

**The Medical Potential of Nanotechnology: Possible
Applications in the Treatment of Neurological Diseases
Such as Parkinson's**

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PASS WITH MERIT

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Abstract

The main focus of this paper is on the potential for nanotechnology to provide novel therapeutic approaches to neurological diseases. I will concentrate specifically on Parkinson's Disease (PD) as it is a commonly occurring condition with a clear need for novel therapeutic approaches to treatment, and also has a range of potential applications for nanotechnologies. I will suggest that the unique properties of some developing nanotechnologies, namely the nano-electrode, nanotubes, and buckminsterfullerenes (or buckyballs), may make them suitable for use in developing new treatments for PD.

Introduction

Nanotechnology is the relatively new area of technology concerned with the properties and uses of structures engineered with at least one dimension measuring at the nano-scale (roughly speaking 10^{-9} - 10^{-7} metres, or 1 to 100 nm, the scale at which individual molecules and molecular structures are measured). The application of some of these new technologies to medical problems could become crucial in the future: due to their minute size they have the potential to overcome some current barriers in medicine by allowing for safer and more precisely targeted treatments. For example, one hope for the future is that nanotechnology may enable us to deliver therapies to specific (individual) cells, something that cannot be done using the larger scale technologies available today. This has the potential to improve the quality and speed of patient treatment, to minimize side effects and damage to other bodily tissue and possibly to lead to a better post-treatment quality of life.

Current research in nanotechnology is focusing on its possible uses in development of biosensors, as tools for microscopic surgery and as a potential method for highly specific drug delivery. For example "quantum dots" (semiconducting nano particles with unique optical properties) are being used in the development of highly sensitive cellular imaging, and carbon nano-tubes (tubes, with a diameter of only a few nanometres consisting of a regular covalently bonded carbon structure) are being used as "scaffolds" to enhance growth of bone and other biological tissue. Another piece of nanotechnology research is focusing on the use of buckminsterfullerenes (more commonly known as buckyballs or simply fullerenes) in drug delivery. Buckminsterfullerenes (named after the architect Buckminster Fuller, who became famous for his geodesic domed buildings) are an allotrope of carbon with the molecular formula C-60 where the carbon atoms are arranged as the vertices of a polyhedral, near-spherical, hollow nanoparticle. Current research is focusing on their theoretical use as vehicles for drug delivery to specific sites within the body. Much of this research is directed towards delivery chemotherapeutic drugs directly to tumours with minimal harm to other bodily tissues; however once developed this technology has the potential to be applied to a variety of medical fields.

Parkinson's disease is progressive neurodegenerative disorder that affects 120,000 people in the UK alone, predominantly those over the age of 50, and has no currently proven disease-modifying therapy. The immediate cause of PD is believed to be loss of dopaminergic neurons and consequent depletion of dopamine from specific regions of the brain. Degeneration of dopaminergic neurons is associated with the presence of cellular aggregates of the protein α -synuclein, known as Lewey bodies, although we currently lack a precise

understanding of how these may cause the neurodegeneration. Dopamine is a neurotransmitter involved in fine control of many motor functions, hence reduced dopamine leads to many of the characteristic symptoms of PD such as tremors and jerky movement.

Nanotechnology: Potential for Development of Novel Therapies

I will suggest in this paper that three separate developments in nanotechnology have the potential to be used in the treatment of PD.

Firstly, I will discuss the potential of nanoelectrodes and nanowires in delivering deep brain stimulation (DBS), a symptomatic treatment applied to some PD sufferers whereby electrical stimulation is applied via electrodes implanted in specific areas of the brain. Nanoelectrodes differ from conventional electrodes as they are generally below 100nm in diameter. They are constructed from carbon nanotubes; hollow tubes consisting of regular formations of covalently bonded carbon atoms). These tubes have the properties of semiconducting materials stemming from the arrangement of their electrons in the molecular structure. The carbon-carbon bonds in nanotubes are similar to those present in graphite, with delocalised pi-bonded electrons responsible for conferring electrical conductance. Indeed, a nanotube is perhaps best thought of as a single layer of graphite structure rolled into a cylindrical shape; the cylinders vary in diameter from 0.5 to 1.5 nm, but can be up to several cm in length. Nanotube synthesis involves applying specific pulses of high energy to a graphite target under controlled conditions. For instance, discharging a high current through graphite electrodes can produce nanotubes; this is currently the most used method for production and could also be a viable method for larger, possibly commercial scale production. Nanotube synthesis is an area of rapid change, and it would be surprising if one or more methods for commercial scale production were not available within the next few years. Nanowires are electrically conducting, insulated wires at the nano-scale. Such nano-scale conductors would be ideal for transmitting the electrical impulses from a neuro-stimulator to the site at which the nanoelectrodes are implanted. There are emerging developments in nanotechnology making manufacture of insulated nanowires a possibility in the near future. One approach involves the use of electrically conducting organic materials, mixed with non-conducting molecules to form crystals in the shape of a nanowires. This method has succeeded in growing the crystals into a regular shape, but a complete nanowire of sufficient length has yet to be synthesised. An alternative approach focuses on the use of a silicate material as an outer mould (and insulating sheath) filled with an electrically conductive polymer. Again, this technique has shown promise in small-scale production but has yet to demonstrate that it can be scaled to produce long enough nanowires for any medical or commercial use.

Secondly, I will consider an alternative use of carbon nanotubes as scaffolds to aid in the regrowth of neurones. Researchers have shown that it is possible for nanotubes to act as scaffolds for regrowth of some tissues: for example a study in rat bones has shown that the nanotubes are both compatible with the tissue and can aid in the development of the bones. I will discuss recent exciting developments that could possibly extend this use to enhance neuronal regeneration.

A third possible application for nanotechnology would be the use of buckminsterfullerenes (or buckyballs) as a drug delivery system to deliver dopamine to the brain through the blood brain barrier, and possibly help to combat the movement related symptoms associated with the disease. Buckminsterfullerenes are molecules of carbon-60 that form a regular near-spherical shape consisting of 12 pentagons and 20 hexagons with atoms of carbon forming the vertices (hence they look much like an old fashioned football, and are hollow in the centre). They can be synthesised in much the same way as carbon nano tubes, specifically by passing electricity through graphite rods in a helium filled environment. Buckyballs are formed and they gather at the graphite electrodes as soot (about 10% of the soot formed is the carbon-60 molecule). As with the nano tubes, it should be possible to commercialise this process thus making buckyballs an available nanotechnology for possible medical use.

Deep Brain Nano-Stimulation

Deep Brain Stimulation (DBS) is a widely applied symptomatic treatment for advanced PD (and for some other motor-degenerative disorders). DBS provides electrical stimulation to certain parts of the brain, allowing for relief (at least in part) of some of the more debilitating problems associated with neural degeneration (for example, DBS has been proven to improve motor control). Currently DBS involves the implantation of a conventional electrode, which is connected (via a lead) to a battery-powered neural-stimulator (also known as an implanted pulse generator). The neuro-stimulator passes high frequency electrical pulses along the lead to the electrode, which then directly stimulates the selected areas of the brain (those associated with motor control for example). Although the precise mechanism of action of DBS (and its effects, if any, on dopamine levels) is not known, the treatment often provides effective symptomatic relief and can enhance patients' quality of life substantially. However, there are potential side effects with DBS: some of these are neuropsychiatric (for instance hallucinations, depression and cognitive dysfunction), some relate to complications of the neurosurgery involved in device implantation (such as bleeding within the brain, and swelling of tissue).

It is possible that nanoelectrodes have the potential to be a more effective delivery system for DBS than conventional electrodes. Nanoelectrodes would theoretically be able to stimulate a more precise area of the brain than the larger electrodes, and this would be likely to give the therapy a higher success rate, and to reduce side effects. Insulated nanowires could theoretically be used in place of the conventional leads, so that the entire process of implantation could be accomplished at the nano scale. This approach would require the development of precise techniques for nano-electrode implantation, and would also be helped by more precise identification of specific brain areas that benefit from DBS, where the stimulation could then be targeted (to some extent the latter development may result from initial trials with nanoelectrode DBS). One benefit would potentially be to minimise side effects that may be caused by stimulation of areas adjacent to those required for treatment, both as a result of more precise delivery of the pulses to the target area, and the reduced total currents that would need to be applied. Another potential advantage is that the requirement for lower electrical currents would, at least in theory, increase the period of time between

battery replacement surgeries and therefore increase the patients' quality of life. However, this latter effect may be counteracted by the nanowire having increased resistance, as resistance of a wire is inversely proportional to cross sectional area. This may use up battery life and mean that surgery to replace the neuron-stimulator may occur more often, instead of less. Another obvious benefit would be reduction in the surgical trauma required during device implantation. Currently a hole of about 15mm in diameter is needed to insert the electrode and lead. Inserting a nano-electrode and nano wires in place of the larger electrode and current lead could minimize this and therefore, at least in theory, make the surgery safer as the smaller surgery would lead to decreased risk of common surgical complications such as haemorrhage and infection. It could also have the benefit of reducing damage caused to neural tissue adjacent to the path of the electrode as it is inserted deep into the brain.

Nano-Scaffold

The "Bucatini Project" pioneered by the University of Milan-Bicocca have used a novel form of nanotube composed of a mixture of two biodegradable plastics as "nano-conduits". Integrated into these tubes was a gel containing natural growth factors. These nano-tubes were then implanted into the damaged spinal cords of rodents in the hope they would act as a bridge for neuron and axon regeneration. After a period of 6 months the researchers found that the tubes had acted as "conduits" and nerve fibres had grown through some of the tubes: hence some of the rats treated did display a slight increase in movement due to the tubes bridging the damaged axons and the gel to enhance the neuron regeneration. Another study has shown that neurons not only grow around these tubes but can also interact with them. This research has suggested that the nanotubes lead to increased electrical activity within the neurons themselves. This kind of research suggests that nanotube implantation has the potential to enable rapid post-surgery improvement as, whilst damaged neural tissue regenerates, the nano tubes can enhance neural connectivity, transmitting impulses within the brain in much the same way as their biological counterparts.

These are immensely exciting findings and open the possibility of application of this technology to neurodegenerative conditions such as PD. Implanting such tubes into the brain, could stimulate ineffective or dormant dopaminergic neurons to re-grow and reconnect, possibly providing a genuine disease modifying treatment for PD. Ideally the dopamine producing area of the brain could be targeted for implantation of neurone-stimulating nanotubes, and the dopamine insufficiency could be reduced or overcome significantly reducing the motor related symptoms of PD.

Implantation of nano tubes could, however involve potential drawbacks. Firstly, techniques for the precision surgery required in order to implant them into the specific area of the brain will need to be developed. Current neurosurgical techniques would probably not offer sufficient precision, and may be potentially life threatening in the aging population who stand to benefit most from the therapy. It may well be that any proposed use of nanotubes for this purpose would have to wait for development of suitable techniques in micro-neurosurgery that would decrease the risk/benefit ratio sufficiently to make such intervention a viable therapeutic option.

Secondly the data to demonstrate convincingly that neuronal growth will ensue has not yet been obtained. Although the experiment in rats gives opens up this possibility, human cells may react differently; it is clear that many years of further research will be necessary before we could obtain sufficiently compelling evidence to undertake trials in PD patients. It is also true that age may be an issue (the mean age for onset PD is 60 years): the older a person the less their capacity for renewal occurring in the body, and it may be that a limit on the age at which sufficient neuronal pathways could be reformed may restrict the utility of this approach to PD

However, since current statistics show that one in between 5 and 10 percent of PD sufferers are “young onset”, where symptoms begin between the ages of 20 and 50, even if unsuitable for the elderly this surgery would have the potential to improve the quality of life for a significant number of sufferers.

Combining Nano-Therapies

One intriguing possibility is that some combination of these two technologies (DBS and neuronal regeneration using nanotubes) could be most effective. Thus it is possible that implantation of carbon nano tubes into the brain attached, initially, to a neuro-stimulator may be an even more promising approach to promote neuronal regeneration than nanotube implantation alone.

Researchers have shown that rat neurons, cultured *ex vivo*, can interact with carbon nanotubes to produce viable, neuronally active networks (University of Trieste, Italy). Researchers are currently working on exploring this development for *in vivo* use to cure central nervous system related diseases (for example Epilepsy). Researchers are currently working on exploring this development for *in vivo* use to cure central nervous system related diseases (for example Epilepsy). This study showed not only that carbon nano tubes are biocompatible but also that the nanotubes were able to bridge the gap between neurons (by conducting neuronal impulses) whilst regeneration was occurring.

It has been shown that mild electrical stimulation can increase the speed growth of neurons in mammals. For example one study stimulated the brains of mice for an hour using a mild electrical current then measured the amount of neuronal generation both by the mice who had had received brain stimulation and those who had not. After a three to five days, it was shown that the brains of the animals that had received the stimuli had at least double the neuronal growth of control group.

This research suggests that carbon nano tubes able to carry electrical pulses for deep brain stimulation may also help to promote neuron growth. This growth could possibly help to overcome some of the motor control problems and even slow or reverse progression of the disease.

Nano-Scale Drug Delivery

Scientists have hypothesized that hollow nano-balls (buckminsterfullerenes) may be able to carry therapeutic substances within them which would otherwise be unable to cross the blood brain barrier. It has also been hypothesised that the buckminsterfullerenes could release them at specifically targeted sites within the brain. Not only would this lead to more effective treatment of the affected area, it

would reduce the amount of medicine needed (as all would go to the target site) and reduce the potential drug related side effects in the rest of the body.

The neurotransmitter dopamine helps to control fluidity of movement. In PD the dopamine producing areas of the brain are primarily affected (resulting in the motor symptoms pathognomonic features of the condition). Thus, if it were possible to target dopamine-containing buckyballs to affected areas of the brain, and to engineer release at these sites, this may constitute a highly specific, novel therapeutic option. With currently available technology, however, this represents a significant challenge. Whilst it has been shown that buckyballs are able to cross the blood brain barrier, there is no currently available methodology for either synthesising dopamine-containing C₆₀ molecules or for engineering such specific release. It has been shown that metals can be implanted within the “carbon cage” of a buckminsterfullerene by soaking the graphite in a solution of the metals salt before continuing the process of synthesis. Therefore an extension of this technique may enable synthesis of buckyballs containing small molecules, such as dopamine or other drugs, in the future. Targeted release however is likely to prove a more difficult challenge. Buckminsterfullerenes are extremely stable structures that require high energies to disrupt the covalent bonds and release the caged molecules. One possible approach would be to use small traces of other elements during synthesis, the idea being that their incorporation into the buckyball may make the overall structure less stable. It may be that such a destabilised structure could be induced to break open by use of energy pulses targeted at the required sites of action. These could possibly be administered by a laser or ionising radiation source. Another potential solution could be the use of implanted nanoelectrodes to deliver pulses of current that would be designed to provide the required energy. In this way, it is possible that therapy combining all three of the nanotechnologies I have discussed could provide a greatly enhanced treatment option for some PD patients.

However one major drawback for this treatment option is the possibility that buckminsterfullerenes are toxic. It has been shown that buckyballs in aqueous solution have the potential to form free radicals that can interact with the phospholipids in cell membranes causing the membranes to rupture and ultimately killing the cells (which, although useful for treatment of cancer is not the desired result around healthy body cells). Researchers at Rice University located in Texas have, however found a way to reduce this by substituting different functional groups onto the buckyball structure. Potential toxicity, of course, represents a general problem for all untested therapies, including nanotechnological approaches. Extensive safety evaluations (using a combination of *in vitro* and animal models) would be needed before any of these technologies could be used for human clinical trials.

Conclusion

Overall I believe that nanotechnology has many potential roles in the future development of treatments for diseases that require novel therapeutic approaches. Carbon nanotubes could provide a way to bridge gaps between damaged neurons to both help them in regrowth and to enable a temporary connection to be forged whilst the regeneration takes place. Nanoelectrodes and

nanowires could cause less damage to brain tissue in deep brain stimulation and therefore minimize side effects. And, possibly, a combination of the two approaches could mean that increased neuronal growth was stimulated during DBS, providing simultaneous symptomatic and disease modifying therapies that have the potential to increase quality of life for PD sufferers.

Buckminsterfullerenes offer a possible route for crossing the blood brain barrier to help with the delivery of drugs; however, research into this approach is at a very early stage and it is clear that significant new developments (for example in eliminating potential toxicity, and in allowing targeted release of contents) will be required before this potential can be realised.

In summary, it is clear that nanotechnology has the potential to revolutionize treatment in many areas of medicine, and there are distinct technologies emerging from many current research projects that could be applied to the treatment of PD. The dynamic pace of current research into this area will ensure that our capabilities in the nanotechnology field increase rapidly. Such developments, combined with concomitant enhancement of our surgical techniques and instruments, and increased understanding of the pathology of diseases are likely to lead to dramatically improved therapies for many chronic conditions such as PD.

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