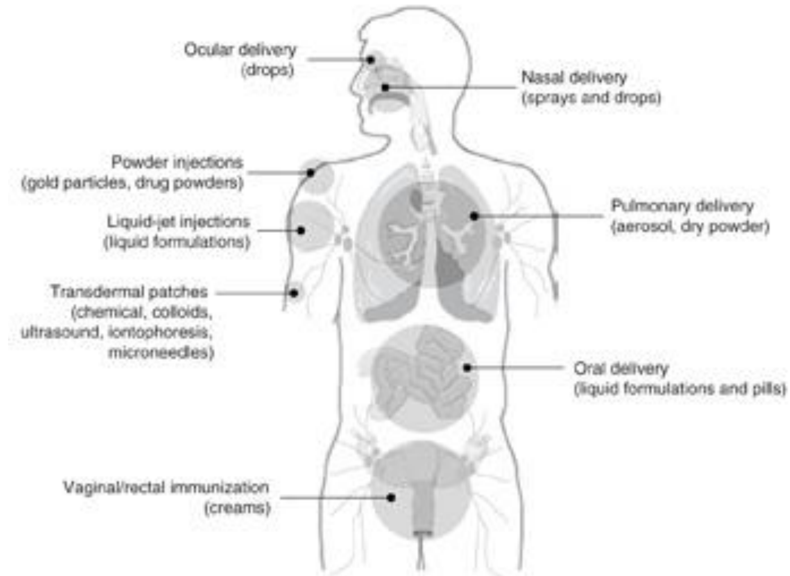
DRUG DELIVERY AND ETHICAL ISSUES INVOLVED WITHIN NANOMEDICINE



BY

DOUGLAS DONNACHIE

PASS

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ABSTRACT

Research has been undertaken to understand an area of current exploration which will surely improve our society in the future. This paper will explore the origin of nanotechnology and the promise of effective and precise drug delivery methods. This paper will also address and discuss the many ethical issues of such methods and perhaps the problems faced by such new technological advances. Moreover, the paper will seek to find the true potential within the health service and society in aiding people overcome problems which are currently an issue. Finally, I shall sum up my findings and give my opinion.

INTRODUCTION

Nanotechnology is at the forefront of our advancing era and brings excitement to many areas, such as chemistry, communications, computing, aerospace, consumer goods and plenty more. For example, computers and machines will inevitably become smaller and products such as self-cleaning windows will become readily available, since the nanoparticles make materials ultra smooth resulting in non-stick surfaces. However, my research interest lies in the applications of 'nano' within medicine.

The word Nanomedicine derives its name from the Greek word *nanos*, which means "little old man" or "dwarf" and is a billionth part (about the size of six carbon atoms in a row). To put in context, the diameter of a human hair is 200 000nm and a 'nano' sized particle is a hundred times smaller than an erythrocyte (red blood cell). At the moment, medicine is the science of diagnosing, treating, or preventing disease and other damage to the body or mind working at a cellular level. In the future, as suggested by the definition of Nanomedicine in *The American Heritage Science Dictionary* medicine may manipulate and change the structure at a molecular level.

The origin [1] of the concept or proposal of 'Nanomedicine', which had sales reaching 6.8 billion dollars in 2004 and is expected to have a significant impact on the economy in the future, has only recently evolved in the last decade. It is a successor of a speech given by physicist Richard Feynman on 'nanotechnology' at an American Physical Society meeting at California Institute of Technology on December 29, 1959. He named this idea *"There's Plenty of Room at the Bottom"* in the view of delving into, back then, the realms of a 'smaller world' and being able to manipulate individual atoms and molecules. Then, by 1986 Dr. K. Eric Drexler, born April 1955, proposed and promoted the technological significance of the nano-scale phenomena. Most significantly in '*Engines of Creation: The Coming Era of Nanotechnology*' he foresaw the capacity and use of 'medicinal robots' which would help clear the capillaries in man to industrial use such as environmental scrubbers that would clear pollutants from the air.

In the 1990's, demonstrated by the work of Richard E. Smalley (1996), 'Buckminsterfullerene C60', also known as the 'buckyball', was discovered. Its size and ability to conduct electricity really well due to the chemical properties of each carbon atom having a free electron, proves useful in nanotechnology for computers and their semiconductors. Furthermore, as manifested by the website http://www.chm.bris.ac.uk/webprojects2002/knowles/, C60 has several other properties which may prove useful in the future of medicine. For instance, C60 has the capacity to absorb light and then release it at a different frequency, as heat or transfer the energy within it, to another molecule. In addition, it's able to convert oxygen into highly toxic oxygen which alongside its other properties could conceivably treat cancer by attacking it within the localised area.

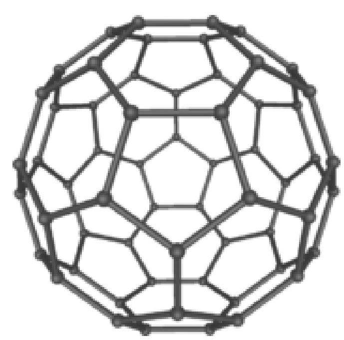

Figure 1: C60

Around the same time, [2] carbon nanotubes were believed to have been discovered by Sumio Iijima of NEC in 1991. Carbon nanotubes are hollow, nanometer sized tubes composed of carbon graphite and display exceptional strength, electrical properties, as well as efficient thermal conductivity.

Consequently, [3] nanotubes are currently being used in tissue engineering since the carbon nanotubes can act as scaffolding for bone growth. Likewise, in the Kanzius cancer therapy, single-walled carbon nanotubes are inserted around cancerous cells which are then excited by radio waves, which results in the nanotube heating up and killing the surrounding cells. The theory behind the actual treatment is fairly simple, (http://www.kanziuscancerresearch.org/about/). A cancer patient is injected with gold nanoparticles with each nanoparticle having an antibody attached to it. It then takes about 45 seconds for the nanoparticles to completely circulate around the body. The nanoparticles are delivered by blood vessels into a malignant tumor. Each antibody attaches itself to a molecule on the surface of the cancer cell, in a similar manner to the lock and key theory, and this results in the nanoparticles being drawn into the tumorous cells. The patient is then exposed to radio waves which are able to penetrate the body and strike the nanoparticles. This causes the nanoparticles to heat the cancer cells and fortunately this results in killing the cancer. Preliminary findings show that 100% of cancer cells are destroyed and that there is no damage to the surrounding healthy tissue. With these positive results, we may, in the future, see and hear more of this type of life changing procedure and hopefully prevent the 7.6 million (published by the American Cancer Society) people who are dying of cancer each year.

Nanotechnology has the capacity to influence all aspects of society – including medicine. The use of nanomedicine, in the future, could include advanced drug delivery systems, new therapies, medical diagnostics and be used in 'in-vivo' imaging. In addition, further down the line, the speculative field of molecular nanotechnology believes that cell repair machines could revolutionize medicine and the treatment of patients in a radically new way. This revolution in treatment is all based on the sheer size of the 'nano' ('dwarf' – a billionth part) and scientists having the understanding and vision to create life saving products and uses in treatment. The relative size of a nano-particle compared to that of a cell will revolutionise present day methods of treating and diagnosing a patient and that makes it important and relevant to medicines' future.

DISCUSSION

Traditionally, drug delivery has been administered [4] by non-invasive peroral (through the mouth), topical (skin), transmucosal (nasal, vaginal, ocular and rectal) and inhalation routes. However, some may have to be delivered by a needle via an injection due to the medication being susceptible to enzymatic degradation or it cannot be absorbed into the systemic circulation efficiently. As a result, these methods are susceptible to reduced bioavailability since more often than not they're not focused on the target of need – currently it's believed that more than $65 billion are wasted each year due to poor bioavailability. The definition of bioavailability from *Merriam-Webster's Medical Dictionary, 2007* states that it is 'the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity.' Therefore, this leaves huge scope for improvement in both having a more effective application and targeting of the medicine with the added bonus of reducing future costs.

Subsequently, we turn to nanoscale particles capacity to maximise the delivery of drugs by having cell targeting precision. Methods such as the Kanzius cancer therapy could be used and become more prevalent in society by copying nature and its methods. For example, antibodies within the body work by attaching to antigens on the surface of cells and pathogens. This works as the antibody has a complementary specific variable region to the antigen on the cells surface. Thus, we can mimic this and use it to our advantage of creating specific antibodies and attaching them to nanoparticles so they're able to adhere to the cell surface of a cancer cell or an area of need. Accordingly, the nanoparticle can then release the medication into the cell precisely where it's needed. An additional advantage of this over traditional drug delivery is that the regulated drug release can eliminate the problem and minimise damage to other tissues and other localities.

Moreover, due to the size of nanoparticles it would enable them to travel anywhere within the body, including through cell membranes and into cell cytoplasm where the drug would be able to obtain the greatest results. Conjointly, the nanoparticle could be lipid based which would enable easy passage through the phospholipid bilayer (plasma membrane) of cells thanks to the membranes lipid nature. Currently, drugs are relative large particles (comparing to molecular level) and are occasionally flushed from the body resulting in a patient needing to use high doses. Therefore, the creation of nanoparticle drug delivery systems would be hugely beneficial in reducing dosage as it would target the site with minimal wastage.

Triggered response is another way for drug molecules to be used more accurately and efficiently. Drugs are placed in the body and only activate on encountering a particular signal. For example, the drug wouldn't be released until it had reached the target area and it would know that it had arrived at its destination due to the chemical signals released by the target cell and the antigens on its surface, thus reducing the effect on healthy tissues which were once affected. This would result in the drugs having fewer side effects on patients, earlier discharges from hospital and fewer complications which would all dramatic cost benefit for the NHS, if 'nano' were to be incorporated within drug delivery systems.

Continuing, if drug delivery does happen to be successful in using nanoparticles, it could be applied to diabetes (although only a theory). It's estimated that 285 million people [5], correlating to 6.4% of adults' population, live with diabetes (2010). In addition, by 2030 it's predicted that 438 million people will have diabetes – 7.8% of the adult population. Unfortunately, there are also major side effects with diabetes. Apart from having to watch your diet and blood glucose levels, a diabetic is more likely to be prone to infection, depression, kidney failure, blindness and other problems such as hearing loss and loss of bone density. As a result, there has been a lot of research into creating

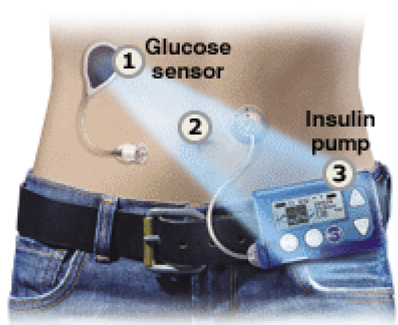

Figure 2: Artificial Pancreas concept

an ‘artificial pancreas’. This would effectively monitor the patients’ blood glucose level and transmit this data to a computer (number 2: in figure 2) which would automatically calculate the correct insulin dose which the insulin pump should deliver. This insulin would then be swiftly injected straight into the blood stream to aid the cells in absorbing the glucose, for the cells to either store it as glycogen or to produce energy immediately.

Another possible future way to help restore body glucose levels back to normal would be through the use of an exceptionally small silicon box, resembling a computer chip, with nanopore sized needles that are large enough for the hormone insulin to be artificially injected into the blood stream. The incredibly small size of this silicon box would make it barely noticeable, especially if implanted under the skin of a diabetic patient. In theory it wouldn’t be prone to infections since pathogens and microorganisms being too large shouldn’t be able to pass through the nanopores. Although this is only a theory, the benefits are clear. For example, overcoming issues such as reduced risk of infection and the ability for the patient to have freedom and live a relatively normal life. The insulin pump would work on demand, when necessary, and one could effectively carry out normal activities such as eating several meals a day and exercising without worry, since the pump would act as a normal pancreas (as it would in a person not affected by diabetes). On the other hand, this would most probably be more expensive than syringes which are currently used to provide insulin artificially and could be prone to technologic malfunctions. Additionally, it could lead to the collection of an enormous amount of individual cellular level data. This could be deemed to be a positive benefit for society and the individual. Conversely, this confidential and sensitive data could be misused by the media or other commercial organisation such as insurance companies against the individual unless rules are put in place.

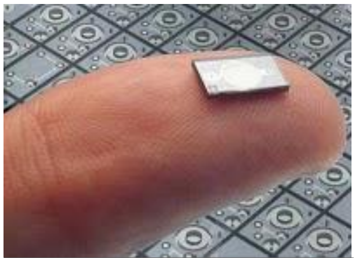

Figure 3: Artificial Pancreas using nanopores for injection of insulin

Ethical Issues

Unfortunately, there are numerous ethical issues with the application of nanotechnology in medicine. Firstly, the toxicity and long term effects on the body because of their size haven’t been confirmed safe yet. It will have to be rigorously tested to pass the ethical standards required to maintain respect and safety for human anatomy. Consequently, it will be necessary to find out whether the application of nanoparticles in medicine is harmful to human health and this will require intensive testing on animals such as rats and mice, which will probably invoke ethical questioning over animal welfare and rights. Campaigners feel strongly against the use of animals for testing due to the issues of inflicting pain on animals that haven’t the ability to express themselves (in a manner towards humans) and reject their participation in testing or relay their emotional and physical state of wellbeing. Correspondingly, experimenting on animals is only acceptable if results cannot be obtained by any other method and suffering is minimised (testing is humane) in all experiments and the human benefits gained outweigh the suffering of the animals. However, this testing could be beneficial to the human race as it would enable the advancement of nanoparticles use within medicine and in the future possibly save the lives of many people suffering from cancer and other life-threatening diseases.

Currently, there have been only two studies published with finding about nanoparticles on animal health. A study at the University of Rochester found that when rats breathed in nanoparticles, the particles settled in the brain and lungs, which led to significant increases in biomarkers for inflammation and stress response. The second study, in China, indicated that nanoparticles induce skin aging through oxidative stress in hairless mice. Although, these cases indicate that the application of nanoparticles may give side effects, the capacity for the advancement in the usage of nanoparticles in medicine is plain for all to see and should be continued, despite the adverse effects on these test animals. This is evident from the theory of using nanoparticles in drug delivery and gaining maximum efficiency from it.

In addition to the animal testing issues there are also religious issues. Some might say one shouldn't interfere with God's creation if nanoparticles were to be used in drug delivery in the future. It could be deemed as 'playing God' and interfering with nature. However, arguably it could also be deemed as helping 'thy neighbour' and looking after the well-being of God's creation since it will allow humans to live a more healthy life. Whichever view you take on this matter, the benefits have the capacity to improve the human species.

Finally, the economic issues are that the investment in nanotechnology is huge. Last year, 2010 (predicted in 2007), [6] it was forecasted that the entire nanotechnology impact was roughly £900 billion increasing from £450 billion in 2008. This investment can only increase. In our current economic climate where government spending cuts are occurring left, right and centre it seems difficult to justify such expense, let alone imagine how and where it will be funded from in order to advance research. Despite this, some would argue that it's an area which is worth the investment since it will hopefully provide a better future, and could generate large incomes and profits for the companies and governments involved. On the other hand, some may argue that it is a waste of money, time and expertise as it's an unproven technology with uncertain and possibly dangerous outcomes. For example; military research and use could bring a new generation of weapons and germ/disease warfare that could have disastrous consequences for health and the environment. In medicine there may be a quantum leap in the treatment of disease and the patient or it could all turn out to be a mirage. We won't know for a number of years, however, the prospect of nanoparticle drugs could be the future of medicine.

CONCLUSION

In conclusion, I firmly believe that nanotechnology and the uses of 'nano' within medicine would appear to promise an exciting and bright future. Conceivably, it could enable people to experience a fuller life without sickness, disease and aging. It offers a range of possibilities such as abstract concepts of 'nanobots' that could accomplish tasks such as the diagnosis and treatment of disease. At the moment, this idea may seem preposterous and utterly ridiculous but many years ago, in the 1700s, if you had said that one day man would be able to go to the moon and walk effortlessly on its surface, people would have thought you were deluded and had '*lost your marbles.*' Since then, there have been six manned landings (between 1969 and 1972) and numerous unmanned landings. If we've managed to accomplish this in such a short period of time, what's to say we can't accomplish more with nanomedicine and its future applications. Another, reason why having 'nanobots' may not seem to be so absurd or ridiculous is illustrated by 'Ken Olson', president chairman and founder of Digital Equipment Corp, who stated in 1977 "There is no reason anyone would want a computer in their home." That does not seem so absurd today and illustrates mans' ability to embrace new technology!

Thus, today's steps are a step closer to a new generation of impressive technology with advanced artificial intelligence beyond belief. Incorporating nanoparticles within drug delivery systems will positively make treatments more effective and prevent unnecessary time, money and expertise wasted each year due to drugs being lost and having poor bioavailability. However, the fear of nanoparticles being too toxic to human health leaves us with a dilemma and extensive research will be required into the safety of exposing these 'dwarf' particles to the human body. Although, this may be overcome by attaching carbohydrates and lipid structures to the nanoparticles 'shell' allowing it to overcome rejection by the body and minimising any toxicity effects by only allowing the release of drugs once in contact with the area of concern (a tumour for example). Despite this, in theory, it should be a more successful delivery system allowing targeting of the drugs and minimising the effects on surrounding healthy tissue(s) and subsequent side effects.

The thought of being able to treat cancer effectively by killing the tumour is a wonderful goal instead of present day invasive and toxic treatments such as surgery, chemotherapy and radiotherapy. However, this is only a dream and perhaps we should be spending our time and money on the large cancers and other diseases that we cannot treat at the moment. Investment in earlier detection could save many more lives by spotting cancers before they become too large and untreatable. Maybe we should be aiming our research and investment on improving present day techniques rather than spending billions on unproven technology. Although, having said that, Kanzius' cancer therapy using nanoparticles reveals that 100% of the cancer cells are destroyed without additional damage to surrounding healthy tissue. This would promote the argument to continue with the research into the use of nanoparticle technology in medicine. In addition, the idea of an artificial pancreas for diabetic patients would be revolutionary bringing positive benefits for the patient and the health service. Creating such a system where it would monitor and deliver sufficient insulin, when specified, would enable the diabetic to have a better quality of life with a more 'normal' lifestyle.

Finally, it seems that nanotechnology is now at the forefront of improving medicine and medicinal application. Fittingly, it seems right to advance in this topical area yet it's extremely important to minimise the ethical issues brought about by research into nanoparticles and its uses in medicine. The major dilemmas that I foresee are that nanoparticles could prove to be toxic for human health and that the technology could fall into the wrong hands to produce horrific diseases or nanowarfare. However, the future benefits of effective treatment with precision delivered drugs are a tantalising prospect and one that we should be embracing.

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