<u>The effect of nanotechnology in developing current medicine to help combat diseases, particularly considering Coronary Heart Disease (CHD)</u>

BY

AMANDA GATWARD
AMY SKELT

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RESEARCH PAPER
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Abstract

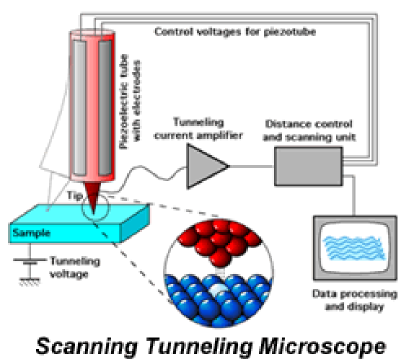
By studying nanotechnology we are able to develop modern medicine, opening up possibilities to manipulate cells and diseases in a way that 50 years ago would have seemed impossible. Coronary Heart Disease (CHD) is Britain's biggest killer, so we decided to see if nanotechnology had a solution to try and reduce its fatal effects, or at least alert people sooner as to whether they are in danger. It was found that nanotechnology could enable doctors, and even patients, to monitor CHD in a less invasive and faster way. Microworms could be developed and placed under the skin to monitor blood flow. Micelles could be used to target plaques in the arteries, and eventually deliver a drug, fumagillin, that can reduce plaque build up. However it does come with some costs, such as fumagillin damaging the brain in high doses. Overall the benefit that these developments could have outweighs the disadvantages by saving thousands of lives each year.

Introduction

What is Nanotechnology?

Nanotechnology is the study and manipulation of materials on an atomic and molecular scale, working with substances less than 100nm (100×10^{-9}m) in size. To put this in perspective a human hair is 80,000nm thick. Manipulating molecules on an atomic scale can dramatically alter the properties of it, for example gold nanoparticles appear red. This is due to the way light interacts with the particles; larger particles absorb and emit light slightly differently to smaller particles because the number of electrons in each molecule differs. This results in the absorbed and reflected frequencies of radiation differing for nanoparticles and normal particles of the same element[1] (J. Winter 2007). Nanotechnology is still relatively new, but from research and applications that have already come of his new science it promises to have huge consequences on future technology, from medical advances to engineering and computer science.

The concept of nanotechnology was first voiced by Richard P. Feynman in a lecture entitled 'There's plenty of room at the bottom'. Though he did not use the idiom 'nanotechnology' Professor Feynman theorised about a time when we would be able to use machines to manipulate matter on an atomic scale. Twenty-two years later in 1981 IBM physicists Heinrich Rohrer and Gerd Binnig invented the Scanning Tunneling Microscope (STM), which could image individual atoms by detecting minute changes to electric currents. Scientists found that they could use the STM to pick up and move atoms. In 1990 IBM scientists used the STM to arrange xenon atoms on a nickel surface to spell their company's logo. This was the first example of manipulating matter on an atomic scale. Subsequent discoveries of carbon fullerenes (60 or more carbon atoms arranged in a hollow cage like structure) including buckyballs and nanotubes laid the foundations of nanoscience[2] (College of Liberal Arts).



A schematic diagram of a Scanning Tunneling Microscope

Figure 1

Carbon nanotubes consist of a single layer of graphite formed into a cylindrical shape. This carbon structure is 1/6 the weight of steel but is 100 times stronger, currently it is the strongest material man has ever made. Its flexibility, conductivity, resistance to heat and chemical stability give it the potential for a wide range of industrial and commercial uses[(2)] (College of Liberal Arts).

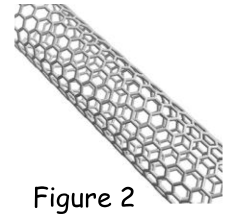


Figure 2

There are already products on the market which are benefitting from developments in nanotechnology. Nanoparticles of zinc oxide have been used to coat glass making it photocatalytic (a substance that absorbs light, and in doing so catalyses a reaction) and hydrophilic ('water loving'). When ultraviolet (UV) radiation is incident on the glass the nanoparticles break down the dirt on the glass. When it rains the hydrophilic properties of glass means that water spreads evenly over the surface, this is the first 'self cleaning' glass[(3)] (K. Bonsor 2011). Carbon nanotubes consist of a single layer of graphite formed into a cylindrical shape. Carbon nanotubes have some amazing thermal, electrical and structural properties which are still being explored and could have many implications for future industry.

The medical importance of Nanotechnology

The importance and relevance of nanotechnology to modern medicine is clear. Being able to work at a cellular level has the potential to treat problems that conventional medicine is unable to. An important factor is the scale of nanotechnology; large scale procedures can be down-sized, making the whole process less stressful for the patient and potentially less risky. Nanotechnology is less invasive and can often go undetected by the body so no response is stimulated[(4)] (D. Chandler, 2011). There will be less risk of infection, especially considering delivery of nanotechnology into the body. If you are able to work on a scale smaller than that of bacteria then the risk of bacterial infection is therefore greatly reduced. As it is already improving computer technology, using this technology medical machinery in hospitals can also be improved to work more efficiently. Nanotechnology is seen as the way forward as there is only so much that conventional medicine can do.

Nanotechnology is now being looked at to solve many medical problems. New ways are being developed to monitor substances in the blood stream using microworms that remain under the skin but are too small to be detected by the body so it will not trigger a response. This would allow 24 hour monitoring, changing the way blood testing is carried out[(4)] (D. Chandler, 2011). Carbon manipulated on a nanoscale has been recently discovered to be able to produce a structure called graphene, which is very small but strong. It has been found that when combined with single stranded DNA it fluoresces when it comes into contact with certain diseases. This opens up the possibility of it being used to diagnose diseases such as cancer[(5)] (Science Daily, 2009).

Coronary Heart Disease (CHD) is the biggest killer in the UK, killing around 94,000 people per year[(6)] (NHS, 2010). CHD is caused when fat is deposited in the coronary arteries, limiting blood flow to the heart muscle, causing it to degenerate over time due to lack of oxygen to the cells. It is mainly a problem for developing countries where food with high saturated fat comprises much of the diet. Saturated fat is high in Low Density Lipoproteins (LDLs) which build up in the artery walls. Obesity and smoking increase the risk of CHD developing and it can be linked to genetics; those with a family history of CHD have a higher risk of getting it. CHD is a degenerative disease and there is no effective treatment for it, however there are ways of preventing CHD from developing. A healthy lifestyle and a diet low in saturated fat and high in High Density Lipoproteins (HDLs) will prevent build up of fat in the arteries.

Nanotechnology has already begun to enable scientists to develop new ways of combating CHD. Researchers in Santa Barbara have already begun to use nanotechnology in mice to detect plaque build up in arteries[(7)] (understandingnano.com, 2009). Micelles (lipid-based group of molecules that form a sphere) were intravenously injected into the mice, which had been fed on a diet high in fat. These Micelles bound to the surface of the plaque and fluoresced when scanned. Researchers found high fluorescence was found in areas where there was most build up[(8)] (D Peters et al., 2008). Matthew Tirrell notes that there could be therapeutic advantages to this.

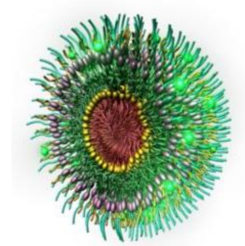


Figure 3

Discussion

Nanotechnology has the potential to revolutionise the way we deal with diseases such as CHD. The work by scientists is already opening doors to new possibilities for treatment in the future.

Monitoring CHD

Research into microworms that are small enough to be undetected by the body but also have the ability to remain in place could be developed further to help doctors monitor patients at risk from CHD. These microworms could be placed in or near the patient's coronary arteries to monitor blood flow and amount of oxygen in the blood. If this research was able to develop, then there is the potential to create microworms that can send information about the blood supply and oxygen levels to a machine outside of the body. If the blood supply was to suddenly drop then the machine could send information to the nearest hospital about the potential heart attack the patient might be having. Admittedly this technology is a long way off, however current research and the pace at which technology is advancing gives the potential for microworms to be placed in coronary arteries and not be moved or trigger the body to react. Thus, allowing twenty-four hour, non-invasive, monitoring to be carried out. It could also be possible to insert a microworm into the cardiac tissue to monitor electrical impulses of the heart, and could send information to a machine which would create a trace similar to that of an electrocardiogram (ECG). This could be used to monitor patients in hospital who have undergone heart surgery. Whether this technology can then develop to be able to send signals to an external machine relies quite heavily on nanotechnology developments in the computer world. However computer chips and machines are continuously getting smaller so it may one day be possible.

A stepping stone to the above technology could well come from recent research into graphene. It has been found that graphene can bond to single stranded DNA to form a DNA biosensor, which when placed in body fluids, such as blood will fluoresce in the presence of certain diseases. Further research into this material could enable a biosensor that reacts to the presence, or absence of specific drugs. This could potentially be used for patients, especially the elderly, who need to take regular medication. The microworms would monitor the blood to ensure that the medication is of the right quantity so doctors can adjust prescription doses if necessary. Also it could fluoresce if the medicine is not detected in the blood stream; this could be due to the patient forgetting to take their medication or the medication not being absorbed into the blood stream. The fluorescence could remind the patient to take their medication or if they have already done so, to then consult their doctor if, after a certain time period (for example an hour), the medication has still not registered. Red is the universal colour for danger, so the microworm could be made to fluoresce red under the skin. However, red may not be an obvious colour against some skin tones so perhaps a brighter colour should be used. This would only be feasible if it was placed just under the skin as if it were any deeper it would not be seen.

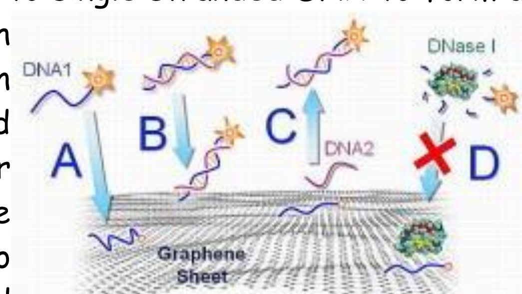


Figure 4

The microworms could also be used to monitor substances in the blood stream. This would be an alternative to current blood tests, the microworms could inserted into the arm, because of the nano-scale of this technology it would non-invasive and it could be possible that the patient may not even feel it. Researchers are currently looking into ways of integrating nano-electrics into living cells to understand processes within cells. Silicon chips smaller than cells have already been produced[(9)] (M. Berger 2010), giving the aforementioned technology the possibility to develop. Developments in similar technology could lead to a microworm with a nano computer chip which, when placed in the blood stream, could monitor components in the blood plasma, such as white blood cell count. This information could be sent back to a computer. This would make blood testing quicker and simpler, potentially giving a diagnosis the same day, which would allow treatment to start sooner. Due to the small scale of the technology, the needle required to insert the microworm under the skin would be smaller than current medical needles. This would reduce the risk of bacterial infection as certain bacterium would be too large to enter the puncture made by the needle. The microworm could also monitor LDL levels, so the doctor is aware of the potential of the build up of plaque in the arteries. This technology could also be used for monitoring glucose levels in diabetics.

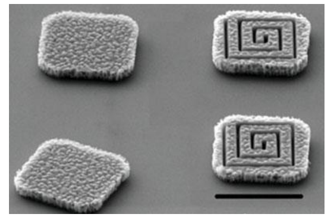


Figure 5

Preventing CHD

The direct cause of Coronary Heart Disease is the build up of plaque in the arteries. Scientists have been experimenting with fumagillin, a drug which in high doses causes damage to the brain, but can reduce plaque buildup in the arteries. As mentioned previously, nano-micelles have been used, which attach themselves to the plaque and fluoresce when scanned. To advance these findings further these two innovations could be combined; if micelles attached to the plaque could release a small dose of fumagillin to combat the buildup then this technology could be used to combat CHD.

In order for such technology to be developed, more research would have to be done into how micelles, once attached to the plaque, would release their dose. Research has already been conducted into entrapping hydrophobic drug compounds inside micelles to form an aqueous solution. It is also suggested that this could protect the drug from digestion by enzymes[10] (ISPharma). If fumagillin could be entrapped inside the micelles in a similar way to this, then the drug could be transported round the body without damaging the brain. If the micelles were resistant to enzyme action it could also be possible for the micelles to be taken orally instead of being injected into the blood stream which would reduce the chances of infection. Once attached to the plaque the micelles would need to discharge their dose. This could be achieved by using a trigger to break down the micelles. Recent research has used hydrogels to transport drugs through the body, these hydrogels 'swell' once triggered by stimuli such as magnetic fields to release their dose[11] (C.T Volgelson 2001). Using such technology the micelles with fumagillin entrapped in them could travel around the body and attach to the plaque on the arterial walls. They could then be stimulated using a magnetic field or even using ultrasound to release their dose to effectively target the buildup of plaque.

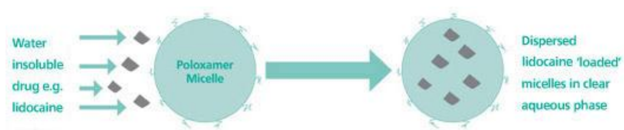


Figure 6

This would reduce the danger of fumagillin damaging the brain, only small amounts of the drug may be required to effectively target areas of plaque buildup, as the micelles attach to plaque there is less of a risk of the drug being released elsewhere in the body and enables specific targeting of plaque. As micelles used in research fluoresced when scanned their progress around the body could be monitored in a similar way.

Repairing heart tissues

There is substantial damage done to the cardiac tissue when a blockage of the arteries occurs, this tissue continues to degrade over time until the heart can no longer function. The ability of nanotechnology to work on a cellular level means that tissue repair technology could be a possibility in the future. Research has already been done using nano-fibre scaffolds to restore neuropathways in the brain which allowed cells to re-grow and restore some of the brain function[12] (AZNano.com 2006). These nano-fibre scaffolds biodegrade over time. It may be possible to advance this technology further, using stem cells on a nano-scaffold to re-grow cardiac tissue. Another alternative would be to use hydrogel. Recent research at the Institute of Bioengineering and Nanotechnology has created a hydrogel which could act as a scaffold for stem cells to grow. It is noted that these stem cells could potentially differentiate into cardiac tissue[13] (Nanowerk 2010). It could be possible, therefore to use nano-scaffolds to link heart tissue together and to form a structure for the hydrogel with the stem cells to adhere to; once the tissue had grown the nano-scaffolds would decompose leaving a fully functioning heart. This relies not only on the advancement of nanotechnology but also the development of stem cell research.

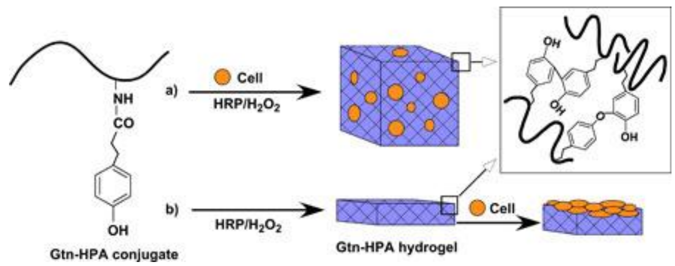


Figure 7 – *formation of Hydrogels by enzyme-catalysed oxidation for (a) 3D and (b) 2D cell growth/differentiation.*

Disadvantages

- Though hydrophobic drug compounds have been entrapped in the micelles it may not be possible to entrap fumagillin in the same way. Fumagillin is a very harmful drug and so extensive research needs to be done to ensure that micro doses of this drug would not have any affect on the brain, or indeed, any other part of the body.

- There is also the possibility that some patients may react adversely to treatments.

- Repairing of the cardiac tissue also relies on the advancement of stem cell research so that the stem cells can be 'programmed' to differentiate into the required tissue.

- The use of microworms to monitor the blood supply and to send readings to an external machine relies heavily on technological advancements of nanoscience in computer technology. It would also require the patient to have a machine in the near vicinity for the microworms to send the readings to.

- There is also a question of where the microworms should be placed in the body; if close monitoring of the blood supply to the heart was required then placing a microworm in the coronary artery could potentially be risky and would require the patient to be operated on.

- The financial cost of such technology must also be brought into consideration. If nanotechnology treatments are expensive they may be limited on the NHS. As it currently stands, in countries such as the USA, where there is no national health service, those on low incomes could not afford such treatments.

Ethics

Much of the current research going into nanotechnology solutions to repairing heart tissue is being done through stem cell research, which is very controversial. The use of embryonic stem cells in research is a highly contested subject. Some people do not agree with growing body parts; it can be argued that scientists are 'playing God'; trying to replicate what only God can create. Other nanotechnology applications could include military weapons, even to the extent of bio weapons which attack certain cells, which some may strongly object to. There are dangers that scientists will not know the full effects of nanotechnology on the body, and some may object to having computer chips inside them.

Conclusion

Nanotechnology has the potential to revolutionise the technology we use day to day. Its ability to manipulate matter on an atomic scale opens up many possibilities for the future, from computer science to industry. From a medical viewpoint nanotechnology could enable modern medicine to advance into the realms of cellular exploration. By exploring on a nano scale we could be able to further understand processes in the body and find new ways to combat disease.

CHD is one of the biggest killers in our country; nanotechnology may hold the answer to fighting and preventing CHD and other heart related problems. Research into micelles, microworms and Hydrogels could be the first steps towards preventing CHD. In our research we came across some difficulties with the developments proposed, including the dangers of fumagillin on the human body, and whether it would be possible for graphene to fluoresce in the presence or absence of certain drugs. Future developments which may overcome these problems could include using a material similar to graphene which in the absence of particular chemicals in the blood will fluoresce. Though fumagillin is a harmful drug using nano-doses of this compound greatly reduces the risks, and further research could be conducted to ensure that, when used in the human body, no damage is done.

Though there is still some way to go towards a solution to CHD, it may one day be feasible to use nanotechnology to combat CHD and diseases like it.

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Fig.1- Scanning Tunneling Microscope (http://www.utexas.edu/cola/progs/sts/the-nano-future/science/a-brief-history-of-nanotechnology.php)

Fig.2- carbon nanotube (http://www.nanoid.co.uk/nanotube_filter.html)

Fig.3- multifunctional micelle designed by research team (http://www.understandingnano.com/nanoparticle-targeted-drug-delivery-arterial-plaque.html)
Fig.4- fluorescent-tagged DNA interacting with functionalized graphene (http://www.understandingnano.com/graphene-dna-biosensor.html)
Fig.5- SEM image of a intracellular polysilicon chip, Scale bar ~3μm. (http://www.nanowerk.com/spotlight/spotid=15292.php)
Fig.6- Micelle drug delivery system (http://www.ispharma.plc.uk/mice.php)
Fig.7- formation of Hydrogels by enzyme-catalysed oxidation (http://www.ispharma.plc.uk/mice.php)