TO WHAT EXTENT CAN NANOTECHNOLOGY HELP IN THE TREATMENT OF ATHEROMA?

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ABSTRACT

The human heart is, for me, the most fascinating entity known to man. It functions day in, day out, and relentlessly pumps volumes of blood round our relatively huge bodies. Thus, being such a complex and important organ, there are a plethora of things that can go wrong which result in very complex issues for a doctor to treat. There are obviously already many ways by which modern medicine goes about trying to solve such problems and prevent them from arising in the first place. During initial research into nanotechnology in medicine, I found that 'NanoMedicine' has a variety of ways in development for protecting the human heart.

I want to try and explore as best I can in this paper what role nanotechnology can play in helping prevent myocardial infarction by namely, combating atheroma in the major blood vessels surrounding the heart.

INTRODUCTION

By definition nanotechnology is 'the branch of engineering that deals with things smaller than 100 nanometres (especially with the manipulation of individual molecules)' [1]. A nanoparticle is a particle one billionth (10^{-9}) the size of a metre and if, by definition, we can engineer and order particles this size to carry out a role specific to our needs, then we can tackle whatever issue it may from a cellular level. This truly opens up a whole new world for any person remotely involved in science, medicine or engineering. Thanks to landmark discoveries such as buckminsterfullerene and its consequent by-products such as nano-tubes, we are now able to engineer and manipulate right down to the size a billionth of a metre; the ramifications of which are unprecedented. Nanotechnology has brought forward advancements in fields such as 'self-cleaning' windows and even allows us to fine tune the taste of our food. But what if we can use our knowledge of the 'nanoworld' to effectively arm ourselves against mans' largest foe, disease.

Thanks to the developments in nanotechnology scientists now have the almost 'God-Like'/ supernatural ability to manipulate and influence activity at a cellular level, this could not be more useful than in the field of modern medicine, after all, disease and consequent illness derives from body's cells and how it is they function, singularly or as a whole such as a tissue or organ. We now, as doctors and scientists, have the uncanny ability to treat a person and to be so incredibly specific to the area(s) needing attention it makes drugs such as paracetemol and other conventional modern day drugs look like a 'Hit and Hope' method for curing and ailment. We can now literally get to the root of problems at the cellular level to diagnose, prevent, administer help and research diseases we once could only see the effects of on a much larger scale.

In this paper I am specifically going to look at the role of the nanotechnology in the detection and treatment of arterial plaque which may consequently lead to atheroma development and result in myocardial infarction.

Atheroma is the hardening of the inside of the coronary arteries due to the formation of arterial plaque. An atheroma begins when the inner endothelium of a coronary artery becomes damaged for a number of reasons, most noteworthy high blood pressure. The damaged cells then induce an inflammatory response causing monocytes, a form of white blood cell, to enter the artery wall. This entry causes the white blood cell to change characteristics and become 'macrophages'. 'The macrophages ingest oxidised cholesterol, slowly turning into large foam cells- so described because of the appearance numerous vesicles take on to accommodate their high lipid content'. These foam cells, through time, die off to cause further inflammation of the arterial wall. 'Intracellular microcalcification deposits' form within the surrounding smooth muscle cells, mainly around the cells adjacent to the atheroma. Over time there is a further build up of macrophages, lipids (causing consequential 'fatty streaks' beneath the atheromatous plaque) and connective tissue which then harden to form the fibrous arterial plaque known as 'atheroma'. [2] Atheroma can lead to myocardial infarction in mainly, one of two ways. The arterial plaque can rupture thus damaging the endothelium of the artery leaving a rough surface to which platelets and fibrin accumulate. This forms a blood clot. The blood clot may stay at the site of damage and reduce blood flow to the heart via the artery in question or may break off, travelling down arteries to narrower vessels on the heart (or anywhere in the body for that matter). If the blood supply is blocked to the heart then the cardiac muscle has a restricted supply of oxygen meaning after time cells will die off causing parts of the heart to die leading to myocardial infarction. The other possible outcome is an aneurysm, meaning a balloon like swelling of the artery thanks to restricted blood flow from the atheroma plaques. The aneurysm may burst thus causing a haemorrhage and consequent myocardial infarction.

As it stands today, means and methods of treating and preventing atheroma development and atherosclerosis are somewhat hit and miss. On top of the well publicised 'lifestyle modifications such as weight management, good dietary habits, smoking cessation and regular physical exercise' [3] there are few actual medical treatments that aim to combat the atheroma and remove arterial plaque at the heart of the problem. Instead, current medical treatments focus mostly on symptoms of atherosclerosis and not the development of the atheroma itself. Treatments include minimally invasive angioplasty surgery in order to expand arteries that have been narrowed as a result of a nearby atheroma all the way up to extremely invasive by-pass surgery to create a blood flow to the heart away from the most severely affected vessels [4]. If nanotechnology, an art form at the forefront of medical engineering, can find a way to effectively combat the formation of arterial plaque, a problem that has plagued medical professionals for an age then surely it would be one of the greatest medical breakthroughs seen to man?

DISUSSION

Coronary heart disease is *the* most common cause of premature deaths in the UK accounting for 28,000 premature deaths in the UK alone in 2008 [5]. So, as all great scientists do when they have a problem, I will now go through in detail all the possible solutions, involving nanotechnology, that are on the table in order to go about solving the issue at hand.

Plaque Attack

As described in the introduction, arterial plaque is our main foe in the fight against atherosclerosis and its symptoms. Therefore, surely this should be one of our primary objectives when it comes to the development of nanotechnology being used for the treatment of coronary heart disease.

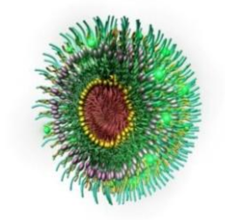

Figure 1 Multifunctional micelle with peptide coating

Engineers at the University of California have developed a nanoparticle specifically designed for the treatment of arterial plaque [6]. Their aim is to form a drug-delivering nanoparticle to attach to the arterial plaque of a patient. The research in question was simply focussing on getting the nanoparticle to attach to the plaque in the first place. The nanoparticle in question is formed from a collection of lipids that come together to make a sphere-shaped nanoparticle called a 'micelle'. The surface of the micelle needs to be able to bind to the arterial plaque effectively in order to stay there. It does this with an outer coating containing a peptide (piece of protein) that bond to the plaque. Their investigation involved inducing atherosclerosis in mice by feeding them a high-fat diet and then injecting them with the micelle, allowing it to circulate for three hours. The team could then investigate as to where the micelle had attached and, as a result, if the micelle would be an effective drug-delivery system. Erkki Ruoslahti, professor at the University says '*One important element in what we did was to see if we could target not just plaques, but the plaques that are most vulnerable to rupture. It did seem that we were indeed preferentially targeting those places in the plaques that are prone to rupture.*'[7] If these nanoparticles are not only able to target the arterial plaque, but the plaque that is most prone to rupture which may cause further complications surrounding the heart, then we as scientists can surely exploit this feat of engineering in order to effectively treat the areas involved with atheroma and atherosclerosis.

We now effectively have a scaffold. Through research and development we have the beginnings of something that may go on to revolutionise medicine through the way drugs are delivered to our bodies, more specifically, the parts of our bodies that need it the most. It not only has ramifications on cardiac medicine but on illness as a whole. For example, if a patient was presented with a malignant tumour in early stages of rapid cell replication, we may, using the scaffold put forward by Ruoslahti and his team, have the ability to 'load' a suitable micelle with a relevant drug. If a micelle was to be loaded with an antifolate drug (a drug that impairs the effects of folic acid, a substance key to rapid cell growth in malignant tumours) such as methotrexate then the drug can easily be administered to the patient and target the specific tumour in question. As a result the drug is administered quickly, efficiently and is almost immediately at the site at which it is needed; the tumour. As we progress with the engineering of nanoparticles and marcelles, we may have the ability to tailor an individual micelle to certain different areas of the body needing treatment and thus personalising and refining treatment of disease for each individual patient.

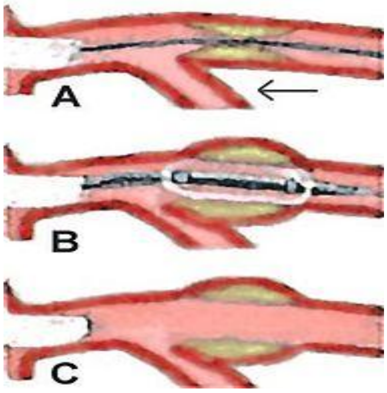

Figure 2 Diagram depicting the use of coronary stent in angioplasty surgery.

Signed, sealed, delivered...

After the research and findings at the University of California, the next step was to exploit the engineered nanoparticle able to locate, bind, and remain on arterial plaque in the arteries, and use it to deliver specific drugs to the area in question.

The previous method used in medicine, and still being used today (that the nanoparticle will perhaps go on to replace) is the use of a 'stent'. In cardiology, there are three main forms of stent used in affected arteries. A bare-metal stent can be used to expand and open up a previously 'clogged up' artery due to atheroma or may be used temporarily during heart surgery in order to open the arteries up for analysis. These do their job but are somewhat primitive and only screen the problem, not solve it. More commonly used at present (after being found to be more effective than bare-metal stents) are drug-eluting stents. These are placed within the lumen of the effected artery and slowly release drugs that inhibit 'cell proliferation' [8] (the growth of an organ/tissue due rapid multiplication the cells) around the atheroma. The final form of stent is a coronary stent used during the procedure of 'angioplasty'. Angioplasty is a surgical procedure used to open up the lumen of arteries previously impeded by arterial plaque from atheroma. Angioplasty achieves its aim of widening the lumen well but it does not hydrolyse nor remove the arterial plaque, it simply moves it to one side.

The aforementioned developments in nanotechnology now give a realistic opportunity to develop a drug delivery system that is not only more effective than a primitive 'stent' but more precise, cost effective and patient-specific. Researchers at MIT and Harvard Med School have developed a nanoparticle called a 'nanoburr'. The nanoburr, much like the micelle, locates and binds to the damaged arterial wall, however this goes one step further as once it has attached to the wall, it slowly releases a drug payload over several days. It is made up of 3 layers; an inner core containing a complex of the drug to be delivered, a middle layer made of the fatty material 'soybean lecithin' and finally an outer PEG polymer coating to protect the nanoburr during transit in the bloodstream. The nanoburr has a surface coated in small protein fragment that act as 'hooks' allowing it to join to the damaged tissue. When damaged, the basement membrane of the arterial wall is exposed and so this is what nano-engineers designed the nanoburrs to target once in the bloodstream. In order to establish the best protein in which to coat the nanoburr, researchers screened a number of short peptide sequences to see which binds most effectively to the basement membrane. They found the most effective sequence to be a 7-amino-acid sequence dubbed 'C11' [10]. At the time of the most recent published work on this research going to press, the researchers were at the point of conducting a two week test on rats using the nanoburrs in order to find the most effective dosage of the drug payload. The drug being used during research is 'Paclitaxel', a drug that combats atheroma specifically by inhibiting cell division and the growth of scar tissue that consequently blocks the artery.

The nanoburr, having undergone early tests on rats, was found to be able to effectively locate the basement membrane through intravenous injection. If the nanoburr was to undergo further development and somewhere down the line, be used in modern medicine, its implications could be huge. For example, it can be used together with stents for a more effective means of combating arterial plaque or even without a stent at arterial locations that may not be suitable for a stent such as a fork in the arteries. The nanoburr was found to be able to release its drug over a 12 day period, meaning a patient would no longer have to undergo repeated invasive surgery thus serving as the perfect alternative to procedures such as angioplasty [11].

Another further use of the nanoburr in the treatment of atherosclerosis may be to use it for the delivery of the drug 'Fumagillin' as proposed in a paper published by scientists from the Washington University School of Medicine. [12] As a drug, fumagillin inhibits the growth of small, secondary blood vessels that grow within the vessel walls and penetrate the atherosclerotic plaque. These small vessels feed the arterial plaque enabling it to grow along with various nutrients and fats. If the blood supply to the rapidly developing plaque was to be removed it is proposed that this may significantly stabilise the plaque and reduce the number of them in the affected area.

CONCLUSION

Nanotechnology as a whole offers a world of unrivalled detail, infinite possibilities and incredible uses for a modern doctor fighting their battle against disease. At the start of this paper I set out attempting to discover to what extent nanotechnology could help in the treatment of atheroma; one of the most common causes of coronary heart disease and therefore a huge factor in attributing to the shameful figures of premature deaths in this country.

At the root of the problem lies the formation of the arterial plaque; this is the main target for drug-baring nanoparticles carrying loads such as Fumagillin or Paclitaxel. Thanks to the development of the micelle, we are given a primary means of transport by which we may carry our drug to the effected site. The micelle is a pioneer in the use of nanotechnology and medicine as a whole. It allows us to be so precise in what we do and where we deliver drugs that, I personally, feel it may go on to completely revolutionise drug-delivery systems and the way we view the administration of medicine. The micelle allows us to locate and tackle the problem on a cellular level giving us a platform by which to combat the very beginnings of disease, and not just treat the development of one.

The nanoburr took the micelle one step further and used the technology it laid down to deliver relevant drugs the plaque. It located and effectively ‘stuck’ to the plaque in the subject’s body. At this point the nanoburr was able to remain in its desired location and slowly release its drug that, unlike any stent being used today, actually worked at combating the arterial plaque by either inhibiting cell division or restricting the flow of blood to the plaque. This for me is where the nanotechnology being developed for use in the treatment of atheroma really comes into its own and seriously outshines the most popular techniques being used by doctors worldwide today. The use of a stent is merely us ignoring the problem and literally pushing it to one side. I am in no way criticising the effect the stent has had on modern medicine, it has no doubt saved countless numbers of lives yet I just feel that through the development of the nanotechnology explained in this paper, it comes across as primitive and outdated. Nanotechnology is progress in its purest form when it comes to medicine. We now have to opportunity, not immediately, but with further extensive research and development, to move from one form of treatment to a form more effective and a lot easier to administer than its predecessor.

In conclusion relating back to my original question, ‘To what extent can nanotechnology help in the treatment of atheroma?’, I feel as it stands at the moment, we simply have the foundations for what could go on to be a huge leap forward in drug-delivery systems in general. When it comes to the treatment of atheroma, nanotechnology could very well play a huge role in the way we look at treating the arterial plaque and other contributing factors to the illness. Nanotechnology may act as both a substitute alongside current procedures and treatments or may go on to be a freestanding solution to the formation of atheroma. Overall I feel we have in front of us a revolutionary way of saving people’s lives and we must invest time and money in its development in order to unlock nanotechnology’s true capabilities in medicine.

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Fig 1. Computer image of engineered micelle. Credit: Peter Allen, USCB College of Engineering.
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Fig 2. Diagram depicting process of angioplasty.
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