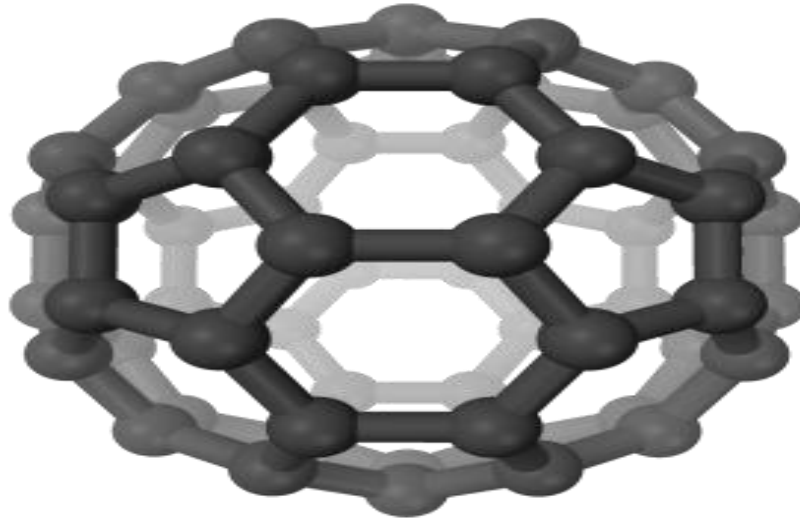


Nanomedicine: A new field for a new era



**By
Zain Ebrahim
Komal Makwana**

**PASS WITH MERIT
(98 words over limit)**

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Abstract

Nanotechnology has become an exciting prospect for medicine with the ability to revolutionise it to the extent that we would be able to cure many diseases that are currently incurable. Nanotechnology can improve medicine in many ways but in this paper we are going to focus primarily on its applications in Alzheimer's and secondary, its applications in Multiple Sclerosis. Affecting around 550 000 people in the UK alone, they have become increasing worries over the last century. We believe that by using nanotechnology, these diseases can be cured and this paper will focus on the mechanism, ethics, benefits as well as problems revolving around these cures. Evidently, these ideas would not be able to be put into practice until research and development in nanotechnology progresses significantly; however, the benefits it would have and the number of lives it would save make it an idea worth researching and developing.

Introduction

Nanotechnology is the science of manipulating matter at a molecular and possibly even atomic scale. It refers to structures that are between 1 nanometre (a billionth of a metre) and 100 nanometres in size. The idea of manipulating matter at a molecular level was deliberated by Richard Feynman who discussed it in a lecture in 1959. The actual term "Nanotechnology" was devised by a professor from Tokyo University, Norio Taniguchi. He used the term in a paper he wrote in 1974 regarding ion-sputter machining. He stated that "Nanotechnology mainly consists of the processing of, separation, consolidation, and deformation of materials by one atom or by one molecule." [1] This concept was promoted by Dr K. Eric Drexler in his lectures and in books such as "Engines of Creation: The Coming Era of Nanotechnology" (1986). [1] This led to a revolution in nanotechnology with the invention of the scanning tunnelling microscope and the birth of cluster science in the 1980s. Several years later, fullerenes were discovered and carbon nanotubes soon followed, making this concept of nanotechnology a reality. These developments have led to many ideas and inventions in molecular devices and machines in many areas like pharmaceuticals, medicine and physics.

The application of nanotechnology in medicine is a field of its own known as Nanomedicine. Nanotechnology can provide us with the solution to many medical problems and may also provide us with methods of cure of particular diseases, the latter of which is what this paper addresses; the use of nanotechnology to cure or alleviate Alzheimer's and Multiple sclerosis. There is on-going research regarding the use of nanotechnology in medicine and several ideas have been posed; ideas which could revolutionise treatment in medicine.

Drug delivery, a method that uses nanoparticles to deliver drugs to specified regions, is currently a topic of research that provides us with exciting prospects. The nanoparticles would be able to deliver drugs, heat, light or any other substances to regions that require treatment. This is significant because it would mean that the drugs would only go to the specified region and this region would be treated directly without causing any harm to healthy cells. The nanoparticles would have to be engineered in order to recognise damaged or tumorous cells, perhaps via DNA scanning.

An example of this method in use is with cancer cells where nanoparticles carry chemotherapy drugs directly to the specific cells and no other cells. The early detection is thought to work as nanoparticles can attach to proteins and other molecules which would allow detection of disease indicators at an early stage. Nano sphere Inc. is currently developing the use of gold nanoparticles which have shown in a clinical study its ability to detect four different nucleic acids, which would enable the nanoparticle to scan and recognise cells for any abnormalities. (2)

Another idea related to Nanomedicine revolves around the concept of the Buckminster fullerene and its ability to block allergic response. These fullerenes are able to inhibit a cellular process which results in the release of the allergic mediator. This would prevent cells from triggering an allergic response. The reason the fullerene is able to do this is because of its unique ability to bind to free radicals due to its distinctive structure. [3]

Nanorobotics is another field of nanotechnology that is currently undergoing research. The value for it in medicine would be invaluable as they would be able to be navigated to the part of the body that needs to be treated and then work as artificial repair systems. For example, in the brain, an artificial neuron repair system could be used. Firstly, a Functional MRI [4] or a PET scan [5] would need to be conducted in order to identify the areas of the brain that have been affected by the disease. Any damaged neurons would show up on the scan, depicting which neurons need repairing or replacing. Nanorobotics can then be used to attempt to artificially repair these cells. These would be made of carbon fullerenes due to their immense strength and relative inertness. To avoid any response from the immune system, the nanobots would have a smooth, flawless coating. [6] The nanobot would emit signals so that doctors operating it would know its exact location and would, in turn, send ultrasonic signals to the nanobot. [7] As nanotechnology involves the building of designs molecule by molecule, it could lead to the repairing of it by the cells or construction. The nanobots would carry the miniature tools to do the repairs inside the cell. The repairing of cells could mean returning the cells to normal and making the person once again healthy.

Moreover, nanobots would be able to identify different types of cells by checking the antigens of the cell surface. The use of chemotactic sensors keyed to the specific antigens on the target cells would be enable the nanobots to do this. If this idea is developed it could be used to repair specific diseased cells by programming the nanobots to do so. (2)

Discussion

The primary focus of this paper is the applications of nanotechnology in Alzheimer's disease, a progressive disease that results in cerebral atrophy; however, we will also lay some focus on Multiple sclerosis and its mechanism and treatment using nanotechnology.

What is Alzheimer's disease?

Alzheimer's is a neurodegenerative disease which is caused by cerebral atrophy that affects 1 in 14 of people above the age of 65 in the UK. The risk is proportion to age; people above the age of 80 have a 1 in 6 chance of developing this condition. It is the most common form of dementia which affects around 570 000 people in the UK alone, 60% of which are Alzheimer's sufferers. The prevalence of Alzheimer's was 26.6 million sufferers globally. This figure is expected to rise by 2050 to the extent that there'd be 1 in 85 sufferers worldwide. This is why around £17 billion is spent annually on research and treatment of Alzheimer's in the UK. [8] Moreover, there is no definitive method of diagnosing Alzheimer's as yet except for a post mortem autopsy but this has many ethical issues surrounding it.

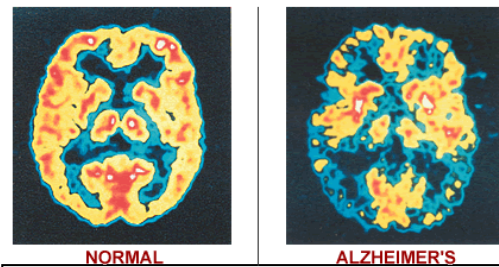


Figure 1: PET scans show how Alzheimer's affect brain activity. The blue and black regions in the right image depict reduced brain activity. *Image courtesy of Alzheimer's disease Education and Referral Centre*

Despite the fact that the progression of Alzheimer's is dependent on the individual, there are three general stages to Alzheimer's; mild, moderate and severe. Mild Alzheimer's is characterised by a group of symptoms including confusion, loss of memory, speech impairment and regular mood swings which lead to deteriorating mental abilities. This, if left untreated, can further develop into the moderate stage which can be characterised by suffering from hallucinations, delusions, incontinence and obsessive behaviour. The severe stage of Alzheimer's includes symptoms such as weight loss, complete loss of memory, difficulty in day to day activities and increased susceptibility to infection. The latter of which tends to be the cause of death in Alzheimer's sufferers; with most cases of death being due to infections such as pneumonia arising due to the disease, meaning that although Alzheimer's usually isn't a direct cause of death, it can still result in a shorter life expectancy. [8]

Causes

Although it is most commonly associated with old age (due to the fact that susceptibility increases with age), its exact aetiology is unknown. However, several hypotheses have been proposed, the most common of which is the amyloid hypothesis, first proposed in 1991. This states that Alzheimer's is caused by beta amyloid proteins which deposit in the grey matter of the brain and form senile plaques, as you can see in figure 2. Plaques like these can usually be broken down by the brain; however, in Alzheimer's, the plaque cannot be broken down, leading to

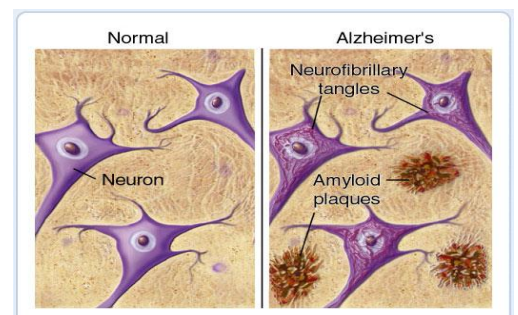


Figure 2: Amyloid plaques and neurofibrillary tangles are indications of Alzheimer's disease. *Image courtesy of www.ahaf.org/assets/images/plaques_and_tangles_border.jpg*

the degeneration of brain cells. However, an experimental vaccine was found to be able to clear amyloid plaques in human trials but this had no effect on the dementia, possibly because the brain cells had already been damaged and weren't replaced. [9]

Due to this, the theory was updated in 2004 to include a different type of protein and a different type of plaque when deposits of beta amyloid plaque didn't correlate with the loss of neurons. This new theory suggested that tau protein irregularities initiate the disease. Different types of tau protein (hyperphosphorylated tau and other types of tau) supposedly pair with each other, forming what's known as a neurofibrillary tangle inside the nerve cell. This causes the disintegration of microtubules, damaging the transportation systems in the cell. This means that extracellular communication cannot occur effectively, leading to difficulties in neuron communication and eventually, the death of these neurons.

Another theory dictates that Alzheimer's is caused by the loss of myelin. The axon of a neuron is usually covered in a myelin sheath, an electric insulating material that is responsible for increasing the speed at which impulses propagate across myelinated fibres, making it an essential component of the nervous system. In Alzheimer's, this myelin is thought of to be broken down with age. This results in a homeostatic myelination response which, as a side effect, leads to the formation of beta amyloid plaques. [10]

Prevention and Treatment

There is no available cure to Alzheimer's; however, medication to alleviate symptoms is available. These include Aricept (trade name for donepezil), Exelon (trade name for rivastigmine), Reminyl (trade name for galantamine) and Ebixa (trade name for memantine). The former three relate to the cholinergic hypothesis as to the cause of Alzheimer's. This idea postulates that Alzheimer's is caused by a lack of a particular neurotransmitter called acetylcholine. Although this idea is not widely supported, a similar idea states that the lack of this neurotransmitter results in an increase in amyloid plaques and this has received slightly more recognition. These drugs work by maintaining the levels of acetylcholine; however, these are only recommended for patients who are in the mild or moderate stage of Alzheimer's since they aren't very effective. The latter drug, Ebixa, works differently to the other three and is recommended for people with moderate to severe stages of Alzheimer's; however, it has side effects such as dizziness, confusion, fatigue and headaches. Although these ameliorate the symptoms of Alzheimer's, they aren't as effective as we'd like them to be and work for some patients but not others, giving rise to the idea of there being different types of Alzheimer's. [8]

Treatment using nanotechnology

This problem can be solved easily using nanotechnology. The Buckminsterfullerene has already been associated with drug delivery due to its icosahedron shape and hollow interior, which

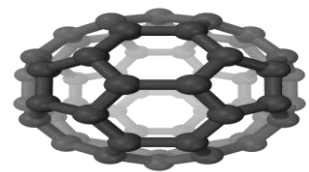


Figure 3: The Buckminsterfullerene has an icosahedron shape which makes it ideal for drug delivery. *Image courtesy of Wikipedia*

allow it to behave as a carrier. This is the fundamental principle in our idea; however, it would be modified to have receptors on its exterior. These receptors would be responsible for detecting the plaques and neurofibrillary tangles and upon doing so, would cause the fullerene to release the proteolytic chemical which it carries. This chemical would hydrolyse the protein plaques and tangles into small amino acids, making it easier for the brain cells to rid itself of these particles, preventing further damage. After the plaque is rid of, another dose of fullerenes would be given. This dose would contain an inhibitor which inhibits the action of this proteolytic chemical, preventing the chemical from lysing any vital proteins.

In order to confirm whether the amyloid plaques had been successfully broken down by the chemical, a PET (Positive Emission Tomography) scan along with Pittsburgh Compound-B indicator would be used. This indicator is a thioflavin that accumulates in areas of the brain where beta amyloid plaques are located, showing these areas on the PET scan. To prevent these plaques from depositing again, another dose of fullerenes would be given which would contain a protease inhibitor of the secretase enzyme that produces beta amyloid proteins. The process by which the fullerenes would reach the cerebral cortex still needs to be considered; however, it is clear that once this idea is put into action, the benefits for treatment of Alzheimer's would be invaluable. [11]

Multiple Sclerosis

Our final idea is related to the myelination theory of Alzheimer's as well as the treatment of Multiple sclerosis. Multiple sclerosis is the most common neurological condition in people aged between 20 and 40, with around 85 000 people affected. Multiple sclerosis affects the central nervous system and in particular, the neurons. The axon of a neuron is usually covered in a myelin sheath, an electric insulating material that is responsible for increasing the speed at which impulses propagate across myelinated fibres, making it an essential component of the nervous system. In MS, the immune system attacks this myelin since it mistakes it for a foreign body. This results in demyelination, disrupting the flow of impulses and therefore damages the neurons. Evidently, if demyelination is the problem then the solution would be to myelinate these neurons again and although homeostatic myelin repair processes already occur in the body, this isn't effective in the sense that the cells responsible for it are low in number and this is where the nanotechnology comes in. [12]

Schwann cells are most commonly associated with the myelination of axonal neurons; however, these are only responsible for myelination in the peripheral nervous system whereas MS affects the central nervous system so another cell must be involved. Oligodendrocytes are the cells responsible for the myelination of axonal neurons in the CNS and although these are thought to be terminally differentiated, they have precursor cells which can still differentiate, called oligodendrocyte precursor cell. [13] Evidently since oligodendrocytes are responsible for the myelination of these neurons, an increase in the number of oligodendrocytes would result in an increase in the rate of myelination and this could be achieved by increasing the number of oligodendrocyte precursor cells. Since myelin

is responsible for electrical insulation, it would make sense if neuronal (and in particular, axonal) electrical activity affected the number of oligodendrocytes that develop in the myelin tract. A recent study showed that the electrical activity of axons in a rat optic nerve affected the number of oligodendrocyte precursor cells and that increasing the concentration of a platelet-derived growth factor stimulates the proliferation of these cells. [14] This suggests that electrical activity in the axons affect the production and release of the growth hormones which control the proliferation of oligodendrocyte precursor cells, controlling the number of oligodendrocytes. This is because increases in electrical activity cause neurons to release ATP which causes a particular cell, known as an astrocyte, to secrete a substance known as cytokine leukaemia inhibitory factor which then promotes the myelination of the neurons [15] (affected by the electrical activity) by the oligodendrocytes, subsequently increasing the number of oligodendrocyte precursor cells and in turn, the number of oligodendrocytes.

Our proposition is to use advanced Buckminsterfullerenes (these have an unbounded electron which is free to move around and carry charge, meaning that it can conduct electricity very well) with receptors to detect demyelinated neurons (differentiating between them via their electrical activity) and electrically stimulate the axons in order to promote the myelination of these neurons by proliferating the number of oligodendrocyte precursor cells and therefore the number of oligodendrocytes via the mechanism described above.

The proliferation of oligodendrocyte precursor cells has a lot of potential since it can differentiate into several other types of cell as well as the oligodendrocytes. These include neurons which can be used to replace the dead neurons in Alzheimer's and in Multiple Sclerosis. Another type of cell that the oligodendrocyte precursor cell can differentiate into is the astrocyte. One important function of the astrocytes was mentioned earlier; that it is responsible for promoting the myelination of neurons; however, another vital function of it is nervous system repair. If nerve cells are damaged (i.e. by plaques or neurofibrillary tangles) these astrocytes would form a glial scar and repair the area by replacing any severely damaged cells. [15] This suggests that the proliferation of the number of these would mean that this function can be performed more effectively, meaning that these could repair or even replace any damaged neurons. To prevent any of these homeostatic repair responses from leading to the formation of beta amyloid plaques, the beta amyloid secretase inhibitor could then be administered.

Ethics of this treatment

There are a few ethical issues that need to be taken into account regarding these potential forms of treatment. Firstly, and most prominently, some nanoparticles have been likened to asbestos and can be lethal if collected in the lungs, potentially causing mesothelioma. This raises the concern of whether the risk of causing other more severe diseases outweigh the need for it to treat Alzheimer's and Multiple sclerosis; two diseases that do not directly

cause death. Since doctors have to pledge not to administer “a deadly drug to anybody” under the Hippocratic Oath, [16] this raises much speculation as to whether it can actually be used in medicine if the harm is too significant.

Moreover, the cost of such treatment would be so steep that only a select few would be able to afford it, making it more of a luxury rather than a worldwide cure. This would raise the ethical issue of equity; everyone deserves to have access to medical treatment that can potentially save their life. In addition, the amount of money required for an idea such as this to take shape exceeds billions of pounds and with frequent natural disasters already inflicting a large amount of damage to countries and their finances as well as global problems such as poverty and starvation (both of which can be solved by the use of money) the question is raised as to whether it is ethically viable to spend so much money researching a prospect that may take years to develop. [17]

In addition, there is also the environmental aspect to take into account. After the fullerenes are no longer usable, disposal would be an issue since these are fairly inert and are extremely small nanoparticles. Combusting it would simply add to the greenhouse effect by releasing carbon dioxide so the best option would be to recycle them; however, this would be fairly costly and fairly hard to do. Additionally, the toxicity of certain nanoparticles would mean that it would be harmful to the environment.

Furthermore, with the ability to repair and even modify cells, it seems plausible that in the distant future a new branch of Nanomedicine involving cosmetics and beauty would develop, with individuals being able to select which characteristics they wanted to change i.e. eye colour. This is similar to the concept of designer babies and could be catastrophic in the sense that many people would develop somewhat artificial characteristics and with the primary difference between robotics and humans being the fact that humans are naturally occurring, this topic would be highly debatable.

Conclusion

Nanomedicine is one of the most promising fields this century and although some may argue that it is unnatural and attempting to replace God by altering things in our body, the aim of medicine in general is to cure or alleviate diseases by administering medication or even performing a surgery; both of which involve the modification of bodily substances.

However, there are a few problems surrounding our ideas. Firstly, nanoparticles have been found to be extremely reactive due to their quantum size and large surface area to volume ratio. The study of this is known as Nanotoxicology. Carbon nanotubes have been found to behave similarly to asbestos and have therefore raised concerns regarding whether they can cause mesothelioma. Moreover, the Swedish Karolinka Institute conducted a study recently which investigated the toxicity of several types of nanoparticles including titanium dioxide, zinc oxide and copper oxide. Titanium dioxide and zinc oxide was found to cause DNA damage and aren't as toxic. Copper oxide was found to be the most toxic and was therefore

identified as a clear health risk by researchers. A lot of research has been put into the toxicity of fullerenes and can be found in “Bio-applications of Nanoparticles”. According to this book, there is substantial evidence to conclude that fullerenes are non-toxic and therefore pose no risk but this may not be the case in our idea especially since our idea makes use of advanced and enhanced fullerenes, meaning that it would compose other compounds too which may be toxic. This could be overcome by constructing it with particles that have been determined to be non-toxic but this still needs to be researched into. [18]

Moreover, the mechanism by which the fullerenes would reach the parts of the brain is still unknown. Although PET scans can indicate where the plaques are, there is no definitive way of navigating the fullerene to these plaques. Perhaps, however, a simple method such as coating it in a layer of a chemical similar to Pittsburgh Compound B which would then enable it to accumulate in the areas of plaque, allowing it to perform its function.

In conclusion, this paper supports any further research and development regarding the use of enhanced fullerenes to carry a proteolytic chemical in the case of Alzheimer’s or an electrical charge in the case of Multiple sclerosis (or demyelination in general) in order to break down any plaques and electrically stimulate neurons to proliferate the number of oligodendrocyte precursor cells and subsequently, the number of oligodendrocytes, neurons and astrocytes. The benefits it would have (including the prevention of death due to increased susceptibility and an improved quality of life) make it a viable form of treatment and although some may argue that the cost of researching into this method and actually developing the technology required is too steep, with £17 billion pound already being spent per annum in the UK on Alzheimer’s research and treatment alone, it is evident that this, once developed, would save money rather than waste it, making it a worthwhile investment. Finally, though some may say that the money would be better spent in solving existing and more imposing problems such as poverty and starvation, people are already attempting to solve those problems and if we only concentrate on the present rather than attempt to invest in our future and revolutionise medicine, we would never be able to grow and adapt to any new conditions that may arise which is why Nanomedicine in general will be an important field since it provides us with the prospects of not only curing Alzheimer’s or Multiple sclerosis but also many other diseases which would otherwise take millions of lives each year. Nanomedicine: a new field for a new era.

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