Nanotechnology and its use in Cancer Research

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Abstract

The applications of nanotechnology have the potential to transform cancer diagnosis, monitoring and treatment. The main premise of nanotechnology in medicine is that it provides a greater precision to current techniques, allowing devices to target specific cells. Currently cancer is diagnosed by MRI and CT scans and is treated either by surgery or a combination of radio and chemotherapy. This paper will discuss how the development of nanotechnology can improve cancer research.

Introduction

"The problems of chemistry and biology can be greatly helped if our ability to see what we are doing, and to do things on an atomic level, is ultimately developed---a development which I think cannot be avoided".[1]

The concept of nanotechnology is defined as the science and engineering involved in manipulating materials on the nanometre scale, where one nanometre is one billionth or 10^{-9} of a metre. To put that into context, the comparative size of a nanometre to a metre is the same as that of a marble to the size of the Earth[2]. Nanotechnology allows advances in medicine and physiology as devices can be designed to interact with tissues on the molecular scale, thus allowing a greater degree of specificity in treatments.

There are two different methods for synthesising materials on the nanometre scale; "top down" and "bottom up." The "bottom up" approach is perhaps the most recognisable when nano-objects are synthesised from molecules which assemble themselves by following chemical laws such as thermodynamics and intermolecular reactions. On the other hand, the "top down" approach is when nano-objects are constructed from a larger object which then has smaller scale details incorporated into them[3].

More than 1 in 3 people will develop some form of cancer in their lifetime[4]. Cancer is a malignant growth or tumour caused by abnormal cell division resulting from incorrect DNA translation or transcription. Factors that affect the risk of developing cancer are: age, lifestyle, carcinogens and genes. Apart from surgery, the two main treatments for cancer are radiotherapy and chemotherapy[5]; both aim to kill cancer cells by either using precisely targeted gamma rays or drugs which disrupt cell division. Unfortunately both treatments damage the healthy cells around the tumour thus causing side effects such as hair loss and sickness. Therefore, there needs to be a more effective treatment which specifically targets the cancerous cells as well as reducing the intensity of the side effects.

According to the National Cancer Institute (NCI) the elderly are 10 times more likely to develop cancer and 15 times more likely to die from cancer than the population under the age of 65. From a scientific viewpoint, cancer and ageing are two opposite phenomena. This is because cancer is due to the overgrowth of cells which will not or can not stop dividing. Whereas, ageing is when the cells no longer divide and have reached the end of its biological life. In spite of this there seems to be a growing link between ageing and cancer as

60% of newly diagnosed malignancies are found in people above 65. The characteristics of the cancer differ with age as well, for example an elderly patient with acute myelogenous leukaemia is more likely to have tumours that resist treatment, and they are less likely to achieve remission than their younger counterparts[6].

Although medical applications of nanotechnology are in its infancy, it can provide new treatments for cancer. The main advantage to nanotechnology being used in medicine is that treatments can become more specific as particles can react with tissues on the cellular level. The particles can be manipulated in such a way as to allow the drug to target the tumour only. This new method of delivery systems could have a significant impact on cancer therapies. Current treatments rely on radiation damaging the effected tissues; however, the treatments lack the precision which nanoparticles can offer. An example of current research on nano-drug delivery systems is CytImmune's development of Aurimune[7]. CytImmune is a nanomedicine company based in America which focuses on using nanotechnology for cancer therapies. Its leading drug is Aurimune (CTY-6091) which consists of gold nanoparticles bound to Tumour Necrosis Factor alpha (TNF) and molecules of Thiol-derivatised Polyethylene Glycol (PEG-Thiol). Aurimune, which is currently undergoing clinical testing, has a size of 27nm and is able to pass through the blood stream without detection by the immune system due to the PEG-Thiol. It is able to target tumours because of the tumour's intrinsic permeability. After reaching the tumour, the TNF molecules located on the nanoparticles are able to kill the cancerous cells. Although this drug is still undergoing testing, it indicates the potential of nanotechnology as new cancer therapies.

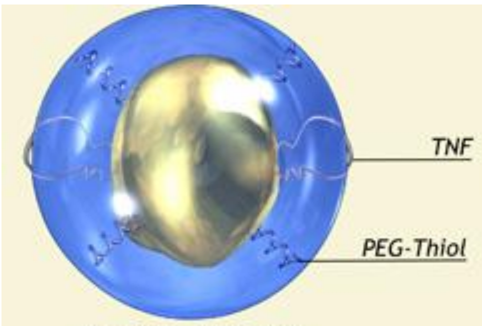

Figure 1: Aurimune (CTY-6091)

As well as nanoparticles, nanotubes are also used in drug delivery systems. They are allotropes of carbon arranged in a cylindrical tube structure[8]. The high tensile strength of nanotubes is due to the sp^2 bonds similar to those present in graphite. These bonds also allow the tubes to be more flexible and durable. TNFs could be placed inside the tubes and be directly delivered to cells resulting in the death of cancerous tissues. Again, this allows the treatment to be more localised so less healthy tissue is damaged and there are fewer side effects.

The application of nanotechnology is not solely limited to drug delivery systems; it also offers developments medical imaging. One example of this is the use of Quantum Dots (Qdots) which are semiconductors with a typical diameter of 2-10nm. When excited they emit photons which as seen as visible light by the eye. The colour of light emitted, which is determined by the wavelength of the photon, can be controlled during production by varying the size of the particle[9]. The advantage of Qdots is that they provide high resolution images and good contrast for electron microscopes. They can be attached to a particular receptor on a cell and can then monitor its processes, indicating any possible reactions that cause cancer. Qdots are also used to mark cancerous cells after this CT scanners are used to detect any tumours. This can be applied to other biological tissues rather than cancerous tissues both in vitro and in vivo[10].

Discussion

The implementation of nanotechnology could vastly improve the approach to cancer. Currently cancer is diagnosed using MRI and CT scans. These techniques could be replaced by cantilevers which are flexible beams that resemble a set of diving boards, built from semiconductor lithographic techniques. These beams are coated in antibodies which respond to the molecular products secreted from the cancerous cell. As a result of the complimentary shapes between the molecular products and antibodies, they bind causing the cantilever to bend due to the increased weight. Each antibody can be specifically designed to allow more than one product to attach to it. In the future doctors can use the change in shape of the cantilevers as an indication of whether a cancerous cell is present and calculate its concentration. This will provide a faster and more accurate detection of cancer cells in the body[1]. An advantage of this method is that it targets individual cells so the area that is most likely to be cancerous can be monitored closely. This process is more time efficient as the doctor can focus solely on the infected area. This research is only in its preliminary stages, so it is likely to be many years before this is applied across the UK.

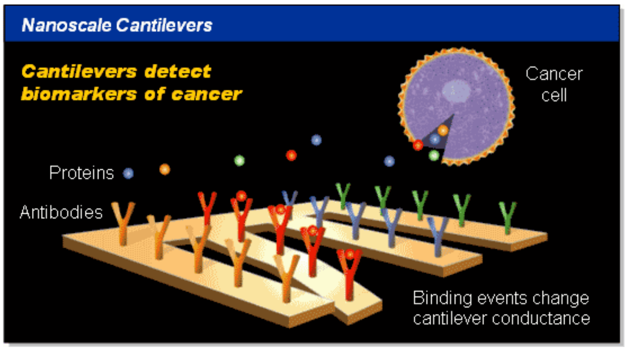

Figure 2: Cantilevers often referred as biomarkers

In Eric Drexler's 1986 book *'Engines of Creation; the Coming Era of Nanotechnology'* he suggests that nanotechnology could advance to such a stage where a nano-scaled machine can transfer reactive molecules into the correct position. Essentially his idea was that machines could be produced on the nano scale and could operate mechanically in the human body by imitating nature. He argued that such radical nanotechnology must be possible as it already exists in cellular biology. Nanorobots would be produced by using hard materials such as diamond. In terms of cancer research the ultimate goal would be to use nanorobots to treat the faulty DNA directly. This could be done by injecting a fluid containing the nanorobots holding the treatment to destroy the cancerous tissues. However there are flaws in Drexler's vision as he has not taken into account that nano objects operate differently to macro objects. This implies that objects that function

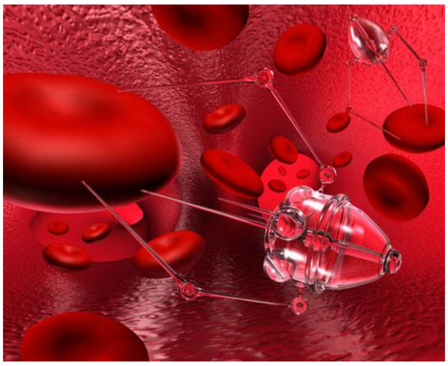

Figure 3: Computer generated image showing a nanorobot in the bloodstream

well in our macroscopic world but will work less and less well as they decrease in size. Movements of the nanorobots would be due to the random movement inside the body; however at the same time it would have to withstand collisions with other molecules. One issue raised by Drexler's theory is that the nanorobots could have the potential to replicate out of control and could possibly 'render all human life extinct'.[2] Although this idea may seem farfetched it triggered doubts into the future of nanotechnology and was dubbed as the 'grey goo scenario'. If nanorobots were to be used in medicine extensive research is needed to prevent such an event from happening.

Nanoshells are another development in nanotechnology which can be used to treat cancer. They consist of a metallic outer layer and a core of silica and can safely enter the body by normal methods of injection. Due to their size, they can selectively target the cancer lesion sites through a phenomenon called Enhanced Permeation Retention (EPR) [3]. To make nanoshells more effective, scientists can modify them by adding molecular glue which conjugates to the antigens on the cancerous cells, consequently disenabling the spread of cancer in the body similar to the effect of agglutination in the immune system. As shown in figure 4, an intense heat is then applied to the area which is absorbed by the nanoshells and selectively kills the cancerous cells. At the same time, healthy cells are left unharmed. At present, treatments do not distinguish between cancer cells and healthy cells; this method offers accuracy as only the nanoshells absorb the heat. In spite of this, it is only a theory so the full side effects of nanoshells are not yet known.

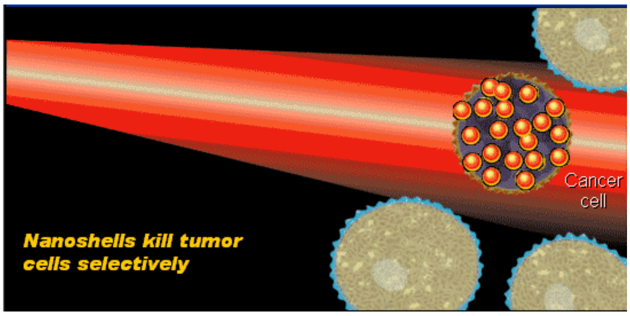

Figure 4: Nanoshells absorbing intense heat

As mentioned in the introduction, nanoparticles could be used as therapeutic agents and in medical imaging. The nanoparticles can bind with the cancer cells, the combined shaped allows it to be more visible during medical scans. This is because the lesion has a more defined shape from the surrounding tissues. The nanoparticles can be easily injected or could be directly delivered using nanotubes to the affected area. The nanoparticles allow for a higher degree of precision in the diagnosis of cancer and give scientists the ability to view cells previously undetectable by conventional methods. Nanoparticles can also pinpoint malignant cells. Similar to the cantilever, the nanoparticles should contain receptors on their cell surface which are complementary to the proteins on the cancer cells. As they would be complementary, each cancer would have a different treatment; the specificity of the treatment would result in a more effective outcome. Perhaps in the future, treatments could be tailored for each patient for example; a patient

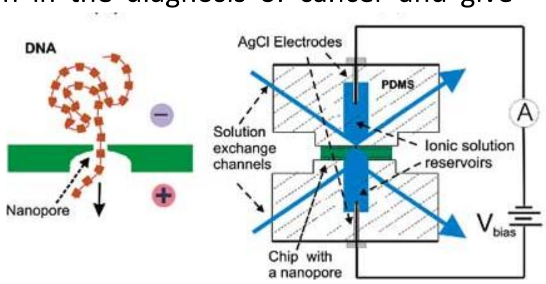

Figure 5: DNA being sequenced using a nanopore

with breast cancer could be prescribed a treatment which includes nanoparticles designed to kill just the cancerous breast tissues.

Nanopore sequencing is a method involving threading DNA through pores which determines the sequences of bases[4]. The idea was first envisioned by David Deamer, of the University of California in Santa Cruz, in the mid 1990s. To allow this process to work, the material is perforated by nanopores and is then placed in a salt solution. The ions present in the solution are able to pass through the pores hence generating a current. The ion current is reduced when a DNA base blocks the gap. The differentiation between the bases occurs due to the different chemical compositions i.e. each base has a unique pore blocking ability. The DNA could be threaded steadily through the nanopore with the variation in ion current being used to distinguish each base. This use of nanopores in DNA sequencing is significantly faster than current methods which involve DNA being split into fragments and then sequenced using gel electrophoresis. This means that in time to come, doctors could sequence their patients' DNA rapidly, indicating any precursors for cancer. Also, this method could be used to show any errors in the patient's genome by comparing it with its "normal genome" at annual check-ups. If a mutation is located, then the patient can then undergo treatment. The benefits of nanopores are that it allows cancer to be detected at an earlier which decreases the chance of the cancer becoming terminal. At the moment, cancer can only be detected visually through any abnormal growths in the body, by this stage, the tumour is already well developed increasing the risk of death.

Before nanotechnology can be integrated into modern health care, the ethical implications must be considered in detail. One of the issues surrounding nanotechnology is its ability to be absorbed to the body. Due to their size, nanoparticles can pass more easily through membranes; one specific example of this is that nanoparticles can pass through the blood brain barrier. This membrane prevents harmful chemicals from reaching the brain. However, currently the potential toxicity of nanoparticles is unknown. Before nanoparticles are implemented in health care, it must be certain that these particles will not have a detrimental effect on vital organs.

Furthermore, there is a lack of understanding of the behaviour of nanoparticles in the body. One possible outcome is that since nanoparticles can pass through membranes easily, it could cause the phagocytes to overload ultimately resulting in inflammation and an increase in susceptibility to other pathogens. Another concern is that owing to their large surface area, nanoparticles may affect chemical processes in the body by absorbing fluids onto their surface. There are other factors which affect toxicity such as its shape, surface charge, aggregation and the presence of certain functional groups in cells. These properties must also be considered during research.

In addition, another point to consider is the life span of nano-objects. At this time, it is not known as to how long the nanoparticles will remain in the body. The nanoparticles may not remain in the body long enough for a successful outcome, on the other hand, the nanoparticles may remain in the body for too long having adverse effects. Therefore, the removal of nanoparticles from the body must be taken into account before being used in medicine. Firstly, the nanoparticles may be removed from the body through natural methods such as excretion. Secondly, the nanoparticles could be traced throughout the body using Qdots, once the treatment has been completed; they could be removed using nanotubes placed on the skin.

As shown in the introduction the majority of cancer patients are over 65 thus showing a link between cancer and age. However their treatment is less intense and aggressive as studies have shown. Those over 65 are less likely to be referred to a specialist when there are signs of malignancy, and are less likely to be given early detection tests at the most treatable stage. Nanotechnology provides detection earlier without causing as much pain as the methods currently used. This means that the aged population have a reduced chance of their cancer progressing to a terminal stage. In addition, elderly care in the NHS is under scrutiny and nanotechnology can provide a more comfortable treatment for them with possibly less side effects.

The costs of these treatments also have to be considered. In times of austerity, treatments involving nanotechnology may not be financially viable for availability across the NHS. It may therefore take many years for the cost of treatments to become low enough for widespread use.

Conclusion

In conclusion, research in nanotechnology is still very much in its initial stages but it has the capability to change medicine. It makes current methods for treatments seem crude, because these methods lack the precision compared to what nanotechnology has to offer. In relation to cancer patients it would enable a faster diagnosis and more efficient treatment.

Furthermore, though these ideas may seem improbable, due to a deficiency in sophisticated machinery in the medical industry; we believe that as technology improves at an almost exponential rate, these advances may become available in the coming decades.

If the development of cancer treatments is to improve at its current rate more money is needed to be invested in cancer research, particularly in nanotechnology. However in the present economic climate the government may 'unnecessarily' cut funding for research. Additionally the life expectancy continues to increase, it can be said that more people would be affected by cancer. So money needs to be allocated to nanotechnology research in cancer as this is a more proficient treatment for the elderly.

Clearly more research is essential, seeing as to date we can not guarantee a certain link between ageing and cancer. The research required to determine the link would be to create a cancer genome project and an ageing genome project so that we can understand the full spectrum of genetic changes which occur in the human body. In addition there are external issues that influence cancer malignancy not just the cells alone. These issues are social, cultural as well as the medical history of the patient. Hence research and studies are needed in these areas before we can implement nanotechnology in cancer patients.

Despite all these concerns regarding nanotechnology, it has the potential to revolutionise our approach to cancer on an international scale. It can also transform lives on a more personal scale by potentially reducing loss of loved ones in families. Nanotechnology has a lot to offer medicine and will become a vital part of treatments in the future.

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Conclusion:

Images:

Figure 1: http://www.cytimmune.com/download/posters/ASCO_Poster.pdf

Figure 2: http://nano.cancer.gov/learn/understanding/nanotech_cantilevers.asp

Figure 3:
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Figure 4: http://nano.cancer.gov/learn/understanding/nanotech_nanoshells.asp

Figure 5:
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