FUTURE DEVELOPMENTS OF NANOTECHNOLOGY FOR CORONARY ARTERY ATHEROSCLEROSIS

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Abstract

Developments of nanotechnology in Coronary Artery Atherosclerosis diagnosis and treatment are today subjects of much research. This paper will discuss the possible roles of nanotechnology devices in the treatment of Atherosclerosis, a cardiovascular disease. The future of its diagnosis is already being explored by nanosystems that could both detect this disease and treat it, thanks to targeted delivery systems and advanced imaging.

Introduction

In 1959, Richard Feynman introduced the idea of miniaturization in his talk “There’s plenty of room at the bottom”. He believed in the rearranging of atoms on a small scale and thus presented endless opportunities to create new devices; setting in motion the wheels that led to the major research we perform today towards revolutionizing nanotechnology. It was in fact Professor Norio Taniguchi who defined Feynman’s ideas as the concept of nanotechnology. Eric Dexler in his book “Engines of Creation”, the first written on this particular subject, further explored and reinforced Feynman’s ideas; laying the theoretical foundation “for the modern field of nanotechnology and articulated the amazing possibilities and dangers associated with engineering at the molecular scale”[2]. Consequently, Dexler is today considered as the “Father of Nanotechnology”. The development of this idea was rather hampered, for the naked eye can only see about 20 macrons and it was only on the 1980s that we were given the ability to see nano-sized particles thanks to ‘Scanning Probe Microscopy’ [3].

Since the first major breakthrough in the 1990s, when the ‘buckminsterfullerene’ was successfully created, medical nanotechnology has widely expanded, becoming one of the most researched fields today. High hopes are set on this mechanism, which is defined as “the study and use of structures between 1 nanometer and 100 nanometers in size”[4]. If one considers the challenge of picking out one single blood cell: this may seem as an impossible task, however the latter measures 2500 nanometers and is therefore seen by nanotechnologists as a rather large particle. That is an example of how amazing and fascinating nanotechnology is. Indeed its application may enable prevention, detection and treatment of many common and dangerous diseases, such as cancer or heart diseases.

One might ask: how are atoms created on such a small scale? In fact, there are several methods. One is the bottom-up approach, which demonstrates an atom by atom assembly: a method similar to bricklaying because one moves the atoms into place one by one, using Atomic Force Microscopy. Within this approach is a method which allows the atoms to unite naturally, this is called “Molecular Self-Assembly”. Another way to produce nanomaterials is by a top-down approach, which refers to the traditional workshop methods for like a sculptor one chisels out materials from a surface, until the desired structure emerges.

This wide field works at a molecular level. Current medical research today involves many different applications of which some are only imagined, where as others stand at various stages of testing in pre-clinical or clinical trials. A first application currently under
development is drug delivery. Many harmful side effects today, are as a result to drugs that do not directly pinpoint the target cell; an example of such a treatment is chemotherapy. The modern application of drug delivery however, could enable nanoparticles to transport the drug to the target cell in order to then apply heat, light or other substances and accomplish its mission. This method therefore reduces damage to healthy cells. Other applications under development are Therapy Techniques, involving ‘Buckyballs’ and ‘Nanoshells’. Diagnostic and Imaging techniques aim, in the future, to detect cancer tumors thanks to iron oxide and gold nanoparticles. Anti-microbial techniques are also being researched and involve anti-microbial agents in a cream that would reduce infections in wounds and reduce the necessity of numerous bandage changes, it uses nitric oxide gas. A final application is that of Cell Repair which would mimic antibodies in our natural healing process, in order to repair damaged and diseased cells. (For more information, see [5])

These applications seem to use natural elements and the scientists themselves appear to have made a conscious effort to not only build new technology but to also understand how they might affect toxicity to animals, humans and the environment. Also, what must be appreciated is that the research does not only involve curing a disease but also aims to prevent and detect damage at an early stage. Whether it be in a very near or more distant future I truly believe nanotechnology will revolutionize methods of both detecting and treating damage to the human body and diseases.

**Discussion**

Coronary Artery Atherosclerosis is the principal cause of coronary artery disease (CAD) and is the single largest killer of both men and women in the United States.

Atherosclerosis is caused by the narrowing and stiffening of the arteries due to fatty deposits known as atheroma, accumulating in their walls. The process that leads to this disease begins with abnormally high levels of excess fats and cholesterol in the blood. These substances infiltrate the lining of arteries at sites of minute damage, forming deposits known as atheroma. This can happen in any artery throughout the body. These atheromatous deposits gradually create plaques (Figure 1). These plaques are made of various substances already

![Figure 1: A) Normal artery, normal blood flow. B) Artery with a plaque build up.](image-url)
circulating the body: calcium, fat, cholesterol, cellular waste and fibrin. This build of substances and the disruption of the blood flow over the plaque, mean that blood is more likely to clot. This consequently narrows and hardens the space inside the artery, reducing the blood flow; sometimes blocking it all together.

Atherosclerosis is as a result to various causes. From my research I have come to the conclusion that the trigger cause is damage to the arterial wall, which in effect enables the atheroma to build up. When observing long-term factors, diet appears to be a major key, for risk factors can be: obesity, high blood pressure, cholesterol, diabetes. Other factors are smoking and a lack of physical activity. This disease appears to affect people of 35 and older, so one can therefore assume that from that age, one is more susceptible to the build of fatty substances. Research has indeed shown that the process begins in a majority of people when they are children, progressively worsening as they grow older.

Symptoms of atherosclerosis are not detectable until an artery becomes narrowed or blocked, in fact, in many cases clogged arteries do not cause any symptoms until a major and dangerous event occurs, such as a stroke or a heart attack. These are caused by the lack of oxygen and nutrients, as a result to the restricted blood flow in the cardiac muscle. When the coronary artery is blocked, one may feel various symptoms: chest pain, shortness of breath, heart palpitations weakness or dizziness, nausea and sweating. Chest pain is also known as angina.

It was estimated that in 2008, 1.4 million men older than 35 in the UK had a heart attack. Also, about 619000 men and 336000 women aged 55-75 had or had had angina.

Various approaches are already available to treat Coronary Artery Atherosclerosis:

1- **Lifestyle changes**: this tends to manage the arterial plaque.
   - Diet: low in saturated fats and cholesterol  →  healthy body weight
   - Not smoking: increases oxygen level in blood and helps circulation
   - Exercise: keeps blood pumping

Medical drawbacks of this however, is that if a person has angina, then the pain is caused and further increased by exercise; so not all patients can take this treatment.

2- **Surgical procedures**: in some cases this may be necessary to prevent an accumulation of yet more plaques.
   - Angioplasty: a catheter with a balloon attached is inserted into the narrowed artery where the balloon is then inflated in order to widen the passage and allow the blood flow.
   - Stent Placement: in some cases the metal balloon remains in an artery to maintain adequate blood flow.
   - Bypass surgery: arteries from other parts of the body can be moved in order to bypass clogged arteries and help the oxygen in the blood reach its destination.
However a major drawback is that these solutions are not always possible. Plaques tend to build up at points where the arterial wall is subject to turbulent flow, meaning in areas where the artery divides (in a fork). Neither balloons nor stents can be placed there in parts of the arteries.

3- **Medication:** the following in fact help control the factors that contribute to the accumulation of plaque.
   - Blood thinning drugs reduce the likelihood of blood clots forming in the artery.
   - Cholesterol-lowering drugs could prevent the creation of atheroma in damaged and exposed areas of the artery

Medication however can prove to be complex and cannot be taken by everyone. It also may have many uncomfortable side effects that change the person’s social attitude.

None of these solutions are able to completely eradicate the dangers of Atherosclerosis, in addition to this; these treatments cannot be applied to all individuals. Although these treatments are certainly beneficial, they are by no means cures. There is no guaranteed way to predict and detect all plaques, even if one is widened, another may later emerge. In addition to this, without nanotechnology, the possibility to reliably detect plaques or indeed, any cardiovascular defect would not be available.

**What nanotechnology could do to the future of Atherosclerosis**

I believe that the development of nanotechnology could bring revolutionary and life changing effects to the clinical consequences of Atherosclerosis, which will enable early detection, possible prevention and indeed a potential cure.

1/ At the University of California in Santa Barbara, they believe in a treatment that could not only detect atherosclerotic plaques, but more specifically those that are most vulnerable to rupture. A plaque tends to rupture where the plaque tissue meets the normal tissue, which is called a “shoulder” [6], a rupture then creates a blood clot which makes the artery prone to a blockage. These plaque-targeting devices are in fact collections of molecules that self assemble to create a micelle (figure 2). The latter is a multifunctional creation which both targets cardiovascular plaque as well as carrying a drug in the same particle directly to its destination.

![Figure 2: Micelle](image)

The difficulties of this research is the cost and therefore whilst also attempting to change lives, these scientists must face legal and administrative issues. However, it would seem the project has been funded for five years of research, costing $18 million. What really draws my
interest and respect is their idea to submerge the concept of delivering the drug to the desired destination whilst also guaranteeing that the nanoparticles remain active in order to treat the target cell. Also, the research plans to enable imaging agents that would help track both the nanoparticle and the therapeutic agent. The scientists and engineers involved appear to have paid attention to both the efficiency of their creation, whilst also enabling a time span that could be needed for the nanoparticle to detect and find the cell. As advanced as technology may be, the body still presents many complications and differences within each individual mechanism, so a longer time span could prevent wasting the devices.

One would think that because these micelles provide long circulation times, that their construction would be prolonged and complicated. However these scientists have adapted the Self-Assemble method (explained previously) of creating micelles which therefore facilitates the construction of these small particles.

As positive and enthralling as this project appears however, one must take into account that its effectiveness has only been proven on mice, on which the plaques were artificially induced. Despite the genetic information similarities between humans and mice, we still have very different mechanisms and therefore none can predict that these micelles will work. However, the confidence projected from various scientists leads me to believe that the possibility of this device becoming a successful discovery is indeed higher than the chance that it will prove to be non-conclusive.

2/ As explained previously, when a plaque is situated on the ‘fork’ of an artery, it is not possible to insert a stent. Harvard Medical School seems to have invested an interest in finding an alternative to the use of stents and have built a nanoparticle that should cling to the artery walls and gradually release the medicine. These particles are coated with minute protein fragments which then allow them to target and stick to specific cells and proteins: these are “nanoburrs” (figure 3). The damage of arterial walls exposes the basement membrane which lines the latter and nanoburrs are specifically targeted to the structure of this membrane.

Figure 3: Nanoburr
The scientists have created this device with a coating of polymer called PEG, which consequently creates a shield for the particle as it travels throughout the bloodstream. As a result, the nanoburr will safely reach its targeted damaged wall in order to release its medicine. This is done over a longer period of time than any of the developments mentioned previously, sometimes releasing the drug over a period of 12 days. I believe this method to be a “slowly but surely” approach, for by releasing the drug over several days, it could be more beneficial and efficient on the long-term scale, for the patient, because this method inhibits cell division and therefore prevents the growth of scar tissues that create blood clots and clog the arteries.

This treatment has been tested over a period of two weeks on rats and therefore, unlike the first development introduced in this paper, it has in fact been tested and is not solely based on the exciting prospect of making a difference.

The two above developments focus on the detection and treatment of the plaques within the arteries. However, Low density lipoproteins (LDL), referred to as bad cholesterol are known to play an important role in the accumulation of substances that build up to plaques. A team at Rutgers University has based its theory on the knowledge that macrophages’ (white blood cells) normal function is as a defense mechanism, yet when faced with LDLs, they have quite the opposite effect, for the macrophages gradually accumulate unhealthy quantities of the substance, becoming a danger to various tissues surrounding the cell, and then initializing the buildup of plaques.

In light of this fact, scientists have deducted that by preventing the contact of LDLs with macrophages they could prevent plaques. Therefore, they have worked on nanoengineered molecules that target the specific receptors on the white cells, consequently blocking the access of LDLs to the macrophages. This device is called a ‘nanolipoblocker’; the name speaks for itself, for in effect, it binds itself to the receptors on the macrophages. Like the first research project, the nanolipoblockers are formed in a micelle structure (Figure 2).

This is a very positive variation to the previous developments I have mentioned, for rather than attacking the plaques, this theory plans to act ahead, therefore reducing the chance of a stroke or heart attack that can create damage to many organisms in the body, including permanent damage to the heart. In addition to this, the nanolipoblocker addresses the recurrence of blockages, for which drugs have not allowed a reliable solution.
Despite the breakthroughs in modern medical developments, the imaging of inside the body has been restricted to mere x-rays, MRI, Cat scans and Echoes. As a result, the detection of Atherosclerosis was rather undetermined and unreliable. Today, thanks to the University of Twente and nanotechnology, a device has been created that enables the monitoring of the increase and decrease of atherosclerosis in coronary arteries: this device is the Intravascular Ultrasound (IVUS).

The concept of this development is the following: it uses a specialized catheter with an ultrasound sensor which then creates images of the calcifications (figure 4), therefore allowing the identification of any form of plaque. Thanks to nanoparticles, IVUS can ultrasound molecular imaging. This device varies from the previous method of detecting damage in the arteries, for it used cardiac catheters that only showed the blood flow within the artery and therefore one can only depict through experience the narrowing of the coronary arteries. This method however was not precise and in many cases it was easy to miss the plaque. IVUS on the other hand is an imaging method that one can rely on and is therefore an improvement to the ‘classic’ catheter.

This development therefore enables the early detection of Atherosclerosis plaques, possibly preventing the symptoms that arise mostly in major events of a heart attack or a stroke, when it is sometimes too late to make a difference in the person’s health. This development has today been clinically tested and proven as a safe and approved treatment. Thanks to the mere vision of the plaques, this development can therefore save lives, demonstrating in my opinion, how amazing and vital science can be.

Figure 4: artery intravascular ultrasound

Of the four developments I have mentioned above, only IVUS has been set in motion, for clinically approved, it has been spread across Europe.
The main common advantages of all these treatments are that they are minimally invasive thanks to the size of the nanoparticles. The patient therefore has no painful permanent scar or even dangers of infection, for the smaller the area of penetrating the skin, the less risk one has of an infection. The treatments are also rapid, the first method being potentially faster than the nanoburrs. However neither the surgeon nor the patient will have to consume a large amount of their time, given that the particles detect the arterial wall damage autonomously. Another positive factor to take into account is the use of natural science used in the research projects, the first and the third theories use micelles which are lipid based and organic; the nanoburrs also use polymer chains.

**Conclusion:**

The future of nanotechnology is an overwhelming prospect, with so many possibilities that look promising. However despite the challenges technology has overcome, some techniques could possibly take years to accomplish and we cannot predict the challenges that might lie ahead: toxicity, human’s different reactions to the treatments…

Already, research has been significantly affected by the ethical debate surrounding nanotechnology in medicine. Some examples of questions to be dealt with are the following: What are the moral boundaries for using human materials and animal models (mice and rats) for this research? What will determine social acceptance of nanotechnological applications in medicine? Are there any moral boundaries of introducing nanotechnology into our world? How should a balanced legal regulation of research and application of nanotechnology look like? As a result to this, any clinical trial put in place first has to endure administrative delays as well as public debates on its ethical issues.

Cost is also an issue and important consideration, for no matter how many lives the developments could potentially save, the cost of research and initial treatment is very high and therefore is one that most people are unwilling or unable to pay. As the technology progresses, we can possibly expect prices to lower, however this seems a fairly distant prospect for the time being. The expense of the research and application of this technology will undoubtedly slow down the progress being made, although if all else fails, work in one area can always lead to developments of another.

Although both molecular imaging and targeted therapeutics are attractive subjects for clinical evaluation, the ultimate role of these technical advances must be established in clinical trials. To date, no solid proof of efficacy has been provided with respect to altering courses of therapy or patient outcomes. The choice of imaging modalities also is broad and remains to be worked out in practice, and it will depend on cost, availability, and the specific application. As is the case for any novel pharmacological agent undergoing clinical trials, the use of
nanoparticles also will require thorough evaluation for toxicity. However, in the era of molecular medicine where early diagnosis and personalized therapeutics may reduce risk and save lives, the promise of these novel technologies and approaches represents a new avenue to disease control that appears to me as extraordinarily compelling.

At this point in time I imagine that the possibility of permanently preventing the build of plaques appears as very slim, for although these developments are able to eliminate detected plaques, it cannot yet permanently prevent damage made to the artery walls and therefore, no matter how many plaques are removed or reduced and how many arteries are widened, there is still the possibility that more will accumulate again. ‘Nanolipoblockers’ on the other hand do show potential, despite the fact that this device only demonstrates to be 75% effective. I feel though that in the future, nanotechnology will enable the visual early detection of artherosclerosis as well as potentially life changing treatment, no matter the method. This would be a major leap in medicine and therefore, thanks to nanotechnology; I have faith and conviction that a medical revolution will take place.
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