Exploring the uses of nanotechnology which have the potential to provide improved treatments, more precise diagnosis and possible preventions of cancer as an alternative to traditional methods used today

BY

CEM PAPAKER

NIALL ARMSTRONG

SAUL CRANDON

PASS

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Abstract

This paper is a brief overview of current and future ways of treating cancer using nanotechnology, while reflecting on the ethical and practical implications of harnessing such an unknown, yet such a promising type of treatment that could shape the way in which cancer is treated in the future. Cancer treatments using substances based on nanotechnology such as BIND-014 and gold nanoparticles are discussed. A brief look into future possibilities of a `Nano-Vaccine' that would prevent the development and spread of cancerous cells is also included.

Introduction

A definition for nanotechnology is given as "… the engineering of functional systems at a molecular scale" [1]. Nanotechnology deals with particles that are less than a few hundred nanometers in size (a nanometre is 10^{-9}m).This means that they can interact with biomolecules directly on the sub-atomic scale. Nanotechnology is a relatively new area of research which started to become prevalent in the early 1980's significantly aided by the development of the scanning electron microscope (1981). An important discovery within nanotechnology was that of Buckminsterfullerene's Buckyball (1986) [2]

According to some people working in the field of nanotechnology physicist Professor Richard P. Feynman is the father of nanotechnology. The possibility of working at very small scale was considered by Feynman who was jointly awarded a Nobel Prize in Physics in 1965 together with the two other physicists. Feynman gave the inspirational talk titled "There is plenty of room at the bottom" on December 29th 1959 [3]. The potential that nanotechnology had in regards with curing diseases has been realised by nanotechnologists and scientists at an early stage that has resulted in a deluge of researchers developing applications of nanotechnology in the field of medicine and some of the most promising research is into possible cures of life threatening diseases, such as cancer.

The term cancer relates to "an abnormal growth of cells which tend to proliferate in an uncontrolled way, and, in some cases metastasise" [4]. Metastasis is the process whereby diseases spread to other areas of the body from the primary cancer [5]. Therefore, it is not surprising that the ability of cancer to metastasise, makes it one of the largest causes of death in the world today.

Tumours caused by the abnormal growth of the cells can be one of two categories, benign and malignant.

Benign tumours usually grow fairly slowly in comparison to malignant tumours and they do not spread to other areas of the body. In addition, they are often 'coated' in a layer of normal cells. The cells of a benign tumour are similar to that of the normal cells found within the body and only become dangerous in certain circumstances; if the tumour grows too large and affects other organs, for example taking up space inside the skull, like a brain tumour. Furthermore, if the tumour becomes unsightly, uncomfortable or releases hormones that affect other areas of the bodily system then the tumour becomes precarious and needs to be addressed.

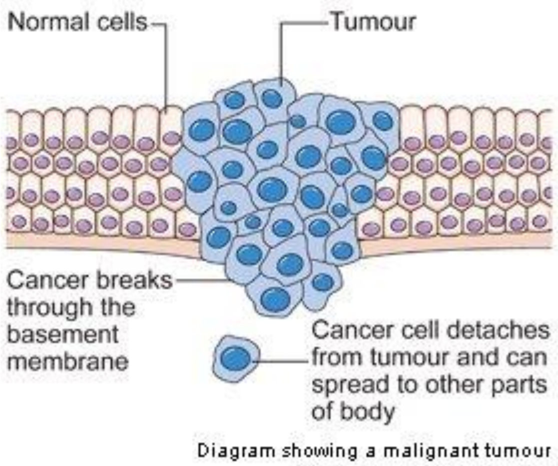

Fig. 1 A malignant tumour spreading in a localized area damaging healthy tissues and penetrating the basement membrane.
Cancer breaks through the basement membrane.
Cancer cell detaches from tumor and can spread to other parts of body.
[6]

Malignant tumours (Fig. 1) are more serious and are very cancerous. Typically they grow much faster than benign tumours meaning that they have the ability to spread very quickly to other regions of the body, thus affecting not only the original site of tumour growth but other places as well. [6]
The main factor that makes cancer harmful in the body is its nature to spread. This occurs when a cancer cell detaches from the tumour (Fig. 1) , therefore, treating cancer early can limit these effects and increase the patient's chances of survival.

The main difficulty posed with cancer is that any cell throughout the body has the ability to develop into a cancerous cell and spread to form a tumour. This makes it very difficult to diagnose and detect a tumour before it has developed. Many types of cancer behave differently in the body, which also adds to the problem of treating the tumour and getting rid of the cancerous cells. Some tumours may grow quicker or slower than the others and produce many different chemicals that may affect the body's function. Also some may spread locally while the others may be spreading to remote areas of the body. The main difficulty is the response to treatments as some types of cancers respond well to drugs/procedures used to control their growth whereas others do not respond to current treatments.
The current treatments that are being deployed on cancer patients comprise chemotherapy, radiotherapy and surgery. The latter tends to be used in the early stages of cancer before it has had a chance to spread to other parts of the body.

Chemotherapy involves using chemical drugs to treat diseases such as cancer.
The chemotherapy drugs, when administered to the patient, can stop cancer cells dividing and reproducing. As the drugs are carried in the blood, they can reach cancer cells anywhere in the body. Unfortunately,, they are also absorbed by healthy cells located in various areas of the body such as the bone marrow, hair

follicles, lining of the mouth and digestive system [7] where the cells are particularly prone to the drugs used in chemotherapy, causing, the distressing side effects that occur when this treatment is in use. However, chemotherapy can be effective in the long term because the healthy cells can repair the damage after a certain amount of time whereas the cancer cells can not, thus causing them to die, eventually.

Radiotherapy is another common treatment which aims to eliminate cancerous cells in and around a specific tumour by killing them.. It works by directing a stream of high-energy particles (radiation) onto the affected tissue, and can be used to treat solid and non-solid tumours. Radiotherapy, like chemotherapy also has side effects because it does not differentiate between the cancerous and healthy cells, either. For this reason, doctors have to carefully balance the dose and timing of the treatment to allow enough time for the normal tissues to recover.

Radiation is used before and after a surgery to reduce the size of tumours and to destroy any cancer cells that may have escaped the surgery,. In recent years doctors and researchers have developed techniques of targeting the cancer more accurately, these include tomotherapy and other radiotherapy based techniques [8]. This has allowed them to administer higher doses of the radiation to tumours while reducing damage to surrounding tissue.

Surgery is the most common form of cancer treatment and is used to remove solid tumours. It often provides the best chance of a cure for many cancers which have not spread. If the cancerous tumour has grown or the cancer has spread away then surgery may still be used in conjunction with radiotherapy and/or chemotherapy. [9]

The latest survey, conducted in 2007, states that 7.9 million people died globally of cancer that year and with populations ever increasing, this figure is set to increase to 11.5 million by 2030 [10]. This data shows large numbers of people are afflicted by this disease therefore treatments for cancer are in high demand making it essential to explore new techniques that may be used to cure cancer more effectively and successfully.. Another reason for increasing research into cancer treatment is that current treatments such as chemotherapy and radiotherapy have distressing side effects and the survival rates following these treatments are still low. Based on the current economic climate, the potential impact of the increase in the number of cancer patients may also place a severe strain on Health Services. This is supported by current research carried out by Cancer Research UK that shows the NHS alone spends £4.5 billion a year on cancer treatment, which equates to over 5% of their yearly budget [11] . Therefore, based on the predicted figures for the future cancer patients given above the associated spending on patient care would also be increased significantly. There are many factors that affect the way that cancer is treated as a disease across the world, could nanotechnology be the answer?

Nanotechnology in Medicine

BIND-014 nanoparticles [12], gold nanoparticles [13] and `Nanobubbles' [14] are nanotechnology based technologies used in medicine to treat diseases such as cancer. The main aims of research and development into nanotechnology treatments are to reduce the side effects of current methods of the treatments of cancer and to increase the efficiency of existing procedures possibly taking the next steps to a definitive cure for cancer.

BIND-014

BIND Biosciences, Inc. a company based in Cambridge, Massachusetts, is a "biopharmaceutical company developing therapeutic targeted nanoparticles to produce best in class drugs" [12]. They are involved in the development and manufacture of nanoparticles with biophysicochemical properties.
Currently BIND Biosciences' most hopeful development is BIND-014 (Fig. 2), a targeted polymeric nanoparticle created to treat solid tumours by locating the unpregulated surface proteins.

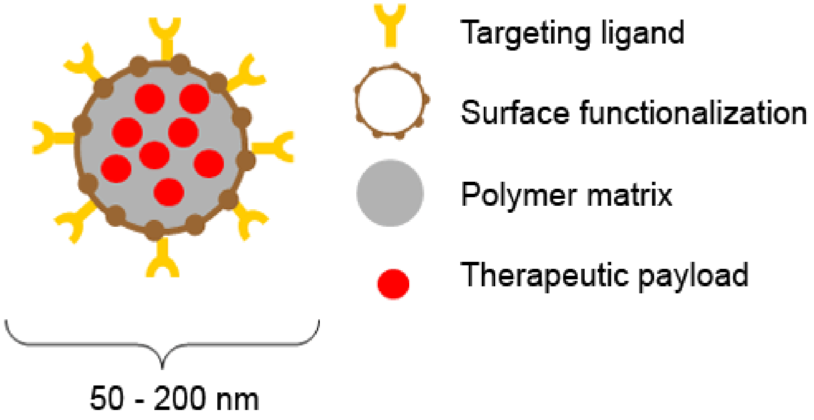

Fig 2
A simplified diagram of the BIND-014 targeted nanoparticles. Targeting ligand, Surface functionalisation, Polymer matrix, Therapeutic payload. [12]

The BIND-014 nanoparticle has 4 main components, each with a particular function to give the nanoparticle its ability to attach to cells and administer drugs and other substances on a cell-to-cell basis.
The targeting ligand component allows the nanoparticle to recognise the target cell associated with the disease by identifying receptors or proteins on the outer cell wall and to attach itself to the diseased cell.
Surface functionalisation is the coating of the BIND-014 nanoparticle which allows it to slip through the immune system undetected. It also provides an area of attachment of the targeting ligand through propriety linkage strategies. These methods allow the drug to be administered evenly and precisely.
The polymer matrix holds the volume of the substance/drug to be directly delivered into the cell in a medium of biodegradable polymers, which is designed to allow the drugs to be administered efficiently.

Finally the therapeutic payload is the substance that is placed inside the nanoparticle which is delivered directly to the cell. Some examples of these substances include small molecules, proteins and nucleic acids, as well as chemotherapy drugs [12].

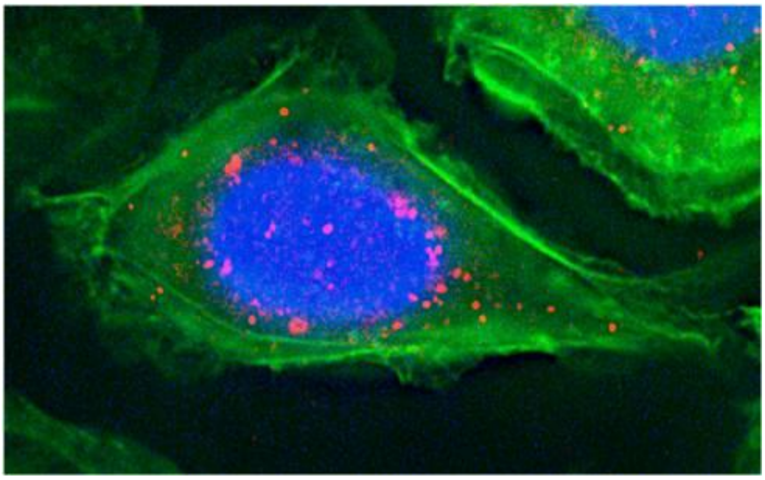

Fig 3.
A fluorescent microscope image showing the BIND nanoparticle entering the cell by endocytosis and delivering the specific drug to the target cell. [12]

BIND-014 nanoparticles are considered to be effective in the treatment of cancer because it allows the chemotherapy drugs to be delivered to specific cancerous cells (Fig. 3) without the possibility of damaging nearby healthy cells. This would allow efficient delivery of the chemotherapy drugs, as opposed to oral chemotherapy and intravenous chemotherapy (into a vein) both of which are not site-specific and often very inaccurate thus increasing the likely hood of damage to healthy cells.

Gold Nanoparticles

Research at the Georgia Institute of Technology (Georgia Tech) and the University of California at San Francisco, has shown that the use of gold nanoparticles may simplify cancer detection. It has been found that gold nanoparticles, when injected into the body do not stick as well to non-cancerous cells as they do to cancerous cells.
Mostafa El-Sayed, the Director of the Laser Dynamics Laboratory and Chemistry Professor at Georgia Tech stated that "Gold nanoparticles are very good at scattering and absorbing light" [13]. Therefore, when these gold nanoparticles are attached to a certain antibody for cancer cells, tumours and areas containing cancerous cells can be identified under a microscope helping to locate the problem areas. El-Sayed stated that "So far, the results are extremely promising" [13]
There is a specific protein known as Epidermal Growth Factor Receptors (EGFR) that is only found attached to cancerous cells, rather than healthy non-cancerous cells. By manipulating the gold nanoparticles and causing them to latch onto the natural antibody our body produces to fight these EGFR (which are appropriately named anti-EGFR), the nanoparticles were found to end up in amongst the cancer cells, thus making these cells `shine' and stand out under a microscope (Fig. 4). The healthy cells do not specifically

conjugate with the gold nanoparticles which means that if a well-defined glowing mass shows up under the microscope, it is probably cancer.

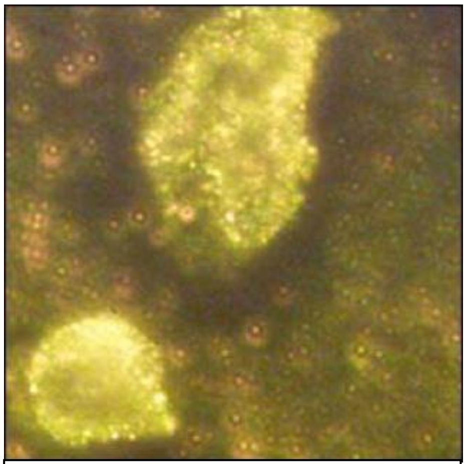

Fig 4.
Two cancer masses, shown up as shining 'lumps' from a view under a microscope, after binding with gold nanoparticles. [13]

El-Sayed said "What makes this technique so promising is that it doesn't require expensive high powered microscopes or lasers to review the results as other techniques require. All it takes is a simple, inexpensive microscope and white light." [13]

The results are also immediate. Once the cells from a tissue afflicted with cancer have been taken and are sprayed with the gold nanoparticles containing the antibody, the results can usually be noticed within seconds. Another major advantage with this technique is that the nanoparticles themselves are not toxic to humans when inside the body, this is very helpful as a previous, similar method was questioned for using semi-conductor crystals to spot cancer cells which were potentially poisonous in the immune system.
It was noted that the gold nanoparticles used, were up to 600% more likely to unite with cells affected by cancer than those that were not. The ideal size for the gold nanoparticles was found to be around 35 nanometres enabling them to work on a cellular scale.
Further research into these nanoparticles shows that they can be used to stop the cells dividing and in some cases can even to kill the cells altogether. The gold nanoparticles can be coated with a certain chemical, arginine-glycine-aspartic acid peptide (RGD) that allows the nanoparticle to be drawn into the cytoplasm of the affected cell and away from healthy cells. Once there, the nanoparticle is brought into the nucleus by a nuclear localisation signal peptide (NLS). It then interferes directly with the cell's DNA (Deoxyribonucleic acid) and prevents further cell division. Apoptosis, (a form of coordinated cell death) then begins, once the cell stops dividing, which eventually causes the cell to collapse. This prevents the cancerous cells from spreading beyond the already damaged region. This is particularly important because the nucleus of a cancerous cell causes them to divide far more rapidly than that of regular healthy cells, hence by preventing this division, it is possible to prevent the cancer spreading to other healthy areas of the body.

The Georgia Tech research team first tested this practice on cancerous cells from the ear, nose and throat which was concluded successful. El-Sayed said that "The cell starts dividing and then it collapses…Once you have a cell with two nuclei, it dies." [13]

The use of these specialised gold nanoparticles has the potential to revolutionise the way cancer is treated and possibly replace traditional methods such as chemotherapy and radiotherapy because gold nanoparticles do not stick to the healthy cells and therefore they do not harm them.

Drug-loaded Nanobubbles

A multifunctional nanoparticle has been created by a research team at the University of Utah which can detect cancerous tumours using ultrasound and simultaneously delivering anticancer drugs to the site in order to shrink them. This nanoparticle was created using an amalgamation of temperature-responding polymers working solely on tumours.

The multifunctional nanoparticle that was created has been engineered to specifically alter its structure in order to form a larger bubble on a micro scale to be used inside the body to combat cancerous tumours. The innovative aspect of these microbubbles is that they respond well to ultrasound so their location can easily be detected using a simple scan. The basic configuration of the microbubbles comprising of small amounts of biologically - compatible polymers created from polyethylene glycol (PEG) allows them to respond to ultrasound. By adjusting the temperatures the original nanoparticle is exposed to, the research team discovered that the particle was stable at room temperature but at body temperature, it was transformed into the microbubble. Thus anti-cancer drugs injected into the nanoparticle would remain there until the creation of the microbubble. The main drug that has been used in this nanoparticle was doxorubicin, a very effective cancer drug used to shrink tumours.

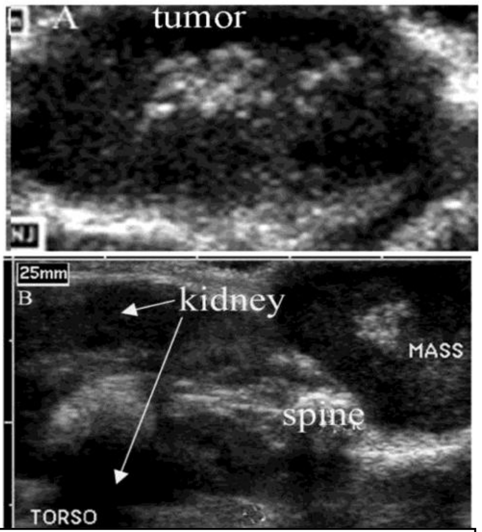

Fig . 5
2 Ultrasound images taken from a mouse., showing a cancerous tumour, labeled “mass” in image (B).
(A) Shows the tumour approximately 4 hours after the drug contained within the micro bubble, has been injected intravenously into the mouse. The microbubbles have begun to accumulate around the tumour.
(B) Shows that the microbubbles are local to the tumour, affecting only the cancer cells and leaving the kidney and other tissues unscathed. [14]

The research team first tested this microbubble on mice that were infected with cancerous tumours. The experiments conducted on the mice were deemed successful due to the fact that the anti-cancer drugs can be retained within the nanoparticles for sustained periods of time, long enough to reach the tumour.

The permeability of the blood vessels surrounding the tumour allows the drugs to seep through and target the mass directly. This is the stage at which the nanoparticles are transformed into the microbubble. Once inside the tumour, the nanoparticles are at the right temperature and have enough energy to coalesce. This can be seen through a simple ultrasound scan (Fig. 5). This allows scientists to see if the drug has reached the targeted site successfully and to monitor its progress. Once the location of the newly formed microbubble has been established and the ultrasound image has been collaborated, the tumour is targeted directly by a concentrated beam of ultrasound which causes the microbubble to instantaneously explode releasing the required drug to the tumour. This minor explosion damages the cancerous cell membranes increasing the drug uptake into the cancerous cells. This experiments showed that the mice used had remarkable deterioration of tumour size and cancerous cells in the affected area after a period of one week that involved two treatments. The research team are assessing the safety of the treatment before making this widely available as well as testing its efficiency [14].

Future Possibilities

Indications from the research we have conducted suggest that nanoparticles will become effective in the treatment of cancer, nevertheless, cancer is likely to remain as a serious disease until improvements to diagnostic methods are also made. It is believed that a future development to counteract these problems would be to devise a "Nano-Vaccine" which might be administered to those most susceptible to cancer.

This "Nano-Vaccine" might be based on a nanoparticle similar to BIND-014. Once it is injected into the body, it would target and envelope the cancerous cells and deliver the anti-cancer drugs that it carries directly. The major difference between BIND-014 and this “Nano-Vaccine” would be that the drug loaded nanoparticles could be injected into healthy patients. They would then respond to cells that start to mutate cancerously thus preventing their growth and spread within the body.

Advantages of the Nano-Vaccine

The “Nano-Vaccine” may be designed to remain in the body for a long period of time thus reducing the need for administering the "vaccine" regularly.

Due to the almost immediate response of these particles, the cancerous cells would be unable to spread making the anti-cancer drugs more effective as there will be far fewer cancerous cells to deal with. The procedure for delivering this “vaccine” would be simple and non-invasive, so it has significant benefits over surgery.

In the long run, it may also result in financial benefits as currently cancer treatments involve extended periods of time within hospitals. This places a large drain on medical funding and with the “Nano-Vaccine” the amount of time that patients spend in hospital may be significantly reduced.

Disadvantages of the Nano-Vaccine

The nanoparticles could have toxic properties and could be potentially harmful in the body.
The cost of developing these nanoparticles to the public may also be high, as a large amount of research would have to take place in order to ensure that the "vaccines" are safe. Developing the Nano-vaccine on a large scale may also add to the cost of the treatment.
The Nano-vaccine could only be used on those who do not suffer from cancer. This means that those with cancer may not benefit that much from the vaccine as it may not be that effective in dealing with tissue that had already been affected with cancerous cells.
Another disadvantage is that, due to the extensive amount of time that the nanoparticles remain active, the nanoparticles could become untargeted or malfunction and confuse the healthy cells with the cancerous ones, thus damaging them by delivering the drug to them.

Ethics

Nanotechnology has many obvious advantages in all aspects of technology, however progress in nanotechnology needs to be controlled and large amounts of research must take place before any advances are made, this is due to the fact that although nanotechnology appears to be a "miracle advancement", there are serious threats and ethical arguments that could occur if the right measures are not taken. A serious risk could be, as different countries will have different access to nanotechnology and research; this could lead to a "Nano-divide", where only some countries have better treatments using nanotechnology while others are still suffering. A further concern for the continued research and application of nanotechnology could be the potential threat of terrorism. Terrorists and other extremist groups could harness nanotechnology which could lead to the development of miniature weapons, explosives, military disassemblers or other dangerous advancements. If this became so, then the effects could be cataclysmic. Governments could also use threats of war or other demands to remove the rules on uses of nanotechnology, gain more nanotech and abuse its delicate research. [15]
As we are in a society where products are developed in one country, used in another and disposed of in another, determining who will receive the products and who will receive the dangerous waste could lead to an argument between countries. The waste of nanotechnological products could be very dangerous and unpredictable, as nanoparticles are self replicating and would be hard to stop. Due to their size it would be hard to keep track of nanoparticles and if they were allowed to replicate uncontrollably (not disposed of properly),

they would constantly expand until their quantities were uncontainable. This idea is known as the “grey goo scenario”. [16]
Due to the scale that Nanotechnology works on, it is possible to engineer extremely small complex mechanisms by building up from individual atoms. Once programmed in this way, these mechanisms can self replicate and, potentially, “new life” can be created from scratch. It is this idea that leads to the possibility of a “grey goo scenario”.
Some religions believe that this potential creation of “new life forms” is effectively “playing God” and this can be seen as morally wrong and it is not appropriate to be used in any field including medicine.

Conclusion

The ways in which cancer can be treated using nanotechnology differ greatly. New methods are constantly being developed and clinical trials have been carried out to ensure that they are useful and safe for widespread use.
Some areas of nanotechnology are often debated such as the behaviour of nanoparticles when they are inside the body. This is a concern and consequently slows the developments in this field. Associated costs in developing nanotechnology for use in medicine, could also be high making it less accessible for people with low income and/or limit its availability on health services such as the NHS (National Health Service). Religious issues are also an area for debate as many religions prohibit interfering with the body's natural function.
It might be possible for some of these issues to be addressed if there was more public awareness about nanotechnology., This might increase research funding and people may be more willing to use nanotechnology once they have a better understanding of it. Perhaps nanotechnology is underrated, as cancer is a worldwide disease resulting in a high death rate. Studies carried out by various researchers have shown that nanotechnology based cancer treatments have the potential to prevent, treat and possibly cure cancer.
The use of nanotechnology in the hospital as a new form of cancer treatment has already initiated debates which should result in certain decisions being made in regards with its use. With more and more people developing cancer, especially elderly people, the sooner nanotechnology can be implemented, the better.
As cancer may affect anyone of any age, preventing the disease appears to be a better way of dealing with cancer. The “Nano-Vaccine” could play a significant role in this respect.

Finally, implementation of nanoparticles in the treatment of cancer is a groundbreaking, new and innovative method, and it could transform the way in which this disease is dealt with across the world, provided that it is proven to be safe for use. Nanotechnology appears to have the potential to revolutionise the world of medicine.

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