NANOMEDICINE: CARRIERS TO HEALTH

BY

STEFFI BERESFORD

PASS WITH MERIT

RESEARCH PAPER

BASED ON

PATHOLOGY LECTURES

AT MEDLINK 2010

Abstract

This paper examines the role of nanotechnology as applied to medicine from the aspect of nanotechnologies as carriers and transporters. The concept of nanotechnology is illustrated and current research of nanotechnology in medicine is discussed. Possible future developments of nanomedicine delivery systems are explored under the criteria of benefit and helpfulness to humans and the surrounding ethical issues are raised. There is recognition that there may be many obstacles to nanomedicine becoming as influential in medicine as proposed and concludes that its introduction should be cautious and led by society.

Introduction

Nanotechnology is set to revolutionise the world and change the world as we know it and probably have a greater influence than the silicon phenomena, medical imaging and computer assisted engineering combined (Herther 2003). It is defined as the development and engineering of useful devices, systems and materials so small that their measurement is lowered to molecular level (Tachung and Wei 2005). This concept of manipulating materials at the molecular and atom level was first presented by the physicist Richard Feynman as long ago as 1959 in his lecture "There's plenty of room at the bottom", in which he concluded "I think this is a development that cannot be avoided" (Freitas 2005). To put this tiny scale into context, the prefix nano means 1 billionth and therefore one nanometre is one billionth of a metre (figure 1). Such microscopic scales are difficult to understand, but to provide some perspective a piece of paper is 100,000 nanometres thick.

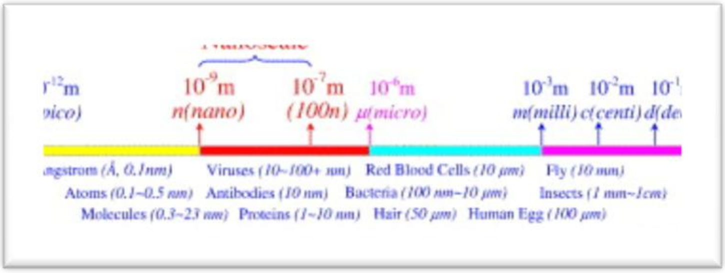

Figure 1

Essentially nanotechnology is the use of atomic and molecular structures as building blocks to create new products. Generally two different approaches are used to construct nano devices, the bottom up and the top down approach (figure 2) (Leary 2010). The first, bottom up method represents an assembly, atom by atom or molecule by molecule as seen in a quantum corral (figure 3), often referred to as nanomanufacturing and is hindered by practicality and speed (Leary 2010). In this process DNA has been used as a construction material (Aslyanbola and Soboyejo (2007).

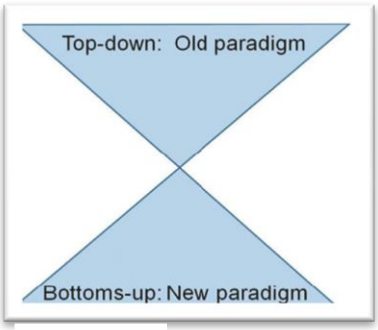

Figure 2

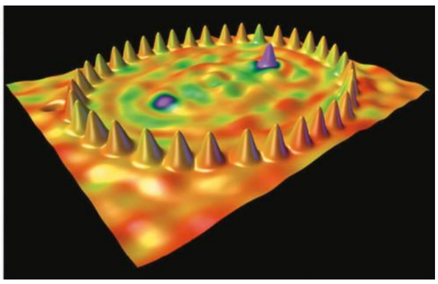
Figure 3

The top down method involves creating smaller devices by using larger ones as a construction tool, usually by moulding or etching. Examples include nanotubes, quantum dots and dendrimers. Leary (2010) has suggested that the bottom up process creates fundamentally different forms of matter and it is not simply an issue of size.

Some of the greatest impact of nanotechnology is happening in the area of medicine and biology, referred to as nanomedicine. In the broad sense it is the application of these nano scale technologies to medicine, mainly for the diagnosis, prevention and treatment of disease, in order to improve the quality of life. Nanomedicine enables the ability to treat, repair and regenerate tissues and organs within individually targeted cells, one cell at a time. The disease is treated and prevented at single cell level using sophisticated nano machines with advanced targeting capabilities, additional feedback control mechanisms and the ability to error check. This approach is in contrast to conventional medicine that reacts to physical symptoms when irreversible damage may have already occurred (Leary 2010).

Nanotechnologies can impact almost every speciality of medicine. Gene therapy has been introduced as a method of treating and preventing defective genes based on the delivery of repaired genes or the replacement of ineffective ones (Verma and Weitzman 2005). The most usual way is to insert a normal gene into the genome to replace the non-functioning gene (Sahoo 2007). Indeed, as reported by Greene (2008) the University of Singapore have developed a nanoparticle that can traffic both DNA and drugs directly to the cells (Figure 4), whilst others have cited gene delivery with the benefit of visualising the delivery through non-invasive, molecular imaging strategies (Liu 2010).

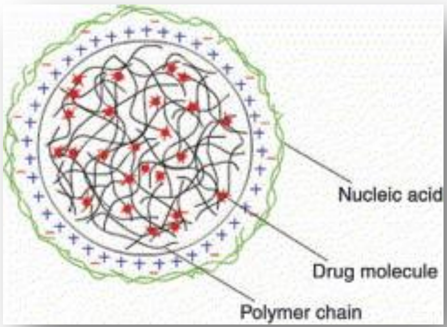

Figure 4

Nanomedicine has proved especially useful for the delivery of drugs. Although today's drugs are molecularly small, there are problems with issues such as solubility, toxicity, maintaining drug concentrations, and the metabolism by for example the acid in the stomach, all which makes the delivery less than optimum and reduces efficacy (Sahoo 2007). Nanoparticles are sufficiently small to enable them to be delivered directly into the cytoplasm having passed through the cell wall, yet programmed to target diseased cells and tissues. The drugs are dispersed throughout the nanoparticles or held in an aqueous or oily cavity surrounded by a single membrane, called a nanocapsule (Aslyanbola and Soboyejo 2008). These multifunctional nanomedicines are particularly useful in the detection and destruction of cancer cells, with targeted drug delivery using magnetic fields to improve the delivery of the drugs (Gould 2008).

Nanotechnologies have been found to have a role through improved imaging techniques. This type of visualisation has been greatly helped by the development of fluorescent probes called quantum dots. These are nanoparticles or nanocrystals that have unique photographic properties not available to common organic dyes that enable the analysis of both single cells and whole organs or tumour masses. It is hopeful that these nanotechnologies in imaging will become more useful by detecting cancer makers present before the cancer has developed (Kawasaki 2005).

Another area of development for nanotechnologies in medicine is patient monitoring devices. These products are able to monitor levels such as glucose, as they circulate in the blood and release insulin as required, avoiding the need for individual monitoring and injections. Similarly, there are suggestions of devices to detect seizure activity and release relevant drugs to prevent an attack (Staggers 2008). Finally, researchers are exploring the development of nanomaterial for regeneration, such as skin cartilage and bone for human use, by either working with the human tissue or perhaps even replacing it totally (Staggers 2008).

This is by no means a comprehensive examination of all the potential capabilities of nanotechnologies to medicine, merely an insight relevant to this paper. The literature is littered with new developments and further hopes of progress. If this is the case the future is revolutionary, but there is a cautionary note since nanomedicine presents many unanswered questions and its progress is dependent as much on society as it is on science.

Discussion

The intention of nanomedicine is to conquer human disease, ill health and aging, but however incredible, it is still in its infancy. Nevertheless, as society debates the latest developments and looks back at past controversies of science and nature, such as in vitro-fertilisation, it has been suggested that nanotechnology is perhaps already embedded into the "social fabric of our life and time" (Murphy 2011). More immediate developments are expected to be in the areas of diagnostics, drug delivery systems and patient treatment (Sahoo 2007), to meet the demands of the aging population, high expectations for a better quality of life and government pressure for efficient and affordable healthcare systems (Nanotechnology 2011). It is these helpful developments of nanomedicine as carriers to health that are highlighted, without ignoring the ethical questions that need to be addressed if nanotechnology is to be a service to human life and improve the way we live.

The potential of drug delivery to human cells using the molecular approach has already been identified. However, there is a case to further develop existing capabilities of nanotechnologies by improving methods and efficacy of drugs delivered directly to diseased cells by a process of miniaturisation, automation, speed and reliability of assays. This is especially applicable to those suffering from cancer where nanocancer chemotherapies can attempt to directly target tumour cells by controlling the nanoparticle size to allow diffusion through the 'leaky' tumour cell, but prevent delivery through normal blood vessels into healthy cells and therefore minimising the effects of potent toxic drugs. A more sophisticated approach would be to build on the multi-step procedure of well targeted drug delivery towards a multi-layered and multi-component design where each layer has a specific function (figure 5).

In simple terms, each layer could be stripped away to facilitate multiple combinations of drugs to targeted cells, whilst programmed to respond intelligently to the type of cells encountered with molecular biosensors for feedback and imaging properties that would enable physicians to be informed on the rate of progress. These targeting, diagnostic and therapeutic benefits would be especially useful to those affected by brain tumours and neurological conditions, which often affect children and young people as the unique membrane that protects the brain presents a particular problem. Drug Loaded particles are able to cross this barrier and attack the tumour. Cell and tissue distribution is modified and results in a more selective delivery system to increase drug concentrations and reduce toxic effects. Similarly the problems of drug release in certain environments that presently destroy the drugs, such as the acidic nature of the stomach can be overcome by the design of novel nanoscale polymer capsules resistant to the effects of the acid.

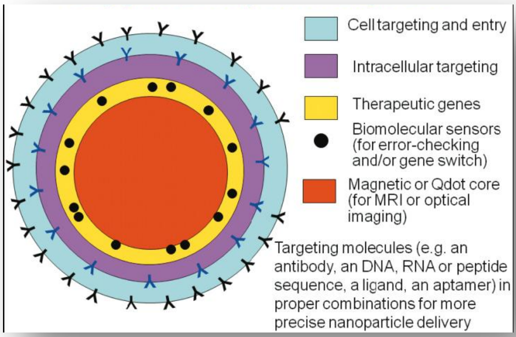

Figure 5

Nanoparticles as carriers have the potential to transport genes around the body to selected targets. A similar multi-layered nanoparticle system structure as seen in figure 5 can be utilised to produce a therapeutic gene manufacturing capability through a series of ordered events at the cell level. The commonest approach is to replace the faulty gene with a normal gene or to repair the existing one that has been damaged in some way. The mechanism works by an upstream promoter sequence that acts as an on/off switch depending on whether there are sufficient gene targets to activate them. The normal gene is inserted anywhere in the genome as a replacement, or repaired through a process of selective reverse mutation to return the gene to its normal function. The application of these techniques are dramatic and exciting as optic nerves for example, could be repaired to restore sight in certain conditions or faulty chromosomes could be replaced to prevent the replication of genetic disorders. Furthermore, reporter genes could be combined with therapeutic genes, such as catalase or peroxidase to enable cells to treat themselves at a cellular level. This capability would demonstrate the feasibility of producing simple gene products in the cells. Indeed, it may even be possible for cells damaged by substances, such as chemotherapy to be returned to normal function or at least to become less dangerous cells by utilising pools of DNA procurers to manufacture therapeutic gene products in the cell, in a way similar to that viruses use to produce viral products.

Remaining with drug therapy, nanomedicine could have a role to play in the control and treatment of HIV, in order to stop the progression towards AIDS. Current treatments have issues with poor solubility and involve daily drug regimes essential over decades, in order to suppress the replication of the virus. The demands of these regimes are liable to poor patient compliance and the risk of viral resistance. As HIV statistics indicate high infection rates, it would be presumptuous to assume that nanotechnologies can cure all and somehow eradicate the disease as quickly as it arrived. In fact it would be futile, as the focus would shift away from the public health and lifestyle message only to perpetuate the disease again. Besides, areas of the highest incidence such as rural Africa are difficult and labour intensive to access. These difficulties could be overcome if nanotechnology can produce a once only drug therapy without the toxic effects which would have the added benefit of being cheaper.

Although the delivery of drugs and genes is perhaps one of the most realistic and useful applications of nanotechnologies, there are potentially further benefits in the early detection and prevention of disease. We have seen how nano scale devices can already be implanted in the body to monitor and then deliver the relevant drug as needed, such as insulin. In future tiny pocket size devices, composed of micro and nanofabricated components could receive information from small circulating implants that have the capability to transport, but also sample mixing, detection and data processing, to continuously monitor health, in preference to data produced at a point in time. These implantable devices with nanobiosensors can be used to monitor chronic conditions such as anaemia, cardiovascular disease and arthritis, or other conditions, such as Parkinson's and Alzheimer's disease to provide information of potential problems, rather than current practices of treatment based on reactions to symptoms. Individuals with these conditions are likely to have a telecommunication facility to transmit diagnostic and disease monitoring process directly to physicians.

A more generalised population use of such devices would be the concept of biological robots which are synthetic microbes designed to produce useful vitamins, hormones and enzymes when an individual has a deficiency, or in more dangerous situations, absorb and metabolise poisons and toxins into harmless substances. Furthermore, women who are affected by poor bone health in their later years could be especially targeted with implants during the teenage years that remain dormant until the time when they recognise that additional calcium and vitamin D are required to maintain bone health and only then release specified amounts on a regular basis to prevent the pain and disabilities of osteoporosis.

These home monitoring devices could easily become as common as a mobile phone today and a 'must have' gadget for the well and healthy, giving an individual a wealth of technical information about the status of their health, such as a constant reading of their blood pressure, levels of electrolytes, or even the sighting of malignant cells through enhanced magnetic resonance imaging. Individuals would have to accept a level of responsibility, such as monitoring the data and making decisions as to how to act. As it is likely that even doctors will fine it difficult to define what is normal and what is abnormal with the availability of such ultrafine levels of sensitivity, ordinary people will be confused and excessively anxious over results that may be insignificant. This raises the ethical questions of what is "health" and when is a person well. Suddenly these terms become indefinable and ordinary people have immediate access to sheets of data on themselves, none of which they fully understand or can possibly be expected to interpret. Surely the human race would turn into a race of neurotics, obsessed about their health surrounded by realms of information that can only lead to questions about confidentiality and privacy, none of which is helpful or a good for individuals.

The potential is there to change the carrying function of the human circulatory system and replace red and the white cells with ones that are programmable and more efficient carriers, through the use for diamond nanorobotics, the strongest substances available. Devised to mimic current red blood cells, small gas sensors are attached to the outside of the cell to let the nanorobot know when oxygen is required and carbon dioxide needs to be excreted. Mechanical white blood cells too, detect a bacterium then transport the pathogen to an ingestion port for destruction. The advances would be advantageous in many conditions, including the need for blood transfusions, premature babies susceptible to infections and respiratory problems, and those with chronic lung disorders, like emphysema. To complicate the issue further, these technologies could enhance those who are healthy, such as the athlete to become a super athlete, or military personnel to see infra red light. Scientists could add and subtract constituents according to the need, for example for high altitude climbing the level of oxygen carrying capacity could be increased, or even adapt the bodies of the military for improved combat, by for instance, a greater capacity artificially generated for faster clotting. However, it raises the ethical question as to whether nanotechnologies should extend life and therefore the line between living and non-living becomes less clear. The ethical concern focuses around whether we are attempting to treat disease or is nanotechnology trying to create "superhumans". These are moral judgements that are less clear in today's society and need to addressed and resolved before the capability to achieve these techniques is reached, and not the other way round. A code of practice that regulates the work scientists undertake encourages scientists to be more transparent about their progress and question its validity within the arena of public opinion (Rainhold 2007), but even then, in such a multi-professional advancement, interpretation of this code can vary across disciplines.

As a result of these advances, nanotechnology could change the system of healthcare as we know it. As efficient carriers of nanotechnology they could avert almost all known lethal conditions including cancer, heart disease, infections and genetic conditions. It is hard to predict how soon these nanotechnologies will become standard practice, but as they do, ways in which individuals access healthcare will alter. Hospitals would change dramatically, as there is no need for numerous investigations, surgery or care. The role of doctors will change to case co-ordinators, working more closely with scientists and other disciplines and the availability of more precise, targeted data will impact on their critical thinking and decision making role. Initially, until the benefits of prevention, mass production and distribution become realised, even the simplest of nano-devices are likely to be expensive and available only to the rich and wealthy. Ways of making these technologies available to all on the grounds of benefit is of great ethical consideration, assuming that society wants this type of medicine. It is suggested that if nanotechnologies do not fit in with the aspirations of society they will be rejected and raise scepticism, just as the GM foods were rejected, yet if there is a perception of benefit, only then do they become acceptable.

However, nanotechnology applied to medicine is not like the latest iPod Nano, since it raises ethical concerns that could have far reaching consequences to the human race and are ultimately not helpful. One such concern is the use of nanomaterials in humans. Currently little is known about them and how their composition reacts with human tissue and the long term effects of these therapies. They consist of a range of compounds that differ in size, shape, and chemistry that make them highly desirable, yet possibly dangerous. Disastrous immune responses are as possible as them entering the nuclei through the cells and interfering with the genetic material. Indeed the lessons from the devastating consequences of thalidomide should not be forgotten. For this reason, carefully designed clinical trials that include assessment inside and outside human tissue are vital with long term reviews, prior to the routine use of nanotherapies and not after they have become accepted treatments. Nevertheless, at some point human trials are necessary and then the question will be raised as to whether it is immoral to use materials that so little is known about.

The fundamental ethical question for nanomedicine, is whether nanotechnology is to make humans better or is it to be used it to make "better humans" by advancing its capabilities beyond what the medical condition presents (Bruce 2006). This is a complex ethical debate and focuses around our perception of human life. Certainly there are some who would argue that human brilliance, able to reverse deformities, restore the senses and prolong life indefinitely, is contrary to religious and cultural beliefs. Humans with these conditions should be accepted and valued for what they are and therefore there should be restraint on what is technically feasible. Alternatively, it could be argued that humans have been given these abilities and therefore it would be negligent not to use them to promote the welfare of the race. The potential danger is that the freedom to use nanotechnologies unlimited would create the opportunity to adapt humans by implanting all the desirable aspects and excluding the not so good, leading to a race that was fashion built.

Furthermore, there are ethical concerns around the impact that nanomedicine will have on society and the environment. They can be considered as a tool for the generation of wealth, as health care costs are reduced and people enjoy eternal good health. However, the inevitable over population and the subsequent effects of overcrowding, poverty and inadequate resources to generate a basic standard of living will become a societal issue. There is also the ethical issue as to whether we should be spending vast sums of money on this type of research when there are thousands of people who still require basic healthcare. The third world has insufficient food, vaccines and everyday medicines for treatable conditions that have been proved to be effective, and at a small cost in comparison to the nano budget that has no guarantees of success.

Conclusion

The paper has highlighted the current nano revolution and speculated about some future developments of nanotechnologies as carriers of health improvements. Particular emphasis has been given to what would be in the interest of human good and the extraordinary potential beyond, in order to illustrate the ethical issues that nanotechnology precipitates.

However, the possibility that the capabilities of nanotechnology have been over inflated cannot be discounted. It is evident that there is a great deal of the use of the word "will", when actually nobody really knows as yet, and can only speculate. This applies equally to the projected benefits, as it does the toxicity and harmful effects. Equally, it is not irrationally to suppose that nanotechnologies in medicine are not as advanced as the smallest nano gadgets and therefore this type of technology in medicine will be a long time coming. Ultimately, it may just gradually become absorbed into our medical spectrum one development at a time, over a protracted period of time, rather than this sudden phenomenal shift that nanotechnology presents today. Besides, time may demonstrate that nanotechnologies are only able to partially meet current predictions and not able to fulfil their promise.

It is suggested that such a revolution should be introduced slowly and sensitively, keeping close to the philosophy that theses technologies, like others before, should do no harm. Thorough and intensive trials can test their safety, whilst society debates about what the human race wants from nanotechnologies and who would benefit most.

References

Aslyanbola, B., Soboyoejo W. (2008) For the Surgeon: An Introduction to Nanotechnology. In Journal of Surgical Education, 65, 1555-161

Bawa, R., Johnson S., Emerging Issues in Nanomedicine and Ethics. In Allhoff, F., Lin P., (Editors) Nanoethics Emerging Debates, Dordrecht, Springer

Bruce, D., (2006) The Question of Ethics. In Nano Today, 1, 6-7

Freitas, R. A., (2005) What is Nanomedicine? Nanomedicine, Nanotechnology, Biology and Medicine, 1, 2-9

Gould, P., (2008) Multi-Tasking Nanoparticles Target Cancer: Nanomedicine. In Nano Today, 3, 9

Greene, M.E., (2008) Nanoparticles Deliver the Goods: Drug Delivery. In Nano Today, 1, 16-17

Herther, N.K., (2003) Nanotechnology, Genomics and Biological Computing. The 21st Century World of Computers www.infotoday.com/online/julo3/index.shtml

Leary, J. F., (2010) Nanotechnology: What is It and Why is Small so Big? In the Canadian Journal of Ophthalmology 45, 449-456. http://pubservices.nrc-cnrc.ca

Liu, G., Swierczewska M., Lee S., Chan X. (2010) Functional Nanoparticles for Molecular Imaging Guided Gene Delivery. In Nano Today, 5, 524-539

Kawasaki E.S., Player A. (2005) Nanotechnology, Nanomedicine, and the Development of New, Effective Therapies for Cancer. In Nanomedicine, Nanotechnology, Biology and Medicine, 1, 101-109

Murphy, P., Munshi D., Kurian A., Lakhtakia A., Bartlett R.V. (2011) Nanotechnology, Society and Environment. In Comprehensive Nanoscience and Technology, 5, 443-476

Nanotechnology, Ethics and Nanomedicine – Analysis of the Issues and Principles to be Faced by the Medical Application of Nanotechnology www.azonano.com/Details.asp?ArticleID=1705

Rainhold, C., (2007) A Code of Ethics for Scientists? In Nano Today, 2, 1

Sahoo S.K., Parveen S., Panda J.J. (2007) The Present and Future of Nanotechnology in Human Health Care. In Nanomedicine, Nanotechnology, Biology and Medicine, 1, 20-31

Staggers N., McCasky T., Brazelton N. And Kennedy R. (2008) Nanotechnology: The Coming Revolution and its Implications for Consumers, Clinicians and Informatics. In Nursing Outlook, 56, 268-274.

Tachung, C., Yih P., Wei C., (2005) In Nanomedicine, Nanotechnology, Biology and Medicine, 2, 191-192

Verma, I. M., Weitzman M.D., (2005) Gene Therapy: Twenty First Century Medicine. In the Annual Review of Biochemistry, 74, 711-738