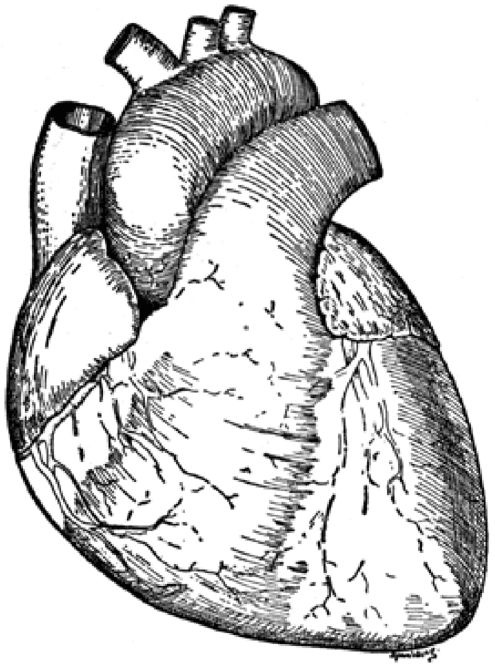
The Applications of Nanotechnology in Coronary Heart Disease



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PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2010

Abstract

Nanoctechnology is showing promise to become the foundation of future medicine. It offers high specificity in drug administration and an improved ability to image the body. This paper hopes to explore nanotechnology's potential in relation to CHD.

Background

Coronary heart disease (CHD) causes the deaths of millions of people every year. In 2004, nearly half a million were killed by CHD in the USA alone. The coronary arteries supply oxygen and glucose to the heart muscle (myocardium). CHD restricts this supply leading to tissue death and myocardial infarction. The main risk factors of developing the disease are from lifestyle: lack of exercise, poor diet (high in cholesterol) and smoking. The cost to the NHS in dealing with CHD is extensive. In 2006 the total cost of dealing with CHD in the United Kingdom was £4,273,738,000 and in the EU reached nearly £24,000,000,000 (ref10). This includes the costs of drug and surgical treatment.

CHD arises from the formation of atherosclerosis. This is caused by deposition of low density lipoproteins (LDLs) which are products of obesity which settle under the endothelial lining of the artery, also known as the intima. LDLs are derived from the synthesis of triglycerides and cholesterol in the liver, which are then released into the bloodstream. They cause the smooth lining of the intima to rupture, forming scar tissue, which creates friction with red blood cells (particularly with the presence of nicotine). Subsequently a thrombus can form, leading to transmural myocardial infarction.

Existing drugs are not unsuccessful in helping patients diagnosed with CHD. Aspirin has proved effective in treating the common symptom of chronic chest pain, angina, when stable, while beta blockers can manage cardiac arrhythmia in its less stable forms. In addition, there are surgical methods available to break up a developed atheroma. Angioplasty is a procedure in which a balloon catheter is positioned at the location of the atherosclerotic plaque in the coronary artery. This expands and alleviates the constricted vessel to allow blood flow to the artery. The implantation of stents is also in practice in the UK; stents are a wire mesh of steel which function the same way as a balloon catheter. In more serious circumstances, a bypass graft is used to direct blood flow via a surgically implanted artery to the site of heart tissue damaged by lack of oxygen and glucose.

Nanoparticles

Nanoparticles are man-made structures engineered for specific uses. Their size is of the order of 10^{-9} to 10^{-7}m. Reseach is being carried out into their uses in medicine and industry. The buckminster fullerene was discovered in 1985 by Robert. F. Curl., Sir Harold W.Kroto and Richard E. Smalley; it is a truncated icosahedron of a Carbon$_{60}$ molecule. Since its discovery, the 'buckyball' has been found to have antioxidant properties, that enable it to be effective in the treatment of neurodegenerative disorders and CHD(ref9). However, the applications of nanotechnology are limited as the field of mesoscopic quantum mechanics is very young, therefore, the mechanisms by which these particles interact with eachother and other matter is relatively unknown. Progress is being made, and rapidly so in this particular field of physics, however it may still be many years before the discoveries currently being made can be fully understood and applied to medical nanotechnology.

Nanoparticles in Coronary Heary Disease

Nanoparticles may be the new foundation of vascular medicine. Currently, most vascular obstructions are treated using a metal stent to widen the afflicted vessel and to deliver drugs to the blockage, as explained above. Whilst the stent is very useful, it cannot always be used, for example at the fork of an artery. In such a situation, more invasive and dangerous procedures must be used. The stent is also an imperfect treatment as in certain cases; an atheromatous plaque can continue to grow through the gaps in the mesh of the stent and blood flow can become as restricted as before the treatment. This is known as restenosis. However, recently researchers at Harvard Medical School and Massachusetts Institute of Technology (MIT) have developed a nanotechnological treatment for conditions such as Atherosclerosis and Thrombosis. This treatment involves a newly engineered kind of nanoparticle, which has been given the name 'nanoburr' due to its ability to bind to damaged vascular tissue. It is hoped that the particles will be used in conjunction with or in place of vascular stents (ref13). Unlike stents, these particles need not be implanted to a specific location, and can work perfectly well at the branches of two arteries.

The particles work by binding to damaged vascular tissue and then releasing paclitaxel, a mitotic inhibitor (ref15), which prevents the growth of thrombi around an atheroma. They are able to differentiate between healthy and damaged sections of the arterial endothelium because when the endothelium is damaged, the structure upon which the endothelial cells rest, the basement membrane, is exposed. The researchers at Harvard and MIT covered the particles in a sequence of amino acids named C11, which they showed to be most effective at binding to the exposed basement membrane (ref13). This sequence sits on top of a protective coating of polyethylene glycol, which is necessary to ensure the safety and structural integrity of the particles as they travel through the circulatory system. The middle layer of the particles is comprised of a fatty substance, soybean lecithin which covers the core of the particles. This core is an ester-like complex of a polymer of lactic acid, polylactic acid (PLA), bonded to the drug that the particles are to release. The team of researchers discovered that the duration of the release of the drugs could be mediated by modifying the length of the PLA chain. They found that the longer the chain, the slower the drug would be released, which could be useful to cardiologists in tailoring patient-specific treatment. The mechanism by which the drug is released is known as ester hydrolysis; in this reaction, a molecule of water reacts with the PLA/paclitaxel complex. During the reaction, the water splits up, donating a hydrogen atom to the PLA molecule, and a hydroxide group to the paclitaxel. This reaction breaks the bond between the PLA and the paclitaxel, leaving the latter free to leave the nanoparticle and to treat the affected area. Such treatment may be more favourable to patients and, indeed to their doctors because it involves no surgery. The particles can be made up in solution, and administered intravenously with no need for additional procedures.

Discussion

'This is a very exciting example of nanotechnology and cell targeting in action, which I hope will have broad ramifications' - MIT Professor Langer on 'nanoburrs'.

Nanoparticles offer broad developments in future medicine. In particular there is huge potential for nanoparticles that can be adapted for treatments other than CHD. The basement membrane is only exposed when the intima has ruptured due to an atheroma. Initially nanoburrs will be limited to delivering medication to reduce the swelling of the damaged tissue, or to break down the atheroma. After this procedure further medication may be delivered by additional nanoparticles to repair the established damage to the intima, which would strengthen the lining of the coronary artery. There are many possible applications of nanoburrs aside from the treatment of CHD. The same method of drug delivery using nanoburrs can be used in the prevention of an ischemic stroke as the nanoburrs would act similarly in delivering a dose of a drug that could break down an atheroma in one of the arteries (e.g. carotid) (ref11). Nanotechnology has developed not only nanoburrs for drug delivery, but nanoparticles to aid imaging, important in determining the location of the atheroma. Nanoparticles can now be synthetically made to be seen by MRI scanners (ref14). When the lining of the intima has ruptured, the blood naturally creates a thrombus containing fibrin. Nanoparticles can be made to bind to the fibrin which can be picked up by the MRI scanner and show the location of the ruptured artery. It is reasonable to suggest that in future nanoparticles, combining the merits of nanoburrs and imaging nanoparticles could be manufactured. These hybrid particles could simultaneously image and breakdown the thrombus, allowing the success of the treatment to be measured quickly and the need for further treatment determined.

Nanoburr technology has the potential to revolutionise treatments for conditions other than CHD. Cancer could also be targeted. Paclitaxel, the drug administered by nanoburrs to inhibit cell division in plaque, is also used in cancer treatment. Currently, nanoburrs rely on the exposure of the basement membrane to find the site of atheroma. As the basement membrane is not exposed by cancer, Paclitaxel delivery by nanoburrs cannot currently treat cancer cells in the same way as plaque, but if nanoburrs were to become programmed to source the chemo attractants emitted by cancers, this flaw could potentially be overcome.

Effectiveness and Safety

Before a new medicine can be licensed, it must pass rigorous clinical trials which thoroughly and meticulously examine any possible risk it may pose to patient and public health. Usually, this is involves considering the side effects and how they may affect people with different conditions and disabilities. These new nanoparticles may, however, potentially pose a risk to non-patients.

Were some of these particles to be accidentally exposed to a small cut or laceration in an otherwise healthy person, they would bind to the basement membrane of that person’s blood vessels. In this case, the particles would release their dose of paclitaxel, or whatever else they may have been modified to contain; it is worth noting, however, that in such an eventuality, the particles would almost certainly be in very small quantities and concentrations. The risk is simply not known as it has not been researched.

There is a very real risk posed by nanoparticles escaping into the environment, as there is not enough known about how they interact with natural and synthetic chemicals in the environment, such as nitrate fertilisers or chlorate bleaches. Whilst it is well known how individual amines, peptides and polypeptides interact with such chemicals, very little is known about the chemistry of mesoscopic peptide based structures, especially ones as new as these.

The fundamental benefit of nanoburrs over conventional drug treatments is that the high specificity of the drug delivery system greatly increases the efficiency of the treatment. There would be reduced risk of side effects from a drug delivered by nanoburrs as it would only be released at the site of the damaged artery. Furthermore, the procedure to place a stent at the location of an atheroma is considerably more invasive, requiring much greater surgical skill and dexterity and an in-patient stay; inconvenient to both the patient and the hospital. If nanoparticles replaced current surgery, the NHS would be able to treat patients with CHD with much greater efficiency, with reduced hospital stays allowing for faster rotation of patients and a lower likelihood of hospitals working to, or past, full capacity.

However, using nanoparticles in medicine is not without drawbacks. It could take many years for nanoparticles to be produced cost effectively. During this time their credentials as potential CHD fighting drugs must be rigorously tested and mass production is not viable until this is done. Obviously, this will entail a significant cost. Even after technology has improved enough for nanoburrs to be created on a large scale, it could take another decade before clinical trials conclude that they can deliver safe and effective treatment for CHD. However, most modern treatment has an element of risk, be that as a result of drug side effects or surgery. The benefits of future treatment using nanoparticles may outweigh the risk of the side-effects it could produce.

Ethical consideration

'The great breakthroughs in science followed one after the other so rapidly, there wasn't time to take stock, to ask the sensible questions...There was no way to reverse the process. How can you ask a world that has come to regard cancer as curable, how can you ask such a world to put away that cure, to go back to the dark days?' Kazuo Ishiguro, in his novel "Never Let Me Go".

While Ishiguro addresses a fictional matter, his words have relevance in what we see today. In a time where cures are appearing and evolving constantly, it could be argued that we are living in the period he describes, and that as we develop areas of medicine such as nanotechnology the 'sensible questions' must be asked.

Dr Donald Bruce, author of 'Ethical issues in Nanomedicine and Enhancement: Overview'(ref4), agrees with Ishiguro, he feels that nanotechnology has the ability to damage 'humanity, in all its rich diversity' and that for this reason, those developing such technology must first address and consider the varied ethical issues associated with this kind of scientific advancement. These relate not only to medicine and the environment but religion, society, economics, even politics as several of these issues would arouse global question or concern.

From a religious point of view, nanotechnology's ability to alter the prognosis of disease and lengthen human life, certainly far past Psalm 90.10's 'threescore years and ten' could be troubling. Many religions take the view that human life is a sacred gift, provided and taken solely by God, and extreme intervention of any kind (in this case that provided by nanotechnology) undermines this, and therefore God, an argument that has been presented often in the case for euthanasia(ref1).

Possible implications for society

Given that combating CHD with nanotechnology has the potential to dramatically alter the prognosis of the disease's sufferers, certain ramifications will arise that can be examined not only from a religious perspective, but also from a social or economic one. Nanoburrs are expected to be used primarily in the treatment of heart disease particularly that resulting from atherosclerosis. Statistically atherosclerosis is prevalent in the obese, smokers and those who consume excessive alcohol (ref8). It could be argued that this raises concerns over the financial viability of using nanoburrs as a standard treatment of CHD, as to a greater or lesser extent, CHD in these patients is a self-inflicted illness arising from a behaviour that may, or may not be addressed. In the case of the latter, some would say that these patients have ignored the widely publicised risks of their condition and that multiple treatments for illnesses arising from 'lifestyles choice' should not be treated as a priority of the NHS and its budget. However, it could be argued equally that increased understanding of genetic and psychological factors of addiction and obesity(ref12) would mean that declining treatment to these people is simply declining aid to those most in need of it. Declining treatment to these groups could also produce accusations of social unfairness as procedures for obesity, smoking and high alcohol consumption are all most common in those from the most underprivileged backgrounds (ref6).

The elderly are also associated with a high risk of developing CHD and bring about separate issues relating both to funding and ethics. The elderly are a group who are economically inactive, and unlike children or the unemployed of working age have no potential to be so in future. This, in combination with the fact that the elderly have a relatively short remaining lifetime, (even with medical intervention) means that the unpopular topic of relating the costs of medical treatment to the resulting benefits must be broached. To take a wholly objective look at the treatment of the elderly, it is almost undeniably an area of medicine less financially sound than others, where patients contribute more to their treatment costs. This is despite the fact that the current elderly have contributed earlier in their lives, as inflation and increased life expectancy produce a deficit. Many may argue that finance is secondary to equality and that all should be treated as a matter of principle, providing the same argument with the elderly as other risk groups. This issue is perhaps at its most debatable when global figures are examined. While it seems to almost all within the world's most developed countries a callous and unjust thing to withhold treatment from an elderly patient, the developing world could no doubt question why the rich wish to prolong human life past the age of 90 and treat diseases inflicted of their own volition, while allowing 8.1 million children under 5 to die annually (6.6 million from either Africa or South Asia). These figures hold great weight if it is to be argued that treatment is to be despatched on an egalitarian basis, as 22 million of the world's infants are not protected by the vaccines offered routinely to those in the UK and USA.

Assessing 'quality of life' is important in managing elderly care. While such concerns are present in all areas of medicine dealing with chronic illness, they become particularly prevalent in the elderly. While all patients with chronic illness undergo long term treatment, elderly patients are often treated for a multitude of conditions which become increasingly numerous over time(ref5) as the body reaches a state of rapid decline. The financial aspects of such treatments have previously been examined so now patient welfare must be taken into account.

The fundamental aim of medicine is to preserve a patient's wellbeing, both physical and psychological, though in some cases these two ambitions conflict. This problem becomes increasingly contestable as technology evolves to allow patients to be kept alive. The procedure surrounding 'do not resuscitate' has become extremely complicated. In the past, it has been relatively simple. If a patient's condition was irreversible and the benefits of resuscitation would not outweigh the suffering or small lifespan of the patient after, then the majority involved could agree that not resuscitating a patient was a sensible action. Now however, the ethics of keeping a chronically ill patient alive are becoming a grey area. New technology means that patients are more likely than ever to recover, and their lifespan after treatment becomes increasingly promising. An ethical issue arises, as it becomes increasingly the case that an elderly patient recently treated for one life threatening condition will return shortly with another and another after that. Some would argue that waging war on age related illness is conducive to nothing- it results only in frequent hospitalisation that achieves only temporary relief and a great deal of discomfort to the patient. Despite physiological, psychological decline and poor quality of life, medical staff will increasingly be unable to tell patients or their families 'there's very little we can do', simply because the action of keeping a person alive - that is maintaining supply of oxygen and glucose to vital organs- has become increasingly possible. This ability to keep a patient living in the most basic sense will inevitably cause distress for families or carers awarded positions like power of attorney, who must make decisions concerning another person's welfare.

In short, it could be said that increasingly age is the chronic illness in itself and heart disease, diabetes, cancer and other related conditions are merely its symptoms, which, like those of hay fever can be fought recurrently and whenever needed because of the simplicity of their treatment. This in turn makes patients' decisions difficult. They know they have a 'right to life', where everything possible must be done to keep them alive if that is what they wish, but whether this 'right to life' is simply the right to be a physically functioning, albeit bound to hospital or to have 'quality of life', whatever that may be. If all possible must be done, when disease becomes curable (as Ishiguro notes) it becomes impossible to withhold this cure. If nanoburrs are to fight heart disease in the near future and cancer in the foreseeable one, ethical decision will become ever more complex and fraught. Furthermore, the western world must face rapid population increase, due to loss of impact of its two greatest killers (ref7). For this reason, some would argue that to prolong human life so hugely is irresponsible in its current lack of sustainability; as future fuel and food supplies are continually coming under question.

Overpopulation is not the only environmental repercussion potentially stemming from nanotechnology. In their paper, Anders Braun and Steffan Foss Hansen note possible ecotoxicological characteristics of nanoparticles (ref2). As Foss Hansen and Braun note, current pharmaceuticals contaminate our waste water, ground water and importantly drinking water; feasibly, nanoparticles will do the same, with effects that cannot yet be ascertained, but which could have some of the most serious repercussions as discussed above, in nanoparticles infecting lacerations.

Conclusion

Having examined nanotechnology's potential to alter the face of medicine, it seems impossible to believe that nanotechnological treatments are not to become common place medical procedures in the next century. They have the ability to cure, or certainly manage much more efficiently, diseases that are currently debilitating and in the long term fatal; thus alleviating unnecessary patient suffering, saving lives, and reducing NHS costs arising from extensive hospital stays. To say that nanotechnology will be behind the future's miracle cures is a statement with many merits, but with several faults. We have discussed the huge potential for nanotechnology to treat diseases previously associated with a small chance of recovery and relatively short term manageability. However, to say that these treatments will be widely available in 10, maybe even 20 years could be a false statement. Clinical trials and rigorous testing will be required before nanotechnology can be certified safe for public use and the environment. While this time span is around 15 years (combined research and clinical trials) (ref3) , nanotechnology - being a revolutionary form of treatment, rather than a mere adaptation or modification of a pre-existing drug - could be subject to testing that doubles this time span, particularly with the relatively unknown effects nanoparticles could have environmentally, as noted by Hansen and Braun. This is not to say that Nanoparticles are not to come into use, as discussed, nanoburrs' potential to replace bypass surgery and stents deems them one of the most promising medical developments of the century. Heart disease's exponential growth as the UK and USA's greatest killer renders demand for effective treatment methods high - certainly as current treatments are both ineffective and associated with a higher incidence of side effects (due to a low ability to target only the affected area) in too high a percentage of patients. Despite the ethical issues arising from nanotechnology in general, and in particular nanoburrs, many will believe that developing this new technology is the only way to overcome CHD, while ethical issues can be addressed as they occur as many future effects are speculative and unpredictable. To conclude, it seems that nanotechnology is an area that must be explored for the progression of medicine, its development having broad ramifications for a range of treatments from cancer to head trauma. At the same time however, it would be irresponsible not to consider potential ethical issues, before we leave behind Ishiguro's '*dark days'* and further accept nanotechnology as a widely used treatment.

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