Nanotechnology and possible future impacts on Cardiovascular Medicine

By

Zain Iqbal
And
Siddhartha Mohan

PASS WITH MERIT

RESEARCH PAPER
BASED ON PATHOLOGY LECTURES
AT MEDLINK 2010
Abstract

Following making use of the Medlink virtual pathology materials online that introduced me to nanotechnology. I have further probed into the world of nanotechnology and its possible uses in medicine and bioengineering. I have placed particular emphasis on its application to help combat the diseases and problems that face the human heart. Nanotechnology gives us hope of combating problems that face the cardiac system such as valvular heart disease, coronary artery grafting, atherosclerosis and pulse rates that are controlled by the use of pacemakers. As with any great medical advancement there are many barriers to overcome however, the future looks very promising for nanotechnology.

Introduction

Nanotechnology is a rapidly developing branch of technology that revolves around manipulating individual atoms and molecules of less than 100 nanometres in size. Nanotechnology was first suggested by Richard Feynman, the highly renowned quantum physicist in 1959, at the annual meeting of the American Physical Society. Here he uttered the awe inspiring words 'There's Plenty of Room at the Bottom'. In his talk, Feynman discussed the importance of nanotechnology and how its use could benefit mankind in a number of ways particularly how it could improve existing machinery such as the electron microscope. The speech at the time was very evocative and thought provoking, but the crude tools available meant such revolutionary ideas were confined to theoretical physics.

The actual term nanotechnology was popularised by Eric Drexler in his 1986 book, Engines of Creation, where he envisaged a time of nanomachines operating on a molecular level. The Engines of Creation appealed to the general public enticing them with the possibility of what nanotechnology could behold, the book sparked huge interest even if it did hold some worrying projections, such as the 'Grey Goo' theory. Later on in the same year, Drexler went on to form the Foresight institute where he continued to be a leading voice on the possibilities that nanotechnology could hold.

In 1996 Richard Smalley and his research team went on to find a molecule formed from a cage of 60 carbon atoms. Buckyballs (or fullerenes) as they came to be known, closely resembled the geodesic domes of the architect Buckminster Fuller hence the name (Figure 1). It is believed that other atoms can be trapped inside fullerenes which led to scientists in the early 2000's investigating the possibility of binding certain antibiotics to the structure and using them to target resistant bacteria and cancer cells such as melanoma. The possibility of using such molecular machines allows researchers to work on a cellular level or perhaps even smaller, within a specific cell, allowing integration between technology and medical treatment on a level that has not been seen before.
The first recipients of minute medical technology were diabetic rats, it was hoped that scientists would be able to treat the condition on a cellular level, eliminating the need for constant insulin monitoring. The technology involved a silicon box, one tenth of a millimetre across, which contained collagen sponge impregnated with insulin producing cells from mammals. The box had tiny holes twenty nanometres wide allowing glucose to enter for detection and insulin to be released, the holes acted as a filter making it impossible for large, complex molecules such as antibodies to enter meaning no immune reaction could be triggered. This showed the future of medicine as being as minimally invasive as possible allowing patients to recover from their problems quickly and fully.

Currently research by many people is working towards using nanotechnology to assist with drug delivery, diagnosis and treatment, tissue regeneration as well as imaging. The very nature of nanotechnology allows materials and equipment to be designed with a high degree of precision in order to achieve maximal therapeutic effects with minimal side effects.

In drug delivery there is hope that nanotechnology can be used to make drugs more specific for example to enter tumours, as large traditional medicine are unable to enter the tumour pores. Due to the size of nanoparticles they will be able to enter such tumours and help against the fight with cancer.

Nanosized markers can be used in diagnostics to detect the smallest quantities of a substance, down to individual molecules allowing early treatment of many diseases such as cancer. The idea of 'Lab-on-a-chip' technology to help miniaturise and speed up the analytical process of diagnosing has been used in the pharmaceutical industry yet at this moment it is still very expensive- as new technology tends to be.

Imaging methods such as MRI scanning uses quantum dots, which are highly fluorescent semiconductors nanocrystals that are excited by a range of wavelengths. The fluorescence
of these quantum dots allows them to be detected even after division, making them particularly useful for cell tracking, for example through the blood or lymphatic system.

Within the last few years micro machines have been developed that spontaneously form muscle, allowing it to move very slowly using the muscles for movement. This device could in the future lead nerve stimulatory based around muscles, making it possible for paralysed patients to breathe or mechanisms to remove plaque from coronary artery walls.

Soon, it will be possible to manually engineer tissue and organs from cells provided by the organ recipient using a scaffold built from bio compatible materials. This will not only help address the shortage of medical organs but will eradicate the problems of organ rejection. The field of neumorphic engineering has also looked into nanotechnology in order to use it to improve the durability and recovery of injured neurons.

It is my belief that the path that nanotechnology follows in the future will be paved by our desire for improved healthcare and medicines.

**Discussion**

The primary aim of this paper is to evaluate the possible future role that nanotechnology can play in helping the human heart to continue beating. The heart is a wonderfully complex and beautiful organ that beats over 2 billion times in a lifetime and is essential for human survival. In this paper I will address the impact of nanotechnology on the follow issues regarding the cardiac system:

- Valvular Heart Disease
- Coronary Artery Grafting
- Atherosclerosis
- Pacemakers

**Valvular Heart Disease**

In the United Kingdom as with many other countries around the world the population is increasing in age due to better medical treatment, education and living conditions, meaning the human heart has to work longer than it was evolutionary designed for. It is often true that the valves in the heart face general wear and tear and so with elderly populations' heart valve engineering has become an important area for research.

Actual valve repair is the preferred method of treating patients who have severe heart disease but a large number of valves are not suitable at all for repair and must be
replaced. There are many different types of heart valves (Figure 2) but they fall under two broad categories- prosthetic (mechanical, stainless steel alloys or silicon) and bioprosthetic (human or animal valves). Prosthetic heart valves have excellent durability and will often last a lifetime whereas bioprosthetic valves must be replaced.

![Figure 2](image)

The one on the left is a mechanical valve
The one on the right is a bioprosthetic valve

The main disadvantages concerning the use of prosthetic valves are thromboembolism, the necessity of anticoagulation therapy, haemorrhage and endocarditis. Due to the natural design and nature of bioprosthetic valves they do not require long term anticoagulants and have better hemodynamics, their main disadvantage is the lack of durability and capacity to grow. As years have gone on there have been continuous and very significant improvements with the design and performance of mechanical and tissue valves, yet none are able to match the normal human heart valve.

However, nanotechnology offers the opportunity of being able to bioengineer human heart valves with better durability than bioprosthetic valves and less chance of complications than with prosthetic valves; indeed many circles agree they could possibly be better than normal heart valves. It is a real possibility that the patient's own cells could be used to specifically tailor a valve to the right shape and dimensions required creating a normal heart valve that would last a lifetime.

The main advantage of engineering valves from a person's own cells is there would not be any rejection by the immune system as there would be no foreign material. Therefore the valves would be able to grow or regenerate, just like normal organs and tissue meaning that if the treatment was used in children there will be no need for further operations or replacements as they grow older.
Iqbal + Mohan- Nanotechnology and possible future impacts on Cardiovascular Medicine

I believe that in order for tissue engineering of valves to be a feasible idea, a scaffold will have to be constructed on which the valves can be grown and the appropriate cells from which the valve can grow need to be identified. The ideal scaffold would have to be entirely biodegradable, extremely malleable, immunologically inert and must provide the conditions needed for cell replication. Due to the job that the valve must undertake it has to withstand high pressure and so must be very strong. Current suggestions regarding biological scaffolds include extracellular matrix and fibrin gel.

In regards to the appropriate cells, stem cell research could be used as cells from the patient’s bone marrow have great potential into differentiating into many cell lines and tissue. However, the cells would need to be forced onto the scaffold to obtain optimum results, as shown by the research into animal urethra replacement using both passive and active seeding.

**Coronary Artery Grafting**

Coronary artery grafting currently involves removing a vein from the leg however, the vein would not last as long as a synthetic artery as the structure of the vein is not usually under high pressure. Techniques are currently being developed such as using a patient’s own cells to grow replacement blood vessels by using a scaffold material that imitates extracellular matrix, thus providing a structure on which the blood vessel can grow. In theory, this idea should be able to be applied to the situation surrounding replacing the coronary artery by using nanotechnology.

The scaffolds contain biochemistries that promote cell adhesion and control cell growth. The major drawback of a tissue engineered graft is the great deal of time that it takes to grow the vessel and so would be unsuitable if vessels were urgently needed for a coronary bypass.

Scientists such as West RR have been designing new improved signalling ways to increase the growth rates of cells and to make the grafts more resistant to recurrence of disease. Using nanotechnology, the nanoscaffoldings can be designed to guide tissue repair and replacement in vessels more specifically than biochemicals. Nanofiber meshes may help to avoid patency problems common especially in small synthetic grafts.

Nanotechnology has also provided us with the possibility of adding proteins onto the scaffolding in order to regenerate the surface tissue matrix of the prosthesis. Growth factors could also be embedded into the scaffold enhancing tissue regeneration and stimulating continual growth and repair. Therefore, it may be possible to produce coronary
arteries for replacement, stimulating the proteins that make up the tissue and allowing interaction with surrounding tissue thus allowing tissue regeneration.

Atherosclerosis

The number of people living with coronary heart disease (CHD) is increasing year on year with the latest figure from the NHS estimating that 2.6 million people are suffering from the condition in the UK. Early diagnosis and appropriate treatment could help the UK maintain this disease at a more manageable level and prevent the illness become much more severe. One of the main causes of CHD is atherosclerosis which is the build up of fatty substances (atheroma) within the walls of the coronary arteries, thus leading to restricted blood flow to the cardiac muscle of the heart. As blood transports oxygen around the heart, a lack of blood will lead to the heart becoming starved of oxygen which is the cause of angina, irregular heart rhythms and even cardiac arrest.

In the long term, it is possible that a robotic device could be produced that is small enough to pass through the bloodstream. This 'nanobot' would be based on the silicon box used by scientists to rid rats of diabetes (as mentioned in the introduction) - in essence it must be able to carry drugs and release them at a specific point. A computerised impression (Figure 3) has been included beneath for possible interpretation on what the 'nanobot' would look like. The drug would be injected directly into the atheroma, causing the fatty deposit to break apart and not affect the surrounding tissue. This may conjure images of ‘sci-fi’ movies but let us look deeper into how this may be a possibility.

![Figure 3](image)

The first issue would be how to get the 'nanobots' into the circulatory system, this can be solved by using existing intravenous infusion techniques. Depending on the patients it would be very much like any other injection, where the 'nanobot' would be injected into the bloodstream finally finding its way to the coronary arteries. The second issue would be how the 'nanobot' could distinguish between atheroma and normal tissue. This could be achieved by
the 'nanobot' constantly sampling the blood vessels until it detects the chemical composition of the atheroma, to which its response would be to anchor itself to the atheroma. The circulatory system of the human body is like a fast flowing river and so it would be important for the 'nanobot' to anchor itself to stop it flowing away or being moved by the beating heart. The next step would be for the 'nanobot' to trigger the release some of the drug into the fatty deposits, this would be administered via the legs shown on figure 3. Due to a diffusion gradient, the infusion will not require energy eradicating the need for the 'nanobot' to have a way of transferring energy. The trigger mechanism could either be self automated by the 'nanobot' detecting a fatty deposit or could be controlled outside by some form of radio signal. The final stage would be for the 'nanobot' to release itself from the wall and continue injecting the drug into other fatty areas once all the drug has been injected it will no longer bind to the walls and be filtered out of the body by the kidneys. Once the 'nanobot' has been released out of the patients urine it could be analysed by a physician on how much drug has been released, showing whether more treatment was necessary or not.

The above mentioned use of nanoengineering for medical purposes may seem a little farfetched but it is certainly a possibility. Many would argue that instead of investing billions into developing such technology could it not be more practical to address why and how people can prevent atherosclerosis in the first place. The main factors causing atherosclerosis are smoking, high blood pressure, high cholesterol level, diabetes and doing little exercise. Perhaps by people taking a little more care in what they eat and how much they exercise we would not have to spend billions on such research.

The process of how the 'nanobot' would work is relatively simple the main difficulty is in actually designing it! Some may consider it to be utterly ridiculous to develop it to fight something that people can prevent by looking after themselves however, if such a device comes into use through nanotechnology it could be used for many different things such as fighting tumours, performing simple operations or biological warfare.

**Pacemakers**

The human heart is a great piece of engineering that is reliant on electrical impulses that are first generated in the sinoatrio node (SAN) in order to work and function. The electrical impulse spreads across both atria but is stopped between the atria and ventricles by non-conducting fibrous tissues. The impulse is then forced through the atria ventricular node (AVN) where there is a slight delay as the atria contracts. The impulse
then travels down the septum through the perkinje fibres allowing the ventricles to fully contract, forcing blood into the aorta and pulmonary artery.

Unfortunately, the electrical impulses of the heart may not work properly and so a pacemaker (Figure 4) may be fitted. A pacemaker is a small electrical device that controls the speed at which the impulses are generated thus the speed at which the heart beats. Pacemakers are the current treatment for long term heart problems that cause the heart to beat slower than normal, they are reliable have few side effects but they do make an impact on the quality of a life a patient can have.

A pacemaker tends to be installed using invasive surgery, carrying all the risk that surgery has with it such as infection, internal bleeding etc. The operation involves puncturing an artery so that an electrical lead can be placed into a heart chamber leading to risks such as blood clotting or human mistakes leading to problems such as a punctured lung. The body may also try and reject the pacemaker as it is a foreign object. The pacemaker senses if electrical activity is slower than normal via the electrical lead implanted in the heart and will take over sending pulses at a pre programmed rate, which is set using radio signals.

Patients may face dangerous problems even after the surgery for example in the world around us there are many electromagnetic rays that can accidently reprogramme a pacemaker such as metal detectors, MRI scanners and even mobile phones. Other problems including the possibility of a pacemaker becoming dislodged if hit too hard due to a car accident or physical contact ruling out any contact sports. The batteries of a pacemaker tend to have a limit of 5 years meaning that a patient will have to undergo an operation again to have it replaced. However, the main problem is that the electrical impulse speed cannot be varied, so when exercising it cannot be made to speed up. There have been recent developments where pacemakers are fitted with sensors to detect movement, or an increase in breathing rate etc but these have proven to not be very reliant. The ultimate aim would be to produce a device that could respond in the same way as body cells meeting the needs of the user.
Nanotechnology provides great benefits to people in the field of pacemakers and controlling the electrical impulses of the heart. Normal pacemakers are implanted outside the heart with a wire leading into the SAN however, if a small enough device could be created using nanoengineering it could be placed into the SAN through keyhole surgery, making the whole procedure as less invasive as possible leading to a better recovery. A smaller device imbedded deep in the heart, would make it a lot less difficult to be knocked out of place meaning a patient can enjoy a fuller life being able to possibly even play contact sports.

As mentioned above, there is a risk of rejection with a pacemaker but if the nano device was surrounded by a thin membrane of only a few cells thick it could trick the body into thinking that it was part of the normal structure thus no immune response would be produced- the cells would be taken from other areas of the body.

Nanocircuitry is a major area of development for nanotechnology and technology is constantly getting smaller, this is the trend that could be implemented on pacemakers. Simple electrical circuits using ‘nanowires’ have already been developed and many computer firms are working on ‘nanochips’ so I believe it is a very real possibility that we will soon see a ‘nano-peacemaker’.

**Ethical Issues**

Application of nanotechnology on humans is ethically a very complex area especially when considering bioengineered tissue. Any advancement will require thorough testing and pilot trials should be conducted in small groups before introduced to the masses. In order for some of the possible advancement I have discussed, long term funding will be required which at this current economic climate is highly unlikely.

Concerns have been raised over the potential for nanotechnology to increase the gap between rich and poor countries due to their varying abilities of taking advantage of nano technology. For example, valvular heart disease due to rheumatic fever exists in many third world countries but they will not be able to benefit from nanotechnology for a very long time.

The Royal Society and Royal Academy of Engineering (UK) has recommended that research councils and the Arts and Humanities Research Board (ARHB) fund a research programme into investigating the social and ethical ideas expected to arise from nanotechnology.
There is not a great deal of understanding at the moment how nanomedicine will interact with human body tissue and so it is also essential for the Health and Safety Executive and Department of Health to establish research into addressing the uncertainty relating to exposure to nanoparticles. The government needs to provide rational, reliable information to the public that is backed up by scientific evidence.

**Conclusion**

Nanotechnology provides a novel and unique way to help us diagnose and treat a whole spectrum of diseases including cardiovascular disease, in a new and safe way. It has been suggested that nanomedicine will eliminate virtually all common diseases and could extend human physical and mental capabilities; on the other hand nanotechnology opens up new avenues for those seeking to create more powerful and effective weapons. Even in times of great economic uncertainty I believe it is important that research labs and governments should focus on advancements to fulfil long standing promises of what nanotechnology can achieve.

The ideas mentioned in this paper are quite complex and would require years of work to achieve as there are many problems surrounding them for example how would the 'nanobot' be able to analyse the difference between atheroma and normal tissue? Currently spectroscopy is carried out using large equipment and a computer and so it seems nigh on impossible to miniaturise this into fitting into a small 'nanobot'. However, research has proven ways of making traditionally large equipment like pressure sensors on a very small scale and so with time and money the possibilities are endless.

In regards to miniaturising the pacemaker there are stumbling blocks such as what would replace the large batteries that are required to power pacemakers. Again, there are developments of nano batteries that are made up of atomic cathodes and anodes that are much more powerful, long lasting and durable. But all of the ideas that I have addressed are theoretically possible and have strong support from members of the scientific community. If the ideas mentioned throughout this paper and hundreds out there are put into practice and actually implemented, our world will never be the same.
References

Ballinger A., Patchett S. (2009) Clinical Medicine, Saunders

BBC Documentary- How to Mend a Broken Heart


Coronary Heart Disease NHS: http://www.nhs.uk/conditions/coronary-heart-disease/Pages/Introduction.aspx


Fullerene: http://en.wikipedia.org/wiki/Buckminsterfullerene

Globes online: http://www.globes.co.il/serveen/globes/docview.asp?did=870997&fid=942

Heartpoint Pacemakers: http://www.heartpoint.com/pacemakers.html


Kumar,P.J., Clark, M.L, Clinical Medicine, Bailliere Tindall, 597

Nanomedicine: http://www.foresight.org/Nanomedicine/index.html


Nanotechnology: http://www.amrc.org.uk/index.asp?id=7422

Nanotechnology, a Hard Pill to swallow http://www.i-sis.org.uk/65/bu/bucl,ins.html

NHS Pacemakers: http://www.nhs.uk/conditions/Pacemakerimplantation/Pages/Introduction.aspx

Pacemakers: http://hrspatienets.org/patients/treatments/pacemakers.asp

Prosthetic Heart Valves: http://cape.uwaterloo.ca/che100projects/heart/files/testing.htm#
Iqbal + Mohan- Nanotechnology and possible future impacts on Cardiovascular Medicine

The Heart: http://www.fi.edu/learn/heart/

The Independent, a huge year for tiny technology: http://www.millenium-debate.org/ind20dec013.htm

There's Plenty of Room at the Bottom: http://www.zyvex.com/nanotech/feynman.html

Tissue Engineered Heart Valves: A potential cure for Valvular Heart Disease
http://www.ctsnet.org/sections/innovation/valvetechnology/articles/article-12.html


Images

Figure 1→ http://www.heart-valve-surgery.com/Images/on-x-mitral-valve.jpg nanotech-now.com/images/buckyball2-large.gif

Figure 2→ http://www.heart-valve-surgery.com/Images/on-x-mitral-valve.jpg

Figure 3→ http://www.sciencephoto.com/images/showFullWatermarked.html/T395190-Nanorobot_treating_infected_cell-SPL.jpg?id=843950190

Figure 4→ http://cache-04.gawkerassets.com/assets/images/4/2009/08/500x_pacemaker.jpg