

Does Nanotechnology Hold the Key to
Curing Parkinson's Disease?



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Abstract

The people most at risk of developing Parkinson's are 50+ years of age so Parkinson's disease is an increasing problem in Britain where there is an aging population (figure 1). By 2034 the number of people aged 85 and over is projected to be 2.5 times larger than in 2009, reaching 3.5 million and accounting for 5% of the total population. Currently, 1 in 500 people suffer Parkinson's disease in the UK, with 7.4 million people being affected worldwide. Recent developments in nanotechnology have brought to light possible uses for nanobots, including a significant future role in neuroscience and neurological treatments. This paper will be looking at how we can utilize nanotechnology to treat and eventually cure Parkinson's disease. This could be achieved by the neural regeneration of the nerve cells in the Substantia Nigra which die off, causing a dopamine deficiency in the brain. We will also examine what the potential pitfalls of nanotechnology in neuroscience could be.

Introduction

Parkinson's disease is a debilitating degenerative disorder of the central nervous system, where the dopaminergic neurons of the pars compacta in the Substantia Nigra die (figure 2). This then leads to the primary symptoms of a Parkinson's sufferer; Bradykinesia, tremors, rigidity, poor balance and the characteristic Parkinsonian gait. Every hour, somebody in the UK is diagnosed with Parkinson's disease, we can expect the rate of diagnosis to increase due to the UK's aging population; 90% of Parkinson's sufferers are over 45 years of age, with the majority of symptoms only appearing over the age of 50. Currently, The National Institute for Health and Clinical Excellence calculates the cost of Parkinson's Disease in the UK to be around £3776 Million annually; this figure is taken from NICE's National Cost-Impact Report '06 and includes the cost of primary and secondary care for Parkinson's Disease. Taking into account the fact that the incidence and prevalence of Parkinson's disease is likely to increase, then the National Cost-Impact is also likely to increase. In light of this, if a cure for Parkinson's disease could be found then not only would the second-most common neurological disorder of people over 60 be successfully treatable, but the National Cost-Impact would be reduced, with secondary care costs being cut significantly. Reducing the economic impact is almost as favourable as the cure itself in the current economic climate.

Whilst reducing the physical capabilities of the sufferer, Parkinson's disease produces high emotional stress and frustration for both patients and their relatives. Parkinson's disease can leave a sufferer unable to manage their day to day lives without constant assistance from relatives or carers; with the sufferer eventually being left unable to perform simple tasks such as cooking, cleaning themselves, dressing themselves and feeding themselves. The loss of independence this brings to the sufferer is unimaginable for those who have never experienced it; this is a major reason why roughly 40% of Parkinson's sufferers will experience depression at some point after their diagnosis. Dementia is also a distinct possibility when suffering from Parkinson's. 30% of sufferers will develop the disorder and further research by Foltynie et al (2005) has found that 1 in 3 Parkinson's sufferers show signs of frontal dysexecutive syndrome (showing symptoms of poor working and short term memory, with a decreased attention span and difficulties in reasoning). Aarsland (2004) has found that 80% of sufferers have severe cognitive impairment after 10 years with Parkinson's.

In order to develop a cure for Parkinson's disease, the cause of the disease must first be known. However, this is easier said than done with a disorder which is 95% idiopathic.

The main cause for Parkinson's is the death of the dopaminergic cells in the Substantia Nigra but it is not known exactly how these cells die. It is not until 70-80% of these cells are dead that the symptoms of Parkinson's disease become apparent. The Substantia Nigra is situated in the mid-brain and is an essential motor centre of the brain; normally the cells here produce the neurotransmitter dopamine which is then transported to the nerve terminals of

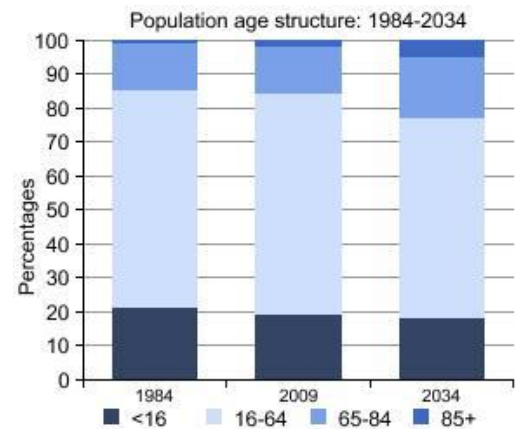


Figure 1

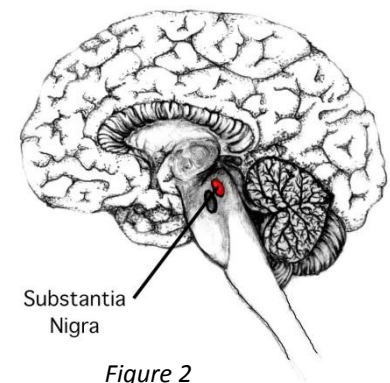


Figure 2

the striatum where it is used as a neurotransmitter. One possible cause for the demise of these cells is defective nucleoli. When investigated, the majority of the nucleoli of the dopaminergic cells which had died were defective, leading to further research. To do this, researchers led by Dr. Rosanna Parlato modified the DNA of experimental mice so that the dopamine producing cells could only form defective nucleoli. The mice were found to develop classic Parkinson's symptoms and the eventual death of the cells which classically die in Parkinson's disease. Currently, it is thought that roughly 5% of Parkinson's cases are due to genetic causes. There are 12-genes presently linked to Parkinson's disease and, although it is extremely rare, it has been known to pass in families from generation to generation due to specific gene mutation. The two main genes suggested, when faulty, are causes of Parkinson's are the Parkin and α -synuclein genes, but other genes majorly linked with Parkinson's include DJ1, PINK1 and LRRK2. The Parkin gene responsible for the Parkin protein is thought to be a cause for early-onset Parkinson's and 18% of early-onset Parkinson's sufferers are thought to have the faulty Parkin Gene. The α -synuclein gene is responsible for the α -synuclein protein, which is the most abundant protein found in Lewy Bodies, the characteristic histological sign of Parkinson's. When faulty the gene causes the protein to aggregate in the Lewy Bodies, causing Parkinson's disease. A Lewy Body is an abnormal aggregate of protein which develops inside the nerve cells (figure 3).

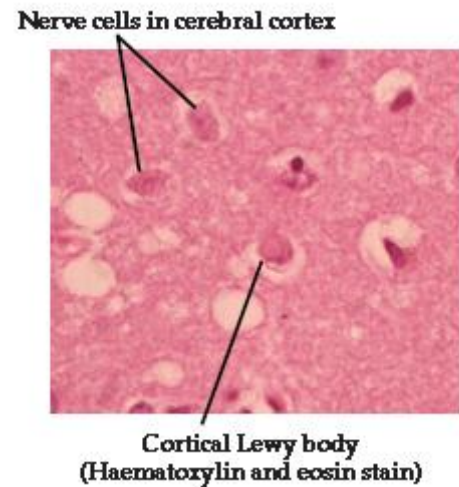


Figure 3

In order to develop new treatments for Parkinson's disease it is very important that we use current treatments and drugs and how they work to improve and evolve the treatment of Parkinson's eventually leading to a cure.

The current treatments and drugs for Parkinson's disease can be seen as clumsy and primarily do not target the actual nerve cells involved, but they seek to mask the symptoms caused by the cells. Current Drugs being used in treatment generally imitate the effect of Dopamine on the Brain. Surgical treatments include Deep Brain Stimulation along with other Lesioning techniques. DBS provides the stimulation necessary to help suppress the overactive nerve cells which cause the tremors of Parkinson's disease. A great advantage of DBS is that whilst suppressing the symptoms, there are no induced-side effects or damage to brain tissue (unless incurred during the positioning of the electrode). Lesioning involves making selective damage on specific areas of the brain, which has been known to help relieve some symptoms of Parkinson's. However, although these treatments may reduce treatments they do not offer the hope of a cure. This is where we believe that nanotechnology can hold the key.

Nanotechnology is a term referring to technology that can involves changing structures at the atomic level, working with materials that are a matter of nanometres in size. This is at the forefront of medical development in the 21st century and we think that there has to be a way to apply this technology to the treatment of Parkinson's, a disease that's so far proved a to be an obstacle medicine can't overcome. By applying the new technologies to the Parkinson's problem and pulling all existing knowledge into one treatment we think a new radical treatment for Parkinson's could be formulated.

Discussion

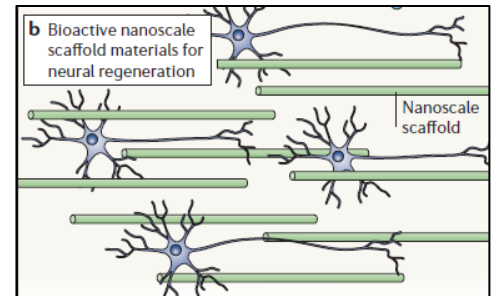
Our idea is based around using nanorobotics to treat and cure Parkinson's disease by initiating the neural regeneration in the Substantia Nigra of the dopamine producing cells. Nanorobotics is a fast developing area of medical treatment with the components of the nanobots being at the microscopic scale of a nanometre. Another definition is a robot that allows precise interactions with nanoscale objects, or can manipulate with nanoscale resolution. Our main concept is that the nanotechnology could be used to provide bioactive scaffolds for the regeneration of the dopaminergic cells (figure 4), or even that nanobots could eventually rebuild the cells themselves during a single surgical procedure.

A nanomaterial scaffold works by mimicking the extracellular matrix of the brain; therefore it would provide a physical or bioactive environment for neural regeneration. Under the physiological conditions, the self-assembly process traps the surrounding environment and manufactures a self-supporting gel in which the neural cells can be encapsulated, allowing the growth of the cells to be controlled. Good examples of the nanomaterials used would be Peptide-amphiphile molecules producing a nanofibre network, or a PLLA (Poly (L-Lactic) Acid) scaffolds with an ultrastructure of PLLA fibres – using PLLA neonatal mouse, cerebellar progenitor cells were able to extend neuritis and differentiate into mature neurons.

Other materials which could be used include nanorough silicon wafers, nanoimprinted Polydimethylsiloxane (PDMS), Electrospun tubes of polycaprolactone and chemically modified multiwall carbon nanotubes. Nanorough Silicon Wafers help to increase the viability and adherence of cells in the Substantia Nigra as proven by Fan YW et al. It was demonstrated that the viability and adherence from wafers with a roughness of 20-50nm increased dramatically as opposed to those of less than 10nm or more than 70nm. This is good as it provides us evidence for the ideal environment for the regeneration of neural cells which can help us develop scaffolds which will maximise neural growth.

Figure 4

Nanoimprinted Polydimethylsiloxane can be used in conjunction with mesenchymal stem cells to produce effective neural cells; this is very good as it would mean that a person's own stem cells could be used to regenerate the diseased area of brain tissue in an effective way. If the cells come from the person who is receiving them then it reduces the problems faced by possible rejection of foreign cells. This would be a much more efficient and fast way of regeneration as the cell bodies themselves would already be there and the cells would only have to specialise with the help of the Polydimethylsiloxane scaffold.



Chemically modified carbon nanotubes can be used as a substrate for cultured neurons. The chemical properties of carbon nanotubes are systematically varied by attaching different functional groups that confer known characteristics to the substrate. By manipulating the charge carried by functionalized carbon nanotubes we are able to control the outgrowth and branching pattern of neuronal processes. Different Polycaprolactone and gelatin nanofibrous scaffolds were tested and the PCL/gelatin 70:30 nanofibre was found to exhibit the most balanced properties to meet all the required specifications for nerve tissue and was used for the in vitro culture of nerve stem cells. The scaffold helped to enhance nerve differentiation and proliferation and acted as a positive cue to neurite outgrowth. It was found that the nerve growth was generally in parallel to the position of the fibres so this would have to be taken into account if it was used in this situation.

Taking the properties of all these materials into account we think that the most sensible choice for a nanomaterial scaffold for the regeneration of the cells in the Substantia Nigra would be nanoimprinted Polydimethylsiloxane because the way that this can be combined with stem cells because it will result in the fastest regeneration of the cells and so the best outcome for the patient.

Although these scaffolds offer fantastic prospects for the treatment of Parkinson's there is still the logistics of working in the centre of the brain to be considered. This is where we suggest combining this technology with the exciting developments being made in the use of Nanobots in the neural regeneration process. These Nanobots will be able to operate on the molecular level of the cells which would be essential to neural regeneration when operating in an area such as the brain that is risky when operating at a macroscopic level. These Nanotech Medical Robots are not available using current technology but with the current rate of development it may soon be a regular part of medical treatment. For example, a cell which is being repaired by a nanomedibot could have its Lewy bodies removed by the bot and any faulty genes (though in only 5% of Parkinson's cases) could be rectified before the cell has died. Even a standardised test could be developed for people who could be considered "at risk" of developing Parkinson's disease, e.g. over the age of 50, a family history of genetic Parkinson's. Then the problem can be fixed using nanomedibots at a much earlier stage and so preventing the occurrence of any symptoms.

When combining the nanotech medical robots with the nanomaterial scaffold the theory is that the nanobots can deliver the scaffold to the correct location, where the cells are dying. The way in which they would do this is by picking up the chemical signals produced by the cells. This has already been proven to work when nanotech medical robots have been used to identify cancer cells. Joseph Irudayaraj has released a paper that documents how using gold nanorods and magnetic particles will make it possible to locate the nanobots within the body using MRI imaging (figure 5). Their route can then be monitored and, in the case of the cancer cell locating probes, they will latch onto cancerous tumors by identifying the protein markers on their surface. When we apply this technology to our treatment of Parkinson's the nanobots would instead look for the dying/dead dopaminergic neurons by seeking out the dopamine that is produced in high concentrations in the Substantia Nigra and then releasing propidium iodide. By firstly seeking out the high dopamine concentration they will be able to locate themselves in the correct region of the brain because not all the cells will have died so this would still be the region of highest dopamine production. Once they are in the correct area, which will have been determined using the MRI imaging, the nanobots can then locate the dead cells by releasing propidium iodide, a fluorescent dye. Propidium iodide cannot pass through the cell membranes of viable cells but can infiltrate dead cells and attach to the double stranded nucleic acid. If the cell that the nanobot latches onto accepts the propidium iodide then it will know that the cell must be dead. However, if

the propidium iodide cannot pass through the cell membrane then this would trigger the nanobot to move onto a different cell.

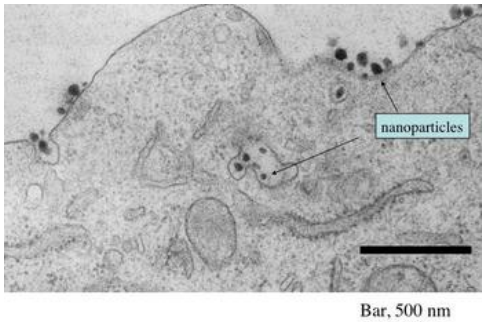


Figure 5

One possible problem with this mechanism is what effect the propidium iodide could have on the remaining dopaminergic cells and how it will affect cell regeneration on the nanomaterial scaffold. It is possible that there is a way that the cells could spontaneously regenerate in response to the presence of the scaffold, however with the material that we are suggesting it would probably be more effective to combine the scaffolds with mesenchymal stem cells so that they can then differentiate into the dopaminergic cells required. Tests would need to be carried out as to how excess propidium iodide affects the mesenchymal stem cells because if the nanobots were repeatedly unsuccessful in locating dead cells then a lot of

propidium iodide could be present. Another issue would be how the nanobots could identify dead cells once the propidium iodide has been released. If the nanobot is attached to a viable cell that doesn't allow the dye to penetrate its membrane then the dye might enter a dead adjacent cell instead. If this were to happen then the nanobot may not be able to recognise the cell as dead once it has latched onto it because it might be too saturated to take up any more propidium iodide. A solution to this would be to only allow each nanobot to latch onto one cell in a treatment but increase the number of nanobots deployed. However, this further increases the ethical issues already present.

There are many ethical arguments that could be had based on our proposed Parkinson's treatment. The most obvious problem is the use of the nanobots which will be able to manipulate our cells at an atomic scale. This is altering the structure of our being at the most fundamental level and we could be seen to be 'playing God'. To create this technology would undoubtedly bring benefits to those afflicted with Parkinson's, but there are also potential dangers. For example, this technology could be used to invent new weapons that could kill thousands of people and sure this would outweigh the benefits of curing Parkinson's disease? What if the nanobots were released into the environment by accident? Without close monitoring these machines would be capable at altering the cells of any biological organism, potentially changing their DNA makeup and changing the ecosystems of the world. Then, looking at our specific treatment, you have to consider the fact that we are dealing with the brain. The brain is the organ which makes us who we are, it is where our personality resides and the potential for catastrophe with any error made is colossal. If the nanobots were lost in the brain there is no way to determine for certain what damage they could cause. We are still unaware what huge areas of the brain are responsible for and so it would be very difficult to explain to patients what the potential risks exactly are.

Looking at the treatment from a slightly different slant another ethical issue would be the proposed use of mesenchymal stem cells in conjunction with the nanoimprinted Polydimethylsiloxane scaffolds. There has long been controversy over the use of stem cells but in this case we are not using embryonic stem cells and they are coming from the patient themselves. If this is still an issue then using another type of scaffold that has more scope for self-assembly in neural regeneration could be an option but this would take more time and could have lower success rates.

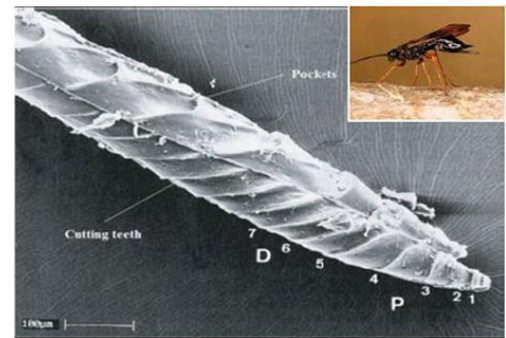
As of yet we haven't discussed how the nanobots will be deployed. In many previous trials the nanobots have been injected into the blood stream in suspension of a fluid. However, in this case injection into a regular artery will probably not be able to get the nanobots into the precise region deep in the brain that we require. Instead we propose taking advantage of an existing piece of technology that is modelled on the wood-boring wasps. In the current DBS treatments electrodes have to be implanted in the brain, however even the slightest movement of these could result in permanent brain damage for the patient. This would also be true of any syringe needle that we used as a probe to deliver the nanobots into the brain. Julian Vincent has found that the design of the wasp's ovipositor is designed in such a way that it can drill through tree bark by producing barely any force. This is done by the reciprocating movements of two adjoining parts which have backwards facing hairs so that they produce less friction upon entering than on removal. Therefore there is no need for any pushing force as the 'drill' is able to pull itself into the material.

Ferdinando Rodriguez y Baenahas applied this technology to the creation of a revolutionary neural probe that will be similar in diameter to that of a syringe needle. This could be used to deliver the nanobots that would be carrying the scaffolds and, if required, stem cells to promote the cell regeneration. Just like the wood-boring wasp, the syringe device wouldn't damage any of the surrounding material on the way in so it avoids some of the risks associated with brain surgery. It will enable the nanobots to be released as close to the Substantia Nigra as possible, closer than using the current technology that would cause too much tissue damage upon entry. Steering can be achieved by

offsetting one of the two parts, resulting in the probe curving in relation to its axis. Rotating the probe around this axis will also provide a 3rd dimension. Further research that has built upon these findings has mimicked the microstructures on the surface of the wasp's ovipositor (figure 6) which would prevent movement of the probe once it has been positioned. Scientists at Imperial College London and the Micro and Nanotechnology Centre (MNTC) are working on a surface texture that can be applied to the device where a series of cantilevers can release the anchoring hooks. It will prevent any migration of the device when it's in position.

Figure 6

The delivery point remaining completely stationary will not only benefit the patient in regards to there being less damage to neurons, but it will also make retrieval of the nanobots easier. Once the nanobots have located the dead dopaminergic neurons and released their nanomaterial scaffolds they will need to be removed from the patient to avoid any damage. If the syringe is in exactly the same position then the nanobots need only to remember their route and retrace it in order to find a safe passage out of the brain. If this isn't possible then the syringe might be able to produce dopamine at a higher concentration than that found in the Substantia Nigra so the nanobots can use the same technology as when they were initially released to seek out the high dopamine concentration and therefore be removed. A possible problem with this would be any adverse effect that the dopamine could inflict on the patient. We would suspect that symptoms might arise that would be similar to schizophrenia as this is caused by increased dopamine. However, research into this would need to be carried out.



Conclusion

To summarise, our proposed application of nanotechnology in the treatment of Parkinson's disease involves the use of nanomedibots to promote the regeneration of the cells of the Substantia Nigra, possibly in collaboration with other nanomaterials and stem cells, to encourage the reduction of the Parkinson's symptoms which cause the major day – to – day issues associated with Parkinsonism.

One of the positive aspects to the treatment is that it could cure a disease that is only suppressed using current therapies. Not only would this alleviate patient suffering, but it would save money that would otherwise be spent on prolonged drug treatments and DBS maintenance. It takes advantage of the potentially world changing developments being made in nanotechnology and applies them in a use that will improve the quality of life of an aging population. It provides a pathway, not only into the treatment and cure of Parkinson's, but also the functioning of the brain on a previously unexplored level which could help us to reach other areas of medicine such as Alzheimer's, as well as giving us the fundamental understanding of the central mechanics behind cell regeneration. Although large investments will have to be made in the development of this technology and in clinical trials, we think that it is worthwhile because of the huge improvement in the treatment of Parkinson's, and also the general technology that will stem from the research.

At this moment in time the technology is still in the early stages of development. With our idea for advanced medical bots being greatly theoretical it is not realistic to assume that these could be implemented in the near future. Instead we will be looking at a period of around 5-10 years before the technology is available to make the nanomedibots proposed, with a further 10 – 15 years of clinical trials before it could be made widely available. Despite this, we do think that nanotechnology holds the key to curing Parkinson's disease.

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Images:

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Figure 2 - <http://www.memorylossonline.com/glossary/substantianigra.html>

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