

FUTURE DEVELOPMENTS
IN THE USE OF NANOTECHNOLOGY
FOR DRUG DELIVERY

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Abstract

Nanotechnology is the ability to build a material or functioning system from atoms, this is still a very new and untested field, but it has the potential to totally change medicine, revolutionising the way in which we diagnose and treat patients. In this paper we explore the possible future use of nanotechnology as an intelligent drug vector that will administer the correct dosage of any drug over a period of several months. We look at the possible developments of this technology into the administration of a female contraceptive drug and for patients without the ability to administer drugs themselves. Our findings were that the use of a nanochip to deliver drugs in these situations could be a successful system, although there are still many issues that must be overcome before it can be utilized in modern medicine.

Introduction

The human body observed at a microscopic level is composed of approximately ten trillion cells, divided into about two hundred different types and specialisations. Each body system can be analysed to a smaller and more minute level, until eventually it all comes down to the interactions of cells, their components and the proteins they produce. This is why nanotechnology has the potential to revolutionise medicine. When something goes wrong with the body, whether it be cancer cells dividing exponentially or nerve cell death in the brain, nanotechnology has the ability to be specific to its target, interacting with cells to diagnose, and treat at an atomic level the source of the problem.

Nanotechnology is the ability to manipulate matter atom by atom to form functioning systems. [1] This concept was first envisioned by Richard Feynman in 1959, he envisaged the use of precise tools to build and operate a proportionally smaller set of tools and so on, until one could build molecules out of atoms. He suggested that because nanoparticles surface area to volume ratio being so high and other quantum size effects, gravity would be less significant and van der Waal forces would have a much stronger affect upon them.

It is now known that nanoparticles display many other unusual properties, which must be considered when using them in medicine, exploiting beneficial properties to our advantage whilst controlling those that may inhibit their potential. [2] Nanoparticles high surface area to volume ratio allows many functional groups to be attached to the nanoparticles. This is useful for future applications of this technology, as it causes the particles to interact as that functional group would in the body, allowing them to be specific and home in on certain cell types and bind to active sites.

Nanotoxicology is the study of nanoparticle toxicity; if you compare a nanoparticle to its regular size form, we find that they are more reactive and biological active. Properties of nanomaterials that affect their toxicity are: chemical composition, shape, surface structure, surface area, charge, solubility, aggregation and functional groups. With so many variables controlling the toxicity of the nanoparticles you cannot generalise health risk of exposure to a single variable; so every nanomaterial must be individually assessed. As future developments into nanoparticles, nanobots and nano forms of drugs draws closer to application in medicine we must know exactly how they will react inside the body to ensure that they are safe before we use them in the treatment of people.

The size of nanoparticles enables them to quickly and easily spread throughout the body reaching tissues they may damage. They can pass through biological membranes

accessing cells, tissues and organs that larger particles could not penetrate: such as the brain, the nervous system, liver, kidneys, spleen, heart and bone marrow. As well as being toxic to human tissue, nanoparticles can be taken up by the mitochondria and nucleus of cells, inducing major structural damage, even mutation of the DNA and cell death. Nanoparticles have been reported to cause oxidative stress, immune responses, allergy and inflammation; damaging proteins, membrane and DNA. The nanoparticles size causes immediate absorption on to the surfaces of some macromolecules, affecting regulatory mechanisms of enzymes and other proteins.

A lot of research needs to be completed: to identify nanoparticles that are non-toxic such as fullerenes C60, to find ways of controlling their movement stopping them from spreading across the body damaging tissue, and to find a safe way of excreting them from the body. [3] These issues and many more need to be resolved to make sure nanotechnology is safe for the future; but currently exciting research is exploring how to use nanobots to diagnose, prevent and treat a number of illnesses where previously there were no visible solutions.

An example of this is the use of nano particles in imaging. Nanoparticles with size tuneable light emission or “quantum dots” as they are known, home in on a specific cell type, such as a cancerous cell. Then when an MRI image is taken the quantum dots are concentrated on the subject. The quantum dots are much brighter than organic dyes, so provide a superior contrast medium resulting in higher quality images. Thus allowing doctors to make better diagnosis and enabling a more accurate view of the location of a tumour so it can be more effectively removed. The problem with this procedure is that the quantum dots are often made from quite toxic elements such as nanoparticles of cadmium selenide, for use on humans a non-harmful substitute will have to be found.

A good example of how ingenuity in the use of nanotechnology has created a simple but effective use of quantum dots is in tumour removal. [4] The quantum dots home in on and seep into cancerous tumour cells, then when an ultra violet light is directed upon the area the tumour glows, allowing the surgeon to more accurately remove the tumour. Flesh welding is a new technique in surgery, where gold coated nanoshells are dabbled along the seam of the two pieces of flesh, after which an infra red laser beam is traced along the seam activating the nanoparticles. In tests this technique has fused two pieces of chicken meat into one single piece. In a heart transplant flesh welding could be used to quickly re-stitch the blood vessels to minimise blood leaks, significantly reducing the risks of the operation.

Kanzius RF therapy is a cancer treatment being researched to replace radiation and chemotherapy. [5] In this treatment gold nanoparticles home in on and attach to cancer cells, then when radio waves are passed through the body it heats up the metal and cooks the cancerous cells, but not any of the surrounding healthy tissue. This non invasive cancer treatment has no identified side effects, and is reported to be coming close to human trials.

In the future scientists aim to create multifunctional nanobots that have artificial intelligence with the ability to repair cells or detect damaged cells and infections. This technology is still in very early research and development; but more basic molecular

machines have already been tested, which mimic the functions of macroscopic processes.

There are many diverse and creative uses of nanotechnology in medicine currently being researched, showing that with such a new and untested technology doctors are having to think outside the box to see its applications. In this paper we aim to present our application of nanotechnology: an intelligent vector for the delivery of drugs as a viable future for medicine. There is currently research in progress into the use of nanoparticles, such as buckminsterfullerenes to safely transport an encapsulated drug directly to the exact area of the body the drug needs to be delivered. However, in this paper we aim to take this idea further by using the principle of molecular machines to make this vector intelligent and self administering.

Discussion

The use of nanotechnology in the future as a means of drug delivery to patients is an exciting breakthrough in medicine. This is when the nanoparticles are engineered to deliver drugs, heat or any other substances to the required cells and indeed the idea of nanotechnology also creates new opportunities for implantable drug systems. [6]

‘Pharmacy on a chip’ is one of the most exciting parts to the drug delivery system; it is a chip implanted into the body which releases drugs at set intervals. [7] [12]

Robert Langer was part of a group of scientists at the Massachusetts Institute of Technology who created a microchip that holds several doses of drugs. These can be released at specific intervals and can last up to several months depending on the quantity of drugs. The chip itself is about as long and as wide as a fingernail and at the nanoscale level slivers of silicon are drilled and wells are created which are filled with drugs. [8] The reservoir wells are covered by either a gold or polymer membrane which can be programmed to release and let the substance out. [9] Langer’s initial chip prototype had about 36 drug reservoirs which could be filled with the specific dosage of different drugs and it was sealed with a polymer cap; as the cap degrades the calculated amount of the drugs required is released into the bloodstream.

Langer said, “In medicine, delivery is critical, this is one feasible nano-approach to putting the right medicine exactly on target”, this is where the chip can be programmed to release the drugs at the precisely right location to create maximum effect. [10] A future area that could be considered using this system would be a chip with a statin drug located in the liver to keep cholesterol levels low for patients with a risk of coronary heart disease.

He also commented in 2003 that it is “the first completely degradable system” for drug delivery which doesn’t require a power source or any outside stimulus to release the drugs. [8]

The major advantage is that it can be taken once and last for a specific period of time of some length; this means the patient does not have to worry about taking any tablets or injections on a daily basis.

A similar design is one of a nanostructured material called BioSilicon by pSividia and has nanosized pockets. The drugs are put into these pockets and covered over by a layer of silicon; the silicon dissolves and a minute amount of the drug inside is released into the body. The amount of the reservoirs opened can be controlled so the right dosage can be given as well as the time it takes for the silicon to dissolve. [11]

This means it can hold all different types of medicine, vary the doses and release the drugs at certain time intervals. The major difference between this and the pharmacy on a chip is that it requires a power source and this means it will have to be regulated and checked for any malfunctions. Another problem with this design is that silicon does not break down completely in the body and eventually actually has to be removed.

With this technology the possibilities it could be used for are limitless but two areas it could have a major impact are:

1. Female contraception
2. Patients who have difficulty taking their medication

Pharmacy on a chip could be used as an alternative to current contraception methods as an easier way to prevent pregnancy. The present pharmacology options for contraception include:

- The oral contraceptive pill (otherwise known as the birth control pill) includes a combination of oestrogen and progesterone that tricks the body into thinking it is pregnant which then results in no ovulation and consequently no egg cell is released. Disadvantages women find with this method is that it has to be taken daily and they can forget to take it. [16]
- The intrauterine device (IUCD) is another form of birth control and is placed in the uterus; there are two types of this device. The copper IUD works by affecting the mobility of sperm cells which prevents them reaching the egg cell. This stops fertilisation taking place. The other type is hormonal IUS and it prevents menstruation taking place so no egg is released. The device normally lasts 5 years and is usually taken by mothers of families who no longer want any more children. The advantage of this method are it is a reliable form of birth control with little reported failure rates but the disadvantage is the procedure is very intrusive for the woman and is not usually recommended for females who would like to have a family in the future. [17]
- The depo-provera injection is another alternative method; it lasts about 12 weeks and prevents fertilisation by preventing ovulation through the hormone progesterone. It also inhibits sperm penetration by changing the thickness of the cervical mucus. The disadvantage of this is that it is not suitable for women with needle phobias and also a major side effect is that it can cause thinning to the bones, especially in younger females. [18]
- The Implanon is a rod that is implanted into the arm just under the skin and lasts 3 years and it releases progesterone into the blood stream throughout that time and prevents ovulation. The Guardian reported in January 2011 that nearly 600 women who used the Implanon device had become pregnant. In addition many had complaints about scarring, device failure, incorrect fitting and other problems. Many women also complained of being able 'to feel it in their arm'. [13] [14] [15]

The pharmacy on a chip for contraception could solve some of these problems and be a more effective form of contraception as its implanting into the body removes any human error with regard to remembering to take the contraceptive; it is far less intrusive than some other methods and it has the possibility of removing the side

effects that can cause immediate or longer term health issues. It would release the drugs oestrogen and progesterone over a specific period of time to stop the release of eggs from the ovaries and thus preventing pregnancy.

The second major use of this technology could be to ensure those patients who would normally have difficulty in taking medication would be able to receive their correct dosage automatically. There are a myriad of health related issues that can make the administration of drugs a difficult and complex issue for some patients. Disabling conditions such as Blindness, Multiple Sclerosis or Motor Neurone Disease can inhibit the safe self administration of medicines. The elderly may have problems with dosages due to increasingly poor dexterity or dementia and indeed patients with learning disabilities or other conditions that can prohibit normal functioning can also have difficulties taking medication.

The implanting of a pharmacy on a chip device in patients with the conditions as described above could ensure that the correct dosages and medication could be applied without the hindrances that can result from their conditions. This could make the daily routines of such patients very much easier and indeed even be cost saving as less nursing time would be needed to administer the medicines at prescribed times.

Whilst there are tremendous advantages in developing this nanotechnology for the two areas described above there are also some major issues which could hamper or indeed prevent these developments.

Firstly there is the major issue of cost. Being a new and untried technology there would need to be a large investment of finance into the practical development of the nano chips, in testing their effectiveness and running pilot programmes. Furthermore the manufacturing process and the cost of some of the materials involved in this process have the potential to be very high, particularly when the chips would need to be bespoke, that is designed specifically for each patient. Whether the high start up costs when compared to the improvements in the health of patients could be justified would be firstly an economic decision taken by the developer as to whether they could recoup their costs and make a profit, particularly at a time of economic restraint and cuts to health provision in many countries, as well as an ethical decision taken by Health authorities as to whether the gains for the health of the patients justifies the financial costs.

The second issue that would be of concern with these developments would be ensuring patient safety as the chips once implanted would be difficult to remove. If, for example, the nano-chip was replacing 4 different drug doses and the patient began to have an adverse reaction to one of them, it would be difficult to ascertain which one was causing the ill effects. It would not simply be the replacement of a particular drug dose but would need the removal of the whole chip if that was possible. If it proved too difficult to remove the chip then the side effects could be extremely dangerous to the health of the patient. To deal with this problem; before the pharmacy on a chip was implanted into the body trials of each of the drugs would be taken first and then it could be transferred to chip form.

When the nanochip is applied to contraception ethical considerations must be made. Contraception is the prevention of the nuclei of the sperm and egg fusing in

fertilisation to form an embryo, which would develop into person. Some people believe that contraception is wrong as it is against their religious beliefs, or because they believe that we do not have the right to deny that potential person the chance to life. Studies have shown that with the introduction of contraception the number of unplanned pregnancies and therefore abortions has increased, this is because no method of contraception is 100% effective. [19] Many people are opposed to abortions as they believe that once the embryo is formed it is effectively a person, so should have the rights of a person, therefore terminating the pregnancy is murder. In this case because evidence shows contraception has led to an increase in abortions, they would argue that contraception is ethically wrong. However in the modern world contraception is here and is unlikely to go in the future. So would it not be better to have a more effective form of contraception with a higher success rate, less unplanned pregnancies and fewer abortions?

Some people have attributed the use of nanotechnology in medicine to be “playing God”, creating materials that do not appear in nature and using them to directly affect the natural systems in our bodies. However, most people agree that nanotechnology is justified if it is used only when medically necessary. The main ethical issue with this use of nanotechnology is whether it is right to create an artificial method to regulate the body. [20] Is it right to make a machine so much a part of you that you are never without it, and it controls something as vital as doses of drugs?

Conclusion

Nanotechnology is soon to become a major part of modern medicine as reflected in the variety of applications currently being developed. Its use in drug delivery could revolutionise the way we take drugs and the effectiveness of the drugs that we take. This is because once the pharmaceutical chip is implanted into the body it will deliver the correct dosage of drugs over a specific period of time. Areas of medicine that will particularly benefit from this are: contraception and patients who have difficulty in taking their medication.

However, there are also major problems with this treatment including the initial cost of producing the chip, which would have to be designed individually to its recipient; and that once implanted into the body it cannot be removed this may cause problems if the patient is allergic to the drug, or if the drug is no longer required. Another major issue is that we do not know yet how nanoparticles will react in our bodies and whether this will be the same for everyone. This technology is so new there is little experimental data about its unintended and adverse affects. We cannot accurately predict how nanoparticles might affect body processes, reactions and tissues. Research needs to be undertaken to ensure that they are safe in both the short term and the long term, as there may be unforeseen future consequences.

Current methods of female contraception such as Implanon, progestogen injectables, the IUCD and the oral contraceptive pill have varying success rates and serious side effects. The use of nanotechnology to administer the oestrogen and progestogen drug into the body means that there is no need to take a daily pill, which if people forget to use results in the main cause of unwanted pregnancies. The chip will be developed to solve this problem without the unwanted side effects of other forms of contraception.

In conclusion we believe that the use of a nanochip, to administer drugs independently over a period of months has the potential to offer the beneficial solution to a number of medical issues. It may be that it is a long time before this system is put into production, but it will be a fundamental part of the revolution of nanotechnology in medicine.

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