



## Nano-based Cell therapy for AD and PD

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### Abstract

The most prevalent neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). Both AD and PD are classified as proteinopathies where misfolded amyloid- $\beta$ , and tau proteins in AD and  $\alpha$ -synuclein in PD are noticed. The main AD hallmarks are memory loss where the loss of dopaminergic neurons and the development of Lewy-bodies are found in PD. The defects in the motor neuron activities, however, can be noticed after the loss of dopaminergic neurons by 50-70% in the Substantia nigra (SN) region. Emerging Evidences are there to suggest that misfolded protein tangles and/or plaques have prion-like proteins which are the major factor causing the pathogenesis. Additional factors that can affect pathology of these diseases include oxidative stress, mitochondrial damage, inflammation, and age-related cell death. Chronic inflammation is also universally thought to play a central role in the initiation and progression of PD.

At present no such real therapies are yet available for the cure of AD and PD, besides some palliative treatment. However, efforts are in the process to find some effective therapies using transplantable neural cells, gene therapies, and some nanomaterials, for better targeting across the blood-brain barrier. Nanomaterials, further can increase the drug half-lives, protect cargo from immune detection, and provide a physical structure that can support cell growth.

**Keywords:** Alzheimer disease, Parkinson's disease, Nanoparticles, Macrophages, Cell therapy

### Abbreviations

Angiotensin-converting enzyme 2 (ACE2)

Alzheimer's disease (AD)

Aminopeptidase N (APN)

Amyloid- $\beta$  ( $A\beta$ )

Blood brain barrier (BBB)

Brain-derived neurotrophic factor (BDNF)

Central nervous system (CNS)

Dopaminergic (DA-ergic)

Glial cell derived neural factor (GDNF)

Human coronavirus 229E (hCoV-229E)

Interleukin-1 $\beta$  (IL-1 $\beta$ )

Inducible nitric oxide synthase (iNOS)

Lewy bodies (LB)

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Macrophages (MΦs)  
Monocyte chemotactic protein-1 (MCP-1)  
Neural Stem cells (NSCs)  
Parkinson's disease (PD)  
Polyethylene glycol (PEG)  
Poly (lactic-co-glycolic acid) (PLGA)  
Arg-Gly-Asp (RGD)  
Reactive oxygen species (ROS)  
Substantia nigra (SN)  
 $\alpha$ -Synuclein ( $\alpha$ -syn)  
Severe Acute Respiratory Syndrome (SARS)  
Tumor necrosis factor- $\alpha$  (TNF-  $\alpha$ )

## Introduction

Protein aggregation is a typical phenomenon in both Parkinson's disease (PD) and Alzheimer's disease (AD). In particular, PD is characterized by the deposition of aggregated misfolded  $\alpha$ -synuclein ( $\alpha$ -syn) protein, which is known as Lewy bodies (LB) in dopaminergic neurons, and thus causes severe motor dysfunction [1]. On the other hand, AD where the cognitive process is typically lost is diagnosed with the abnormal accumulation of amyloid- $\beta$  (A $\beta$ ) plaque and tau neurofibrillary tangles in the brain [2]. Supporting evidences are there to clarify the proteinopathy due to the accumulation of pathological  $\alpha$ -syn, A $\beta$ , and *tau* that spreads from cell-to-cell [3-12]. The  $\alpha$ -syn aggregates localize in the mitochondria and induces mitochondrial fragmentation and decreased membrane potential [13-15]. In AD, the aggregation of A $\beta$  peptide results from the oxidative stress from dysfunctional mitochondrial reactive oxygen species (ROS) [16-18]. Further, abnormal hyper-phosphorylation of microtubule-associated *tau* protein leads to the formation of *tau* tangles with prion-like activity. In both the diseases, AD and PD, expression of inflammatory cytokines have been noticed which may cause the protein aggregation and cell death. However, inhibition of amyloidosis in both AD or PD with small molecules and antibodies exhibit only a little success [19-21].

Traditional therapeutic drugs usually have off-target effects. Nanomaterial formulations can ensure targeted delivery and also can overcome the blood brain barrier (BBB) during delivery of the actives [22-25]. Additionally, composite nanomaterials can be developed to ensure the new cell growth in PD and AD [26]. In this review, we will explore the current field of nanomaterials for therapeutic application of cell-based therapies in PD and AD.

## Present Treatment Strategy

Except some palliative treatment, like using Dopa/ Dopamin, currently, there is no curative therapy for PD or AD. However, efforts are in progress to regenerate the neuronal

growth, axonal extension and to repair the damaged cell in both the diseases using some neurotropic factors like BDNF, GDNF. Nanomaterials like scaffolds, PLGA are thoughts to be used not only for targeted delivery of the neurotropic factors but also to increase their half-life and to improve the motor function and dopaminergic neuron restoration without showing any toxic effects *in vivo* [27-29].

Further, maturation of neurons can be done, *in vitro*, by using scaffolds pretreated with RGD and heparin before administration to an *in vivo* system [30]. In this regards, various scaffolds are being made using alternating amino acid sequences, which support neuronal growth and differentiation [31, 32]. Humanin peptide, which is known to inhibit A $\beta$ -related cell death in AD can be delivered successfully with polymersomes (PEG-PLGA) [33].

**Cell Therapy:** Cell therapy of PD by transplantation of stem cells has been proposed earlier. However, there are enough demerits in that approach, like availability of enough cells for transplantation, probability of future development of carcinoma, and so many other logistic challenges including the cost of the treatment.

**Neural Stem cells (NSCs)** have been considered as the preferred cells for transplantation as those can produce dopamine, the active principle for PD/AD treatment [34-36]. Besides the production of Dopamine, NSCs possess the ability to control the level of dopamine in the synaptic cleft as it contains the Dopamine catabolizing enzymes, and as a result offers a less probability of having future neural tube defects that can result from the excess unused floating dopamine in the Substantia Nigra (SN region). Further, NSCs can also be used as a vehicle for delivering other neuron co-stimulatory drugs, and/or chemotherapeutic agents. In fact, NSCs have been found to deliver neurotrophic factors to the CNS and promote neuron integrity and regeneration [37-40].

**Macrophages, another possible therapeutic cells against PD/AD:** PD is believed to be the result of chronic inflammation [41, 42]. MΦs, the main regulatory immune cells that act in the periphery have the ability to polarize either to its M1 type or to M2 type under the influence of environmental factors [43]. M1 type of MΦs while is pro-inflammatory, and releases several chemokines, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF-  $\alpha$ ), and monocyte chemotactic protein-1 (MCP-1), and iNOS, the M2- MΦs produce anti-inflammatory cytokines, like IL-10, IL-4, IL-13, and promote tissue repair [44-47]. During the inflammatory disease progression, M2-MΦs are gradually replaced by M1-type [48]. With the similar note it is believed that somehow in the brain MΦs are polarized to M1-type during the pathogenesis of PD. In fact, MΦs and neutrophils are able to cross the blood brain barrier, and secrete proinflammatory cytokines (e.g., ILs, TNF $\alpha$ , IFN- $\gamma$ ), which can cause the development of PD [49].

**Use of Nanotechnology for Targeted Tissue Delivery:**

As an extension of the targeted cell therapy, the use of nanovehicles to carry NSCs along with the neurotropic factors across the Blood-Brain Barrier (BBB) have been proposed [50-53].

- Liposomes:** Liposomes are capable to encapsulate both the hydrophobic and hydrophilic drugs into its hollow core and deliver them to the disease sites [54-56]. Long-circulating liposomes, like PEGylated liposomes, can also be prepared by coating with polyethyleneglycol [58]. In clinical trials with the treatment of histoplasmosis, meningitis, and neutropenia, PEGylated liposomes showed better efficacy with less side effects [59].
- Polymeric Micelles:** Amphiphilic polymeric micelles are made up of PEG-PCL, poly(styrene) or PLGA [60]. These type of block copolymers are, indeed, approved by FDA for the targeted drug delivery [60]. In that hydrophilic shell, hydrophobic drugs can stay protected from the surrounding environment. By designing the cell-specific ligands and attached to the polymer can make the polymer to be directed towards the specific cell types [61].
- Nanoviricide®:** It is comprised of a polyethylene glycol (PEG) and alkyl pendants. The alkyl chains while make a flexible core the PEG forms the hydrophilic shell and imparts non-immunogenicity. The resulting polymeric materials form stable micelles with chemical groups that are uniformly distributed along the polymer chain. This polymeric chain attaches with the virus-specific ligands like chemical moieties, peptides, antibody fragments or other proteins (Fig. 1). Recently, NV-CoV-2, a biopolymer designed and made by Nanoviricide® (Shelton, CT) are potentially active against many viruses including Corona virus [62]. In the antiviral therapy of corona virus, NV-CoV-2 is covalently bonded with antiviral small chemical ligands similar to S-protein which binds to the cognate cellular receptor, ACE2. NV-CoV-2 also can bind the other SARS receptor, Aminopeptidase N (APN), and showed inhibitory activities against the the human coronavirus 229E (hCoV-229E) which uses APN receptor for binding to the cell.[62].

**Conclusions and Future Perspectives**

The treatment of PD is still controversial as there is no defined diagnostic tool for the early detection of the disease and also their pathological pathway. Pharmacological therapy, in fact actually starts when the patient notices the difficult motor activities, and at that point 50–70% of dopaminergic neurons actually have already been lost which makes it practically impossible to cure [62]. Current therapies are mainly focusing on palliative treatment and/or slowing down and reversing the abnormal motor symptoms.

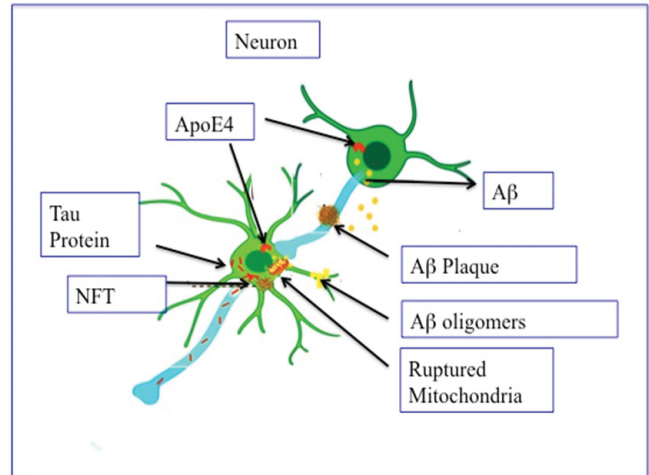


Figure 1A: Key Players for AD Pathogenesis

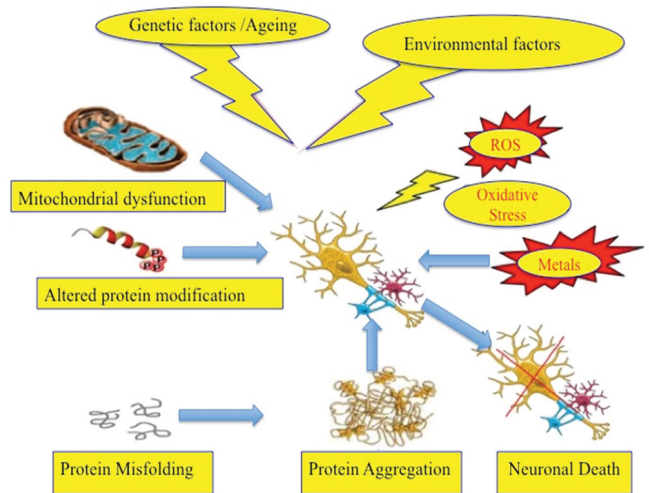


Figure 1B: Key players of PD

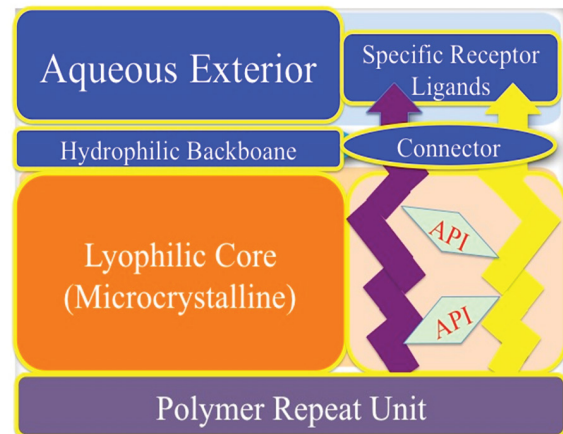
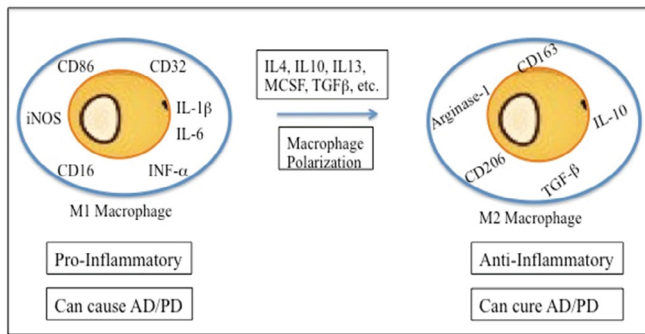
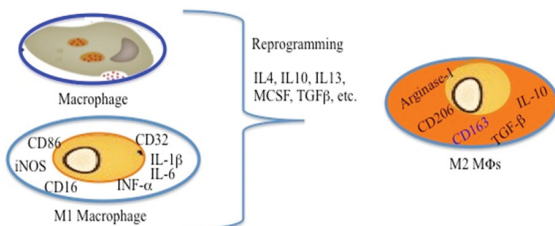


Figure 2: Schematic Design of Nanoviricide Biopolymer

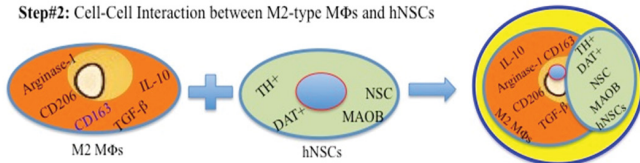


**Figure 3:** Reprogramming Macrophages to its M2 type for AD/PD Therapy

**Step#1:** Macrophage Re-polarization to its M2-Type in cell culture



**Step#2:** Cell-Cell Interaction between M2-type Mφs and hNSCs



**Figure 4: Step# 1:** Macrophage Repolarisation to its M2-type in cell culture dishes in Presence of reprogramming cytokines. Grow the cell until enough amount of M2-Mφs are obtained.

**Step#2:** Cell-Cell interaction between M2 type Mφs and hNSCs to get a unique cell which should express anti-inflammatory cytokines, as well as dopamine.

Several studies have demonstrated that nanosystems could potentiate sustained release of the repurposed PD drugs with no side-effects, and increase the effectiveness of the therapeutic agents. Moreover, they can be used for effective delivery to the target across the BBB. Great efforts are still in the process to develop new effective PD therapeutics, like safinamide and opicapone which may decrease motor fluctuations [63-66],  $\alpha$ -syn target therapies [67], and neural stem cell transplantation therapies, and gene therapy [68]. Our Plan of Action is to create a Novel Therapeutic Module for PD and AD. Accumulation of M1 type of macrophages in the brain is the key player of PD onset [69]. Repolarization to its M2-type by cytokines, nanoparticles or both could be the effective components the strategy that could be deployed for PD therapy (Fig. 2). The DA-ergic NSC cells while will replenish the loss of neural cells the anti-inflammatory cytokines can also be the used as a vehicle of the M2 polarizing cytokines (IFN $\gamma$ -GMCSF, IL-10, IL-4, TGF- $\beta$ , IL-12, etc.) to re-educate M1 type to M2 type. Thus, in combination, therapeutic benefits could be achieved for the PD victims.

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## Consent for Publications

Both the authors have agreed to submit this paper for publication.

## Ethical Approval

Not applicable

**Conflict of Interest Statement:** The authors declare no conflict of interests.

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