

Role of nanobiotechnology in Parkinson's disease

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Abstract: Nanotechnology, employing the use of engineered materials with the smallest functional organization on the nanometre scale in at least one dimension, is one of the most new and innovative developments in contemporary science and is set to revolutionize the future of medicine. A further innovation in nanomedicine has been manufacturing drugs as nanoparticles as they are thought to be absorbed more easily into the body because of their size. It could offer easier methods of locating and targeting specific cells on a nano-size level, on an atomic scale, and delivering drugs to these cells. This is good because mostly, very powerful drugs are needed to kill mutated cells e.g, tumor cells, and these drugs would be hazardous if they came into contact with normal functioning cells. So nanotechnology could provide devices to limit and reverse neuropathological disease states, to support and promote functional regeneration of damaged neurons, to provide neuroprotection and to facilitate the delivery of drugs and small molecules across the blood-brain barrier. All of them are relevant to improve current therapy of Parkinson's disease (PD).

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INTRODUCTION

James Parkinsons was the one first described a group of symptoms that later became known collectively as "Parkinson's disease", over 200 years ago¹. Talking about Parkinsons disease, it starts at a molecular level (a genetic defect and/or an environmental agent yield to a misfolding of proteins) with consequences at the cellular level (dysfunction of the ubiquitine proteasome system and mitochondria with free radical formation and protein aggregation leading to the apoptotic death of dopaminergic cells), which in turn produces biochemical and neurophysiologic disturbances, particularly dopamine deficiency in the striatum and in other nuclei, and increased firing rate with abnormal firing pattern in the sub thalamic nucleus (STN) and internal segment of the globus pallidus (Gpi)². The clinical expression of all these disturbances is Parkinsonism. It was observed that there are several unmet needs regarding to this disease, which require urgent solution to improve the care of patients.³ The main obstacle in treatment of PD, is that there is no way of curing it currently; treatment can only offer temporary symptomatic relief¹.

In United Kingdom PD is seen as a progressive neurological condition seen at a prevalence of 1 in every 500 people. So it is vital to develop effective treatment strategies. In this regard nanotechnology is a new progression in medicine which may be used to help treat this common disease¹. This review is a brief incursion into the future of PD. It is, thus, something speculative yet a good intellectual exercise for basic researchers and neurologists, which might positively influence the future of a patient with PD.

Nanotechnology and PD

PD is known to be a complex disorder whose keyword is variability^{1,4}. That's the reason its diagnosis is not straightforward. To date, there is no specific test to confirm the condition; therefore it needs to be diagnosed by a specialist, however the symptoms can be controlled by prescribing pharmaceutical drugs, a variety of therapies and also surgery in very rare cases⁵.

Role of nanotechnology in the diagnosis of PD Lab-on-a-Chip

In the last ten years, much new advancements have been made in the medical nanotechnology in relation to diagnosis of Parkinson's disease. One of the most recent and influential innovations in this sphere is the discovery and creation of nano-sized chips, known as "Lab on a Chip", with the potential to diagnose disease rapidly⁶ (Figure 1).

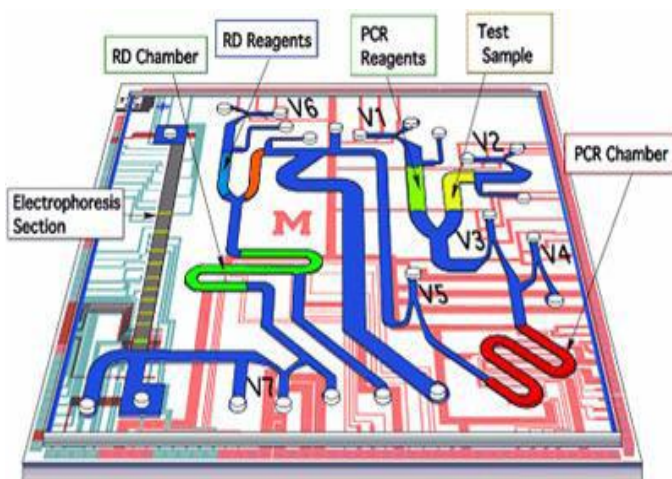


Figure 1: Lab on a chip.

Since their discovery in 1990s, a great amount of research has been carried out into the new-found lab-on-a-chip. Now-a-days these specialized scientific instruments have decreased drastically in size, i.e., they are grown up to one millionth of their original size, scientists can employ many tiny “laboratories” on this chip. Scientists concluded that these silicon chips can analyze many different things all at once e.g. blood samples, tissues etc, and from this information, diagnosis of many diseases such as PD is possible⁶.

Aptamers

Aptamers represents another breakthrough in the nano-technological domain. Aptamers bind to specific target molecules, and are made up of oligonucleic acids or peptide molecules. Aptamer are classified into two types nucleic acid aptamers and peptide aptamers. Nucleic acid aptamers are usually engineered using Systematic Evolution of Ligands by Exponential Enrichment (SELEX), also referred to as in vitro selection, enabling them to bind to different molecules in the body. Recently, the first aptamer based drug has been legalized by the, U.S. Food and Drug Administration, which could be used to treat age-related macular degeneration. It has been found that Parkinson's disease is one of the many that has the potential to be diagnosed by aptamers, particularly the RNA (Ribonucleic Acid) type of aptamer⁷.

PET scan

One of the most reliable scan to assist in the diagnosis of Parkinson's disease is Positron Emission Tomography scan (PET scan). Currently, alpha-synuclein has been shown to accumulate in the blood plasma of patients with Parkinson's disease, and can lead to the formation of Lewy bodies (Figure 2), causing damage to neurons and cell death, hence interrupting dopamine pathways in the brain⁸. It was found that this key information concerning alpha-synuclein could be used to carry out further research into new aptamers. In this regard, RNA aptamers, which could combine with the alpha-synuclein in the blood plasma, would be much more effective due to their higher affinity. Attaching a reporter sequence could be just as effective, if not more accurate, to determine when the aptamer has bound to the alpha-synuclein in the blood plasma. This would allow researchers to establish whether or not there was alpha-synuclein in the blood plasma, and therefore whether the patient had Parkinson's disease. A possibility which could be introduced in the future, would be the use of a PET scan in conjugation with RNA aptamers, and so as the PET scan checks dopamine activity in

the brain, these two could be used together to ensure that the diagnosis is much more accurate⁸.

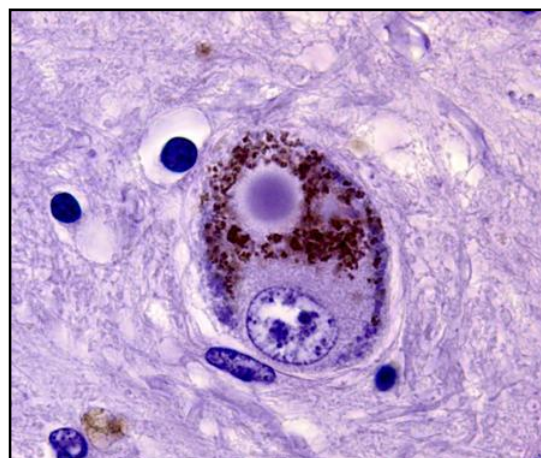


Figure 2: A Lewy Body.

Nanotechnology and PD therapy

As mentioned earlier that in PD multiple neurotransmitter systems are involved, so this means the use of many drugs every day. So, the PD patients are not happy with the prospect of taking 10 or 12 tablets every day. In other words a “magic shotgun” rather than many “magic bullets” would be welcomed by patients. Side by side the main goal would be to develop a tablet containing all the necessary drugs in the precise doses, to be taken once a day. Such a tablet should improve motor, emotional and cognitive symptoms present since the onset of the disease without causing either motor (dyskinesias) or psychiatric complications. All this can simply be summarized in one phrase: different needs in different patients and in different moments in the same patient. Nonetheless, it is likely that nanotechnology will offer tools of finer precision to manipulate complex biological systems with greater selectivity and timing than a gross pharmacological approach. These achievements could contribute decisively to the improvement of drug therapy in PD.

Parkinson's disease can be controlled, to some extent, by a variety of pharmacological therapies, the three most established of which are Levodopa, dopamine agonists and Monoamine Oxidase-B (MAO-B) inhibitors.² However, each of these three treatments encounters a number of issues. Levodopa has both the greatest symptom control and the most detrimental side effects of the three drugs; there is evidence that it may lead to increased motor complications and other adverse effects that could also be caused by dopamine agonists and MAO-B

inhibitors⁹. MAO-B inhibitors may also provide symptomatic relief in the early stages of Parkinson's disease instead of Levodopa, but only provide restricted amount of symptom control. Levodopa, sometimes have limited solubility and may break up before reaching their intended destination. Therefore, despite numerous recommendations and guidelines for use of these drugs with regard to treatment of Parkinson's disease, there is still a tremendously large scope for improvement¹⁰.

Bucky ball

One of the most interesting advancements in nanomedicine is the system of drug delivery based on tiny structures that are engineered nanotechnologically, where the drug can be dissolved, absorbed or dispersed in the matrix of the nanoparticle. A possible alternative to this would be a vesicular system in which the drug is carried in an aqueous or lipid carrier within the walls of a hollow particle. Fullerenes are carbon isoforms arranged in spherical cage-like structures of size range 0.7-1.5nm. The first to be discovered was buckminsterfullerene, also known as a "buckyball", by Curl, Smalley and Kroto in 1985; it consisted of 60 carbon atoms¹¹ (Figure 3).

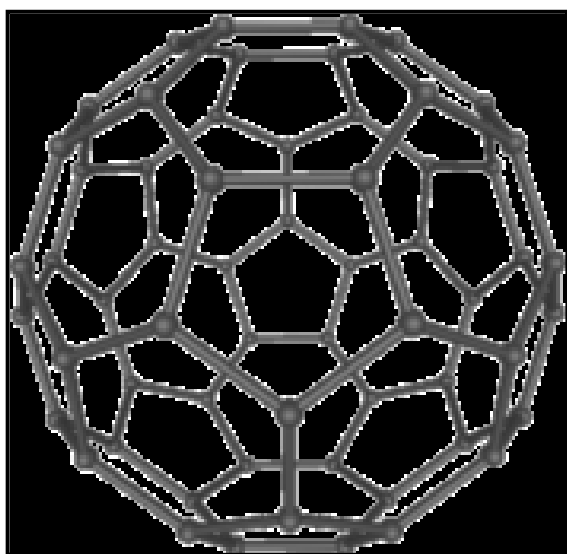


Figure 3: A Bucky ball.

Furthermore, by using tubes rather than spheres, smart bio-nanotubes of tubulin coated with lipids could encapsulate a drug (for example Levodopa), and use the electrical charges of different cellular structures to "open" the nanotubes, releasing the drug, at the desired site within the body¹². Now-a-days, nanodiamonds are also an area of active research in drug delivery, due to their large surface

area and tendency to cluster. It has been found that drugs could be attached to the surfaces of individual nanodiamonds, remaining inactive while the nanodiamonds are clustered together. Then once these particles reach the intended site of delivery, the clusters break apart and release the drug load.¹³ Recently, a novel biodegradable brain drug delivery system, i.e, the lactoferrin conjugated poly-ethylene glycol-poly lactide-polyglycolide (PEG-PLGA) nanoparticle (Lf-NP) was constructed, and was found to be a promising drug delivery system with reasonable toxicity¹³.

Now it is evident that Polymer nanoparticles have an extraordinarily large surface area that presents diverse opportunities to place functional groups on the surface¹⁴. These "smart" surfaces and materials could enable the development of better systems for in vivo drug delivery. So, in this regard, researchers found that dopamine containing liposomes, after stereotactic implantation in the striatum, can produce both behavioral recovery and enhanced striatal dopamine levels in a rat model of PD¹⁵.

Further advancements in the drug delivery, employing nanotechnology principles, in the case of PD, involves the use of deep brain stimulators that are routinely implanted in the STN¹⁶ or the Gpi opening up the possibility of simultaneously delivering well-chosen drugs (glutamate antagonists, cannabinoids, and others) or other molecules (trophic factors, enzymes, etc.) that are able to modulate the activity of output structures of basal ganglia.

Finally, implanting biosensors in the striatum and other brain nuclei to monitor the levels of dopamine and other neurotransmitters could be of interest¹⁷. Now-a-days this could be done by minimally invasive surgical techniques and the directing of the biocompatible sensor by magnetic nanoparticles. This biocompatible sensor together with the magnetic nanoparticles could be directed to the specific area of the brain by an external magnetic field. Although this guidance could be done by a permanent magnet, a more complex set-up would be preferable for patients, and, therefore, the external magnetic field could be applied by magnetic resonance-like devices.

This could be ended with the fact that there are significant advantages of using nanostructures as drug delivery vehicles opposed to more traditional delivery mechanisms. These advantages include; high stability, the possibility of transporting both hydrophilic and hydrophobic drugs, high carrying capacity due to greatly increased surface area, better bioavailability, systems that allow controlled release

rates or release upon an external stimulus and the possibility to exploit a range of patient-friendly delivery routes¹⁸.

Role of nanotechnology in gene therapy of PD

As with the concept of gene therapy, in case of gene therapy for Parkinson's disease involves the administration of standard, "healthy" genes into a Parkinsonian patient with defective, "faulty" genes with the aim to trigger the cells within these genes to begin producing dopamine.¹⁹ Furthermore it is anticipated that these healthy genes begin to adapt the malfunctioning cells by making alterations to them that trigger the production of dopamine within them to resume. So if such a process can be achieved effectively with little or no complications, then this way of treatment could be a valid way of controlling or ceasing the symptoms of Parkinson's disease. In doing so, neurotrophic factors (factors that help to prevent the death of neurons) and proteins that work to amplify dopamine production e.g., Glial Cell Derived Neurotrophic Factors (GDNFs), encourage the neurons to grow and thrive and can prevent further damage being caused to these cells¹⁹.

Localized delivery of genes and trophic factors avoiding the use of viruses

In the last few years, scientists have endeavored to directly deliver the genetic material into the areas of the brain that require them for development and repair. However, many such trials have proven that this method is impractical, because it is too difficult to maintain the correct levels of the molecules in the correct regions of the brain. Considerable side effects were noted, decreasing the suitability of this method with regard to treating Parkinson's disease, so now an alternative to the use of neurotrophic factors is the introduction of proteins that increase the levels of dopamine produced within the brain specifically enzymes including dopa decarboxylase and tyrosine hydroxylase. These proteins would act as an alternative to Levodopa, dopamine agonists and MAO-B inhibitors. These proteins instead of being delivered by injection (which would simply mean that the proteins were unable to enter the necessary cells due their inability to penetrate the cell walls) are delivered by the gene therapy techniques into the cells. So now it is evident that this would effectively create a new dopamine production centre within the brain, representing a revolutionary step concerning the treatment of Parkinson's disease²⁰.

The genes encoding either the neurotrophic factors or dopamine manufacturing proteins are inserted into the viruses. The recombinant viruses enveloping the genes are injected directly into the

defective areas of the brain and are able transport the therapeutic material to the sites within the brain where it is needed. However it was found that these recombinant virus vectors are at high risk of being recognized as foreign material by the body and therefore being subjected to an immune response. Furthermore, mutagenesis of the virus vectors may lead to the formation of tumors during carcinogenesis and even death²¹.

Talking about the most non-viral vectors, these are considered safer but they lack the high transfection efficiency obtained with viral vectors. For effective gene therapy, a genetic payload must be delivered to the targeted cell-tissue, then enter such cell and get transported to the nucleus to achieve expression. The initiating event, which is the entrance of the genetic material into the cell without the use of a viral vector, is limited because of the need to supply the DNA to the surface of the cell in sufficient concentration to effect entrance. In this regard, ultra fine silica nanoparticles, functionalized with amino groups, have been shown to bind and protect plasmid DNA from enzymatic digestion and to effect cell transfection in vitro^{22,23}. Recently, the possibility of using ORMOSIL nanoparticles as a nonviral vector for in vitro gene transfection has been found²⁴. Using such nanoparticles, researchers have delivered genes into the brains of living mice with an efficiency that is similar to, or better than, viral vectors and with no observable systemic or neurologic toxic effects²⁴. The results were found to be highly promising, but the long-term toxicity of nanoparticles has to be monitored.

In the past few years, these gene nanoparticle complexes are applied to models of PD. Using these complexes it was found that, currently delivered genes (with viral vectors) in the striatum or the STN of PD models or human beings, such as those encoding the production of tyrosine hydroxylase, cyclohydrolase¹, aromatic amino acid decarboxylase^{25,26} or glutamic decarboxylase²⁷ could be administered with this new approach. Also, the trophic factors could be released, important for dopamine cell survival (i.e., Glial Derived Neurotrophic Factor (GDNF), Brain Derived Neurotrophic Factor (BDNF), etc.) or molecules involved in the development of dopamine neurons, such as sonic hedgehog or Nurr1, in the nigrostriatal pathway^{28,29}. Many alternatives to these delivery systems are being explored now-a-days. Thus, genes can be delivered in liposomes administered intravenously and pegylated immunoliposome delivery of the tyrosine hydroxylase gene has already been shown to alleviate behavioral deficits

in rodent models of PD^{30,31}. Side by side, other research is looking at how quantum dots might spur growth of neurites (immature neuron sprouts). Biocompatible quantum dots are semiconductor nanocrystals that can be used as a biolabelling tool but also as a key building block for complex bioprobes. They have the ability to bind target selective molecules and therapeutic molecules, enabling efficient delivery of treatments via a 'probe' to the diseased area. Scientists are now employing many approaches to add adds bioactive molecules to the quantum dots, in a way to provide a medium that will encourage the growth of neurites in a directed way³².

Researchers proposed a technique involved condensing DNA plasmids into nanoparticles, enabling them to be delivered to the brain as a means of ceasing or preventing the degeneration of the nervous system. This technique is non viral and therefore the issues highlighted during trialing of viral vectors are less likely to occur using this method. In this technique polycations are used to compact individual molecules of plasmid DNA to form compacted "DNA Nanoparticles" (DNPs) (Figure 4).

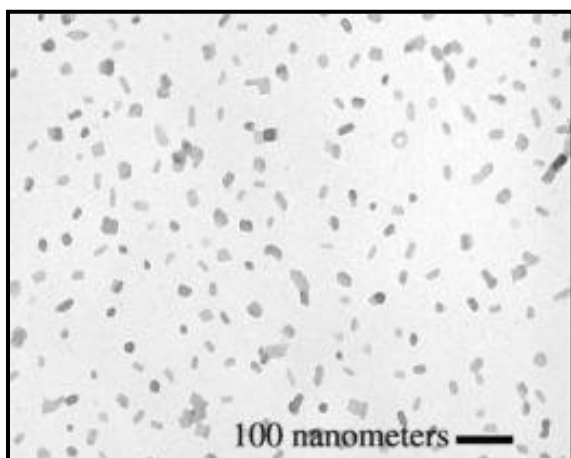


Figure 4: DNA nanoparticles.

In theory, these particles can then be injected directly into the brain of patients with Parkinson's disease as an alternative to use recombinant viruses. In addition to avoiding immune response and subsequent disastrous side effects, using DNPs instead of alternative methods ensures that even if the DNPs are injected into the targeted area of the brain, rather than inside specific cells, they are able to effectively penetrate and subsequently enter the correct area cell. This can be achieved because unlike hydrated DNA, the DNA plasmids, once

compacted, are small enough to cross the nuclear membrane pore of post-mitotic cells once they have passed through the cell wall and the cytoplasm. Studies undertaken by Yurek involved injecting compacted DNPs directly into the brains in order to carry GDNF protein to the sites that required it as an alternative to the use of virus vectors. Results confirmed that immune activity within the site of injection was negligible and this interference was found to be as a result of the injection process rather than the DNPs themselves. This minimal immunogenic response to the injection DNPs suggests that nanotechnology could be used to create an effective non-viral alternative to overcome the issues presented by virus vectors.

Neuroprotection and nanotechnology

One of the therapeutic fields in nanotechnology is Neuroprotection. Neuroprotection refers to any therapy attempting to stop or slow down the death of neurons, however any such therapy should be directed to interfere with some of the mechanisms involved in neuronal death.^{33,34} Neuroprotective therapy of PD is still theoretical, but it is based on the concept that the three to four hundred thousand at-risk dopaminergic neurons in the human substantia nigra can somehow be protected from the complex degenerative process that causes premature cell death and depletion of dopamine. Once identified and shown to be effective, neuroprotective drugs could be used in patients with early clinical signs of disease or potentially even prior to the appearance of disease in those shown to be at genetic risk³⁵.

It was found that potential neuroprotective strategies would act by interfering with the expression of the abnormal gene product (RNAi, antisense therapies) avoiding the misfolding and aggregation of misfolded proteins (vaccination, reinforcement of ubiquitine proteasome system and chaperones, reinforcement of free radical scavengers systems, avoidance of microglial activation, immunization, reinforcement of mitochondrial activity and excitotoxicity antagonism, among others) and interfering with the signaling pathways leading to apoptosis^{36,37}. It was concluded that any neuroprotective strategy should be applied as early as possible in order to obtain the maximal benefit.

Selegiline and rasagiline (both monoamine oxidase inhibitors), dopamine agonists, and the complex I mitochondrial fortifier coenzyme Q10 have been evaluated in clinical trials and are receiving the most attention as possible neuroprotective agents. Also, water-soluble derivatives of buckminsterfullerene (C60) derivatives (fullerenols) are the main achievement

of nanotechnology for neuroprotection³⁸. It is evident that fullerenols have antioxidant properties but they also inhibit the activity of glutamate receptors and exert antiapoptotic effects. Studies on one class of these compounds, the malonic acid C60 derivatives (carboxyfullerenes), indicated that they are capable of rescuing mesencephalic dopamine neurons from toxin-induced degeneration³⁸. Despite these promising results in vitro, in vivo data are scarce so further research relating to in vivo trails need to be performed.

In recent years it was found that neuroprotection in PD could also be achieved by stimulating neurogenesis and migration of new cells to SNpc (and other affected nuclei). In mature mammalian brain, certain areas retain the capacity for neurogenesis³⁹. One such area is the sub ventricular zone (SVZ) of the lateral ventricle. The SVZ contains a population of slowly dividing stem cells that generate faster-proliferating neural progenitor cells⁴⁰. Recently, Bharali et al.²⁴ provides evidence as to how nanotechnology could stimulate the proliferation and migration of endogenous stem cells, which are converted to dopaminergic neurons once in the correct place and environment by way of receiving the appropriate signals. These amino-functionalized organically modified silica (ORMOSIL)-mediated transfections can also be used to manipulate the biology of the neural stemprogenitor cells in vivo.

Intracellular surgery, in the case of PD can be attained by nanotechnologies⁴¹. Such “nanodoctors” would identify the parts of the cell and molecular signaling pathways that are suffering and might eventually act on them (i.e., avoid and repair DNA damage, remove misfolded protein deposits, increase lysosomal activity, etc.) with an extremely high degree of selectivity and specificity⁴². High frequency deep brain stimulation (DBS) of the sub-thalamic nucleus is the preferred surgical treatment for advanced parkinson's disease⁵². There also exists a possibility of reversing pathology in some cases of PD patients⁴².

Reconstructing the SNpc and the nigrostriatal pathway

The best and most novel therapy for PD is to directly replace, or stimulate re-growth indirectly of damaged and lost cells within the parkinsonian brain. However to fulfil this many problems are encountered because functional regeneration after injury to the mammalian CNS is extremely poor, largely because of the non-permissive environment in the mature CNS. Several barriers to the repair process exist including: formation of scar tissue, gaps in nerve tissue formed during phagocytosis of

dying cells, factors that inhibit axon growth, and the inability of many neurons to initiate axonal extension. So, in the case of PD the main objective of cell therapy should not be limited to replacing the dopaminergic deficiency but to restoring or reestablishing the normal anatomy (connectivity) and physiology (appropriate synaptic contacts and functioning) of the striatum.⁴³

Now-a-days, stem cell-based replacement therapies have prompted high expectations owing to their theoretical capacity for generating millions of well characterized dopamine cells, which once implanted could rewire the nigrostriatal system. In spite of these, the use of cells as a vehicle of molecules essential for dopamine transmission and/or cell survival. Encapsulated cells, genetically modified to release any molecule with these properties, are isolated from immunological attack and continuously release the molecule, and are being frequently used⁴⁴ (Figure 5).

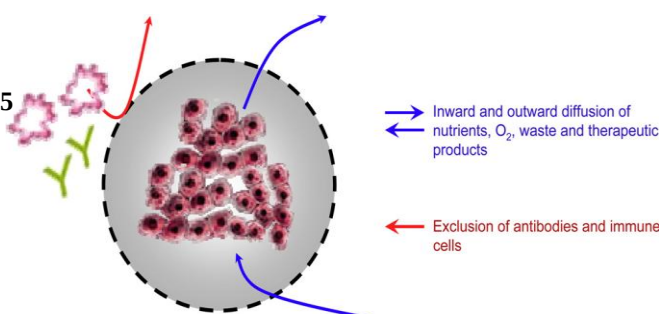


Figure 5: Cell encapsulation technology. Immobilization of biologically active material within a polymeric matrix surrounded usually by a semi-permeable membrane designed to circumvent immune rejection.

Another pragmatic approach is to implant cells able to survive and produce and release dopamine or Levodopa. This happens in the case of human retinal epithelial pigment cells, which produce dopamine. In this technology micro carriers are used that can be linked to cells in order to increase their survival⁴⁵.

Many trails indicated that materials with dimensions greater than 1 mm have not invoked proper cellular responses to regenerate tissue. However, due to their ability to mimic the dimensions of constituent components of natural tissues, like proteins, nanomaterials may be an exciting successful alternative. So, nanomaterials interact much more closely with cells thereby inducing changes in cell functions. For example, carbon nanofibres promote neural growth. Uptil now materials investigated include: nanophase ceramics, metals, polymers, and composites.

Similarly, nanoengineered scaffolds that support and promote neurite and axonal growth are highly promising in this regard^{46,47}. This approach is now being welcome in PD since the implantation of cells cannot be performed in the SNpc owing to the impossibility of implanted cells to extend axonic prolongations long enough to reach their target cells, which are located in the striatum. So, cells are implanted ectopically in the striatum to guarantee the establishment of synaptic contacts with the GABAergic projection cells, as well as with the corticostriatal glutamatergic neurons and with local interneurons⁴⁴⁻⁴⁶. It has been found that the availability of new materials able to promote, guide and protect new axons emerging from implanted cells might allow the implantation of cells in their natural environment, the SNpc. Attempts with trophic factors and co-implantation of peripheral nerve with dopamine cells have shown that bridging the nigrostriatal pathway is feasible and efficacious in animal models of PD⁴⁷.

In recent years, it has been demonstrated that new materials can be of great value in other aspects of regenerative therapies research. One of the main challenges in obtaining neurons with dopaminergic phenotype from embryonic stem cells concerns the differentiation process. Guiding differentiation is a key step once stem cells in the laboratory tend to differentiate in an uncontrolled manner, resulting in a mixture of cells of little medical use. It has recently been shown that by mechanically straining the cells as they grow, it is possible to reduce significantly and almost eliminate their uncontrolled differentiation⁴⁷. This new liquid crystal based cell culture system can transmit desired sets of physical and chemical signals to stem cells so as to control their differentiation.

Challenges

There are numerous challenges associated with nanotechnology applications relating to PD. Nanotechnology allows an intervention at a molecular level and any desired cellular signaling pathway can be targeted. Sometimes we believe that this extraordinary specificity is enough but there is a need for even greater specificity. Furthermore, there is a requirement for technologies that are able to multitask, carry out a diverse set of specific cellular and physiological functions, such as targeting multiple receptors or ligands. For instance, PD is the clinical expression resulting from numerous interdependent molecular and biochemical events affecting numerous and interdependent cell groups in numerous and interdependent basal ganglia and brainstem nuclei. A great cellular heterogeneity and multidimensional cellular interactions in the spatial

and temporal domains underlie the basis of the nervous system's anatomical and functional wiring that is the basis of its extremely complex information processing. This processing is disrupted in disease states and it is important not to cause further disruptions by the application of an interacting nano-device, since the resultant side effects could be severe⁴⁸⁻⁵⁰. Also, long-term effects of nanotechnologies are unknown.

Conclusion and future aspects

As it is mentioned earlier nanotechnology could resolve many of the underlying problems within medicine today and improve a great number of current methods regarding diagnosis, prevention and treatment. Specifically, these developments could be applied to Parkinson's disease. At present little action can be taken to slow up the progress of the disease, so any developments instigated by nanotechnology are likely to be seen as radical. Despite this, nanotechnology poses a number of issues and a degree of risk. It is important that these risks are addressed, especially when the technology will be used within such a vast field as medicine.

Now-a-days, the "Lab on a Chip" procedure cannot be used for Parkinson's disease, even though it can be a very effective for other diseases. In the future however, the "Lab on a Chip" design could be adapted to work for Parkinson's disease – the foundations of the aptamer procedure could be used on a chip which could detect alpha-synuclein in the blood plasma, from a drop of blood on the chip. This could be very effective, but on the contrary, the research into this method would require significant funding.

In recent years it has been noted that the prospect of using nanotechnology for the treatment of disease, particularly delivering drugs to specific sites within the body, is a very real one. It is likely that within the next few years more research will have been undertaken and progress will have been made concerning treatment of disease. Regarding Parkinson's disease exclusively, carbon nanotubes and other nano structures, could be used to deliver treatment drugs such as Levodopa and dopamine agonists. No risks have been discovered as of yet, regarding in vitro use of nanoparticles in diagnosis, however there is some apprehension about possible toxic effects when using nanoparticles for therapeutic purposes. Environmental contamination from manufacturing nano-medical appliances also poses a great risk.

Another use of nanotechnology regarding delivery of treatments is the use of DNPs instead of virus vectors in order to deliver therapeutic genetic material to designated areas of the cell. This

therefore virtually overcomes the major issue of rejection of the new genetic material by the immune system and with further development could eventually be implemented on a large scale into patients with Parkinson's disease. However, a lot more research needs to be done in order to evaluate the effects of this treatment as currently, experiments have only been undertaken on rodents and the effect that gene therapy with DNPs has on humans may be substantially different.

Finally, if a set of ethical guidelines are produced then it would allow nanotechnology to be used within medicine safely and people could benefit from its attributes. In the future, if these ethical issues are resolved and nanomedicine is explored further, it could have a profound impact on the management of Parkinson's disease, and the future of medicine itself.

REFERENCES

- Lang AE, Lozano AM. Parkinson's disease. *N. Engl. J. Med.*, 1998; 339: 1130-1143.
- Schapira AH. Present and future drug treatment for Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2005; 76: 472-488.
- Koller WC, Tse W. Unmet needs in Parkinson's disease. *Neurology*, 2004; 62: S1-8.
- Linazasoro G. Cell therapy for Parkinson's disease, only young patients allowed. *Cell Transplant*. 2006;15:463-473.
- Przuntek H, Muller T. Clinical efficacy of bupropion in Parkinson's disease. *J. Neural. Trans. Suppl.*, 1999; 56: 75-82.
- Johnston TH, Fox SH, Brotchie JM. Advances in the delivery of treatments for Parkinson's disease. *Expert Opin. Drug Deliv.*, 2005; 2: 1059-1073.
- Jayasena SD. Aptamers an emerging class of molecules that rival antibodies in diagnostics. *Clin. Chem.*, 1999; 25: 1628-1650.
- Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science*, 1997; 27: 2045-2056.
- Verhagen L, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias. A 1-year follow-up study. *Arch. Neurol.*, 1999; 56: 1383-1386.
- Jenner P. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. *Neurology*, 2005; 65: 3-5.
- Farnasworth M, Farnandez M, Sabatinni, L. Buckyballs: Their discovery and History. *Plos Biol.*, 2005; 23: 45-67.
- Holister P, Harpour TE. Nanotubes. *PloS Biol.*, 2003; 24: 23-26.
- Mitura S. Nanodiamonds. *J Neuroimmunol*. 2007;1:56-68.
- Olivier JC. Drug transport to brain with targeted nanoparticles. *Neuro. Rx.*, 2005; 2: 108-119.
- Zhang Y, Schlachetzki F, Zhang YF, Boado RJ, Pardridge WM. Normalization of striatal tyrosine hydroxylase and reversal of motor impairment in experimental parkinsonism with intravenous nonviral gene therapy and a brain-specific promoter. *Hum. Gene Ther.*, 2004; 15: 339-350.
- Rodriguez MC, Gorospe A, Linazasoro G, Ramos E, Rodriguez P, Obeso JA. Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *Neurology*, 2000; 55: 45-51.
- Withman RM. Probing cellular chemistry in biological systems with microelectrodes. *Science*, 2006; 311: 1570-1574.
- Siegel RW. Applications: Concolidated Nanostructures. *Science*, 1999; 2: 234-256.
- Horellou P, Mallet J. Gene therapy for Parkinson's disease. *Int. J. Pharm.*, 1997; 15: 241-256.
- Miyoo Y, Jung kim Y, Lee U, Jin paik P, Jong C. Neurotrophic Factor in the Treatment of Parkinson Disease. *Int. J. Pharm.*, 2003; 1: 20-24.
- Kirik D, Bjorklund A. Parkinson's disease: Viral vector delivery of parkin generates model results in rats. *Int. J. Pharm.*, 2005; 15: 727-729.
- Kneuer C, Sameti M, Haltner EG, Schiestel T, et al. Silica nanoparticles modified with aminosilanes as carriers for plasmid DNA. *Int. J. Pharm.*, 2000; 196: 257-261.
- Kneuer C, Sameti M, Bakowsky U. A nonviral DNA delivery system based on surface modified silica-nanoparticles can efficiently transfect cells in vitro. *Bioconjug. Chem.*, 2000; 11: 926-932.
- Bharali DJ, Klejbor I, Stachowiak EK. Organically modified silica nanoparticles: a nonviral vector for in vivo gene delivery and expression in the brain. *Proc. Natl. Acad. Sci. USA.*, 2005; 102: 11539-11544.
- Carlsson T, Winkler C, Burger C. Reversal of dyskinesias in an animal model of Parkinson's disease by continuous L-DOPA delivery using rAAV vectors. *Brain*, 2005; 128: 559-569.
- Available from: <http://www.clinicaltrials.gov/ct/show/NCT00229736>
- During MJ, Kaplitt MG, Stern MB, Eidelberg D. Subthalamic GAD gene transfer in Parkinson disease patients who are candidates for deep brain stimulation. *Hum. Gene Ther.*, 2001; 12: 1589-1591.
- Airaksinen MA, Saarma M. The GDNF family: signalling, biological functions and therapeutic value. *Nature Rev. Neurosci.*, 2002; 3: 383-394.
- Wagner J, Akerund P, Castro DS, Holm PC, Canals JM, Snyder EY. Induction of a midbrain dopaminergic phenotype in Nurr1-overexpressing neural stem cells by type 1 astrocytes. *Nat. Biotechnol.*, 1999; 17: 653-659.
- Pardridge WM. Tyrosine hydroxylase replacement in experimental Parkinson's disease with transvascular gene therapy. *Neuro. Rx.*, 2005; 2: 129-138.
- Fu A, Gu W, Larabell C, Alivisatos AP. Semiconductor nanocrystals for biological imaging. *Curr. Opin. Neurobiol.*, 2005; 15: 568-575.
- Linazasoro G. Neuroprotection and neurorescue in Parkinson's disease: love story or mission impossible. *Exp. Rev. Neurother.*, 2002; 2: 403-416.
- Ravina BM, Fagan SC, Hart RG. Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment. *Neurology*, 2003; 60: 12-34.
- Dugan LL, Lovett EG, Quick KL, Lotharius J, Lin TT, O'Malley KL. Fullerene-based antioxidants and neurodegenerative disorders. *Park. Relat. Disord.*, 2001; 7: 243-246.
- Gross CG. Neurogenesis in the adult brain: death of a dogma. *Nature Rev. Neurosci.*, 2000; 1: 67-72.
- Alvarez-Buylla A, Garcia-Verdugo JM. Neurogenesis in adult subventricular zone. *J. Neurosci.*, 2002; 22: 629-634.
- Morris K. New-wave neurotechnology: small-scale makes big promises. *Lancet Neurol.*, 2004; 3: 202-212.
- Diaz-Hernandez M, Torres-Peraza J, Salvatori-Abarca A. Full motor recovery despite striatal neuron loss and formation of irreversible amyloid-like inclusions in a

- conditional mouse model of Huntington's disease. *J. Neurosci.*, 2005; 25: 9773-9781.
39. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. *Nature Neurosci.*, 2000; 3: 537-544.
40. Orive G, Hernandez RM, Gascon AR, et al. Cell encapsulation: promise and progress. *Nat. Med.*, 2003; 9: 104-107.
41. Subramanian T, Marchionini D, Potter EM, Cornfeldt ML. Striatal xenotransplantation of human retinal pigment epithelial cells attached to microcarriers in hemiparkinsonian rats ameliorates behavioral deficits without provoking a host immune response. *Cell Transplant.*, 2002; 11: 207-214.
42. Windebank A, Yaszemski M. Biodegradable implant as scaffold for nerve regrowth. Abstract at American Academy of Neurology annual meeting. 2004; 66: 6-15.
43. Silva GA, Czeisler C, Niece KLL. Selective differentiation of neural progenitor cells by high-epitope density nanofibers. *Science*, 2004; 303: 1252-1255.
44. Linazasoro G. Cell therapy for Parkinson's disease: only young patients allowed. *Cell Transplant.*, 2006; 15: 463-473.
45. Winkler C, Kirik D, Bjorklund A. Cell transplantation in Parkinson's disease. How can we make it work. *Trends Neurosci.*, 2005; 28: 86-92.
46. Chiang YH, Lin SZ, Zhou FC. Bridging nigrostriatal pathway with fibroblast growth factor-primed peripheral nerves and fetal ventral mesencephalon transplant recovers deficits in parkinsonian rats. *Cell Transplant.*, 2006; 15: 475-482.
47. Lockwood NA, Mohr JC, Ji L, Murphy CJ, Palecek SP, de Pablo JJ. Thermotropic liquid crystals as substrates for imaging the reorganization of matrigel by human embryonic stem cells. *Adv. Funct. Mat.*, 2005; 16: 618-624.
48. Oberdorster E. Manufactured nanomaterials (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. *Environ. Health Perspect.*, 2004; 112: 1058-1062.
49. Sayes CM, Gobin AM, Ausman KD, Mendez J, West JL, Colvin VL. Nano-C60 cytotoxicity is due to lipid peroxidation. *Biomaterials*, 2005; 26: 7587-7595.
50. Borm PJ, Robbins D, Haubold S. The potential risks of nanomaterials: a review carried out for ECETOC. *Part. Fibre Toxicol.*, 2006; 3: 11-34.
51. Kaili H, Yanbin S, Wenming J. Lactoferrin conjugated (PEG-PLGA) nanoparticles for brain delivery: Preparation , characterization and efficacy in Parkinson's disease. *Pharm. Nano.*, 2011; 415: 273-283.
52. Alim BM, Stephan CM, Johan M, Pierre PM. Deep brain stimulation of the sub-thalamic nucleus for the treatment of Parkinson's disease. *Neurology*, 2009; 8: 67-81.