

# Possible Uses of Nanotechnology in the Treatment of Atherosclerosis

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PASS WITH DISTINCTION

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## ABSTRACT

In this paper we will explore how nanotechnology could be used to fight atherosclerosis and lower the risk of coronary heart disease through Magnetic Fluid Hyperthermia or by improving the delivery of conventional drugs.

## INTRODUCTION

“Nanotechnology is the engineering of functional systems at the molecular scale”<sup>1</sup> and has also been described by Professor Norio Taniguchi as the ‘separation, consolidation and deformation of materials by one atom or molecule’. Nanotechnology first theoretical capability was envisioned by physicist Richard Feynman in 1959, and the word was popularised by K. Eric Drexler who, in the 1980’s, spent a decade describing and analyzing nanobots. As our technology has improved, so has nanotechnology which has a growing list of applications in every area of modern day society from engineering to cosmetics, however an area that nanotechnology will aid greatly is medicine. In spite of that nanotechnology was first unintentionally used by the Romans when making red stained glass, they created small gold spheres when mixing gold chloride with glass. These gold spheres were nanoparticles which absorbed and reflected sunlight in such a way that produced a rich ruby colour.

Nanotechnology could open the door for minimally invasive treatments or for powerful diagnostic techniques which would allow us to spot diseases far earlier than we can currently detect them now. In fact, some scientists and doctors are even calling nanobots, “wonder drugs”<sup>2</sup>. The two most useful properties of nanoparticles are firstly that they can be constructed on an atomic scale so produce ‘tailor-made’ particles and secondly it is the fact that nanoparticles are so small that they can access areas of the body that traditional medicines can’t due to their ability to pass through cells. The term nanoparticle usually refers to a man made object of between 1 and 100 nm in size, to give you an idea of scale animal cells are usually between 20,000 and 40,000nm. At the moment nanotechnology is still in the early stages of development and currently is used in cosmetics and suns-screens.

The area that we are going to look at is the ability for nanotechnology to help those with CHD (coronary heart disease) caused by atherosclerosis. Atherosclerosis is the formation of fatty deposits or ‘atheromas’ in the walls of arteries leading to narrowing of the arterial lumen.<sup>3</sup> The endothelium of an artery can be damaged by several things, most often by high blood pressure or by carbon monoxide from smoking. When this lining is damaged white blood cells pass through the lining into the media layer and encourage the production of smooth muscle. At the same time they can also absorb oxidised LDL (low-density lipoprotein) and are turned into ‘foam cells’ which form the core of an atheroma. Atheromas also contain dead blood cells, platelets, cholesterol, fibres and sometimes high levels of calcium<sup>4</sup>

Atherosclerosis can lead to several serious conditions including coronary heart disease (CHD), peripheral vascular disease and stroke, depending on the location of the atheromas.<sup>5</sup> Atheromas narrow the lumen of arteries by pushing the lining of the wall inwards and so reduce blood flow through the artery, but if the atheroma bursts through the endothelium into the lumen a blood clot (thrombus) is formed. A thrombus can completely stop blood flow and if it happens in a coronary artery it will cause a myocardial infarction (heart attack) or even heart failure.<sup>6</sup>

An unfortunate feature of atherosclerosis is that the first symptoms are often extremely serious, for example angina or a myocardial infarction, so by the time it is diagnosed the patient may have already suffered long-term or fatal damage to their heart.

Coronary heart disease caused by atherosclerosis is one of the biggest killers in the developed world; it is thought that twice as many people die as a result of atherosclerosis induced CHD than from all cancers combined.<sup>7</sup> So as you can see it is important that we find an efficient treatment.

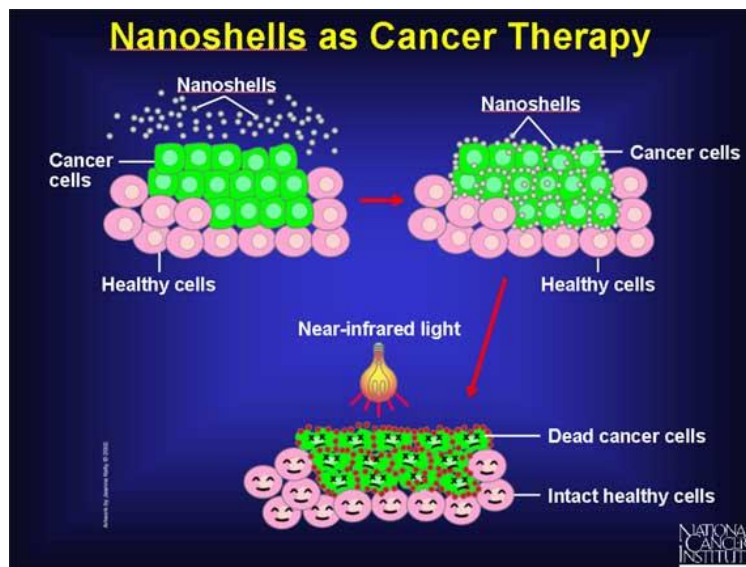
At the moment there are only a few ways to overcome an atheroma: surgeons could remove a vein from another part of the body and attach it to the affected part of the heart allowing the blood to pass through reducing the pressure in the artery and supply the heart tissue with ample oxygen, known as Coronary Artery Bypass Grafting, or a Balloon Angioplasty where a balloon is inserted to relieve narrowed arteries, allowing blood to flow through providing oxygen to all part of the heart again. However, with both of these there are risks that other atheromas forms near the present atheroma, because of the high LDL, (low density lipids) levels in the blood. Also current surgical interventions for atheromas can be extremely invasive leading to an increased risk to the patient and a longer stay in hospital. While several drugs are also used to help treat atherosclerosis and its symptoms, they are not always effective and require high and frequent doses of medication for an extended period of time.

## DISCUSSION

Nanotechnology could play a multitude of roles within the prevention, early diagnosis and treatment of atherosclerosis. We have focused on two methods that could be used to make atheroma treatment much more effective while at the same time less invasive.

Our first proposal for a possible treatment of atherosclerosis is an adaptation of a cancer treatment that is currently being trialed called Magnetic Fluid Hyperthermia. In 1957 Gilchrist et al. published a paper exploring ways of treating Lymph node tumors that were missed when a primary tumor was surgically removed.<sup>8</sup> His main proposal was for the use of magnetic materials, such as magnetite ( $\text{Fe}_3\text{O}_4$ ), in hyperthermia treatment. These materials, which can be heated using magnetic fields without affecting the rest of the body, were usually only taken up by cancerous cells so when the material was

heated only the cancerous cells were heated along with them. The cancerous cells can be destroyed by heating them to a temperature of between 42-45°C for around 30 minutes<sup>9</sup>



**Figure 2:** <http://www.understandingnano.com/nanoshells-cancer-therapy.html>

With the advance of nanotechnology scientists have been able to improve MFH by using nanoparticles. The size of these new nanoparticles allows them to more easily travel through cells and reach the target tumors; this reduces the number of particles needed as less is wasted. As well as using magnetic nanoparticles and magnetic fields to destroy tumors, nanotechnology has opened up the opportunity of using gold ‘nanocages’ and lasers to perform a similar function.

Research done at the University of Washington, St Louis has demonstrated that these nanocages, around the same size as a virus, can be very effective in treating cancerous tumors, although a major problem with both MFH and gold nanocage treatments is that not all of the material ends up in the target tumors. In Xia’s and Welch’s trials on the effect of gold nanocage treatment on tumors in mice only around 6% of the nanocages entered the tumors.<sup>10</sup> However, nanotechnology can also provide a solution to this; the nanoparticles can be engineered to actively ‘seek’ their target by attaching antibodies or ‘bio-linkers’.<sup>11</sup> These antibodies would be small molecules, attached to the nanoparticles, which can only link to certain cells in the human body, which have the corresponding antigens. So, for example, when the nanoparticles include antibodies designed to attach to cancerous cells, the nanoparticles can only heat cancerous cells meaning less healthy tissue is affected.

We think that this kind of treatment could easily be adapted to use against atherosclerosis. By attaching nanoparticles to antibodies that can seek out atheromas we could theoretically inject a solution containing the nanoparticles into any major vein where they would soon travel through the heart and into the major arteries, including the coronary arteries which are the main sites of atheroma formation. Here the nanoparticles could travel through the thin endothelium layer of the arterial wall and then enter the atheromas, where they could now be heated using a magnetic field or a specific frequency of laser (depending on the type of nanoparticle used) causing the atheroma to break down. In order for these nanoparticles to be able to find atheromas a specific target needs to be selected, our suggestion is that the antibodies are adapted to seek out foam cells which are one of the main constituents of atheromas and are not commonly found elsewhere in the body. For this suggestion to work, research would need to be done to identify a characteristic of foam cells that is not shared with normal white blood cells, which could be targeted by the nanoparticles. For example, if the antigens on the cell surface membrane of a white blood cell change when it changes into a foam cell than these antigens could be targeted by receptors on the nanoparticle. If foam cells are a viable target for the nanoparticles, treatment for atherosclerosis could happen at a much earlier stage than with current treatment. Foam cells are one of the earliest components of atheromas to form,<sup>12</sup> so our treatment could attack atheromas long before any symptoms could present. By treating atheromas while they are still in their 'fatty steak' stage and before they begin to narrow the lumen of the coronary arteries, many cases of angina and myocardial infarction could be prevented.

The treatment should work on atheromas at all stages of development, however once the atheromas reach a certain volume we are not sure what will happen to the broken down materials. When smaller atheromas are broken down by the heating we are fairly certain that the body would be able to deal with the small bits of material that will enter the blood stream, either by reabsorbing it around the body or by removing with the kidneys and liver. However, when atheromas with a larger volume are treated the body may not be able to remove all of the broken down material and it may end up forming a thrombus in smaller blood vessels elsewhere. So while we can safely assume that the treatment itself would only affect the atheroma whilst leaving healthy tissue untouched, without the resources to conduct tests and simulations it is impossible to predict what side effects the breaking down of the atheroma may have after the treatment.

Another application for nanotechnology in the treatment of atherosclerosis would be the use of targeted drug carriers. We think that nanoparticles could be used to deliver the conventional drugs used in the treatment of atherosclerosis in order to make them more effective. Nanoparticles can be created that can carry drugs directly to the area where they work. This means a higher percentage of the drug administered reaches its target and therefore lower doses can be used. An example of this is the work of Winter et al.,<sup>13</sup> they conducted an experiment on the relative effectiveness of Fumagillin when administered freely and bonded to a nanoparticle. Fumagillin is a drug that prevents the development of minute blood vessels that grow through the arterial wall and 'feed' new atheromas. They found that by using a nanoparticle to administer the drug they could lower the dose by as much as fifty thousand times. Being able to lower the dosage is extremely beneficial in this case as high doses of Fumagillin can have adverse side-effects so by lowering the necessary dose the nanoparticles also make the treatment better for the patients. Work by Padney et al. further backs up the effectiveness of nanoparticle administration, they found that in mice infected with Tuberculosis they needed to give them 46 daily doses of anti-TB drugs before their organs were clear of the infection while they only had to give them 5 doses of the nanoparticle-bound drugs in the same time to have the same effect.<sup>14</sup>

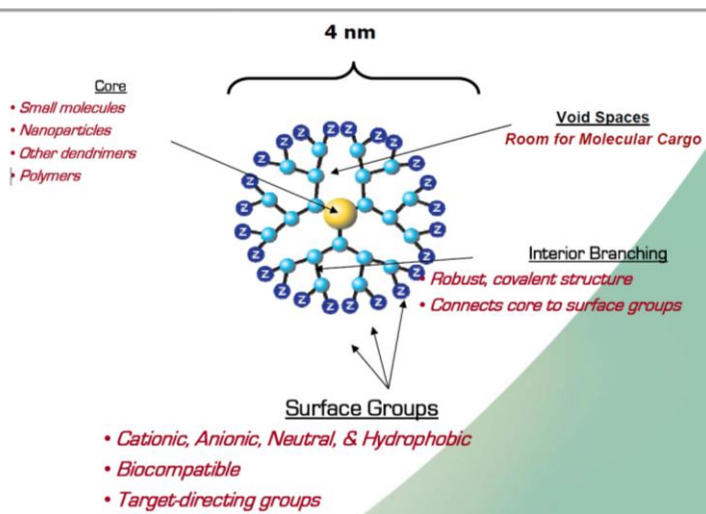
A wide range of drugs can be used to fight atherosclerosis, some of which act upon the atheroma or its surrounding while some take effect elsewhere in the body. Statins have the reputation of being one of the more effective drugs to treat this condition; they work by inhibiting the 'HMG-CoA reductase'<sup>15</sup>

enzyme which is responsible for the production of cholesterol in the liver, research also shows that statins can reduce the amount of LDL (low-density lipoprotein) that becomes oxidised<sup>16</sup>. Cholesterol is one of the components of arteriomas, whilst oxidised LDL can cause white blood cells to turn into foam cells. On top of these properties statins are anti-inflammatory, anti-thrombotic<sup>17</sup> and are able to lower the risk of endothelial dysfunction all of which makes them more effective in preventing the formation on growth of arteriomas. However, it is because of the variety of effects that statins have that means that they are more difficult to incorporate in to a nanoparticle drug delivery system. Attaching a drug to a nanoparticle makes it the drug more effective by increasing the amount of it that reaches its target, however statins work on several different areas of the body; the liver, the arteriomas and components of the blood. This means that statins would only be effective on one target, unless of course the drug was added to several different nanoparticles; each one specialised to target one part of the body.

Nitric Oxide would be a far simpler drug to use in a drug delivery system. Nitrous oxide's primary use in atherosclerosis care is to dilate arteries by acting on the smooth muscle in the arterial walls. Increasing the lumen size of arteries helps to negate the adverse effects caused by the arterial narrowing that results from arteriomas. Administering nitrous oxide doesn't really treat the arteriomas themselves but helps prevent dangerous symptoms such as myocardial infarctions that can happen as a result of decreased blood flow to cardiac muscles due to arteriomas. Increasing the lumen of arteries also lowers blood pressure, which means less damage occurs to arterial walls and so arteriomas don't grow so quickly.

Beta-blockers and ACE inhibitors both lower blood pressure by relaxing blood vessels and slow the heart rate. These effects mean that these drugs are effective at reducing the symptoms of atherosclerosis and slow the formation of arteriomas.<sup>18</sup>

Scientists around the world have suggested dozens of different designs that could be used to carry different drugs; we're going to look at two broad types; dendrimers and polymer micelles. Dendrimers are globular or spherical nanostructures which can be designed to carry drugs attached to their surface or contained within their structure. They can be built to very precise specifications due to their construction process; they are built on an atomic structure 'upwards.' As they range in size between 1 and 10 nm they are much smaller than most cells<sup>19</sup> and so can pass into or through cells in the body easily in order to reach their target site. Antibodies or other targeting molecules can be added to the surface of the dendrimers so that it can find its target cell before releasing its payload of drugs. Figure 3 shows the structure of a dendrimer including the different sites where it could hold drug molecules.



**Figure 3:** <http://dnanotech.com/dendrimerOverview.pdf>

On the other hand, polymer micelles form due to hydrophobic interaction between polymer segments when added to a liquid. They can also be used to carry drugs around the body to a target site due to the ability of scientists to add polymer segments that can target specific cells. The outside of the micelles is generally hydrophilic and so the micelles are soluble aqueous solutions, enabling them to move around the body easily. Micelles ranging from 50 nm to 220 nm can encapsulate non-water soluble drugs to be administered intravenously.<sup>20</sup> As polymer micelles are much larger than dendrimers they could carry larger drugs such as the statins.

As each drug mentioned treats atherosclerosis in slightly different way, it may be more effective to use a solution of nanoparticle carriers to deliver a combination of drugs instead of just one. Each drug would have to be attached to a nanoparticle with antibodies that can send it to different parts of the body, it would be no use attaching a nitric oxide molecule to a dendrimer which targets cells in the liver. Usually it may be unadvisable for a patient to take a wide range of drugs at the same time but due to the extremely low doses made possible by nanotechnology someone could take a combination of drugs without fear of over-medicating. With further research and an improvement in finding ways to target nanoparticles, this 'cocktail' of drugs could be used to prevent atherosclerosis in high-risk individuals before symptoms even present.

As with most major advances in medicine, nanotechnology raises a set of ethical concerns. Firstly, the NHS is already struggling financially and might not be able to afford these new, expensive treatments and so they might only be available in the private sector. With such a common and dangerous disease such as atherosclerosis is it fair that only the more well off sections of our society could afford to have possibly life-saving treatment? However, our opinion is that nanotechnology could in fact save the NHS money in the long run. After the initially high cost of researching the treatments, we think that the savings made by reducing the amount of wasted drugs could balance out the cost of running a treatment program. On top of this we feel that by using our effective yet minimally invasive treatment ideas patients with CHD would have shorter stays in hospital and wouldn't have to undergo expensive operations, saving the NHS even more money.

Finally, if patients can be cured of a life-threatening disease by a simple injection, what is their motivation to lead a healthy lifestyle? We think that people should take more responsibility for their own health instead of just relying on hospitals to fix their lifestyle related diseases, therefore we propose that these treatments would only be available to a patient after they had made progress to improve their diet, exercise regime and had quit smoking. Of course this wouldn't apply in emergency situations!

## **CONCLUSION**

The biggest problem that faces our proposed treatment is how to identify and manufacture antibodies or other molecules that could be attached to nanoparticles in order to guide them to the right locations in the body. With our suggested use of MFH a malfunction in the targeting system could have a catastrophic effect on healthy tissue in the body, particularly if the nanoparticles target healthy white blood cells instead of the foam cells in the atheromas. Research into how to guide nanoparticles more accurately to their targets is currently happening around the world so it is feasible that soon it would be possible to attach targeting molecules to the nanoparticles knowing that they would definitely find the current cells and not accidentally harm other tissue.

Another problem that faces nanotechnology in general is that we don't yet fully understand the long term effects that nanoparticles may have on the human body or the environment. For example, the environmental toxicologist Eva Oberdörster found that exposing fish to relatively low doses of fullerenes (a type of carbon nanoparticle) caused extensive brain damage<sup>21</sup> which suggests that nanoparticles entering the body might have other effects to the ones we intend.

However, we don't feel that these fears should prevent research into the medical benefits of nanotechnology. Nearly all medical treatments involve side-effects or risks in one form and we still use them so why should we treat nanotechnology any differently? As long as proper precautions are taken and any associated risks are negated as much as possible we feel believe that nanotechnology will revolutionise medicine and bring great benefits to the health of society.

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