

**NANOTECHNOLOGY**

**INVESTIGATING THE POSSIBILITIES FOR  
THE APPLICATION OF NANOTECHNOLOGY  
IN THE MODERN TREATMENT OF CANCER**

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## Abstract

Research into the development of nanotechnology in cancer treatment has brought around many questions, but also promotes a hope in the future of treatment for neoplasia. Through the work in drug delivery to and the detection and imaging of tumours all aspects of nanotechnology are assessed for their quality and utility in this paper. It is hoped that it will shed light on the new science that is nanotechnology and that in the future it will hold a prominent place in the treatment and detection of many other diseases.

## Introduction

Nanotechnology is the movement and manipulation of materials on an atomic and molecular scale. Nano means one billionth, and typically around 4 atoms can fit side to side in one nanometre. To put it in other words, a nanometre is roughly the same size as 1/80,000 of the diameter of a single human hair.

The first example of use of nanotechnology dates back to 30BC when an ancient artefact named the Lycurgus Cup was made. By using transmission electron microscopy it is revealed that the glass used to make the cup contained nanoparticles of gold and silver giving the cup a unique characteristic. When illuminated from the outside the cup's colour was green but, when illuminated from the inside the colour of the cup changed from green to red. It is most likely that the unique properties of this ancient Roman piece were created by accident as there are surviving pieces from the same era that appear to be failed attempts at recreating this effect.

In 1908 a German physicist named Gustav Mie came up with the theory of light scattering by the use of particles. Mie's theory helped scientists to realise that the size of particles determines the colours that we see. He then went on to invent a method of calculating the size of particles by determining the light they scatter. His calculations never really caught on as they were so complicated and too long for practical use until around the 1990's when the supercomputers became available. The basis of Mie's theory is used in the modern world today by researchers in predicting and determining the size of nanoparticles. Richard Feynman first introduced the idea of nanotechnology in 1959 during one of his talks entitled 'There's plenty of room at the bottom'. The term 'nanotechnology' itself came from a professor at Tokyo University of Science, Norio Taniguchi; it first appeared in one of his papers in 1974. He stated "Nano-technology

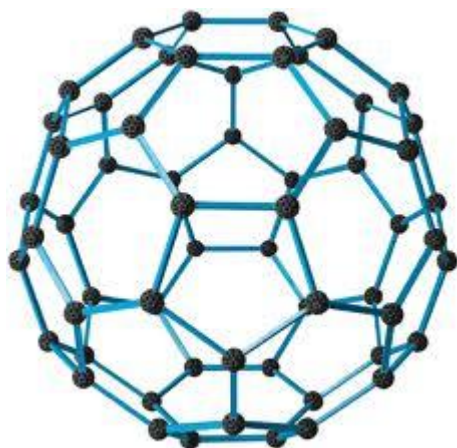


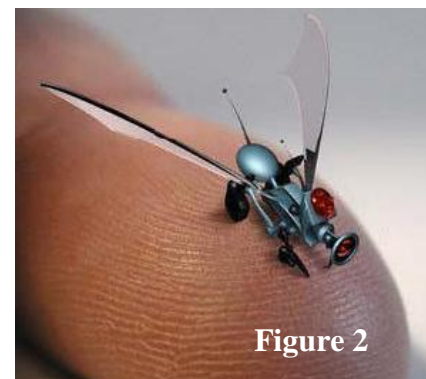
Figure 1

mainly consists of the processing of, separation, consolidation, and deformation of materials by one atom or by one molecule." The next major breakthrough came in 1985 when Richard Smalley, Robert Curl, James Heath and Sir Harry Kroto discovered C<sub>60</sub> (a carbon nanoparticle)[figure 1]. It was named Buckminsterfullerene, after the American architect Buckminster Fuller. C<sub>60</sub> was more commonly known as a "buckyball" due to its spherical-like structure. The molecule was proven to survive collisions at speeds of 20,000 miles per hour and above. Researches are currently investigating the use of buckyballs as drug delivery systems. Smalley, Curl and Kroto won the 1996 Nobel Prize in Chemistry for their discovery. In 1988 came the discovery of quantum dots. Dr.

Louis Brus and his team discovered nano-sized crystal semiconductor materials.

They proceeded to call them quantum dots, and their work eventually contributed to the understanding of the Quantum Confinement Effect.

From the making of nanobots (figure 1), the healing of spinal injuries to the delivery of drugs and the unclogging of arteries, nanotechnology is medicines hope for the future. Researchers identified a biological marker for Alzheimer's disease and have been able to detect minute concentrations of it using nanotechnology (i.e., bio-barcode process developed by C. Mirkin and colleagues). If successful, this could be the first tool for early diagnosis of Alzheimer's disease. Experiments are also being undertaken to use this bio-barcode process for other diseases like AIDS and many forms of cancer.



The most exciting new use of nanotechnology in medicine is the use of nanoshells in the modern treatment of cancer. In recent times, cancer is one of the major causes of death all around the world despite the huge investment and human resources dedicated to the investigations. According to official figures published in 2005 by the National Statistics office, the incidence of cancer in England and Wales has risen by around 20% in men and 30% in women since 1970. Between 1950 and 1999, the proportion of deaths due to cancer rose from 15% to 27% for men and from 16% to 23% for women. According to the study, as mortality from heart disease, stroke and infectious diseases has fallen, more people now die from cancer than from other major causes of death. One in three people there will develop cancer during their life and one in four people will die from the disease. It is these statistics that are the rising force behind the use of nanoshells in medicine, as the new developments could vastly improve the lives and chances of those suffering with cancer.

## **Drug Delivery**

One vital use of nanotechnology in cancer treatment is the synthesis of tiny capsules. These capsules are made of nanoparticles and can be used to transport drugs, heat, light and other substances such as radioactive material to specific cells, such as cancerous cells. These spheres are formed by moulding nanoparticles around solid micro particles, which can either be the desired drug, or another material which will be removed, leaving an empty container, to later be filled with the desired substance. The micro capsule is then coated in a slippery, non-stick coating. This coating is vital as in recent attempts to create drug delivery capsules, the capsules clumped together and became stuck. Another new innovative feature is the exit hole that has been made so that the drug or substance can escape from the sphere.

One of the most recent developments is the creation of a tumour killing drug created by CytImmune, one of the many new examples which are appearing to target cancer cells to deliver chemotherapy. This method of administering the tumour killing agent tumour necrosis factor alfa (TNF) will significantly reduce the damage caused by TNF to the healthy cells in the body. The particle consists of a gold nanoparticle attached to a molecule of TNF. This is then attached to a molecule of Thiol-derivatized polyethylene glycol (PEG-THIOL). This final molecule allows the nanoparticle to be hidden from the immune system, so it doesn't become attacked and broken down in the

bloodstream before reaching the site needed. The combination of molecules is called Aurmine.

The nanoparticle of Aurmine works in a variety of ways. Primarily, the particle is designed to be too large to enter most healthy blood vessels. However, the trick that allows the particle to reach cancerous tumours is that tumours induce blood vessel growth (angiogenesis) and so there is an increased gathering of larger blood vessels than would be found in healthy tissue surrounding the tumour. Also these blood vessels surrounding tumours become leaky because of the immense pressure put on them by the fast growing tumour. This allows the particle to exploit the enhanced permeability of the vessels to enable the nanoshells to exit the blood stream at the site of the tumour passively, preventing damage being done unnecessarily to the rest of the body. Another vital characteristic of Aurmine is the fact that the TNF binds to the tumour, so it can effectively destroy the area and prevent the cells from spreading. This use of nanotherapy has currently just completed Phase 1 of clinical trials, and now is looking to Phase 2. This second phase involves incorporating other chemotherapy drugs into the nanoparticle, as it is shown that this is when the TNF is most effective. Also trials are being held where a molecule of Paclitaxel, another chemotherapy drug is attached to the surface of the Aurmine.

Another exciting new use of nanotechnology is the use of nanoparticles to transport heat to thermally destroy tumours (Figure 3). J.Donald Payne, President and CEO of Nanospectra states that: "We believe a principal benefit of this approach may be highly selective and rapid tumour destruction with minimal damage to surrounding tissue and no systemic toxicity." The company has created AuroLaser Therapy which aims to thermally destroy cancerous cells by using particles activated by a near Infra-red laser. The AuroShell particles work in a similar way as the Aurmine. The shells are specially designed to strongly absorb wavelengths in the near infra-red (NIR) range of the spectrum. The shells consist of a casing made of gold nanoparticles, as the gold has useful properties such as Plasmon resonance and scattering. Most importantly the gold nanoshells can be tuned to the specific near infra-red wavelength so the properties of the nanoshells can be activated without opening up the body.

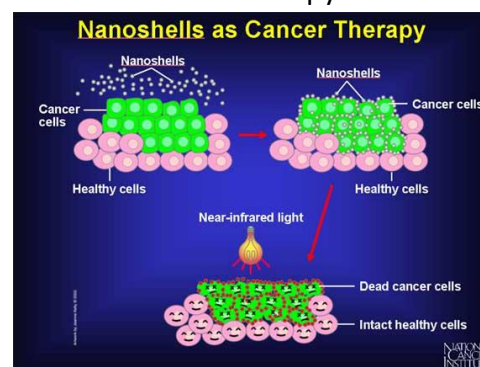


Figure 3

When the shells are injected, these particles have been shown to accumulate in the tumour due to the leaking blood vessels surrounding the tumour, called the enhanced permeability and retention (EPR) effect. This effectively destroys tumour when illuminated with an NIR laser. The surface of the nanoshell can also be covered in tumour-targeting moieties to further decrease the chance of damage to healthy tissue. After the shells have accumulated, the area of the tumour is illuminated with laser, and the NIR wavelength travels easily and with minimal disruption through the layers of human tissue. The nanoshells then absorb this light and this starts an interaction known as surface Plasmon resonance. During surface Plasmon resonance, the electrons on the gold surface of the nanoshell begin to oscillate as they are excited by the energy from

the NIR laser. The gold can be altered so its electrons will oscillate at a certain increased frequency, so the increased magnitude converts the light energy from the NIR laser and turns it in to a blast of heat to thermally destroy the tumour. Gold and silver both have equally good surface resonance, but gold was chosen as it is very unreactive and poses a much smaller threat to the body. The therapy has currently only been tested on those with tumours in the soft tissue of the head and neck once other treatments have failed them.

Also, nanotechnology has created a way in which X-Rays can be used advantageously to destroy cancerous tissue. The treatment via Nanobiotix has similar goals to that of Aurmine and AuroLaser. The company behind Nano x-ray therapeutics, Nanobiotix, wishes to resolve the biggest drawback of radiation treatments for cancer, the damage to the surrounding healthy tissue and the many side effects that can include irritation to the skin and mucus membranes resulting in crusting to the skin, nausea and also increasing the risk of future cancer. There is a big push for the completion of Nano x-rays clinical trials as about half of all cancer patients go through some form of radiation therapy, and Nano x-rays could play a major part in reducing the damage done to patients all over receiving radiation therapy. Nano x-ray consists simple of a hafnium oxide core that is the source of the therapy, but only when its electrons are excited by an external beam of x-rays. The crystalline structure of the nanoparticles prevents it being broken down by the body to ensure that it reaches its destination. The nanoparticles only have an effect when activated by an incoming beam of x-rays. The rays are absorbed by the nanoparticles, and in turn electrons with an increased amount of kinetic energy are formed and free radicals are created. It is these free radicals that interact and destroy the cancerous cells.

These techniques of using nanotechnology in drug delivery provide a new way of attacking cancerous tumours in the future. It may be a few years before these techniques are seen in our hospitals, but it offers an insight into the future of medicine, and the possibilities nanotechnology holds.

However, in relation to the veterinary field, it is often important to remember the mental wellbeing of our animals before continuing with these treatments. Though the treatments offer our pets a new hope, we mustn't forget the stress and strain we are putting our pets under by undergoing these treatments. Though side effects in treatments such as chemotherapy are much less severe in pets as they are in humans as a smaller dose is used, many pets still suffer from side effects such as vomiting and diarrhoea. Though this is not too severe in the short term, some animals may have to be treated with chemotherapy for the rest of their lives so is it really fair to keep these animals alive if they will never regain their full lease of life? I believe that in the cases where chemotherapy and other similar treatments are the only option, often it is not fair to put our pets through this. If the animal is still young, with many years ahead of them in health, then it should be considered. But when the animal is in the later years of life, I do not think that prolonging the animals suffering simply because of the owner's pain in losing them is right. This topic is one severely debated by veterinarians, and can only really be decided by the owner following a full discussion with their vet on their pet's individual case.

## **Diagnostic and Imaging**

Nanotechnology not only plays a key role in the delivery of drugs, but also in the diagnostics of the disease itself. Nanoparticles can be used in imaging to highlight the diseased area in the body, which comes in extremely useful in cancer especially. This screening allows for the direct treatment of the damaged cells without harming the surrounding healthy ones, which is a problem with chemotherapy and radiotherapy today.

Quantum dots are starting to be used for diagnostic testing of samples and it is thought that in the future they will also be used to locate cancerous tumours in the body. At the minute, the quantum dots (qdots) are used to enhance MRI scans. Iron oxide nano particles are used and are coated with a peptide that enables them to bind with cancer tumours. Once they have formed the bond with the cancer tumour, the image that is created is greatly enhanced, due to the iron oxide. The qdots may also have colour added, which allows scientists to track the spread of cancer as the qdots attach themselves to the cancer cells. The progress of these nanoparticles can now be tracked using infrared lymphangiography. This allows the scientists to gain a deeper insight into how the cancer divides and spreads throughout the body during the progression of the disease. This is especially useful in studying Leukaemia as it allows scientists to tag blood cells, which enables them to distinguish between leukemic and non-leukemic cells, and observe how they divide. Clinical trials on qdots revealed that the nanoparticles with a diameter of twelve nanometres were better suited to the extremities of the body, fingers, feet, etc., whereas those of six nanometres in diameter were more efficient in the mammary glands. This may be because the blood vessels flowing to the extremities are a lot wider to increase the blood flow as the blood pressure will not be as high in these areas, whereas the mammary glands are in close proximity to the heart and therefore only a small artery diameter is required to acquire the necessary amount of blood so smaller diameter nanoparticles are needed.

Nanoparticles are also able to attach themselves to proteins and other molecules, which is why they are becoming increasingly important in diagnostics. Recent clinical trials are studying the use of gold nanoparticles and magnetic nanoparticles. It has been proven that both can detect certain nucleic acids, with the latter also able to identify certain proteins and many other materials. Carbon nanotubes work in this way as well. If attached to cancer cells, the nanotubes are able to be detected by Raman spectroscopy. This allows for the location and destruction of the cancer cell.

Dr. Kas, University of Texas, Austin, have developed a machine that deforms cells to test their elasticity, which is a specific property of each type of cells cytoskeleton. The elasticity can be used to identify cancerous cells and indicate different stages of neoplasia, rapid cell growth. The machine contains two optical fibres in microfluidic flow chamber, which can cause cells to stretch as a high powered nano-laser passes straight through. Different types of cells can be identified by the way in which they stretch. This

will allow scientists in the future to be able to distinguish between cancerous and non-cancerous cells.

## **The Future of Nanotechnology**

Advancement in nanotechnology is one thing that is certain for the future. What is uncertain however is how the benefits and consequences of this advanced technology will affect us. It brings great opportunity for both the application and the abuse of the science. The technology brings hope for a cleaner and more efficient way of running machines in the future. Possibilities for cheap and effective solar energy systems as well as a renewable zero carbon emission source of fuel. With nanotechnology, the advancements of computers are guaranteed, with the ability to make components for computers on an atomic scale. There is also great hope for the medical industry. Developments such as nanoshells and quantum bring a sense of anticipation that nanotechnology will be able to destroy cancerous cells and viruses without worry of damaging the surrounding healthy tissue.

However with these advancements comes the threat more dangerous and technologically advanced wars. The potential for the quick production of cheap and dangerous weapons brings the worry of superior military systems. Also the advancements in weapons may make them more accessible, meaning that the world we live in becomes a more dangerous place.

Nevertheless, I believe that the main threat is currently hidden from view. Studies are already appearing showing unseen problems with the applications of nanotubes in seemingly harmless products such as tennis rackets. Studies of nanotubes are arising that show they may carry a similar health risk to asbestos. Asbestos was another wonder material that took the world by storm before things turned sour after it was discovered that the fibres contained in it were found to cause lung disease.

A team of researchers split mice into 4 groups and injected varying lengths of the nanotubes into each group. One group was injected with short nanotubes about 5 microns in length, one with long nanotubes about 20 microns in length, one with asbestos and one with small carbon clumps. Those injected with short nanotubes or carbon clumps remained relatively unharmed. However those injected with long nanotubes developed lesions on the lung lining similar to those that had been injected with asbestos. When foreign particles such as dust or smoke land on the lining of the lungs, cells known as macrophages arrive to engulf these particles and remove them. However the long nanotubes, similarly to the asbestos fibres, are too long for the macrophages to remove, and these resulted in lesions on the lung. It is severely hoped that nanotubes do not follow the path of asbestos, as with asbestos, the lesions caused eventually became mesothelioma, which is a deadly form of cancer.

So far there is no evidence that nanotubes pose any threat when in the form of a bicycle or a golf club, but the fear comes from the making of these products, or even when these products become broken down in later life. "I think there is clear evidence for caution in how they are used and handled," said Andrew D. Maynard, chief science adviser to the Project on Emerging Nanotechnologies at the Woodrow Wilson International Centre for Scholars in Washington. It has been suggested by many that nanotubes should be subjected to the same rules and regulations as asbestos, at least until further tests have been completed.

## **Conclusion**

Nanotechnology has progressed further and faster than anyone could have imagined ten or twenty years ago. The speed of this development is thanks to the dedication and funds that have been pumped into this area of research with such enthusiasm. I believe that the continued advancement of this technology could lead to many more exciting possibilities in the future, such as a reduction on our reliance on non-renewable fuels such as oil and coal. The technology could lead an era where cancer is no longer a death sentence, and where we approach the disease with a cure in hand.

This development however is by no means certain. With the current economic climate being in such turmoil, it is possible that the budget surrounding such research may be cut, either partially or completely. These cuts may result in the slowed progress of the technology, and may cost thousands of lives if the treatment of cancer and other such diseases is compromised. Without the constant research and funds for these projects, the full developments of these technologies cannot be expected to become achieved. Without these funds, vital research involving the issues revolving nanotubes and other such problems cannot be fully unveiled. This may lead to problems in the future such as those in the manufacturing industry falling ill due to inhaled nanotubes, or if these stories are false but are not fully proven, then it could result in the loss of faith in the industry.

Another problem faced by the industry is not only the falling funds or speculation about the implications of the technology, but the importance the industry is patrolled with vigilance to ensure that developments do not occur in the wrong direction. If nanotechnology fell into the wrong hands, it could be disastrous for the whole Earth.

Nanotechnology holds a power that could be deadly if released into the weapons industry.

Overall, as aspiring medical and veterinary students, we believe that the most important applications of the technology are advancements in the direction of the curing of disease and the improvement of diagnostic imaging. These medical reforms could lead to an increase in life expectancy of both animals and humans, and more importantly we believe, it could lead to an increase in the quality of life enjoyed by those in their last days.

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