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Recent Research Developments in Parkinson's Disease

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Abstract

Important research developments have recently occurred in the understanding of Parkinson's mechanisms and the symptomatic therapy of the disease. This article reviews such developments and their place in the disease's therapeutic armamentarium. It also assesses their potential contribution(s) to our search for the root cause(s) of the disease. Improved symptomatic therapy has taken place for both motor and non-motor systems with the progressive development of several therapeutic drugs. This article also explores new research vistas including the role of gene therapy in the search for Parkinson's disease-modifying therapy and neuroprotective treatments such as neural transplantation, stem cell transplantation, and transcranial magnetic stimulation. In this context, our two interacting brains (brain-in-the-skull, brain-in-the-gut) should underpin Braak's hypothesis as to the origin of Parkinson's. In the search for disease-modifying therapies, the article reviews the two therapeutic strategies currently followed, the epidemiological findings and large clinical prospective trials reporting a *correlation* between a reduced occurrence or prevalence (or both) of PD and the consumption of compounds such as caffeine or nicotine. The three different principles of therapeutic action are addressed: active and passive immunotherapy, modulation of alpha-synuclein aggregation, and enhancement of autophagy of alpha-synuclein. Nanotechnology is newly proposed for directly delivering therapeutic drugs at the right brain locations in the right dosage amounts.

Keywords: Alzheimer's disease; Lewy body dementia; nanomedicine; neuroradiological imaging; neurodegenerative diseases; multiple system atrophy; Parkinson's disease; progressive supranuclear palsy

Abbreviations: Abbreviations: AD: Alzheimer's Disease; APD: Anti-Parkinson Drugs; BBB: Blood-Brain Barrier; BPB: Blood-Protective Barriers; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; DBS: Deep-Brain Stimulation; DLB: Dementia with Lewy Bodies; EEG: Electroencephalogram; FDG-PET: Fluoro-Desoxyglucose PET; GCS: Glucocerebrosidase; GWAS: Genome-Wide Association Studies; IMDS: International Movement Disorders Society; MAO: Monoamine Oxidase; MAPT: Microtubule-Associated Protein Tau; MRI: Magnetic Resonance Imaging;; MSA: Multiple System Atrophy; ND: Nanodevices; NDD: Neurodegenerative disorder; NIH: (U.S.) National Institutes of Health; NINDS: (U.S.) National Institute of Neurological Disorders and Stroke; NM: Nanomedicine; NMS: Non-Motor Symptoms; NP: Nanoparticles; NT: Nanotechnology; OS: Oxidative Stress; PD: Parkinson's Disease; PET: Positron Emission Tomography; RBD: REM Behavior Disorder; REM: Rapid Eye Movement; RES: Reticulo-endothelial System; SPECT: Single-Photon Emission Computed Tomography; TMS: Transcranial Magnetic Stimulation; TRBG: Tremor, Rigidity, Bradykinesia, Gait and posture.

Disorders mentioned: Alzheimer's disease; Brain abscess; Cerebral edema; Dementia with Lewy bodies; De Vivo; Epilepsy, HIV encephalitis [38]; Meningitis; Multiple sclerosis: Multiple system atrophy; Neuromyelitis optica (Devic's disease); Parkinson's disease;

Parkinson syndrome; Prion; Prion-like diseases; Progressive multifocal leukoencephalopathy; Psychosis (dopaminergic-induced); Rabies; Systematic inflammation; Trypanosomiasis.

Drugs Cited: Amantadine; Caffeine; Carbidopa; COMT-inhibitor; Donepezil (*Eisai*); Droxidopa (*Northera*); Duloxetine (*Cymbalta; Xeristar*); Inosine; Istradefylline (*Nouriast*); *Isradipine*; L-dopa; Levodopa; Mannitol; MAOB-inhibitor; Melevodopa; Naloxone; Nicotine; Omigapil; Opicapone (*Ongentys*); Oxycodone; Pimavanserin (Nuplazid); *Rasagiline*; *Selegiline*; Safinamide (*Xadaco*); Tozadenant; XP066 (*Rytary*); *Under development*: ANLE138b; NPT200-11. *Under clinical testing*: NPT100-13a.

Introduction

Nearly two centuries after the description of the cardinal motor symptoms of Parkinson's disease (PD) and more than a century after the identification of the two neuropathological hallmarks of the disease, two advances have changed the field. The first was the discovery that a mutation in the gene for the protein alpha-synuclein causes a rare form of autosomal-dominant PD, identifying the genetic component of PD and explaining the presence of pathological alpha-synuclein-aggregations in the Lewy bodies in the *substantia nigra*. The second was the confluence of the Braak's staging and the "dual hit theory", positing that PD is a late-stage phenotype preceded for years, if not decades, by three prodromal stages. While testable in the clinic, it faced conflicting results; furthermore, the long time lag required militates against its general acceptance.

Based on the above findings, and perhaps for the first time in the history of the disease, the focus of drug development has then shifted away from transmitters, transmitter-related receptor agonists and antagonists, and transmitter-synthesizing and degrading enzymes. It is now centered on the chemistry, synthesis, transport, aggregation, and degradation of alpha-synuclein and other proteins involved in neurodegenerative disorders (NDDs), such as MAP-Tau or amyloid-beta. A 20-year-long effort in neuroscience and drug development appears at last to provide the first therapeutic results. Unfortunately, notwithstanding the importance of these new developments and the associated research efforts and clinical trials, we will not be closer to identifying the root cause(s) of the disease and, therefore, not closer to a cure.

After a succinct historical background [7, 15, 19, 23, 31], I will discuss the new therapeutic developments in the form of improved symptomatic therapies for both motor and non-motor systems, identifying their mode of action, and phase of development. Drugs approved for other indications but now also tested for PD will likewise be reviewed. However, these compounds and techniques only allow fine-tuning of the available symptomatic therapy and do not represent a major innovation of the type needed.

Beginning in 1997, the world of PD research began changing dramatically with contemporaneous advances in genetics and nanomedicine. Three genetic discoveries (PARK1, LRRK2/PARK2/PINK1/DJI, and GCS-4) have changed the world of PD or, at least its genetic component, leading to a search for a PD-modifying therapy. So far, no important adverse effects have been reported but the clinical usefulness of gene therapy remains to be established. Neuroprotective treatments will also be reviewed including neural and stem cell transplantation and transcranial magnetic stimulation. Several nutrients have been proposed as possible treatments; however, there is no evidence that vitamins or food additives improve symptoms.

Two disease-modifying therapeutic strategies are currently followed, one based on epidemiological findings and large clinical prospective trials and the other based on the above genetic discoveries. The former has reported a *correlation* between a reduced occurrence or prevalence (or both) of PD and the consumption of compounds such as caffeine or nicotine. As a result, a dramatic shift in the strategy for developing a new PD therapy has taken place targeting alpha-synuclein protein synthesis, degradation (such as autophagia, lysosomal, or proteasomal degradation), protein aggregation, and propagation in the nervous system. Finally, 20 years after the discovery of PARK1, the academic and pharmaceutical-industrial-scientific community can offer the first candidates with a potential for a disease-modifying effect on PD.

Several lines of research suggest that mitochondria may play a role in the development of PD. Their abnormalities are major sources of free radicals often referred to as oxidative stress including free radical damage to DNA, proteins, and fats. Their contribution to PD will also be examined.

Lastly, considering the possible links between PD and the blood-brain barrier, it is suggested that employing the principles, methodologies, and procedures of nanomedicine/nanobiotechnology could benefit the treatment of PD in that therapeutic compounds could be delivered at the right brain locations in the right dosages and regimens. The foundations for this proposal are here laid down in the hope that they will be taken up and investigated.

Historical Background

Slightly more than 200 years after their description, the four cardinal motor symptoms of PD (tremor, rigidity, bradykinesia, gait and posture imbalance – our acronym TRBG) are still the basis of the clinical diagnosis of the disease. For more than 100 years, we have known the two neuropathological hallmarks of the disorder, the so-called Lewy bodies containing aggregations of the protein alpha-synuclein and the loss of midbrain neurons containing pigmented-melanin. The latter reflects the neurodegeneration of dopamine-producing neurons in the *substantia nigra* leading to a marked dopamine deficit in the striatum.

Since 1961, L-dopa, a symptomatic dopamine-replacement therapy, has been available for PD. As L-dopa, the precursor of dopamine and subsequent dopamine agonists are highly effective in reducing motor symptoms, PD was for a long time predominantly considered a "movement disorder". This focus was even enforced by three developments: (1) the unraveling of the motor circuitry of the basal ganglia, (2) its imbalances in PD, and (3) the dramatic therapeutic effect of deep brain stimulation (DBS) of the subthalamic nucleus or the *globus pallidus*. These symptomatic therapeutic achievements may explain why the development of therapies for the wide range of disabling "non-motor symptoms" (NMS) that PD patients experience throughout the disease has been neglected. Also, research efforts on the development of disease-modifying drugs were largely performed in acute toxin-induced rodent models (although PD is not known to occur naturally in any species other than humans except perhaps, according to Smeynes, in ducks!). Unfortunately, the neuro-scientific results of these efforts failed to translate into clinically successful drugs. Thus, apart from a few cases of toxin-induced Parkinson syndromes, firm knowledge at the molecular level on the etiopathogenesis of PD was lacking until the year 1996.

However, between 1996 and 2006, two discoveries have changed the field: (1) The discovery of a mutation in the gene for the protein alpha-synuclein (that is the presence of three alleles instead of two alleles, leading to the production of 150% of normal alpha-synuclein) causes a rare form of autosomal-dominant PD. It is the cause of the genetic component of PD and the explanation of the presence of pathological alpha-synuclein-aggregations in the Lewy bodies in the *substantia nigra* and (2) the publication of the Braak staging of PD which, combined with the "dual hit theory", proposed that the manifestation of motor PD symptoms is a late-stage phenotype preceded for years, if not decades, by three prodromal stages. While important contributions, I do not believe that these developments and the associated research efforts and clinical trials will identify the root cause(s) of the disease.

Up to 2016, we still had no treatment to stop or even slow down the progression of the disease. Available therapy so far had been symptomatic. Now, however, and for the first time in the history of the disease, as a result of our greater understanding of the genetic and neuropathology of the disease, substances with a *potentially* (emphasis added) disease-modifying effect are under development. This enhanced understanding is leading to research that is revolutionizing the understanding of PD.

Based on these findings, the majority of cases with PD (the so-called idiopathic form of PD) were assumed to present an alpha-synucleinopathy. Drug development thus shifted its focus from transmitters, transmitter-related receptor agonists and antagonists, and transmitter-synthesizing and -degrading enzymes to the protein chemistry, synthesis, transport, aggregation, and degradation of alpha-synuclein and other proteins related to neurodegenerative disorders (NDDs), such as MAP-Tau or amyloid-beta. A 20-year-long effort in neuroscience and drug development appears at last to provide the first therapeutic results... but these developments and the associated research efforts and clinical trials may (will?) not identify the root cause(s) of the disease.

New Therapeutic Developments

With the above situation in mind, efforts over the last 20 years to develop new therapies for PD can be divided into two categories aimed at: (1) improving symptomatic therapy of motor and non-motor symptoms and (2) addressing potential mechanisms of PD, with a focus on the protein alpha-synuclein, its chemistry, synthesis, aggregation, degradation, and interaction with other proteins to develop a disease- modifying treatment. I addess below in detail these developments.

Improving symptomatic therapy of motor systems

To improve the available symptomatic therapy for motor symptoms, several drugs have recently been approved or are still under testing. These developments include:

- Improvement of the pump device for infusing L-dopa in the jejunal cavity (available since 2017-18), and
- Approval of a long-acting (5- to 6-hour duration of action) L-dopa (currently available in the U.S. under the trade name Rytary).

Table 1 lists the newly developed symptomatic therapy for motor systems and motor complications employing a dopaminergic mode of action including four newly approved drugs for PD. It details the mode of action of the drug, its phase of development, some comments on the approved dose and its potential reimbursement whether in the European Union (EU) or in the U.S. It also provides the corresponding references for those who may wish to refer directly to the sources of information used in drafting this Table.

Compound	Indication	Mode of action	Phase of development	Commentary and approved dose	References
Melevodopa/ Carbidopa	Motor	Modified form of L-dopa soluble tablet	Approved	Marketed in Italy	Zangaglia *et al*. (2010) Fasano *et al*. (2014)
Opicapone *Ongentys*	Motor wearing-off	COMT-inhibitor, long-acting, add-on to L-dopa	Approved	Reimbursed in EU 50 mg/day	Ferreira *et al*. (2015) Roccaet *et al*. (2016) Fabbri *et al*. (2016)
Safinamide *Xadago*	Motor wearing-off	MAO-B-inhibitor, glutamate modulator, add-on to L	Approved	Reimbursed in EU, active comparator study to other MAO-B-inhibitors not available 50 or 100 mg/day	Stocchi & Torti Cattaneo *et al*. (2016) Borgohainet *et al*. (2014) Borgohain *et al*. (2014) Schapira *et al*. (2013) Stocchi *et al*. (2012)
"XP066" *Rytary*	Motor wearing-off	L-dopa/ Carbidopa (4/1) long-acting, extended-release	Approved	Reimbursed in USA 95, 145, 195, 245mg L-dopa capsules	Yao *et al*. (2016) Mao & Modi (2016) Waterset *et al*. (2015) Hsu *et al*. (2015) Stocchiet *et al*. (2014) Pahwa *et al*. (2014) Hauser *et al*. (2013)

Source: Oertel and Schulz (2016)

Table 1: *Newly developed symptomatic therapies for motor systems of Parkinson's disease*

Symptomatic therapy for motor and non-motor systems

Likewise, Tables 2 and 3 list the symptomatic therapy developed for motor symptoms and their complications and non-motor symptoms utilizing a non-dopaminergic mode of action in two situations:

- In the case of drugs approved for PD: This includes 5 newly developed drugs; and
- For drugs approved in another indication but now tested in PD. This includes 3 newly developed drugs.

All of the above drugs are in advanced stages of clinical trials.

Symptomatic therapy for non-motor systems

In 2011, the International Movement Disorders Society (IMDS) published a comprehensive evidence-based medicine review of the therapy for non-motor systems (NMS) as guidance in treating the individual NMS in PD. Since then, increased efforts in this field have led to the approval of new therapies:

- For the treatment of dopamimetic-induced psychosis in PD: The 5HT2A inverse agonist Pimavanserin has been approved in the U.S. Thus, for the first time, an alternative to the currently employed antipsychotic compounds Quetiapine or Clozapine is available.

Compound	Indication	Mode of action	Phase of development	Commentary	References
Amantadine Extended-release	Motor dyskinesia off-time	NMDA-receptor antagonist, long-acting	Phase III completed	Registered in 2017/8/9 as 340 mg/day	Pahwa *et al*. (2015), (2016)
Droxidopa L-Threo-3,4-Dihydroxy-Phenylserine *Northera*	o Motor and non-motor freezing o Neurogenic orthostatic hypotension	Noradrenaline precursor		Approved in Japan and USA Capsules: 3×100 mg max. 3×6 (max. daily dose 1,800 mg)	Hauser *et al*. (2014) Espay *et al.* (2014) Mathias *et al*. (2001)
Istradefylline *Nouriast*	Motor wearing-off	Adenosine 2A receptor antagonist	Phase III positive Phase III ongoing in EU	Approved in Japan 20 mg/once daily (40 mg/daily possible)	Vorovenci & Antonini (2015) Kondo *et al*. (2015) Pinna (2014) Mizuno *et al*. (2013) Pourcher *et al.* (2012) Factor *et al*. (2010) Mizuno *et al*. (2010)
Tozadenant	Motor dyskinesia wearing-off	Adenosine 2A receptor antagonist	Phase III ongoing		Michel *et al*. (2015) Hauser *et al*. (2014) Perez-Lloret & Morello (2014)
Pimavanserin *Nuplazid*	Non-motor psychosis	5HT2A inverse agonist	Phase III positive	Approved in the USA 2x17 mg/ once daily	Cummings *et al*. (2014) Hacksell *et al*. (2014)

Source: Oertel and Schulz (2016)

Table 2: *Newly developed symptomatic therapy for motor and non-motor systems - Drugs approved for Parkinson's disease*

- For the severe pain syndromes: The slow-release preparation of Oxycodone/Naloxone has been successfully tested in PD. Furthermore, the precursor of noradrenaline Droxidopa, also known as L-threo-DOPS, has been approved for the treatment of neurogenic orthostatic hypotension, one of the troubling autonomic symptoms in advanced PD and even more so in multiple system atrophy (MSA), another alpha-synucleinopathy.

Compound	Indication	Mode of action	Phase of development	Commentary	References
Donepezil *Eisai*	Non-motor falls, gait disorder, dementia in PD	Acetylcholine-esterase-inhibitor	Phase IIIb ongoing	Approved for therapy of Alzheimer's dementia	Chung *et al*. (2010) Ravina *et al*. (2005)

Duloxetine *Cymbalta, Xeristar* (University of Toulouse, France	Non-motor pain	SSNRI	Phase III ongoing	Approved for therapy of pain and of depression	
Oxycodone/ Naloxone *Targin* (MundiPharma	Severe pain syndrome in PD	Opioid	Phase III positive	Approved for therapy of pain	Trenkwalder *et al*. (2015)

Source: Oertel and Schulz (2016)

Table 3: *Newly developed symptomatic therapy for motor and non- motor systems - Drugs approved in another indication, now tested in Parkinson's disease*

- For deep brain stimulation: A large recent study has shown beneficial effects of this neurosurgical procedure on non-motor symptoms (NMS). Given the major impact of NMS and therapy-related non-motor complications on the quality of life for PD patients and their partners, this field needs priority in future clinical trials [3, 5, 6, 8, 34].

In summary, these compounds and techniques allow fine-tuning of the available symptomatic therapy of motor and partly of non-motor systems in PD. However, they do not represent major innovations. True, highly needed innovations would be:

- A compound with disease-modifying properties to slow down, if not stop, the progressive pathophysiology of PD (that is, most likely the spreading of the alpha-synucleinopathy in the central, peripheral, autonomic, and gastrointestinal nervous system of patients with PD).

- The use proposed by this author of nanomedicine principles and technology to cross the blood- brain barrier (BBB) and deliver the appropriate compound(s) at the right location and in the right dose.

New Research Vistas

Beginning in 1997, the world of PD research began changing dramatically with contemporaneous advances in genetics and nanomedicine.

Gene therapy and the search for Parkinson's disease-modifying therapy

Gene therapy typically involves the use of a non-infectious virus (i.e., a viral vector such as the associated adenovirus) to shuttle genetic material into a part of the brain. The gene used leads to the production of an enzyme that helps to manage PD symptoms or protect the brain from further damage [10, 29].

In 2010, there were four clinical trials using gene therapy in PD. So far, no important adverse effects in these trials have been reported although the clinical usefulness of gene therapy has not yet been established. Three genetic discoveries have changed the world of PD or, at least its genetic component [26, 28, 35]:

- PARK1: For the first time, though a very rare instance, an autosomal dominant mutation (termed PARK1) that is responsible for the protein alpha-synuclein was described. Shortly after this discovery, alpha-synuclein aggregates were identified in the Lewy bodies in the post-mortem *substantia nigra* samples of patients with idiopathic PD. Therefore, the majority of patients with idiopathic PD are now considered to suffer from alpha-synucleinopathy.

- LRRK2, PARK2, PINK1, DJ1: By 2016, at least eight monogenic causes for PD had been evidenced. The autosomal dominant forms relate either to a mutation of alpha-synuclein or to LRRK2, whereas autosomal recessive forms (PARK2, PINK1, DJ1) cause

mitochondrial dysfunction.

- GCS-A: A small percentage (3–7%) of patients with idiopathic PD were found to carry a heterozygous mutation for the gene glucocerebrosidase-A (GCS-A). Further, besides the role of alpha-synuclein, genome-wide association studies (GWAS) have confirmed the importance of the microtubule-associated protein tau (MAPT) in the etiopathogenesis of PD [32]. Still further, at least 28 genetic risk (susceptibility) factors have been identified and, likely, this number will further increase in the future. These discoveries have already had a major impact on the development of new therapies, especially regarding *potentially* disease-modifying compounds.

The Braak staging of Parkinson's disease (revisited)

Based on the distribution of the Lewy bodies in the nervous system, Braak et al. postulated that, as defined with its motor symptoms, "*PD is most likely a late-stage phenotype of a disease which has been going on for decades*" [4].

The advantage of the Braak hypothesis is that it can be clinically tested. By carefully screening and following-up patients at risk for PD, clinicians can identify a subgroup of patients with prodromal PD who present with and develop the sequence of symptoms related to the postulated prodromal PD stages. This type of study may lead to the discovery of endpoints for future neuroprotective trials in prodromal PD.

However, the hypothesis has its limitation for the *post-mortem* analysis of PD brains has shown, for example, that the density of Lewy bodies in the medullary areas is lower than in the cortex. Also, a similar distribution of Lewy neuropathology is observed in patients with incidental Lewy body disease (that is, individuals with the hallmark Lewy pathology in brain who did not present with motor Parkinson features) when they were alive. This observation does not appear to be consistent with a caudorostral spreading of alpha-synuclein aggregates. But, if Lewy bodies are considered a mechanism to reduce the amount of soluble toxic alpha-synuclein oligomers in the cell, then, the density of Lewy bodies in a given brain area may reflect its "defense" capability. In addition, if the caudorostral ascending process is tightly linked to the connectome of the involved structure, the *locus coeruleus* with its lack of connections to the basal ganglia and, on the other hand, its strong projections to cortical areas, might drive the alpha-synuclein load of cortical areas many years longer than the *substantia nigra* might influence the alpha-synuclein load of the basal ganglia.

The spreading hypothesis

Combined with the "dual hit theory", the Braak hypothesis proposes that PD starts either in the olfactory bulb and related areas or in the gastrointestinal system. Thus, a pathological agent would retrogradely reach the *substantia nigra* via an only recently discovered connection between it and the olfactory bulb. Alternatively, it may move retrogradely from the gastrointestinal system up to the dorsal motor nucleus of the vagal nerve and would then propagate upwards in the brainstem reaching the *locus coeruleus* complex. Over the next 5 to 10 years, it would finally affect the *substantia nigra* [25].

The search for prodromal stages

In the clinical situation, according to Braak *et al*., manifest PD is preceded by years, if not decades, by prodromal phases (the phases related to an early or premonitory symptom of the disease). To screen for prodromal (premotor) phases, the non-motor system hyposmia, constipation, depression, and the REM sleep behavior disorder (RBD) are now considered prodromal indicators. Whereas the first three are sensitive but not specific, RBD is now accepted as the most specific phenotype of the PD prodromal phases with a risk of more than 80% to convert into PD, or dementia with Lewy bodies (DLB), or less frequently into multiple system atrophy (MSA) 10 to 15 years later [9, 36, 37].

Similar research on prodromal stages takes place with "at-risk relatives" of Parkinson patients, who are either heterozygous for the LRRK2 gene or are homozygous for one of the autosomal-recessive genes for mitochondrial dysfunction in PD (PAKR2, PINK1, DJ1).

Our two interacting brains – Etiologic modulations of neurodegenerative and gastroenteric diseases

Humans live in a symbiotic relationship with the commensal indigenous microbial communities living within them, forming an

integrated ecosystem. Our two brains (brain-in-the-skull, brain-in-the-gut) communicate bi-directionally through the gut-brain pathway (or axis). Dysbiotic states of the gut microbiome can be correlated with neurodegenerative disorders, contributing to or modulating their etiology(ies) but *not* being their root cause(s). Effects on neurodegenerative and gastroenteric diseases include, in particular, Parkinson's (and Alzheimer's) disease. They also include effects of the selective serotonin re-uptake inhibitors (antidepressant medications meant to cause chemical changes in the mind showing gastrointestinal side effects, irritable bowel syndrome, osteoporosis, and developmental disorders such as autism). In the same manner that connections between the brain and spinal cord lesions indicate multiple sclerosis, connections between the gut and enteric nervous system lesions may explain gastroenteric diseases. Cutting-edge research is currently investigating how the second brain also mediates the body's immune response. The above considerations are germane to the Braak hypothesis and should be considered in parallel with it.

Neuroprotective Treatments

Investigations on neuroprotection are at the forefront of PD research. Several molecules have been proposed as potential treatments. However, none of them have been conclusively demonstrated to reduce degeneration. Agents currently under investigation include:

- *Anti-apoptotic* (Omigapil, CEP-1347);
- Antiglutamatergic;
- *Monoamine oxidase* (MAO) inhibitors *(Selegiline, Rasagiline);*
- *Promitochondrials (coenzyme Q10, creatine);*
- *Calcium channel blockers (Isradipine);*
- *Growth factors* (GDNF); *and*
- *Vaccines*; A vaccine that primes the human immune system to destroy alpha-synuclein *PD01A*, developed by the Austrian company Affiris, has entered clinical trials in humans.

Neural transplantation

Since the early 1980s, fetal, porcine, carotid or retinal tissues have been used in cell transplants in which dissociated cells are injected into the *substantia nigra* in the hope that they will incorporate themselves into the brain in a way that replaces the dopamine-producing cells that have been lost. Although there was initial evidence of mesencephalic dopamine-producing cell transplants being beneficial, double-blind trials to date have indicated that cell transplants produce no long-term benefit. An additional significant problem was the excess release of dopamine by the transplanted tissue, leading to dystonias.

Stem cell transplants

Stem cell transplants are a recent research target because stem cells are easy to manipulate and, transplanted into the brains of rodents and monkeys, have been found to survive and reduce behavioral abnormalities. Nevertheless, the use of fetal stem cells is controversial. It has been proposed that effective treatments may be developed in a less controversial way by the use of induced pluripotent stem cells taken from adults [33].

Transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (TMS) temporarily improves *Levodopa*-induced dyskinesias. Its usefulness in PD is an open research topic [11, 27].

Nutrients

Several nutrients have been proposed as possible treatments; however, there is no evidence that vitamins or food additives improve symptoms [1, 2].

The Search for Disease-Modifying Therapies

Two therapeutic strategies are currently followed. The first is based on epidemiological findings and large clinical prospective trials reporting a correlation (emphasis added) between a reduced occurrence or prevalence (or both) of PD and the consumption of compounds such as caffeine or nicotine. Table 4 cites examples of these generic substances with a postulated disease-modifying potential for PD.

Compound	Indication	Mode of action	Phase of development	References
Caffeine (University of Montreal, Canada)	Motor early PD	Adenosine-receptor antagonist	Phase IIIb ongoing	Wills *et al*. (2013) Postuma *et al*. (2012)
Inosine (Michael J. Fox Foundation)	Motor early PD	Precursor of urate, antioxidant	Phase Iib ongoing	Bhattacharyya *et al*. (2016) Ascherio *et al*. (2009)
Isradipine – STEADY-PDIII (NIH-NINDS, Novartis, University of Chicago)	Motor early PD	Dihydropyridine calcium channel blocker	Phase IIIb ongoing	Simuni *et al*. (2016) Simuni *et al*. (2013)
Nicotine – NIC-PD (Parkinson Study Group: Germany, USA). MJFF, IPF, NP, DPG, Novartis Germany)	Motor *de novo* PD	Cholinergic, modulation of α-synuclein aggregation?	Phase IIIb completed	Oertel *et al*. (2016) Quik *et al*. (2008) Hong *et al*. (2009)

Source: Oertel and Schulz (2016)

Table 4: *Therapy with compounds of disease-modifying potential (generic substances)*

The second approach departs dramatically from the first one, taking advantage of groundbreaking genetic discoveries related to the alpha-synuclein protein: synthesis, degradation (such as autophagia, lysosomal, or proteasomal degradation), aggregation, and propagation in the nervous system. Finally, 20 years after the discovery of PARK1, the academic and pharmaceutical-industrial-scientific community can offer the first candidates with a potential for a disease-modifying effect in PD.

Three different principles of therapeutic action are addressed: (1) active and passive immunotherapy, [13, 18, 20], (2) modulation of alpha-synuclein aggregation, and (3) enhancement of autophagy of alpha-synuclein (Table 5).

Active and passive immunizations

The first therapeutic approach mimics a strategy that has been followed in Alzheimer's disease (AD) for the last decade, namely, active and passive immunizations. This immunotherapeutic strategy relies on the following three assumptions:

- Alpha-synuclein is trans-synaptically spread and can be accessed in the extracellular space;
- Sufficient numbers of antibodies released against alpha-synuclein reach the brain; and
- Antibodies trap the alpha-synuclein aggregates.

Compound	Indication	Mode of action	Phase of development	References
Immunotherapy				
Active immunization (Affiris)	Motor	IT	Phase II ongoing	Schneeberger et al. (2016) Manoutcharian *et al*. (2016)

Passive immunization (Biogen; Parthena/ Roche)	Motor	IT	Phase II in preparation Phase II in preparation	Weihofen et al. (2016) Bergström et al. (2016) Kalia et al. (2015) Games et al. (2014) Spencer et al. (2016)
Alpha-synuclein aggregation modulators				
NPT200-11 (UCB/Neuropore)	Motor? likely in *de novo* PD	ASAM	Phase I in planning	Koike et al. (2014) Szoke et al. (2014)
NPT100_18a (Neuropore)	Not applicable	ASAM	Preclinical testing	Wrasidlo et al. (2016)
ANLE 138b (MODAG)	Motor? likely in *de novo* PD	ASAM	Phase I in planning	Deeg et al. (2015) Levin et al. (2014) Wagner et al. (2013)
Alpha-synuclein autophagia enhancer				
Nilotinib *Tasigna off-label* use (Georgetown University; MJFF)	Motor non-motor	"Tyrosine kinase inhibitor" ASAE	Investigator-initiated trial – open-label small pilot study - randomized controlled trial in planning (MJFF-USA, Cure PD Trust, UK)	Pagan et al. (2016) Hebron et al. (2014) Hebron et al. (2013)

Source: Oertel and Schulz (2016)

Table 5: *Therapy with compounds targeting alpha-synuclein*

Today, active and passive immunization trials are underway in phases I and II. These treatments have passed the safety level testing, and the first data on phase II trials were awaited in 2017-2019. One limitation of active and passive immunotherapy, that is the low amount of antibodies passing the blood-brain barrier, may be overcome by coupling antibodies to the peptide penetratin, as has recently been reported in a mouse PD model.

Modulation of alpha-synuclein aggregation

In the modulation of the alpha-synuclein aggregation approach, modulating the aggregation of alpha-synuclein aims to block or reduce the aggregation of its monomers to oligomers or later on to fibrils. Following this principle, two drugs (ANLE138b, NPT200-11) near very early development. The former compound can reduce the aggregation of alpha-synuclein (it also extended survival in a mouse model). The latter compound reduces aggregation of alpha-synuclein at least *in vitro* and, according to public information, should have reached the very first safety testing in humans. A third compound (NPT100-18a) can displace alpha-synuclein from membranes but is still in preclinical testing.

The advantage of these small molecules is that, in variance to antibodies employed in immuno-therapeutic attempts, they readily pass the blood-brain barrier. Nonetheless, in analogy with the case of the beta amyloid plaques in Alzheimer's, the clearing of these protein accumulations may not be therapeutic and may perhaps even worsen the disease.

Enhancement of autophagy of alpha-synuclein

In the third approach, autophagy enhancers of alpha-synuclein are being newly developed and in preclinical testing. Screening of libraries of registered compounds may well reveal further potential members of this group. Again, notwithstanding their potential ability to clear the alpha-synuclein protein accumulations, I do not believe that such compounds will treat the root cause of PD and may not be curative.

In summary, the shift from symptomatic to preventive therapy has proceeded along five lines:

- ***Passive immunization***;
- ***Active immunization;***
- ***Modulation of alpha-synuclein aggregation;***
- ***Small molecules***: Two small molecules that function as alpha-synuclein aggregation modulators; and most recently
- ***Autophagy enhancer***: An autophagy enhancer with a known adverse profile (which is already registered in the field of oncology).

Thus, for the very first time, the possibility of a "disease-modifying therapy" appears to be testable in PD. However, *disease-modification is not cure*! Taking together the discoveries on the genetic background of PD and the Braak staging hypothesis, new avenues for drug development and clinical testing have opened up. In the next few years of clinical testing, potential disease-modifying compounds will be tested in the early stages of motor PD. Here, *de novo* PD patients who never received a symptomatic therapy will be recruited and should present with a unilateral asymmetric very mild motor symptomatology.

"True" neuroprevention being the prevention or delay of the conversion of a prodromal to a motor stage, corresponding parameter(s) and biomarker(s) have yet to be discovered. Such a parameter must be responsive to therapy, even in the prodromal stage, to qualify as a primary endpoint for pivotal registration trials. In these efforts, biomarkers are studied in several organs or systems: central and peripheral nervous system, the skin, and the salivary gland. Major efforts are placed into different imaging techniques with sophisticated magnetic resonance (MR) methods, nuclear medical ligands for the dopamine transporter, single-photon emission computed tomography (SPECT) or fluoro-desoxyglucose positron emission tomography (FDG-PET). At least in the next few years of clinical testing, potential disease-modifying compounds are and will be tested in the early stages of motor PD.

Mitochondrial Research

Mitochondria are the energy-producing components of the cell and abnormalities in the mitochondria are major sources of free radicals (molecules that damage membranes, proteins, DNA, and other parts of the cell). They may play a role in the development and progression of PD. This damage is often referred to as oxidative stress (OS). It has been observed in PD brains. Some mutations that affect mitochondrial function have been identified as causes of PD. While mitochondrial dysfunction, OS, inflammation, toxins, and many other cellular processes may contribute to PD, the actual cause of cell loss or death in PD is still undetermined.

On the other hand, hundreds of genes involved in mitochondrial function have been found to be less active in PD so that drugs targeting them could perhaps slow the progression of the disease.

Animal Models

PD is not known to occur naturally in any species other than humans, although animal models that show some features of the disease are used in research. In the early 1980s, the appearance of Parkinsonism in a group of drug addicts who consumed a contaminated batch of the synthetic opiate MPTP led to the discovery of the chemical MPTP as an agent that causes Parkinsonism in non-human primates as well as in humans. Models based on toxins are most commonly used in primates. They employ rotenon (an insecticidee, *paraquat* (a herbicide), and *maneb* (a fungicide). Transgenic rodent models that replicate various aspects of PD use the neurotoxin 6-hydroxydopamine to target and destroy the dopaminergic neurons in the *substantia nigra*.

The Nanomedicine Approach

In separate publications [12, 14], I discussed the fact that of the approximately 400 known neural disorders, a number of these may be due to a disruption or failure of the blood-brain barrier (BBB), including particularly Parkinson's, but also Alzheimer's, epilepsy, brain abscess, cerebral edema, De Vivo, HIV encephalitis [30], meningitis, multiple sclerosis, neuromyelitis optica (Devic's disease), prion and prion-like diseases, progressive multifocal leukoencephalopathy, rabies, systematic inflammation, tripanosomiasis, and others. In the case of Parkinson's, the penetration mechanism of the BBB is still rather unknown.

The brain protective barriers

There are five protective barriers (BPB) that hinder the delivery of therapeutic drugs to the brain. They describe the five main interfaces between the central nervous system (CNS) and the periphery. These include:

- The blood-brain barrier proper that extends down the spinal cord;
- The brain-cerebrospinal fluid barrier (CSF);
- The brain-inner CSF barrier;
- The brain-outer CSF barrier; and
- The brain-retinal barrier.

Composed of a monolayer of brain capillary endothelial cells forming tight junctions, all interfaces are physical and metabolic barriers that serve to regulate and protect the micro-environment of the brain. Thus, the BBB limits access to the brain to small non-polar molecules by passive diffusion or catalyzed transport of large and/or polar molecules. It hinders the delivery of most pharmaceuticals (diagnostic, therapeutic agents) to the brain.

Possible links between Parkinson's disease and the blood-brain barrier

In the case of PD, we have already reached three important conclusions [39]:

- Dopamine does not cross the BBB so it cannot be taken as a medicine to boost the brain's depleted levels of dopamine. However, a precursor of dopamine, Levodopa, can pass through this barrier to the brain where it is readily converted to dopamine. The administration of this drug temporarily diminishes the motor symptoms of PD. Unfortunately, only a very small amount of the drug (say, 5–10%) crosses the barrier; the remainder is metabolized to dopamine elsewhere in the body, causing a variety of side effects.
- The immunotherapeutic strategy for PD therapy relies on the assumptions that:
    - Alpha-synuclein is accessible in the extracellular space (trans-synaptic spreading);
    - Antibodies against alpha-synuclein reach the brain in sufficient quantity;
    - Antibodies trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space; and
    - Modulating the aggregation of alpha-synuclein aims to block or reduce the aggregation of its monomers to oligomers or later on to fibrils.

Three small molecules mentioned earlier (ANLE138b, NPT200-1, and NPT100-18a) are being developed as PD drugs. In variance to antibodies employed in immunotherapeutic attempts, these drugs readily pass the BBB. Thus, the ability to traverse or bypass the BBB while delivering therapeutic compounds at the right locations in the right dosage amounts would herald a new approach to the treatment of PD. however, this nanotechnology application to PD has not yet been undertaken.

Drug resistance and the possible role of the BBB remain an important research focus [16, 17].

Bioavailability of therapeutic drugs

The bioavailability of therapeutic drugs is determined by the permeability of the BBB to them. Unfortunately, so is the resistance to chemically different anti-Parkinson drugs (APD) for which there currently are no known theories describing it.

Drug Delivery Across The Blood-Brain Barrier

Approaches

I have detailed elsewhere the several approaches available for drug delivery across the BBB [16, 17]. I will not review them again here but, for convenience, I have summarized them in Table 6. The Table also provides a partial listing of therapeutics for drug delivery across the BBB. Separately, Table 7 summarizes the delivery systems employed [12, 14, 39].

Approach	Mediating factors	Results
Mannitol intracarotid diffusion	• Vasodilatation • Shrinkage of cerebrovascular endothelial cells • Modulation of the contractile state of the endothelial skeleton • Junction proteins by increased intercellular calcium	Marked increase in apparent BBB permeability to intravascular substances (factor 10) due to both increased diffusion and bulk fluid flow across the tight junctions
Use of immunosuppressants	• Drugs, metabolic derangements or hypoxic-ischemic injury • Concomitant hemodynamic disturbances (intracerebral hemorrhage or embolic stroke) • Loss of autoregulation of cerebral blood flow • Changes in intracranial pressure due to edema • Inflammation	• Seizures (transient and easily treated) • Lack of EEG data may underestimate the true impact of BBB failure on the breakdown of neuronal control
Physiological approach(es)	LDLRP/Epic (a low-density lipoprotein/related protein) with engineered peptide compound	Improves transcytosis capacity of specific receptors expressed across the BBB

Source (14)

Table 6: *Therapeutics for drug delivery across the blood-brain barrier*

Nanotechnology applications

Various types of nanoparticles (NP) and nanodevices (ND) for delivering therapeutics are available. I will only briefly summarize them.

Nanoparticles:

The layered NP consists of three components:

- A core vesicle with a double-layered membrane. It is filled with water and hydrophilic and/or hydrophobic drugs;
- A multi-layered shell; and
- An exterior shell that targets the NPs to areas identified as PD sites.

Approach	Mediating factors
Chemical systems	• o Lipid-mediated transport • o Pro-drugs • o Lock-in systems
Biological systems	Specific endogenous transporters located within the brain capillary endothelium
Other systems	• Receptor-mediated transport systems, e.g., endogenous peptides (insulin, transferin) • Solid lipids • Polymers • Mesoporous silica • Inorganic

Source (14)

Table 7: *Delivery systems for drug delivery across the blood-brain barrier*

The multi-layered shell of the NP has several purposes:

- Stabilizing the NPs;
- Preventing drug leakage;
- Target the NPs to the PD site;
- Minimizing the interactions of the NPs and non-PD sites;
- Transport drugs that are not easily stored in the core (e.g., highly charged nucleic acids).; and
- Passing unnoticed by the immune system.

The basic process to use drug delivery involves at least three steps:

- Encapsulation of the drugs;
- Successful delivery of said drugs to the targeted region of the body; and
- Successful release of that drug there.

NP-based delivery enables sophisticated tactics to fight disease with improved drug release profiles both spatially as well as temporally while reducing harmful side effects, all of which being enabled by their small size and intricate engineering design.

There are several clinical advantages to these NPs. Specifically, they:

- Circulate throughout the bloodstream without being attacked by the immune system;
- Are non-toxic because they are made of a biodegradable polymer that can be safely metabolized by the body; and
- Can be packed with many small drug molecules that can diffuse out of the polymer core and through the platelet membrane onto their targets in the brain.

Nanocarriers:

Several nanocarriers have been developed for drug delivery at the right address in the brain. However, challenges remain, including how not to let the medicine(s) act before they reach the right place. Thus, to encapsulate the drugs, long-range electrostatic interactions are employed wherein the carrier attracts oppositely-charged medicines. To subsequently trigger their release, magnetic fields, different pH-values, etc., are used. In each situation, however, the problem of efficiency of the drug release remains. Nonetheless, work is still needed to determine the most effective NTs for brain tumors. Table 8 summarizes the various types of NPs and their indication(s):

Nanoparticle type	Indication(s)
Microspheres	
Bionanocapsules	
Radiolabeled polyethylene glycol-coated: • HexaDecylCyanoAcrylate; (HDCA) • PolyAlkylCyanoAcrylate (PACA) • PolyLacticCoGlycolic Acid (PLGA) • Peptidomimetic Monoclonal Antibodies; (PMA)	• Not ready for clinical trials because of accumulation • Coated with polysorbate 80 or poloxamer 188
Magneto-Electric Nanoparticles	Wireless stimulation of cells deep in the brain
Bioavailability-improved nanoparticles and molecules	
Maximization of bioavailability (both at specific places in the body and over time)	Molecular targeting by nano-engineered device targeting molecules and delivering drugs with cell precision

Nutshells: • Platelet-coated NPs • Biocompatible/biodegradable gelatins • Shape-shifting engineered nanoparticles • Nanogels	Targeted by conjugated antibodies or peptides: • Can deliver higher doses of medication drugs to targeted sites in the body • Can deliver multiple drugs bypassing the BBB • Can be tailored to specified sites and nowhere else • Non-sticking, with responsive shell permeability
Liposomes	
Peptides	• Able to cross the BBB through various mechanisms, e.g., Casomorphion (a heptapeptide)

Source [12, 14]

Table 8: *Various types of available nanoparticles able to contain therapeutic drugs*

Table 9 lists the various delivery systems available so far with new nanodevices being under current investigation and to become available in the future.

Nanodevices	Action(s)
Engineered devices: • Improved pharmacokinetic strategies of drug molecules (biodistribution, bioavailability, and controlled and site-specific drug release) • Decreased peripheral toxicity • Influence manufacturing factors (type of polymers and surfactants, particle size and size distribution, and drug molecules) • Limitations of drug amount delivered, and physiological factors [phagocytic activity of the reticuloendothelial system (RES), protein opsonization]	Potential to be engineered to efficiently and more safely deliver drug treatments directly to the location of diseased cells while helping avoid harm to healthy cells that fall victim to toxic drugs administered by conventional means
Miniaturized carriages: • Protein cages • Microbubbles • Multi-shell hollow nanogels with responsive shell permeability	• Created but challenge remains how not to let the medicine act before it gets to the right place in the brain • Triggers for drug release can be external magnetic field, different pH values, etc.

Source [12,14]

Table 9: *Nanoscale devices for drug delivery across the blood-brain barrier*

Magnetic resonance molecular imaging can show how brains age

Utilizing a novel MRI modality ("molecular imaging") that they helped develop, Dr. Aviv Mezer and his team at The Hebrew University of Jerusalem, Israel, saw that different brains age differently. Perhaps more importantly, they evidenced major changes in the molecular makeup of the gray matter in younger versus older subjects, providing a crucial understanding of how our brains age. For example, in some white-matter areas, there is a decrease in brain tissue volume, whereas in the gray-matter, tissue volume remains constant. The result will be that patients will more likely receive correct diagnoses earlier, speeding up when they begin treatment, which potentially could help them maintain an improved quality of life for longer – all via a benign, non-invasive technique.

This new level of information was previously hidden to the medical community because such changes could only be observed *post mortem* with huge differences in the macromolecules in different diseases. By contrast, with this new technology, the changes can be seen while patients are alive. Those changes in brain macromolecules can be used to detect the onset of neurodegenerative diseases, including PD.

Summary and Conclusions

- The discovery of a mutation in the gene for the protein alpha-synuclein has simultaneously provided an element of the cause of Parkinson's disease, that is its genetic component (in both its motor and neuropsychiatric manifestations), and the explanation of the presence of pathological alpha-synuclein-aggregations in the Lewy bodies in the *substantia nigra*.
- The majority of Parkinson patients, even at the very early stage of neurological diagnosis, actually present a late-stage phenotype of an alpha-synucleinopathy.
- The field has steadily shifted away from developments of symptomatic therapy to preventive therapy, with several different options: active immunization, passive immunization, development of small molecules that function as alpha-synuclein aggregation modulators and, most recently, an autophagy enhancer with a known adverse profile.
- For the very first time, the possibility of a disease-modifying therapy appears to be testable. However, *disease-modifying therapy is not cure!*
- Taking together the discoveries on the genetic background and the Braak staging hypothesis, and considering the interactions of our two brains (brain-under-the-skull, brain-in-the-gut), new avenues for drug development and clinical testing have opened-up. In the next few years of clinical testing, we predict that potential *disease-modifying* compounds will be tested in the early stages of motor PD. However, the diagnostic methodology should identify a primary endpoint for clinical neuroprotective trials, not only in early motor PD but also in the prodromal stages of PD.
- For "true" neuroprevention, parameters and biomarkers which reflect the progression of the alpha-synucleinopathy in the prodromal stage have yet to be discovered. Such a parameter must be responsive to therapy even in the prodromal stage to qualify as a primary endpoint for pivotal registration trials. At present, this parameter has not been identified.
- Deep brain stimulation and high-intensity focused ultrasound guided by magnetic resonance imaging still have their place in the therapeutic armamentorium.
- The benefits of neural and stem cell transplantation remain to be established.
- Dopamine does not cross the blood-brain barrier so it cannot be taken as a medicine to boost the brain's depleted levels of dopamine.
- Levodopa, a dopamine precursor, can pass through this barrier to the brain where it is readily converted to dopamine. Unfortunately, only 5–10% of the drug crosses the barrier with much of the remainder being metabolized to dopamine elsewhere in the body, where it causes a variety of side effects.
- The immunotherapeutic strategy relies on the critical assumptions that alpha-synuclein is accessible in the extracellular space (trans-synaptic spreading), antibodies against alpha-synuclein reach the brain in sufficient quantity, and they trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space. However, one important limitation of active and passive immunotherapy is the low amount of antibodies that can pass the barrier; this may be overcome by coupling antibodies to the peptide penetratin and also employing nanotechnology methods and procedures.
- Three drugs are close to or under very early development (ANLE138b, NPT200-11, and NPT100-18a). The advantage of these small molecules is that, in variance to antibodies employed in immunotherapeutic attempts, they readily pass the BBB.
- Being able to traverse or bypass the BBB while delivering therapeutic compounds at the right locations in the right dosage amounts would herald a new approach proposed here to the treatment of Parkinson's disease. This is what nanomedicine and nanotechnology promise to do. However, while the technology is now well known, its application to Parkinson has not yet been undertaken.
- Magnetic resonance molecular imaging, a benign non-invasive modality, can show in living patients what was previously possible only post mortem, namely how brains age, making it possible to detect the onset of PD and other neurodegenerative diseases.

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