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NANOMEDICINES FOR PARKINSON DISEASE: CURRENT STATUS AND FUTURE PERSPECTIVE

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ABSTRACT

Parkinson disease (PD) is the second most common progressive neurodegenerative disorder due to loss neurons in SubstantiaNigra pars compacta. A number of medical and surgical treatments are currently available but the beneficial effects wear off with long term use and many native therapies have severe side effects. Hence novel therapeutic strategies continue to be in the developmental demand. Nanomedicine is an important medical application in Nanotechnology which shows promising future in drug delivery system in Parkinson disease. This review gives a glimpse about current treatment for PD and discuss about the Nano-particle based drug delivery which evades Blood-Brain Barrier. BBB stands as a gateway for drug targeting in the central nervous system. Various potential nanoparticles and nanosystems based therapies are explored and benefits are heaved out. Further with a set of well regulated guidelines, it would allow nanotechnology to be used within medicine safely and people could benefit from its attributes.

KEYWORDS: Parkinson disease, nanomedicine, drug delivery, nanosystems, Polymeric nanoparticles,

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INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disorder following Alzheimers disease, which affects 0.5 – 1% of the population aged 65-69 years and 1-3 % of the population over 80 years of age. [1]. The core clinical features of PD were first described by James Parkinson in his classic monograph "Essay on shaking palsy". Most of the countries experience an ageing phenomenon where the existence of population aged above 65 years are increasing and hence there is an increase in age related neurodegenerative disorders [2]. It has been estimated in 2005 that brain related disease represent 35 % of the total economic burden of Europe[3]. A recent study by Pritchard *et al* found that death related neurological disorders dramatically increased from one to two fold between 1979 & 1997 respectively in developing countries like INDIA which gives a wakeup call to explore new frontiers in neuroprotective research. It has been estimated that 4 million people worldwide have this condition and the incidence increases [4]. Various researches shows that symptoms of PD can be reduced by treatment at early stages of disease onset but as the disease progresses the symptoms get worse. Complete cure for PD is still out of reach [5]. The underlying pathological finding in PD is the loss of nigrostriatal dopaminergic neurons with a resultant loss of neurotransmitter dopamine in the corpus striatum.The prime clinical symptoms of PD are tremor at rest, rigidity, bradykinesia, postural abnormalities and freezing phenomenon [1].

The population of elderly Indians has increased from 5.6% in 1961 to 7.1% in 2001. The elderly population in developing countries is expected to increase from 200-250% compared to a mere 20-40% in developed countries[6]. Following the population census in INDIA, the elderly population was only 24 million in 1961 but now it has been raised to a whooping 77 million in 2001 [7]. Hence it is high time for researchers to find a complete cure for PD. Various surgical and conventional treatment are available provided with side effects (Hallucinations, Confusion & Psychosis) due to more dosage and hence a new era in modern science named 'Nanotechnology' are being explored by scientists and it shows promising results. This review will focus in brief on current medical and surgical treatment strategies and how nanotechnology will have great impact on treatment of PD.

AVAILABLE TREATMENT FOR PD

Pharmacological treatment: Most commonly used treatment for PD is the dopamine precursor, L-Dopa. Unfortunately approximately 50% of patients using L-Dopa develop complications within 5 years of treatment.[8,9] These are mostly severe motor fluctuations (wearing off effect) and dyskinesia (drug induced voluntary movements including choreiform and dystonic movement). Recent results suggest that continuous dopamine stimulation might help in preventing the wearing off effect.[10] Various strategies have been proposed to provide an uniform dopamine supply including new delivery methods like transdermal delivery, increased frequency of delivery and new sustained release formulations.[11,12] Monoamine oxidase inhibitors are sometimes useful as monotherapy for early PD and also can be used with L-Dopa therapy.[13] Their use is sometimes associated with a worsening of L-Dopa's side effects in some patients.[14] Dopamine receptor agonists are potent in controlling primary motor symptoms but because of their side effects (hallucinations, confusion and psychosis) they often are contradicted, especially in older patients.[15] The limited efficiency over the course of the disease and incapacity to stop or revert makes these drugs a treatment of choice.

SURGICAL THERAPIES

Surgical ablation of deep brain structures: Prior to L-Dopa, surgical ablation of deep brain structures was performed. Experimental ablation involves the drilling of holes in the skull of an animal and inserting an electrode or a

small tube called a cannula into the brain using a stereotaxic apparatus. A brain lesion can be created by conducting electricity through the electrode which damages the targeted area of the brain likewise, chemicals can be inserted in the cannula which could possibly damage the area of interest. Thalamotomy was an effective treatment for reduction of contralateral tremor while pallidotomy was found to improve motor symptoms with variable degrees of success [16,17]. Although these therapies are completely abandoned with the introduction of L-Dopa, recently pallidotomy has re-emerged as an option in treatment. Although they are effective in controlling cardinal symptoms, they have serious limitations. Unilateral pallidotomy have no long-lasting effects on gait and balance problems. Bilateral pallidotomy has severe cognitive and psychiatric side effects[18]. Finally, only a small proportion of patients are amendable to surgical intervention.

NANOTECHNOLOGY FOR MEDICINE

One of the most formidable limitations for PD through drug delivery is the restricted entry of drugs to the central nervous system (CNS) by the Blood Brain barrier (BBB). BBB stays as a gateway and allows only small lipophilic molecules to pass by. However large,hydrophobic, charged molecules requires facilitated transport. Due to these strategies pharmacophore designed drugs and even dopamine, a polar compound are restricted to enter the CNS. Schematic representation of transport of molecules across BBB is depicted in Fig 1. Small lipophilic proteins disperse through BBB but they are recognized by P-gp (P-glycoprotein) and exposed to degrading enzymes of the endothelial system. This impediment can be easily overcome by using nanotechnology by packing drugs into small nanoparticles (10-1000nm) which more readily crosses the BBB. [19]. Moreover these structures can evade the traditional degradation lines and target specific CNS structures which reduces systemic side effects [20]. Superlatively nanoparticles will help in automatic drug delivery sensing when medication is needed and delivering it to a specific target [21].

Figure 1

Schematic representation of transport of molecules across BBB

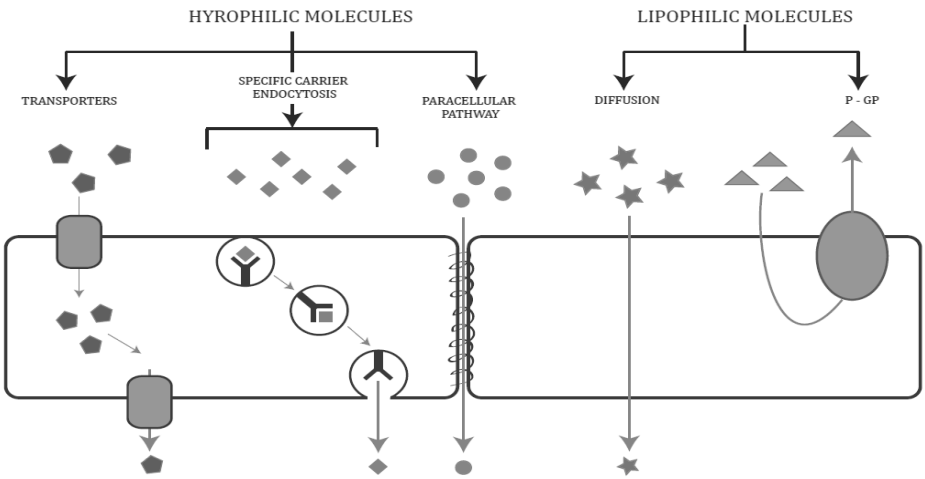


Figure 1: Note : P-gp – P-glycoprotein efflex pump

Interestingly nanotechnology has the potential to reduce and reverse neuropathology as well as regenerate damaged neurons. Nanoparticles has the ability to target signaling pathway, gene products and proteins abbreation involved in neurodegeneration and stays as a unique neuroprotective therapy. [22]. The mechanism in which drugs combined with nanoparticles can be delivered into the cells are depicted in Fig 2.

Figure 2
Steps representing cytosolic delivery of drugs into the cell

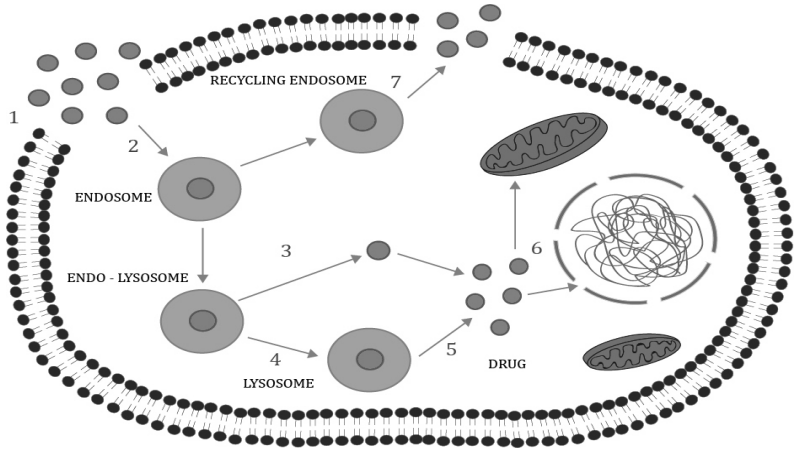


Figure 2:Note : 1. Association of nanoparticles (NPs) with cells, 2. Internalization of NPs via endocytosis, 3. Endosomal escape of NPs or 4) Lysosomal degradation of NPs, 5) Drug freely diffusing into cytoplasm, 6) Cytoplasmic transport of drug to target organelle, 7) Exocytosis of NPs.

CRITICAL FEATURES OF NANOMEDICINES OVER CONVENTIONAL MEDICINES

Apart from obvious application of nanotechnology in medicine, nanomedical approach is fundamentally different. Nanotools are used for nanomedicines which are approximately 1000 times smaller than a cell. Nanomedicines target the tissue, cell by cell. Drug use is targeted and adjusted approximately for individual cell treatment at the proper dose for each cell. The combination of these features is not a simple extrapolation of current methods in conventional medicine. Nanomedicine will represent a huge paradigm shift, resulting in the treatment of disease at the single-cell level in a massive parallel processing fashion using huge numbers of sophisticated nanomachines, not only with advanced targeting capabilities but also with error-checking and feedback-controlled dosing at the single- cell level[23]. This will result in a huge increase in the effectiveness of medicine for the individual patient. By accomplishing this on a larger scale nanomedicine promises to provide a huge and beneficial change for medicine and the health care system.Some of the developing nanomedicine therapies for PD is summarized in Table 1.

Table 1
Summarization of developing nanomedicine therapies for Parkinson disease

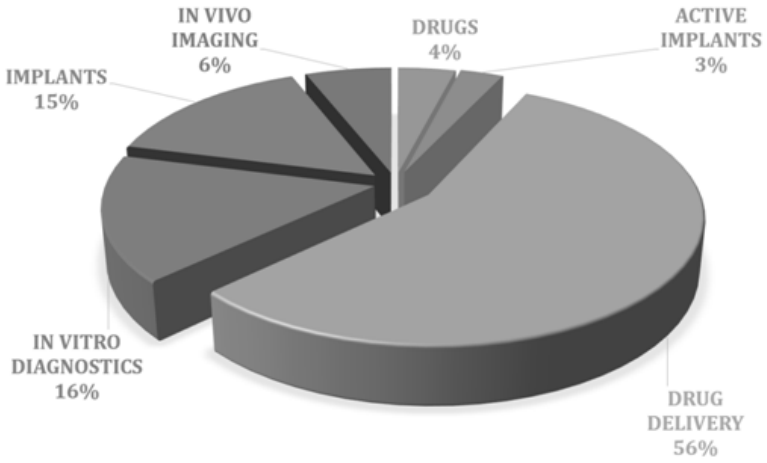
Therapeutic mechanism	Particle composition	Finding	Ref
Antioxidation	Polyhydroxylated fullerene erivative, C60(OH)24	Prevent mitochondrial oxidative damage induced byMPTP in human neuroblastoma cells	[24]
Decrease ROS production	Polyethyleneimine-PEG-containing catalase	Cell-mediated delivery of catalase to brain	[25]
Reduce euroinflammation	VP025 (Vasogen Inc.),hosphatidylglycerolbasedphospholipid NP	Neuroprotective with pretreatment in a 6-OHDA mouse	[26]
Delivery of functionalproteins	Poly(butyl cyanoacrylate)	Delivery of functional proteins to primary hippocampal cultures.Uptake dependent on LDL receptor.	[27]
Improve drug delivery	Bromocriptine crystals suspended in tristearin/tricaprin lipid combination and coated withpoloxamer-188	Improved pharmacokinetics over free drug	[28]

Most of the nanotechnological drug delivery system for neurodegenerative disorders like PD is in the form of polymeric nanoparticles which can pass through tight cell junctions, cross the BBB, achieve a high drug loading capacity and can be targeted towards mutagenic proteins. Most important features of these nanoparticles in CNS drug delivery[29] are

1. Their chemical properties can be easily modified to achieve organ-tissue or cell specific and selective drug discovery.
2. Drug delivery can be controlled
3. Increase in bioavailability and efficiency of incorporated drug by masking physicochemical characteristics
4. They protect the incorporated drug from enzymatic degradation and
5. Very few side effects.

There has been increasing interest in nano based drug delivery system than other nano based techniques and the statistics are shown in Fig 3.

Figure 3
Statistics showing application of nanotechnology in healthcare [30]



POTENTIAL NANOSTRUCTURES FOR TREATMENT OF PD

Few nanoparticels which can be used for drug delivery are discussed below.Polymeric nanoparticles, nanocapsules and nanospheres:Polymeric nanoparticles and nanocapsules range from 10-1000 nm [31] possessing high drug loading capacities and protect the incorporated drugs against degradation and hence the drug reaches the target site specifically. Moreover they are stable and their surface properties can be manipulated in order to escape macrophage recognition [32]. Doxorubicin, used for malignant brain tumors is one of the CNS drug delivered using polymeric nanoparticles [33,34,35]Nanospheres are dense polymeric matrices in which drug is dispersed and nanospheres are prepared by micro-emulsion polymerization [36]. Nanospheres are nanoparticle systems constituted by a solid core with a dense polymeric matrix whereas nanocapsules are formed by a thin polymeric envelope surrounding an oil-filled cavity [37,38-40]. Types of nanoparticles used for drug delivery are shown in Fig 4.

Figure 4
Nanoparticles used for drug delivery in CNS(adopted from Modiet al [23])

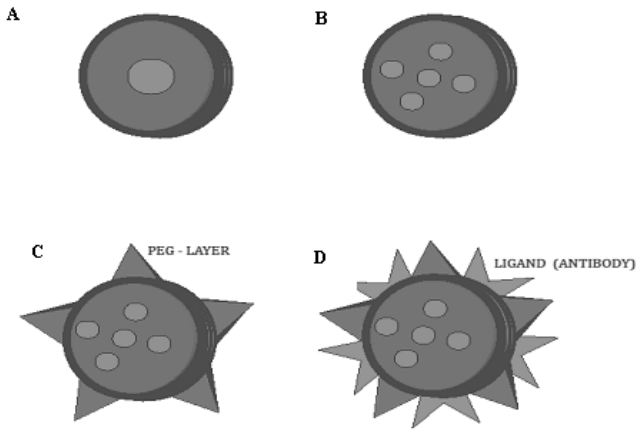


Fig 4:Note: (A) Nanocapsules, (B–D) Nanospheres with drug distributed throughout a polymer/lipid matrix, (B) either without a surface coating or coating with a surfactant and/or PEG layer, and (D) additional coating with antibodies and/or ligands.

POLYMERIC NANOGELS AND NANOSUSPENSIONS

Nanogels are networks of cross-linked polymers that often combine ionic and nonionic polymeric chains and are prepared using an emulsification solvent evaporation approach.[41,42]Nanogels swell in water and are able to incorporate molecules such as oligonucleotides, siRNA, DNA, proteins, and low molecular- mass drugs. The drug-loading capacity is up to 40–60%.Vinogradov and coworkers[43] have encapsulated oligonucleotides within a cross-linked nanogel for delivery across the BBB. *In vivo* studies suggested that the nanogel increased brain uptake of oligonucleotides while decreasing uptake in the liver and spleen. Drug-loaded nanosuspensions are crystalline drug particles stabilized by nonionic surfactants or mixtures of lipids.[44,45] Major advantages of nanosuspensions include their simplicity, high drug-loading capacity, and applicability to numerous drugs for CNS delivery.[29,45].

CARBON NANOTUBES AND NANOFIBERS

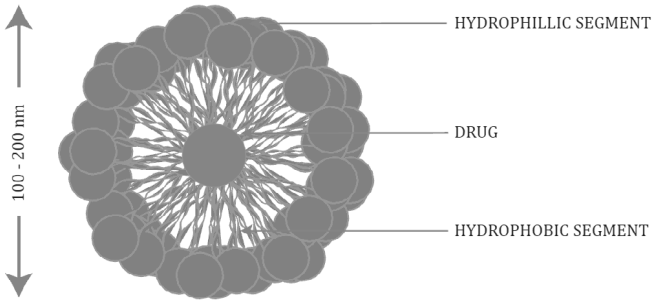
Carbon nanotubes are being explored to improve chronic CNS electrical stimulation.[46]clinically, functional electrical stimulation implants are gaining momentum for the treatment of PD. A significant challenge with the development of recording or stimulating chronic CNS electrodes is device failure associated with the fibrotic response mediated by glial and immune cells.[47] The development of compressed carbon nanofiber–based electrode arrays for CNS neuronal stimulation could be injected at sites of degeneration to provide both a physical substrate and the molecular signals needed to stimulate and support tissue healing in treating NDs.[48]The mechanism involved during carbon nanotube neuronal stimulation may be explicated in terms of an *in vitro* neuronal circuit model that is cultured on nanotube substrates to affect single and multiple synaptic pathway stimulation via the carbon nanotube layers and neuronal–nanotube electrical coupling and adhesion that may facilitate population firing that is strengthened by the appearance of a fast Na+ current, taken to constitute an early sign of axonal differentiation. These interactions may also sustain unconventional electrical coupling, thus unveiling new approaches to the basic understanding of the CNS electrophysiology.

POLYMERIC NANOMICELLES

Polymeric nanomicelles have a core–shell architecture with a hydrophobic core and a shell of hydrophilic polymer blocks (Fig 5). The

core can incorporate up to 20–30% w/w of hydrophobic drugs, thus preventing premature drug release and degradation. The shell stabilizes the nanomicelles and masks the drug from interactions with serum proteins and untargeted cells. Once the target cells are reached drug is released by diffusion. Polymeric nanomicelles are versatile and have been shown to efficiently deliver DNA molecules *in vitro* and *in vivo* although no successful study on their delivery to the CNS has been reported thus far.[49–51].

Figure 5
Polymeric Nanomicelles(adopted from Modiet al [23])



POLYMERIC NANOLIPOSOMES

Nanoliposomes are vesicular structures composed of uni- or multilamellar lipid bilayers surrounding internal aqueous compartments.[52] (Fig 6). Relatively large quantities of drug can be incorporated into liposome aqueous compartments or within the lipid bilayers. Extended systemic circulation times can be accomplished with nanoliposomes with modified surfaces that reduce opsonization in plasma and decrease its recognition and removal by the liver and spleen.[52,53] Evaluation of nanoliposomes for targeted CNS drug delivery has been studied for various applications.[54-57].

Figure 6
Types of Nanoliposomes(adopted from Modiet al [23])

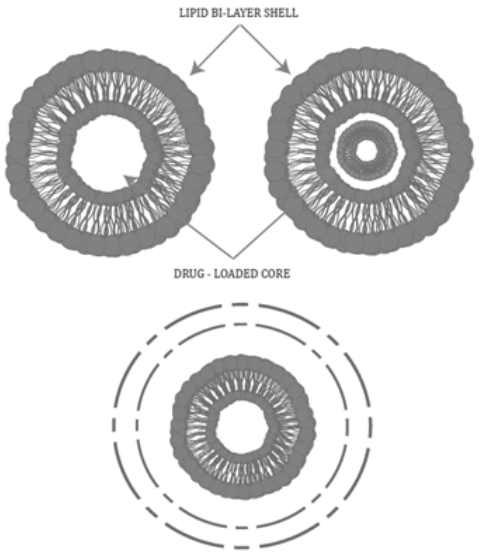


Fig 6:Note: A. small unilamellar vesicles B. multilamellar vesicles and C. stimuli-sensitive nanoliposomes.

NANOSYSTEMS FOR ADVANCED EXPERIMENTAL TREATMENT OF PD

Nanosystem mediated brain targeted delivery of dopamine in PD:

There are number of studies focused on delivering dopamine (DA) to the brain using redox based delivery system for localized release of DA in the brain [58]. Research outcome concluded that DA can be delivered into the brain through localized release and metabolism which exerts appropriate responses. Since DA cannot cross the BBB, these results open a new gateway for treating PD. [53]

CONVECTION – ENHANCED DRUG DELIVERY IN PD

The intravascular administration of drugs has been confounded by the BBB [59]. Hence osmotic disruption has been used temporarily to infiltrate the BBB and allows the penetration of neuroactives.[59]. Though this treatment is effective, controlling the site of treatment remains complicated and limited to a major vascular distribution .[60,61]. Moreover, repeated treatment creates discomfort and morbidity narrowing the use of osmotic BBB disruption therapy but Convection enhanced delivery (CED) technology delivers neuroactives at larger and consistent treatment volume. This technique employs bulk flow of neuroactives through extracellular space of the tissue [59]. Theneuroactives distribution volume is primarily a function of the infusion rate and specific character of tissues. More recently CED is employed in Phase I trials for gene therapy in PD.

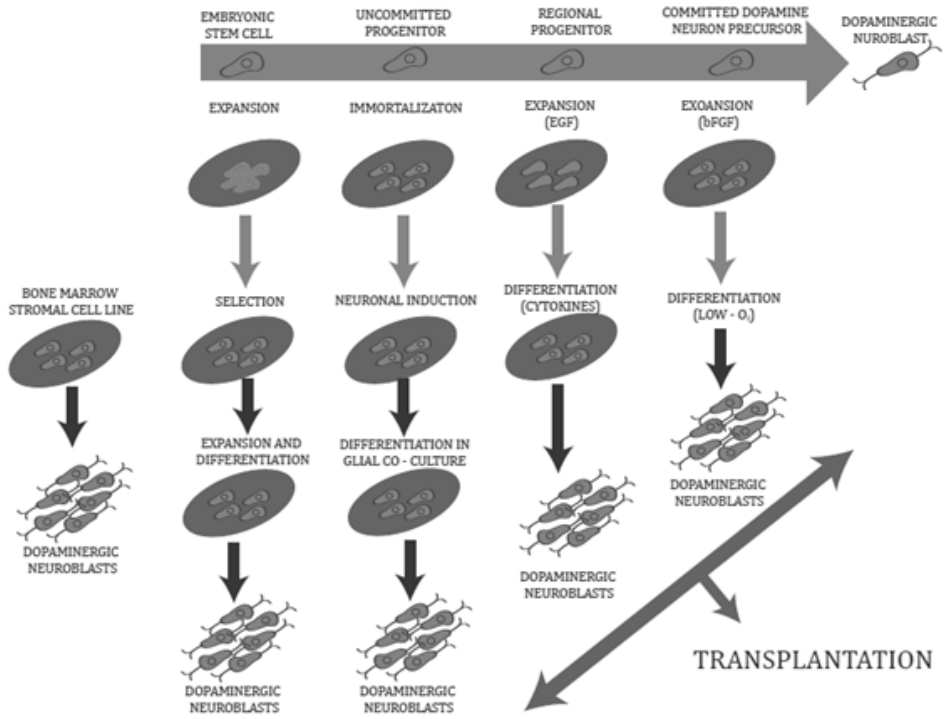
NANOPARTICLE BASED GENE THERAPY FOR PD

An outstanding work by Yurek& coworkers [62] through novel technologies condensed DNA plasmid into nanoparticles for delivery to the brain with a focus on halting neurodegeneration in animal models of PD. They used transduction technique to express a particular gene in the cell by incorporating the DNA in the genome of the cell and making it to express the desired gene product. Furthermore it is possible to utilize neurotrophic factors to revive dormant brain cells and assist them to produce dopamine, which was proved in animal models [63]. This approach is also carried out in advanced PD patients and showed lack of side effects and significant improvement from baseline measured by Tomography [63]. This therapy provides a new platform to transfer a variety of Gene-therapy agents into human clinical trials for neurodegenerative disorders.

NANOFIBERS AS STEM CELL THERAPY IN PD

Polymer based biodegradable nanofibers with scaffold potentially allow stem cells to repair damaged neurons effectively [64] which can be achieved through a combined process electrospinning and customize nanofibre structure into scaffold and inject into the body. The structure is inserted into the target site followed by embedding the stem cells into nanofibers. Nerve cells attach to the scaffold and form a bridge between the brain. As time progresses, scaffold erodes and naturally eliminates from the body leaving the newly regenerated nerves intact [65] which shows great progress for treatment of PD. In another endeavor using stem cells for treating PD, Lindvall and Hagell[66] revealed the genes that initiate and control the DA-producing nerve cellswithin the brain. They managed to develop embryonic stem cells into DA-producing nerve cells in chicken and mousemodels (Fig. 7).However, a significant challengewas that they could not succeed in producing pure samples of the DA-producing cells as they also produced 10–20% of unwanted stem cells.

Figure 7
A schematic showing the use of stem cells and immature progenitors in producing dopaminergic-like neurons for the treatment of Parkinson's disease (adapted from Lindvall and Hagell[64])



CARBON NANOTUBE & NANOWIRE BIOSENSORS IN PD

Carbon nanotubes have recently emerged as a new option which analyzes the potential through possible toxicological implication in the field of Medicine and Pharmaceutics[67]. A careful examination of the carbon cathode used in the arc-discharge process for the production of fullerenes by Iijima S, resulted in the historical discovery of CNTs [67]. Carbon nanotubes, and magnetic iron oxide nanoparticles, gold-coated silica nanoshells, can transform electro-magnetic energy into heat, causing a temperature increase lethal to cancer cells merely by increasing the magnetic field or by irradiation with an external laser source of near infra red light at the very location where these nanoparticles are bound to or internalized within tumour cells [68] .It is interesting to note that among the currently available delivery systems, which include liposome's, emulsions, polymers and micro particles, CNTs have recently gained popularity as potential drug carriers, therapeutic agents and for applications in diagnosis [69]. Nanowires implantable biosensors have been developed for PD treatment. [68]. Biosensors consist of carbon nanotubes and nanowires which are hollow, light weight, chemically inert with superior mechanical strength. They are organized as arrays and designed as nanochips which are not rejected by the human body. Nanochips performs various functions inside the body like monitoring and sensing DA release. First carbon nanotube biosensor was designed by Li &colleagues [69] which monitors the loss of DA and enhances activities between neurites and neurons. Apart from sending the release of Dopamine and contributing to the growth of healthy Dopaminergic neurons, the biosensor also communicates with polymer biosensor attached to the area of the body where tremor occurs. Signal from implanted sensor controls and directs the motion of the

area of the body where exterior sensor is attached. Exterior sensor can be easily placed on the body under wrist watch and the implanted carbon nanotube based sensor detects the sensor attached to the watch and controls trembling and directs the hand movement. [69].

CONCLUSION

Nanomedicine has opened a new gateway for diagnosis and treatment for various diseases and it holds great promise for future health management. Although publication wise nanotechnology accounts only 5% worldwide but this technology is at a budding stage and there are few products in the market. Nanotechnology based drug delivery is one of the most advanced field in nanomedicine and its progress increases. Though there are more expectations from nanotechnology, their medical use should be adequately evaluated for its risk and safety factors. Apart from the progress and promising future, public concern over nanotechnology remains to be a chaos. Hence 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 Parkinsons disease, and the future of medicine itself.

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