

HOW NANOTECHONLOGY AND STEM CELLS CAN BE COMBINED TO
CREATE CURES FOR CHRONIC AND OTHER COMMON DISEASES.

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PASS WITH MERIT

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Abstract

Nanotechnology and stem cell research are currently at the forefront of modern medical discoveries. The ability to manipulate the environment in which stem cells differentiate at a nanoscale allows us to uncover a new level of treatments for a wide range of illnesses. This paper comprises of some of the research that has, and is, currently being carried out into the potential uses of this fascinating new field in modern medicine. In particular it aims to look at the combination of nanotechnology and stem cell research, whilst addressing any ethical and economical issues associated with these, and their potential to aid in diagnosing and treating a number of chronic illnesses, including chronic heart disease, Parkinson's and Alzheimer's.

Introduction

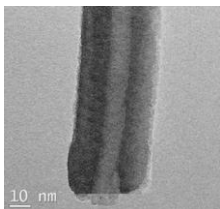
Richard Feynman's lecture, 'there's plenty of room at the bottom' in 1959 introduced an entirely new concept, through his bottom up approach, to a previously unexplored area of science which we have since defined as nanotechnology. He was fascinated by the concept of 'manipulating and controlling things on a small scale.' However, due to technological restraints his ideas would not be developed until the 1980's when, fuelled by the development of cluster science ('the study of the molecular and atomic clusters') nanotechnology truly surged in popularity.

In 1983, it was discovered how molecules containing sulphur can self-assemble on gold surfaces into monolayers which were, on average, a few nanometres in diameter. It was then possible to alter the properties of these layers to develop arrangements that contained more desirable qualities, such as bio compatibility. Currently, self assembling monolayers (SAMs) are used in medicine during cell patterning, the process that determines what stem cells will differentiate into.

Subsequently, the detection of carbon nanotubes (Figure 1) which can be as small as 1 – 2 nanometres in diameter, in 1991, provided great promise for medicine; they are utilised both in scaffolding, which can be required in bone formation or in the growth of artificial muscles. Furthermore, the covalent bonds within their structure enable these tubes to be the strongest and stiffest materials known.



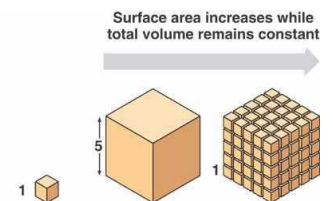
Figure 1



The discovery, rather than the creation of the above substances must be stressed. It is a common misconception that nanomaterials are an artificial material but, halloysite nanotubes (Figure 2) are caused 'by the weathering of aluminosilicate minerals' proving these materials are present in nature.

Figure 2

Nanotechnology was first defined, by Norio Taniguchi, as the science behind materials between 1 and 100 nanometres. What makes them so fascinating is their versatility caused by their high surface area to volume ratio in which the majority of their particles are on the surface, unlike at the macro level where the percentage of atoms at the surface of a substance is considerably lower. This change in ratio can be seen in figure 3. This is significant in solids, as all reactions occur at the surface level, and so due to this afore mentioned ratio, reactions in nanoparticles are much faster and can occur even in inert elements when at the nanoscale. As a result nanomaterials are efficient catalysts and can be used to initiate and speed up reactions. When this effect on reactions is applied to stem cell production, we are able to create environments suitable for the differentiation of stem cells into specialised cells, with the hope of then introducing them into the body.



Total surface area (height × width × number of sides × number of boxes)	6	150	750
Total volume (height × width × length × number of boxes)	1	125	125
Surface-to-volume ratio (surface area / volume)	6	1.2	6

Figure 3

The primary obstacle of stem cell therapy is the inability of the 'injected cells to engraft to tissues'. An attempt to overcome this is to provide a scaffold, created from nanotubes fashioned from synthetic

polymers such as poly(lactic) acid and natural polymers such as collagen and chitosan, which help to direct the stem cells and ensure they differentiate into the desired specialised cell.

Current research into this new field of nanotechnology and stem cells has already shown great promise for nerve cell regeneration, as these are the only mature cells in the body that are unable to replicate themselves. David Nisbet has successfully embedded stem cells into a scaffold created from carbon Nanotubes (CNTs) which, once successfully implanted swiftly regenerate into a new 3D structure. Further research has been conducted into this concept by Tysseling Mattiace et al in which paralyzed mice regained the ability to walk after being treated with nanofibres. We will expand on this later in the paper.

Separately, both nanotechnology and stem cells already have many uses in medicine to aid diagnosis and contribute to finding cures and treatment. For example, SAMs are able to detect NO in the breath, which provides a more accurate method of detecting and hence diagnosing asthma; a disease that affects 1 in 8 children and rising. Whereas adult bone marrow stem cells, as seen in the work of Doctor Walter Giovannini (2010), have been employed to grow new pieces of trachea in recent years. However, the merging of these two areas the potential would be revolutionary within medicine.

Discussion

As we explore the potential applications of nanotechnology and stem cells, it is important we consider the ethical and economical issues that are associated with these developments also. The risks should be analysed to ensure safe and sustainable development.

'In a sample of 1,015 adult Americans, only 29.5 percent of respondents agreed that nanotechnology was morally acceptable'; in the UK however, the figure was much higher at 54.1%. Many of these people who felt it was morally unacceptable believed that nanotechnology was 'playing God' creating synthetic substances. In spite of this nanomaterials have existed naturally for thousands of years; such as, the previously mentioned, Halloysite Tubes. Another example of a naturally occurring nanoparticle is Buckminster Fullerene, which was discovered by R. Smalley, H. Kroto and R. Curl, in 1985, only 25 years ago. This same particle was recently discovered in space by Professor Cami from the University of Western Ontario (2010) in cosmic dust clouds, suggesting these particles have naturally existed for longer than possibly the earth itself. A potential solution to combat these fallacies is to stop the spreading of false ideas by improving the education surrounding this technology.

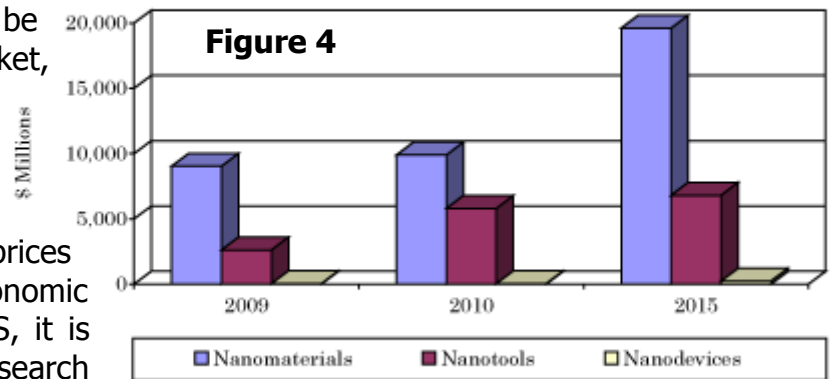
These feelings are reciprocated with regards to stem cell research; however the use of embryonic stem cells generates even greater disputes stemming from the debate whether life begins at conception, as believed by the Roman Catholic Church, or later on in the embryos development. The pressure group, Pro life, a British political party formed by a number of concerned individuals that represent a large number of people opposed to embryonic stem cell research, feel that each embryo is a potential life hence that embryonic stem cell research violates their human rights. However, the potential of nanotechnologies impact on stem cell development, offers the ability to source stem cells from adults over embryonic stem cells, hence overcoming the ethical complications.

Yet another issue of developing nanotechnology is the potential harm it may cause as it is such a new field of research we are still currently unaware of the potential long term effects on both human health and the natural environment. The inability to easily predict the properties of the nanoparticles in comparison to the elements behaviour at a macro scale is due to how small the nanoparticles are, causing them to have increased reactivity. From this uncertainty, there are worries that nanoparticles could cause undiscovered side-effects. Furthermore, as each particle has a very high surface area to volume ratio, originating from their small size, they are ideal catalysts to chemical reactions within

the body, having the potential to cause irreversible damage, by either absorption through the skin or inhalation of nanoparticles that are deposited in the lungs, which can then diffuse into capillaries to be transported around the body, leading to deposits building up in different organs. This has been demonstrated by the work of Ken Donaldson at the University of Edinburgh (2008) in which mice were injected with Carbon Carbon Nanotubes (CNTs) and granulomas were produced within organs as a result of the immune response. However, there is doubt cast over the effect of the inhalation of nanoparticles as a further study conducted on mice by James Bonner (2009) found that 'very little inflammatory or fibrogenic effect was observed.'

It is imperative that the economical concerns of this research are not overlooked, as Nanotechnology's impact on the global economic market is significant (with its 2010 worth set at \$15.7 billion dollars) and this is set to increase to \$26.7 billion dollars as the field develops and strengthens its presence in the science world (see figure 4). Through our research we believe that because of the variability of the nanoparticles the materials produced will become highly successful competition. So other materials that are not made from nanoparticles will not be able to meet the demands of the new market, and a monopolistic market could form. Following this, we believe that hyperinflation would occur, as there will only be a few suppliers to a large population – so they are able to charge prices as high as desired. With the current economic uncertainty and cut backs within the NHS, it is uncertain how they will be able to fund research into nanotechnology's effect on stem cells and so new field may become dominated by the private sector which has more capital available.

SUMMARY FIGURE
GLOBAL NANOTECHNOLOGY MARKET, 2009-2015
(\$ MILLIONS)



Source: BCC Research

this

Although it is vital the possible complications are not ignored, we must also acknowledge the potential of this exciting new field, such as future research into the cures for chronic conditions such as Parkinson's disease, spinal chord injuries, the build up of plaque within the coronary system and Alzheimer's.

With an aging population, Alzheimer's is becoming an increasingly prevalent disease in our society, there are 35.6 million sufferers currently, and this number is set to increase to 115 million by 2050. Unsurprisingly there is a great deal of investigation into cures and treatment for this disease, and the results from nanotechnology and stem cells appear positive. Alzheimer's disease is the permanent loss of neuron cells in the brain as a result of an accumulation of different proteins within the brain, either plaques (beta-amyloid deposits between the nerve cells) or tangles (tau protein deposits within them). Primarily, the Blood-Brain Barrier (BBB) must be triumphed, as an evolutionary protection only permits the movement of fat soluble, non-polar and light weight molecules to enter into the brain. The work of Dr. Paras N. Prasad (2008) has shown how this may be overcome through the attachment of quantum rods to the protein transferrin; the nanomaterial is capable of crossing the BBB. In the future, it is hoped this ground-breaking research will allow these rods to be included in drug delivery or developing a nanoparticle that can cross the BBB unaided. Alongside this progress, the ability of nanoparticles to diagnose Alzheimer's more accurately and less invasively has been a major aim by researchers. As a result of Jorg Kutter's study (2010), a simple blood test, aided by nanoparticles, can test for Alzheimer's rapidly. The nanoparticles used in this test are magnetic and have specific antibodies attached to their surface and so bind to the required molecules. As any excess blood is removed from the sample these molecules are then released by the magnetic

nanoparticles where they are tested to determine whether or not the patient is indeed a sufferer of this disease. It is hoped that by 2015, this machinery will become routine by general practitioners.

It is evident in the above paragraph that the individual ability of nanotechnology to both detect and potentially treat Alzheimer's is monumental. However up to this date, there is no record of nanotechnology controlling the stem cell environment in Alzheimer's research, but it is likely that this is the next step for researchers, as the success of the following studies has suggested that this is a possible reality in the not too distant future.

CNTs have many desirable qualities, including their conductivity which enables them to control the differentiation pathways of mesenchymal stem cells (MSC) to create electroactive cells such as those found in the heart or the nervous system. What is even more exceptional about their properties is that they are able to provide a scaffold without cytotoxicity, meaning they are able to provide a link between healthy cells within the body and differentiated stem cells, providing a successful application of cell therapy.

As previously mentioned David Nisbet's success in anchoring stem cells to a 3D scaffold of CNTs has provided promising indications for the treatment of nerve cell damage. The hope is for these scaffolds to be attached to nerve cells, and provide a channel between healthy nerve cells and undifferentiated stem cells, encouraging them to specialise into new nerve cells to replace those damaged by conditions such as Parkinson disease and spinal cord injuries. This scaffold should then gradually decompose, without creating toxins, and leave behind a new generation of functioning nerve cells. Further research into this is currently being undertaken by the Mental Health Research Institution of Victoria into its ability to be applied to repair neural pathways in the brain.

The research by Tysseling-Mattiace et al, which was briefly mentioned earlier, showcased the capabilities of nanotechnology to manipulate the differentiation of the stem cells into nerve cells, as the mice in the afore mentioned study regained mobility in just 6 weeks, with the scaffold disintegrating after just 8 weeks. During this research, cylindrical nanofibres were able to create an in vivo environment that promoted regeneration between both ascending sensory fibres and descending motor fibres through the site of damage and also reduce cell loss. The injuries sustained by the mice were similar to those sustained from car crash victims, thus giving hope to the future of this treatment and how it could be used to treat humans.



Figure 5

Another possible branch of nanotechnology and stem cell research is in the treatment of chronic heart conditions such as coronary heart disease. Professor George Hamilton and Alexander Seifalian (2009) have managed to develop a new material, consisting of a polymer embedded with special molecules created with the aid of nanotechnology, to construct artificial arteries (as can be seen in figure 5). These nanoparticles are able to encourage the stem cells being circulated in the blood to engraft onto the artery and create an endothelial coating. It has been designed to mimic nature as much as possible and is

able to match its pulse to the natural heartbeat due to its flexibility, whilst remaining strong enough to avoid breaking down. Another advantage of this

material is that it uses stem cells from the patients own body, reducing the risk of rejection and also the need for embryonic stem cells. The hope for this wondrous new material is that in the future we will be able to create 'off the shelf' grafts, stents and devices that are ready to use when required. This means we will be able to reduce the number of bypass surgery which require donor veins from the patients own body, which are not always available, simplifying the procedure, and hopefully reducing the number of deaths from coronary heart disease. It is protected if trials using this method are successful, it could benefit up to

28,000 people each year in Britain alone who undergo operations to widen blocked and narrowed arteries.

It is important, however not to overlook the research of nanotechnology and stem cells into areas, other than for the treatment of chronic, life threatening diseases. A recent study, lead by Robert Guldberg of Georgia Tech's Woodruff School of Mechanical Engineering, found that the use of scaffolding, created by carbon nanotubes, and stem cells combined for treating major

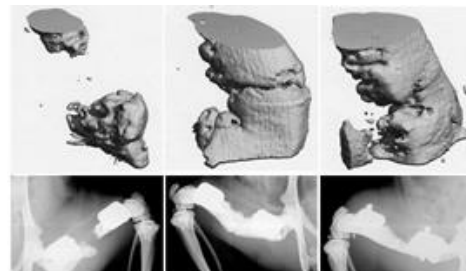


Figure 6

bone injuries resulted in better bone formation and function than by simply using a scaffold alone, as can be seen in figure 6. The study was conducted on rats that had a reduced immune system to prevent the rejection of bone marrow-derived mesenchymal adult stem cells and amniotic fluid foetal stem cells. Two, eight millimetre wide bone gaps were created to supply a suitable scenario in which to test the various treatments. One set of rats was treated with scaffolding alone, but this did not lead to any new bone growth, and only one in nine of the rats treated with both scaffolding and foetal stem cells displayed any signs of new bone bridging the gap. However, four in nine treated with the combination of adult stem cells and scaffolding resulted in new bone growth to bridge the gap, which gives great hope for the potential futures uses of adult stem cells, which are not associated with as many ethical issues as foetal stem cells. To try and understand why so many of the cells had not differentiated to repair the gap in the bones, nanoparticles were used, known as quantum dots, to track the distribution of the stem cells when placed into the body. Unfortunately between seven to ten days after implantation it appeared that the quantum dots had been engulfed by inflammatory cells, known as macrophages, after being released by dead stem cells, suggesting that the stem cells were still being rejected by some cells in the body, preventing differentiation, growth and any potential repair to the site of injury. It was also found that the quantum dots reduced the function of the transplanted cells, therefore inhibiting any possible therapeutic effect they may have had in bridging the gap between bones, yet when the same study was carried out in vitro it showed no defection of the cell viability. This study has provided great anticipation for the future marriage of nanotechnology and stem cells in the treatment of major bone injuries, with the expectation that one day it may be able to provide an alternative to bone grafting operations, which can be an extremely prolonged and painful treatment.

CONCLUSION

The above snapshot of ongoing investigations into nanotechnology and its effect on stem cells to cure and treat widespread diseases indicated that this technology cannot be underestimated. Nonetheless, ethical issues surrounding these controversial areas of research will, we believe, play a vital important role in the future of these fields that show the potential of genuine cures, including Tysseling-Mattiace's work regarding spinal injuries and Parkinson's disease.

Although these treatments seem promising, they are still in the early stages of their development, so the total benefits of this research will only begin to be reaped by our children's or grandchildren's generations.

With a growing and ageing population, where health problems such as chronic heart disease, Alzheimer's and Parkinson's are ever increasing it has never been so crucial to uncover earlier diagnostic tools and better treatments. Nanotechnology alone has already shown huge potential for tackling these problems, and when combined with stem cells, as we have seen, could possibly be revolutionary for the way we currently treat these life threatening diseases, radically changing our health care system by improving its reliability and efficiency.

Nanotechnology is still a very young field, and I believe we have only just begun to see a glimpse of what it is capable of doing. It is unfeasible to predict all of the treatments that the manipulation of stem cells by nanotechnology may uncover, as this research field is still in its infancy.

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