, ommiting the undesired side effects. The nanoshell is an example of targeted treatment. It consists of a glass core covered by a gold shell. To treat a patient, the nanoshells are given intravenously over a number over days. In this time, a percentage of the nanoshells will group in a tumour. A harmless, near-infrared, light is shone through the skin over the tumour. The nanoshells can be varied in width to make the shells absorb light at this wavelength. As the nanoshells absorb more light, they heat up and burn away the tumour, leaving the healthy surrounding tissue unharmed. This process is shown in Figure 1. [5]



Source: Nanospectra Biosciences ROBERT DIBRELL, ERIC BERGER : CHRONICLE

Figure 1

The nanoshells fit into the category of 'nanovectors'. A nanovector is a hollow or solid structure within the 1-1,000nm range, which can be filled with anticancer drugs. On the surface, functional groups can also be attached for the targeting of tumours.[5] Other existing nanovectors include nanocantilevers and nanowires,[6] which focus mainly on the detection of malignant cells.

Convincing evidence has been found to support the effectiveness of the treatment of cancer with nanoshells by bioengineers and physician-scientists (Jennifer West, Susan Blaney, and Rebekah Drezek) at Rice University, Texas (2011). Seven mice with glioma (an extremely invasive brain tumour) were injected with gold nanoshells. They were then left for 24 hours to allow the nanoparticles to accumulate within the tumour. As shown above, a near infrared light was shined for three minutes at the tumour, causing the nanoshells to heat and kill the mass. Progress was recorded in all the mice, but cancer returned in three. The other four were still cancer free 90 days after treatment. [7]

This research has excited many scientists and doctors around the world due to its ingenuity and potential. It has shown that previously thought inoperable tumours may still have a chance at being removed, with less intrusion than before. With this it is hoped that nanoshells can provide an effective regimen to cancer patients, meaning less hospitalized care and faster recovery.

Discussion

It has already been shown that through the use of dendrimers (a chemical polymer with regular and repeated monomers branching out from the centre to form a tree-like structure [8]), scientists have been able to make a multi-functional nanoparticle that can deliver anti-cancerous drugs to a tumour whilst it emits a fluorescent glow. This glow can be picked up by contemporary scanning technology to allow doctors to see the location of the growth.[9] However, although use of dendrimers and the way dendrimers target the tumour are new, the drugs they use are not. Therefore many of the original problems and side effects of traditional chemotherapy protocols are still present. Golden nanoshells have been shown to be highly effective against tumours in mice [7], yet they still come with their own drawbacks. Currently, when using only gold nanoshells, the contrast of the growth in the body is not improved on the MRI machine screen, as a result smaller tumours may be missed and the degree of success of the treatment will remain uncertain. If cancerous cells have become detached from the primary tumour, it would remain difficult to know for sure if these have been denatured. Unlike during surgery, the use of nanoparticles *in vivo* means that the cancer cannot be seen. This means that during the treatment using nanotechnology, the doctor is almost oblivious to the progression of the nanoshells as they burn through the tumour.

Although a rough estimate may be made for the duration of time the near-infrared light should be shone onto the tumour, it will not have the optimum level of accuracy. If the nanoshells are heated excessively, they may go on to burn healthy tissue once the tumour is removed. The heated nanoshells may go on to circulate in the blood and cause damage to other parts of the body. Although the arteries and capillaries of the body could possibly withstand this, other more sensitive areas such as the brain could suffer serious harm.

This paper proposes attaching cancer cell-specific reporter and targeting molecules to the surface of a gold shell and glass core nanoshell in order to make a multifunctional nanoparticle. The gold nanoshells have proven to be able to enter a cancerous mass until needed, yet locating where to place the near-infrared light is difficult as the smaller growths will not show up under normal circumstances. By attaching monoclonal antibodies to the surface of a gold nanoshell, along with a reporter molecule such as fluorescein, further accuracy can be achieved.

As the gold nanoshell enters the tumour, the monoclonal antibodies bind with the cell. As this happens, the fluorescein is caused to glow brightly [10]. These glowing cells can be picked up by contemporary MRI machines, allowing doctors to find even small masses of tumour throughout the body. Precise measurements of the tumour can be made and it can be seen whether or not the cancer has spread. This gives greater information when deciding further actions.

The beginnings of secondary and subsequent tumours are usually caused by cells detaching from a primary tumour and circulating through the bloodstream or lymphatic system. [11] Despite it being possible for the nanoshells to bind with these single cancer cells, it is unlikely that they will show up on a scan. Nevertheless, some cancer cells stick to platelets whilst circulating in the blood stream for protection. [11] This could end up having the opposite effect though, as the mass formed could well end up being large enough to be present in scans. This exciting prospect would permit doctors to know if the cancer has been completely removed, and researchers to follow the progression of cancer *in vivo*.

If cancer cells are detected in the blood stream or lymphatic system, the process can be repeated several times, until the cancer has gone. This has an advantage over other methods of treatment, as it is not aggressive and so is not likely to have a limit to the amount of times the process can be carried out. Alternatively, the infrared light can be placed over the heart. As all blood passes through the heart, the light does not have to follow the tumours around the body, but merely wait for the nanoshells to pass underneath, killing the cancerous cells before they are able to set up a secondary tumour.

Notwithstanding, this unfortunately does not help the doctor or surgeon using the near-infrared light to know when to stop. It is very difficult to tell if what you are cutting into is tumour or healthy tissue, even when you can see the growth. However, although it is difficult, it is not impossible.

Normally, a tissue sample is taken from the body and taken to a histologist. The histologist then identifies whether or not the tissue is cancerous under the microscope. Not only is this invasive as it requires surgery, but it is also time consuming and subject to human error. A faster and more accurate method is to incorporate a mass spectrometer to work hand in hand with the doctor and nanoshells.

As the tumour is burnt by the nanoshells, smoke is produced. By placing a minimally invasive nanotube into the body above the tumour being operated on, it is possible to suck the smoke into a mass spectrometer. As the smoke is sucked up, the smaller molecules naturally separate from the tar due to their latent inertia. These smaller molecules progress through a mass spectrometer for analysis. The mass spectrometer is able to do this due to the changes undergone by the cells.

When the tissue is vaporised, the molecules become charged. As they enter the mass spectrometer, the molecules are accelerated by magnets in a vacuum. Due to the laws of physics, the bigger the molecule, the slower it goes. The molecules are identified in the mass spectrometer according to their weight and final speed when they hit the analyser at the end of the machine. Calculations are then carried out and the tissue is identified as cancerous or healthy (Zoltán Takáts, 2011). [12]

Despite this sounding like a lengthy process, it only takes around 0.9 seconds [12], instead of the usually 40 minutes needed by histologists. This allows real-time, instantaneous decisions to be made by the doctor or surgeon. The mass spectrometer can be wired up to the device that emits near-infrared light; so that when a certain amount of healthy tissue is registered by the mass spectrometer the light cuts out, preventing further damage. This will allow complete removal of the tumour, with minimal side effects.

From here, the nanoshells will pass into the urinary system and be excreted from the body. Further tests can be run and more scans taken to confirm the complete absence of malignant cells, and the treatment repeated if needed. The injection of these nanoshells would also act as an effective diagnostic tool if symptoms were present. A scan could be performed, and any malignant growths would be present on the screen, and treatment could begin immediately. This makes these nanoshells a truly multifunctional and useful tool in the fight against cancer.

Ethics

Nanotechnology has progressed rapidly since its creation, and brought with it many benefits to science. However, as the science leaps ahead, the ethics struggle to keep up. Nanotechnology is more than likely to have huge impacts on society, yet these possible consequences have yet to be fully explored and explained to the public.

Primarily, the potential toxicity to the body is a significant concern. Many biological barriers that would otherwise prevent the passage of larger molecules into vital organs cannot stop nano-sized particles. Furthermore, the phagocytes that engulf foreign bodies are unable to detect anything smaller then 200nm. [13] This enables nanotechnology to circulate freely throughout the body unhindered and unchecked.

This raises questions about what would happen if a nanoparticle accessed an organ that it was not intended to. The body is fully of sensitive and temperamental organs, which can easily be damaged. Although nanoshells have recently been proven to be an effective combatant of glioma in mice, the effects on the human body are currently unfamiliar with scientists. If nanoparticles reached parts of the brain that were previously thought inaccessible, its functionality could be severely impaired.

It has not yet been confirmed how the nanoparticles are removed from the body, if at all. Some scientists suggest that they are excreted, whilst others propose that the liver stores them. [12] Biodegradable masses decompose through the body and are excreted by the kidneys and intestine. As nanoshells are usually composed of a gold coating, thus making it non-biodegradable, studies have shown that nanoparticles have been found to accumulate in organs. This is a concern as it is not known how long the deposits stay and what damage could occur. [14]

Once these nanoparticles are removed or excreted from the body, they will either end up in air or water. The presence of these nanoparticles in the air or water may adversely affect human health or act as a pollutant. Due to the nanoparticles being so small, it is highly unlikely for them to settle on a surface as even the slightest breeze will be sufficient in keeping them afloat.

The extended period of these nanoparticles being airborne increases the chance of them being inhaled by people and animals. The unknown affects, if any, of nanoparticles in the lungs could include problems or illnesses. Due to the nanoparticles having such a large surface area, and therefore a greater reactivity rate, harmful effects on the body could be increased as more reactions occur. Similarly, a normally harmless molecule could become hazardous. [13]

Numerous tests and prolonged research must be completed and conclusive evidence found before it becomes an all-accessible treatment in the NHS, due to the potential damage to the body. Public perception must also be carefully monitored. Doubts and uncertainties expressed by the public may have an unforeseen impact on research. By working alongside journalists and doctors, who are close to the concerns of the public, researchers will be alerted to these concerns and enable them to offer timely explanations.

Intellectual property issues in respect nanotechnology must also be addressed. With the rapid acceleration of the scientific findings, it has taken several years for these problems to be publically discussed. The question of who controls and benefits from the technology is ongoing, as is how it can be integrated with existing patients. Failure to solve these dilemmas could constrict and hinder the accessibility and usefulness to all involved.

Tackling these problems is as important as, if not more so, continuing the research of nanotechnology.

Conclusion

Further development of nanotechnology will doubtlessly be instrumental in the detection and prevention of cancer in the future. This paper supports the utilization of nanoshells as an effective method of diagnosis and treatment. Although some of the ethical issues touched upon may have cause for concern, through further research, and with the progression of technology, they may be resolved quickly and effectively. Fortunately, nanotechnology does not raise as many serious issues as other recent developments in science.

The cost of the research must also be taken into account. The development of this technology is potential millions of pounds away, and a lot more time must be devoted to finding ways to attach the molecules onto the nanoshells. The millions spent now will not need to be spent again if nanotechnology enables the effective removal of cancer. As a result, millions more lives will be saved every year.

Current research supports the possibility that nanoshells may become a viable and widely utilised treatment for many types of cancers. The real-time monitoring of destroyed tissue negates the disadvantage of being unable to see the tumour whilst operating; whilst the increased contrast on the MRI scans gives pinpoint accuracy and the ability to spot mobile cancer cells. This is an amazing ability that can revolutionize medicine.

Public perception and intellectual property issues must continue to be openly and transparently debated in order for the technology to increase the ultimate benefit for cancer patients. Public discussion and involvement combined with scientists from multidisciplinary teams could apply their experience and knowledge to come to a swift and safe decision.

Cancers are a group of devastating and cosmopolitan diseases that affect the lives of millions of people. The human cost of the malignancies justifies the many hours of work and expense of research into nanotechnology for use in cancer treatment. Current research suggests a bright future for the treatment of cancer with nanotechnology at its forefront.

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