HOW CAN MODERN DAY DEVELOPMENTS IN NANOTECHNOLOGY BE USED TO REVOLUTIONISE THE TREATMENT OF CANCER SUFFERERS, AND WHAT ARE THE POSSIBLE DRAWBACKS?

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Abstract

Over the last 50 years, Nanotechnology has gained a higher profile in the scientific community, being seen with 'virtually unlimited potential' - Spencer Abraham(1). It has become one of the most researched areas of science, and more recently, it's applications to medicine are slowly becoming realised. Specifically, diseases such as cancer, in its various form have been identified as one of the main causes of death in the United Kingdom, with a huge 156,723 cases of mortality in 2008 according to Cancer Research UK(2). As a result, cancer treatment is of great importance, and the applications of nanotechnology to this are very exciting. In this paper we will investigate and discuss the ways in which nanotechnology can be applied to the treatment of cancer, as well as consider possible problems and ethical issues, by using a 'gedanken' experiment based on existent research. Our findings were very interesting, from the application of gold covered nanoshells to the use of complex dendrimers for an all in one function as it were. Nanotechnology has definitely secured its place in medicine.

Introduction

Nanotechnology, as the prefix 'nano-' suggests, involves the manipulation of the atomic scale and has been described as 'manufacturing with atoms' - William Powell(3). Hence, it deals with measurements as small as 10^{-9} metres (one billionth of a metre) , where amazingly in reality, the diameters of three typically sized atoms are the equivalent of one nanometre (unit notation is nm). The idea of nanotechnology was first proposed by the American physicist Richard Feynman(4) (Figure 1). Feynman was involved extensively in the development of quantum theory and it's mechanics. On December 29th 1959 at the annual American Physical Society meeting at Caltech, California, Feynman said 'The principles of physics...do not speak against manoeuvring things atom by atom.' He later went on to say that 'it (nanotechnology) is something...that can be done', and most famously suggested there was 'plenty of room at the bottom'. Since this proposition, molecular engineering has progressed, leading to remarkably intricate structures that have been developed with the use of precision equipment, which is used to manipulate individual atoms. An example of such equipment is the Atomic Force Microscope (AFM), developed by IBM in Zurich during the 1980's. The technology is very useful because there has been resolution demonstrated upon the nanoscale, previously unachievable, due to the diffraction limit of electrons or visible light. Instead, the microscope has a 'cantilever' (small beam supported at one end, See Figure 2). Manufactured from silicon, or a nitride of silicon it has a rounded end in order to minimise the risk of damage to the specimen. As the cantilever moves across the surface, it experiences deflective forces, due to van der Waals forces, magnetic forces and so on. As the deflection occurs, a laser beam is reflected off of the cantilever, allowing the degree of deflection to be quantified. To obtain a good image of the specimen surface, the microscope is scrolled across it with extremely sensitive piezoelectric stepper motors. The differences in deflection allow a surface contour image to be developed. Furthermore, in order to manipulate the individual atoms, optical tweezers(6) can be used. Developed by Arthur Ashkin and his colleagues, at Bell Labs during the 1970's, a highly concentrated laser beam is used to attract or deflect microscopic particles, or hold them in a stable position in three dimensions. By using this technology, the tweezers in conjunction with the AFM can be used to manually position atoms in order to form a particular 'designer' molecule of any shape, perhaps for a particular function. As the atoms are brought closer to each other, attractive forces or permanent bonds form between adjacent atoms, allowing the molecule to be constructed atom by atom. This is known as the 'bottom up' approach(6), because small matter is used to make larger material.

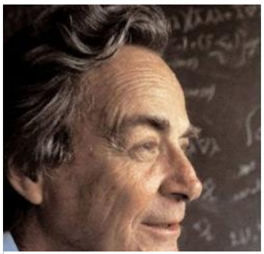

Figure 2

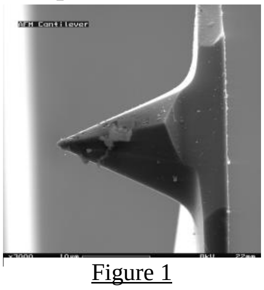

Figure 1

Conversely a 'top down' approach can be used to build small material from larger matter. Nanotechnology has impacted many fields, although medicine is one of the greatest beneficiaries of the technology. Playing an important role is the fact that molecular structures can be fabricated into a particular shape, in order to perform a highly specialised task. Furthermore, as the structures are on the 'nanoscale', their size is of the same order as the average cell, and biological molecules. In due course the products of nanotechnology are capable of interacting with such structures, and influencing mechanisms within the body. One of the areas of medicine in which nanotechnology is having a profound impact is in the detection and treatment of cancers. Cancerous cells(11) are those that are rapidly dividing (proliferation). The body is unable to control this (Figure 3), and the resulting division leads to the development of a 'neoplasm' or 'tumour' in body tissue. Other important characteristics are a loss of the cell's specialised function, known as 'dedifferentiation'. Invasiveness throughout the body, means that the cancerous cells can spread into healthy areas of tissue (due to a secretary enzyme that digests extracellular matrices), thus permitting the cancer to spread. Lastly, the ability of tumours to metastasise, (release of secondary tumours from the primary tumour), into body cavities, the circulatory or lymphatic systems results in propagation throughout the body, creating further tumours. Cancerous cells are especially resilient, as they have mutated, having lost the ability to respond to particular signal molecules or hormones used in cell signalling, resulting in the built in self destruct system of a cell with a mutation or abnormal DNA (known as 'apoptosis') being non-existent. Ultimately, this means that the division of mutated cells is able to progress to form larger tumours. Undetected, tumours may spread throughout the whole body, forming their own blood supply, via a network of arterioles, capillaries and venules, whereby nutrient uptake occurs more efficiently, aiding the tumour's growth. Tumours grow, or spread around the body, eventually interrupting organ function, possibly upsetting the body's chemical mechanisms, or even causing structural damage. The patient will eventually die(7), although the prognosis is dependent upon the aggressiveness of the cancer, and it's type. Medical researchers have harnessed nanotechnology to produce nanodevices. However it has been seen that these devices have had to adhere to one elementary concept of size. If the device is too small, the body may remove it before its potential effect(s) become(s) apparent, while too large and there may be problems with toxicity, and access throughout cells in the body. Developments have occurred both in treatment, and detection of cancers. Firstly, from the work of Alexei Ekimov (1980) and the American NCI (2005) 'Quantum Dots'(8/9) have been developed which are small semiconducting molecules, ranging from 5 nm to 50nm in diameter. The dots have either been engineered to a shape, or to contain an antibody that is complimentary to the antigens that can be found upon the surface of cancer cells, meaning the dots will bind to these cells only. The cadmium cores of the dots fluoresce when subjected to ultra-violet light (Figure 4), with the colour depending upon the nature of the core, as well as the size of the dot itself. These have been seen to allow areas in which cancer is developing to be highlighted, or 'flagged' for treatment. Researchers have also incorporated latex beads upon the surface of the dots which have been designed to bind to a particular sequence of DNA, possibly a mutation that could be responsible for the cancers.

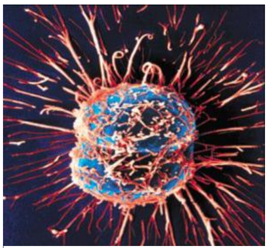

Figure 3

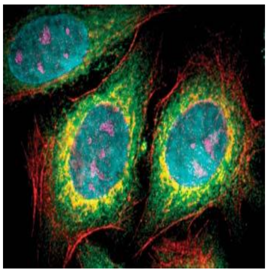

Figure 4

This method of detection is most beneficial, as it can be used more successfully earlier in diagnosis than conventional physical examination techniques, or MRI scanning become effective. Furthermore, according to the work of Christopher Loo, et al (2003) in the journal of TCRT, nanoshells$_{(8/9)}$ can be used to help destroy cancerous cells without risking destroying health tissues. The nanoshells are spherical nanoparticles, that have been engineered with a surface covering of gold atoms. In conjunction with this, to ensure the shells only bind to, and affect cancerous cells, antibodies specific to the antigens of the cancer cells can be incorporated. Once the shells have bound to the cells, high intensity infrared radiation will be subjected to the area in which the cancer is predominant. The radiation is absorbed by the gold atoms, whose kinetic energy increases, generating heat, which has been seen to kill the cancerous cells without damaging healthy ones. According to the work of the American NCI (2003), dendrimers, have been adapted for cancer treatment. Dendrimers$_{(8/9)}$ are roughly spherical, heavily branched molecules, which were discovered in the work of Vögtle (1978, see Figure 5). Due to this elaborate branching, researchers recognised the potential for specific drug carriage (using antibodies as before). They have also successfully developed a series of 'reporters' which are attached to the molecule which bind with particular cell signals, such as those of imminent cell death, meaning that treatment can be monitored, by measuring the amount of a particular molecule in the blood. Lastly, with the previous work of Smalley et al (1996) the well known spherical allotrope of carbon with molecular formula C_{60} known as Buckminster Fullerene$_{(8/9)}$ or 'Bucky Balls' have been used as a method of drug delivery to cells that require this. Although specificity has not yet been achieved, from the work of Naomi Halas (2005) from PBS 'Science Now' the novelty in this discovery is the fact that unlike other nanoparticles, Bucky Balls are excreted whole, meaning that researchers were able to encapsulate potentially hazardous substances, such as radioactive isotopes, knowing that they would be removed soon after. In this way it was found that there were no lingering effects that could detriment or cause cancers in other parts of the body.

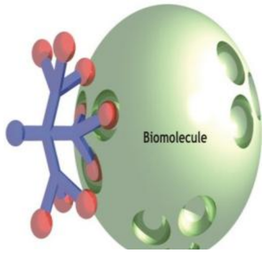

Figure 5

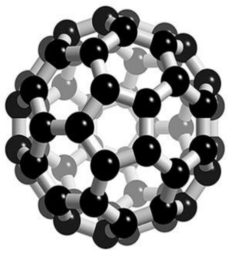
Figure 6

Discussion

Before beginning our discussion regarding possible developments in nanotechnology, we will delve into the problems that are associated with the most recent discoveries.

Functional problems currently facing nanotechnology as a whole

In general, the main problems associated with the current nanodevices are:

- Financial: where due to the requirement of specialist equipment, the current economic climate and the vast amount of time to invest, some may argue that these funds are better spent elsewhere.
- Ethical: where the main consideration is whether or not the treatment is too expensive for use in the National Health Service (NHS), and if so, who will decide who lives, and who dies. The idea of playing god, conflicts with many religious perspectives. Also, how should the technologies be tested?

- Functional: where due to their amazingly small scale, and increasing complexity, the devices may become more difficult to engineer, and use, thus requiring operational skills. Furthermore, if the devices are not manufactured to a critical standard, it may be detrimental to the patient's condition.

We will now analyse different nanoparticles, considering their current uses, their potential for development, limitations, and how these may affect their applications in modern day medicine.

Nanowire(9)

Nanowires (Figure 7) are silicon wires that have been engineered on the 'nano-scale' and have some current uses. Nanowires have been seen to be very useful, as they can be emplyed as a sensor of multiple forms of cancer, such as prostate and breast cancer, because the coating of antibodies upon the wires bind to proteins in the blood that could indicate the progression and development of cancers. Currently this method has been used in blood tests, where a sample of blood is taken, and the nanowire used as an indicator. Upon testing for the binding, the wire is seen to have cancerous cell residues. There is also potential for various developments. For example,

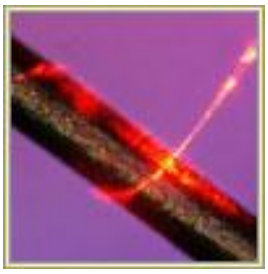
Figure 7

the nanowires could be permanently implanted into the body, in order to act as an indicator that can be used at any time, as opposed to the patient is having to visit a doctor's surgery or hospital. Based on this, it may then be beneficial to implant nanowires in areas where cancer was pre-existent. During the process of rehabilitation, if the cancer returns, the treatment can resume immediately, as opposed to waiting for conventional detection which may be too late in terms of terminal progression. Here, the wire is only being used as a diagnostic device. It may also be possible to create a hybrid nanowire, impregnated with drugs and/or radioactive isotopes, possibly with Bucky-Balls attached. This would allow the continuous treatment of the specific area in which the wire is installed. Being very flexible and miniscule, they could be used in the treatment of spinal cord cancers, a region of the body that is constantly moving. Of course there are problems. For example this technology hasn't been tested for harmful effects if placed in the body for a long period of time (as with carbon nanotubes), as the body's chemical balance may be upset, resulting in detrimental effects to the body. In addition placing the nanowire in a region such as the spine would require the greatest dexterity and would possibly call for the use of specialist surgical techniques and equipment, such as micro-forceps. Furthermore, the implantation may lead to unforeseen complications during the procedure, such as damage to surrounding tissue. This would be very problematic, especially in the region of the ovaries, prostate and the spine, as small errors may lead to infertility or even paralysis respectively. There is also the issue of locating and extracting the wires, without damaging body tissues.

Finally, the longevity of the nanowire is also something that must be considered. If the binding can only occur once, then replacement may be required frequently, possibly raising the question as to whether the treatment is beneficial. Development of a reusable nanowire that could bind repeatedly may be essential.

Nanocantilevers(8/9)

Nanocantilevers (Figure 8) are small beams supported at one end. They contain antibodies that are complementary to cancerous antigens. Upon binding, the cantilever vibrates at a particular frequency, which can then be detected by specialist doctors and equipment. Currently, this device has only been used in blood testing, although there are problems associated with this technique, as every time the diagnostic tool is used, a blood sample must be taken. It may be beneficial to implant the device, possibly securing it to a particular tissue surface, for a longer term, allowing the vibrations to be detected externally whenever necessary, without the need for blood samples. As with nanowires, these devices could be used specifically in the rehabilitation of cancer patients, where if the cantilevers were implanted into tissues nearby affected tissues, it would be easy to deduce whether the tumour had been destroyed, or was redeveloping in order to end or sustain treatment accordingly. However, there are problems with this nanoparticle. Primarily, it may not be a permanent device, as after binding to the antigens has occurred, the antibodies may not 'unbind', meaning that the cantilever becomes useless after this point. Furthermore, implantation into the human body would be very difficult requiring the use of precision equipment, like high powered microscopes, or optical tweezers for the manipulation of the cantilever itself. The procedure may also require some kind of surgery, which may not be received positively by an extremely ill patient. Furthermore, the need for trained doctors and the investment of equipment that can detect the vibrations may be very costly, although despite the initial expenses , movement into mass production with popularity means costs would eventually decline.

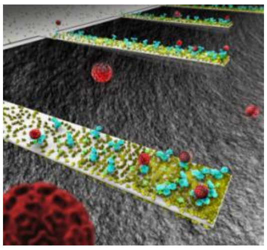

Figure 8

Nanoshells(8/9/11)

Nanoshells (Figure 9) have been seen as advantageous mainly because they contain antibodies allowing specificity to the antigens of cancerous cells. Once bound, they only damage the cancerous cell provided infrared radiation is incident. Further development could employ a combination of antibodies, gold atoms and possibly beneficial drugs, such as analgesics e.g. morphine being placed on the surface of the nanoshells, in order to help relieve some pain during the administration of infrared radiation to activate the device. This would also allow effective drug delivery, as the antibodies would ensure only cancerous cells are targeted. With something this effective in destroying cells there may be some limitations and risks. The biggest problem is that to activate the nanoshells, infrared radiation must be incident upon the device, in order to activate its lethality. However it may not be a well known fact that in adequate quantities, and intensity, infrared radiation can in fact be damaging, since it is a form of ionising radiation. As a result, the use of high intensity radiation of this kind may also contribute to further development of cancers, or at least cause severe discomfort or negative bodily reactions e.g. heat rashes. Another problem could be the cost of manufacturing such specialist particles, although as with most of those researched here, costs will decline as interest develops.

Figure 9

Quantum dots(8/9)

Quantum dots (Figure 4) are molecules that can signal the presence of cancerous cells in the body. They are comprised of various compounds of cadmium, which determine the colour of light it emits. There are however, some significant problems that may be associated with these devices. Firstly, the structure of the device consists of a cadmium core which has been seen to be toxic to humans, from either large doses, or repeated exposure to small doses. The cadmium can be seen to interfere with how the body uses calcium, inhibiting normal cellular functions, and in extreme circumstances the cadmium accumulates in the liver and kidneys as part of the body's attempt to remove it in the urine. To aid toxicity shielding, a polymer coating is applied. However, what if the polymer coating was not manufactured accurately, or waseroded; leaving a small pore through which some cadmium may escape? One solution would be to research another material that could be incorporated into the core, but would still perform the same functions as cadmium i.e. the phosphorescence, without the toxicity. Finally, there is the problem of how the quantum dots would be removed from the body once their purpose is achieved, as the binding of the devices to the cancerous cells may make extraction difficult. Would it be possible to effectively 'program' the device to leave the binding site after a certain period of time has passed, or detach in response to particular chemicals that may be naturally occurring in the body, or could be administered via drugs. It could be a molecule that binds to the antibodies on the surface of the dots, deactivating or digesting them, leading to detachment.

Nanopores(8/9)

Nanopores are minute holes, that are so tiny that they force molecules of DNA to move through them one strand at a time. This means that they can accurately analyse the genetic material of an individual cell for abnormalities in their DNA, compared to a healthy cell, in order to deduce whether they have mutated genes that may contribute to cancer development. Moreover in the future, nanopores may be engineered so that they can be altered in diameter, in response to heat, since the kinetic energy may cause the pore to vibrate and dilate. This would then allow the release of drugs to be controlled, for example if the cancer was becoming especially aggressive, more drug could be released, or conversely less, as in the situation of Bucky Balls that cannot currently be manipulated in this way. It is also a possibility to implant them into cell membranes. However despite their potential, there are associated problems in respect of how the pores would intially be administered into the body in the first place. This may also require specialist training and expensive, specialist equipment, due to their minute size.

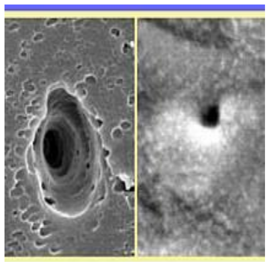

Figure 10

Dendrimers(8/9)

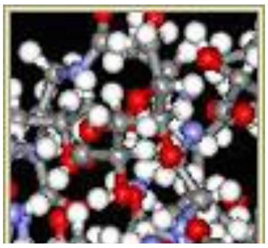

Figure 11

This is the most impressive molecule in nanotechnology to date, as it has the greatest potential due to its multiple branches being part of its molecular structure. Currently, researchers have only had limited successes, having only bound antibodies for specificity and drugs. However, this branching means that many of the previous devices could theoretically be attached to the dendrimer, creating a hybrid molecule that combines the functions of the devices involved. This may result in the creation of many combinations to fight cancer. Quite simply it can combine the strengths of all the other nanoparticles, utilising them together to become much more efficient and effective. Despite the vast sea of possibilities, there are some combinations that appear to be especially promising. Antibodies would create the initial specificity to cancerous antigens. Then, quantum dots could be incorporated as a way of identifying the region of the cancer as well as the position of the dendrimers, to check they are functioning correctly. Next, nanoshells could be connected as a way of destroying the cancerous cells. Furthermore, Bucky Balls could be attached to the dendrimers allowing the specific delivery of drugs, or the irradiation of the cancerous cell via radioactive isotopes, which is also specified. Lastly, researchers contemplated the possibility of a reporter molecule that communicates as to whether the cancer is being destroyed. This could be a potential application of a nanocantilever which could bind to the antigens and vibrate to show presence, then when vibration become less frequent, this would indicate progress. As with nearly all of the other devices, the complexity of this molecule means that it would be extremely difficult and expensive to manufacture in terms of specialised workforce and equipment, although mass production would seek to reduce these. Lastly, like with the other specific devices, one must consider the method of removal, or the possible toxicity of the compounds. This could be overcome in a similar way as before using inhibitors or digestive drugs.

Conclusion

It can therefore be seen that there is vast scope for the development of nanotechnology in medicine, especially in the field of cancer diagnosis, and treatment, with the development and refinement of currently existent nanoparticles. We feel in particular that one of the most promising developments is in the field of dendrimers. These molecule have the potential to become a revolutionary treatment and form of diagnosis and the possibilities are truly impressive, where it has been seen that it may be possible to combine devices upon the branches. Different combinations will allow a cocktail of nanodevices to be administered with their effects being specific to what is needed. However, it is apparent that there may be problems with the attachment of the nanodevices as well as the economics and technicality of production. This field of medicine has come a long way from mere contemplation in 1959, to reality in the 21st century, although one should not fall under the illusion that this is the peak and conclusion of nanotechnological advancements, because there are still various problems that can be overcome, as well as unimaginable potential as to further devices and their applications. Nanotechnology has well and truly secured its place in the development of future cancer treatments and diagnosis.

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