HHS Public Access

Author manuscript

J Neural Transm (Vienna). Author manuscript; available in PMC 2021 August 03.

Published in final edited form as:

J Neural Transm (Vienna). 2020 May ; 127(5): 785–791. doi:10.1007/s00702-020-02167-1.

Parkinson's disease treatment: past, present and future

John D Elsworth, PhD

Yale University School of Medicine, New Haven, CT 06511, USA

Abstract

The substantial contributions of Dr Gerald Stern to past and current treatments for Parkinson's disease patients is reviewed, which form the foundation for an evaluation of future options to control symptoms and halt progression of the disease. These opportunities will depend on a greater understanding of the relative contributions of the environment, genetic and epigenetic influences to disease onset, and promise to emerge as strategies for improving mitochondrial function, halting synuclein and neuromelanin accumulation, in addition to refinement of stem cell and gene therapies. Such advances will be achieved through deployment of improved models for the disease.

Keywords

Parkinson's disease; Pathology; Pharmacology; Stem Cells; Gene therapy; Review

Past

My motivation for embarking on postgraduate work, all those many years ago, was driven by a fascination with the intricacies of brain biochemistry and how chemicals or drugs could affect the balance between different neuronal systems. However, during this time it was my collaboration with Gerald Stern that redirected me from this rather narrow outlook to a goal to pursue meaningful clinical advances for patients with Parkinson's disease (PD). Gerald's compassion for his patients and his dedication to developing new treatments options for them was infectious and moitivating.

The greatest breakthrough in medical treatment for PD so far in our lifetime is the use of L-dopa for treating the symptoms of PD and Gerald was the first neurologist in the UK to administer L-dopa to PD patients, and to establish the first dedicated PD clinic in the country. Gerald was also on the forefront of many other significant therapeutic advances that have improved the lives of those with PD, notably the use of MAO inhibitors (Elsworth et al. 1978; Lees et al. 1977) and directly-acting dopamine (DA) agonists (Stibe et al. 1988). While these successes are well known, it is some of his lesser known studies that illustrate his creativity and drive to alleviate the plight his patients. While doubtless some ventures were never formally reported, the breadth of those that did are illustrative, including studies with PD patients on the effect of amantadine (Hunter et al. 1970), metatyrosine (Sandler et

john.elsworth@yale.edu.

Conflict of interest: The author has no financial disclosure to make or have any conflict of interest.

al. 1972), melatonin (Shaw et al. 1973), thyrotrophin-releasing hormone (McCaul et al. 1974), lithium (McCaul and Stern 1974), baclofen (Lees et al. 1978), electroconvulsive shock therapy (Ward et al. 1980), vitamin E (Stern 1987), and marijuana (Frankel et al. 1990). Further review of his writings also reveals an early appreciation of the potential value of computerized tracking of patients' symptoms (Cassell et al. 1973) and a prescient investigation of nasal administration of therapeutics (Kleedorfer et al. 1991). Early in his career, Gerald held a research appointment under the direction of Dr Mettler at Columbia University, and during this time he was involved in brain lesion studies to advance understanding of the regions involved in generating parkinsonian signs, and interestingly these studies included the subthalamic nucleus (Stern 1966). This experience doubtless influenced his view that surgery had a valuable place in PD treatment (Stern 1969). Since that time of course the subthalamic nucleus has become a major target for DBS in the treatment of parkinsonian motor symptoms (Bronstein et al. 2011; Faggiani and Benazzouz 2017).

These treatment options were designed to relieve the symptoms of PD or mitigate side effects of antiparkinsonian drugs rather than intervene in the underlying disease process. In order to achieve meaningful progress in halting or delaying the progression of cell loss in PD, a greater understanding of the disease process is needed. Gerald voiced a cautionary note about this (Stern 2012a) "If neurodegenerations have a combination of causes, and if those causes are far more stochastic than generally conceded, then this may set limits on what preventative or neuroprotective measures may be possible, as well as on prospects for realistic favourable interventions during the course of a degenerative disease". However, Gerald followed this comment by "Lest the above appear unduly pessimistic, mention was made above to Pandora. Ancient Greek mythology explains that when she opened her box, she released all the evils of mankind. But left in the box was Hope". The progress in the PD research field in the past few years has certainly left us with "Hope" for better treatments and possibly cures for PD in the near future.

Present

All signs now point toward α-synuclein oligomers or fibrils playing a crucial role in the spreading pathology in PD (Stefanis 2012), although it is uncertain what genetic or environmental factors precipitate its aberrant processing or clearance that lead to abnormal α-synuclein deposition in Lewy bodies. It should be remembered though that α-synuclein pathology is not specific for PD, as it is also evident in other conditions such as multiple system atrophy and Lewy body disease (Riederer et al. 2019). Though Alzheimer's disease and PD have been historically considered distinct neurodegenerative entities, there is evidence for Lewy body pathology in and pathological tau aggregation in PD, suggesting some overlap between these two disorders (Desikan et al. 2015). In fact, α-synuclein, phosphorylated tau protein, amyloid beta and other proteins appear to show synergistic effects in the underlying pathogenic processes (Giasson et al. 2003; Jellinger 2011). As with the characteristic amyloid plaques in Alzheimer's disease, the explanation for the presence of synuclein-containing Lewy bodies in PD is controversial. These aggregates could be a key component of the pathology, an endogenous protective mechanism or an epiphenomenon. However, a recent finding has shed some light on the significance of neuromelanin in Lewy

bodies and implicated them as a culprit in parkinsonian pathology. Thus, a rodent model has been developed which overexpresses human tyrosinase, resulting in progressive production of neuromelanin, reaching levels found in elderly human brains. When a particular threshold of neuromelanin is attained, these animals develop PD-like pathology (Vila 2019). If neuromelanin plays a key role in instigating neuronal loss, then PD patients may have greater or accelerated accumulation compared to others. Such a scenario could arise from an upregulation of tyrosinase-related enzymes or elevated levels of cytosolic dopamine, which undergo metabolism and polymerization to form neuromelanin. The vesicular monoamine transporter is recognized as the most important mechanism for controlling intracellular dopamine concentrations, so it is intriguing that an inverse relationship has been observed in human midbrain dopamine neurons between neuromelanin content and vesicular monoamine transporter expression, indicating that more neuromelanin pigment is formed in neurons that have lower vesicular monoamine transporter activity (Liang et al. 2004). The implication that neuromelanin plays a key part in parkinsonian pathology resonates with its ability to chelate iron, which in turn can increase oxidative-stress and may increase the toxicity of environmental or endogenous toxins (Zecca et al. 2004). Indeed, nonhuman primate dopamine neurons that contain neuromelanin are more susceptible to 1-methy1–4-pheny1–1,2,3,6-tetrahydropyridine (MPTP) toxicity than non-melanized neurons (Herrero et al. 1993). Thus, despite neuromelanin being the subject of scrutiny and speculation for many years (Marsden 1983), its biosynthesis may yet emerge as a target for therapeutics in PD and aging.

The proportion of PD cases that can be firmly attributed to identified genetic component generally estimated to be quite small, which has led to the conclusion that most cases can be attributed to environmental factors (Chen and Ritz 2018). Certainly there are identified toxins that can induce PD or PD-like conditions, such as viral encephalitis, exposure to high level of certain metals or particular pesticides/herbicides/fungicides (Chen and Ritz 2018). But encountering such risk factors alone is not enough to account for the development of all idiopathic cases PD. However, polymorphisms in genes not directly associated with PD could translate to differential susceptibility to toxins and blur the distinction between idiopathic and familial forms of PD. Particular attention has focused on the cytochrome P450 enzyme, CYP2D6, which is highly expressed in the liver and certain areas of the central nervous system, particularly the substantia nigra. CYP2D6 is one of the most important enzymes involved in the metabolism of xenobiotics in the body and plays a role in metabolism of approximately 25% of clinically used drugs. The CYP2D6 gene codes for several splice variants and protein products with different catalytic activity. So-called “poor metabolizers”, will incur greater impact than other individuals from environmental toxins that rely on CYP2D6 for metabolism and it is relevant therefore that “poor metabolizers” have an increased risk of developing PD (Ur Rasheed et al. 2017). This is just one example of an interaction between genetics and environment relevant to induction of PD.

Recent advances have revealed a stronger genetic contribution in PD than previously thought, uncovering the role of several PD-related genes in idopathic disease associated with low penetrant mutations. Several recent genome-wide association studies (GWASs) and their meta-analyses have increased the estimate of heritability of PD from the traditionally quoted 1–5% to potentially as much as 30% (Zhang et al. 2018) with discovery of over 40 loci

associated with significant PD risk (Li et al. 2019). However, the identified single nucleotide polymorphisms are usually located in the non-coding regions so that their influence on gene expression and the interaction of multiple genetic risk factors needs to be deciphered. Future approaches using a transcriptome-wide association study (TWAS) should be able to connect putative PD susceptibility genes with specific regulatory functions associated with PD and help prioritize future research (Li et al. 2019).

Another facet that muddies the distinction of environment and genetics is epigenetics, where biochemical modifications to nucleotides in DNA can affect gene expression. Such alterations can be inherited but also can be induced by toxin exposure, lifestyle and even be influenced by the gut microbiome (Bullich et al. 2019). Thus, it seems likely that epigenetic changes play an important role in the etiology and pathogenesis in some cases of PD (van Heesbeen and Smidt 2019), and it is apparent that the synuclein gene is particularly prone to epigenetic modification (Sharma et al. 2019). It is increasingly clear that onset of PD cannot be traced to a single factor and that for most cases it is the result of an unfortunate combination of genetic polymorphisms, epigenetic changes and various environmental factors.

Even though there are several discrete populations of dopamine neurons in brain and synuclein is one of the most abundantly and widely expressed proteins in brain, it is obviously relevant to the etiology of PD that nigrostriatal DA neurons containing synuclein aggregates are preferentially lost in this disease. Indeed, several facets of nigrostriatal DA neurons appear to render them susceptible to damage. This population has particularly high energy demands and low spare respiratory capacity (Pissadaki and Bolam 2013). They have long unmyelinated axons and extensive arborization, making their energy demands much higher than for most neurons (Pacelli et al. 2015). To maintain basal DA tone across the expansive region of their arborization, they fire with slow rhythmic action driven by L-type calcium channels creating large oscillations in intracellular calcium concentrations (Surmeier et al. 2017). As substantia nigra DA neurons have relatively low calcium-buffering capacity, the high intracellular calcium levels favor elevated oxidative stress, which under certain conditions can damage mitochondria (Duda et al. 2016). Mitochondrial homeostasis is achieved by a balance fission and fusion cycles in response to metabolic or environmental stresses (Youle and van der Bliek 2012). Fusion mitigates the burden of partially damaged mitochondria by mixing its components with undamaged mitochondria. Fission creates new mitochondria, and also contributes to quality control by segregating and removing of seriously damaged mitochondria. It is probably relevant to PD pathology that the maintenance of mitochondrial fusion-fission is associated with the function of α-Syn and other PD-related genes (Pozo Devoto and Falzone 2017)

Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α is a transcriptional coactivator that acts as a so-called master regulator of mitochondrial metabolism. An exciting link between PGC-1α and PD pathogenesis emerged several years ago (Zheng et al. 2010). This study involved a genome-wide analysis of data from laser-captured post-mortem DA neurons from PD patients. The gene sets with the strongest association to PD were associated with PGC-1α, and the authors surmised that disruption of PGC-1α may be a root cause of PD. Consequently, the development of drugs targeting PGC-1α pathways has

emerged as an enticing target for therapeutic interventions designed to improve mitochondrial function and progression of PD symptoms. It is clear that in order to harness therapeutic benefit from interventions that adjust PGC-1α function and boost mitochondrial function, a greater understanding of PGC-1α regulation and signaling cascades is needed (Lindholm et al. 2012). One such an approach would be activation of a downstream effectors, such as peroxisome proliferator-activated receptor gamma (PPARγ), known to have antioxidant properties in mitochondria.

The anti-diabetic drug, pioglitazone is recognized as a PPARγ agonist that has promising preclinical results in animal models of PD (Machado et al. 2019; Swanson et al. 2011), although little is known about the precise molecular mechanisms that lead to these neuroprotective effects. We have recently found that pioglitazone administration activates expression in brain of an interesting, but little-studied, mitochondrial enzyme, paraoxonase-2 (PON2) (Blackburn et al. 2020). Located on the inner mitochondrial membrane, PON2 enhances the function of coenzyme Q in the electron transport chain and subsequently reduces the production of reactive oxygen species that can lead to oxidative stress (Devarajan et al. 2011). PON2 is most highly expressed in dopamine-rich regions of brain (Costa et al. 2014) and PON2 deficiency hypersensitizes neurons to oxidative stress induced by 1-methy1–4-phenylpyridinium (MPP+), the toxin generated in vivo following MPTP delivery (Parsanejad et al. 2014). Interestingly, in rodents and primates PON2 expression peaks during development and has fallen by adulthood (Garrick et al. 2016), which coincides with age-related susceptibility of dopamine neurons to the parkinsonian protoxin, MPTP and to methamphetamine in primates (Morrow et al. 2011; Morrow et al. 2012).

Pioglitazone has had mixed outcomes in clinical studies with PD patients (Brakedal et al. 2017; Investigators 2015; Wu et al. 2018), although it should be noted that the lack of a detectable effect in negative studies could be due to the relatively low dose of pioglitazone employed, compared with preclinical studies, and/or the short duration of pioglitazone treatment. In addition, the loss of nigrostriatal DA neurons in particular patient populations may have been too great for a protective effect to be discerned. Thus, it may be too soon to dismiss the potential benefits that glitazone drugs offer in PD, especially in patients with type 2 diabetes or dementia (Lu et al. 2018; Tseng 2018). We suspect that the pioglitazone-induce increase in expression of PON2 in striatum likely contributes to the neuroprotective effects of the drug observed in preclinical models of PD, ischemia and stroke (Cai et al. 2018). We hope that our new data stimulate research into other pharmacological tools to activate PON2 expression in brain and achieve neuroprotection. Stimulation of central PON2 expression in adults promises to be successful and well-tolerated as it relies on reinstating the relatively high levels that occurred during development.

Future

For over the past 40 years there has been hope that replacement of lost DA neurons in PD could translate to an effective and standardized treatment for the condition (Lindvall 2015; Parmar 2018), and Gerald certainly contributed to experimental efforts to make this a reality (Zhou et al. 1997). Clinical trials using transplantation of fetal ventral mesencephalic tissue

to the striatum of PD patients produced variable outcomes, which have been attributed to the number and distribution of DA cells implanted, “contamination” of the implant with cell detrimental to the goals, the health of cells when grafted, the technique used to transfer cells to the brain, the particular patient population studied and the vagaries of the immunogenic profile of donor tissue and recipient host system (Lindvall 2015). Clinical studies were derailed upon the discovery of an increased risk of graft-induced dyskinesia following fetal tissue implantation in PD patients, but have recently been revived in limited capacity upon insight into probable causes of this side effect (Abbott 2014). However, the use of fetal tissue in the treatment of PD still has certain obstacles; the ethical issue that some have related to acquisition of fetal tissue, the limited availability of such tissue and the variable propensity of grafted tissue from one source to be rejected when implanted in the brain another subject. The rapid progress in knowledge of stem cell biology offers to alleviate these barriers, in addition to some of the other stumbling blocks that hindered the implementation of fetal tissue grafting as a reliable approach for treatment of PD. One of the most promising paths forward is the derivation of stem cells from somatic cells (e.g., fibroblasts from skin), and differentiation of these cells to an unlimited number of DA neurons that closely resemble those that naturally arise in the substantia nigra pars compacta. Generation of stem cells from adult cells can be achieved by somatic nuclear transfer or by using transcription factors to reprogram cells to “induced” pluripotent stem cells (iPSCs). The latter type of cell is technically easier to produce than the former and clinical trials or PD are underway using DA neurons derived from iPSCs. Studies in NHP suggest that somatic cells taken from the patient and implanted later as DA neurons (immune-matched) will probably fare better than non-matched or partially matched cells (Morizane et al. 2017), although we have to be cognizant of the potential of matched cells to acquire a foreign signature during its in vitro manipulations. In addition, the potential advantages of somatic nuclear transfer should not be overlooked in the haste to implement iPSC-based therapeutics (Wolf et al. 2017).

In terms of the time for basic science discoveries to mature to clinically useful applications, it is interesting to reflect that 25 years ago a commentary in “Science” on cellular transplantation approaches to PD treatment, concluded “many of those gazing into the future of Parkinson’s therapy see a time when there will be therapies that rescue a patient’s own dopaminergic neurons, making neuron grafts unnecessary. One candidate as a substance for preventing the death of dopaminergic neurons is glial-derived neurotrophic factor (GDNF)” (Barinapa 1995). Soon after this statement the era of neurotrophic factor gene therapy for PD began in earnest (Choi-Lundberg et al. 1997) and while still not yet established as a recognized treatment option for the disease, there is an ongoing GDNF gene therapy clinical trial for PD. Progress in the gene therapy field has been dependent on development of improved vectors. For in vivo gene therapy recombinant adeno-associated viral (rAAV) vectors are now well established, based on their safety and ability to transduce non-dividing cells such as neurons with high efficiency and achieve persistent transgene expression. A challenge for gene therapy of PD has been to target the affected pathways selectivity and sufficiently with minimally intrusive methods. A recent breakthrough has been the engineering of novel AAV capsids, such as the AAV9 and related serotypes (Wang et al. 2018), which have gained popularity due to their ability to traverse the blood-brain barrier

and transduce brain cells following systemic administration. No doubt these new AAV serotypes will be harnessed to deliver other potentially therapeutic genes to the brains of parkinsonian patients, including aromatic amino acid decarboxylase and glutamic acid decarboxylase in addition to neurotrophic factors (Christine et al. 2019; Kaplitt 2019; Kirik et al. 2017).

Mention was made earlier of Gerald's involvement in early studies involving intranasal delivery of small molecule therapeutics (Kleedorfer et al. 1991). More recently it has become apparent that this route can provide convenient access to the brain for gene vectors such as nanoparticles and even stem cells (Aly and Waszczak 2015; Danielyan et al. 2011). This is an intriguing strategy albeit with the potential for "off-target" effects, although with stem cells there is the possibility that chemoattractant signals from the comprised nigrostriatal dopamine system pathway could provide appropriate guidance (Bjugstad et al. 2008; Carney and Shah 2011).

Progress in PD research will rely on the use of appropriate testing models. With animal models, the choice of species employed is a critical factor, as illustrated by well-known example of primate susceptibility to MPTP compared with rodents (Chiueh et al. 1984). A lesser known example was provided with quintessential wit by Gerald (Stern 2012b), where he describes the unique sensitivity of horses to develop nigropallidal necrosis following consumption of the plant, yellow star thistle! Newer approaches to modelling include the ex vivo study of patient-derived induced-pluripotent stem cells and three-dimensional organoid-based culture systems, which permit further insight into Parkinson's disease pathogenesis and potential therapeutic targets (Grenier et al. 2020; Marotta et al. 2020). In vivo modeling has also advanced, now allowing the creation of transgenic animals, including nonhuman primates (Chen et al. 2019; Scaduto 2016), although this is challenging for diseases that stem from multiple genetic loci containing risk variants. Theoretically at least there is the specter of interspecies chimeras from closely related species, such as those between humans and other primates in order to model CNS diseases with complex genetic contributions, using interspecies blastocyst complementation (De Los Angeles et al. 2019); I wonder what Gerald would have thought of that!

Summary

As we peer into to the future of PD research and push ahead without Gerald, we should remember his tremendous spirit and contributions and be inspired by his "Hope" (while avoiding hype) in seeking better treatments and cures for PD.

Acknowledgments:

Supported by AG048918 to JDE

References

Abbott A (2014) Fetal-cell revival for Parkinson's Nature 510:195–196 doi:10.1038/510195a [PubMed: 24919900]

Aly AE, Waszczak BL (2015) Intranasal gene delivery for treating Parkinson's disease: overcoming the blood-brain barrier Expert Opin Drug Deliv 12:1923–1941 doi:10.1517/17425247.2015.1069815 [PubMed: 26289676]

Barinapa M (1995) Researchers broaden the attack on Parkinson's disease Science 267:455–456 doi:10.1126/science.7824944 [PubMed: 7824944]

Bjugstad KB, Teng YD, Redmond DE Jr., Elsworth JD, Roth RH, Cornelius SK, Snyder EY, Sladek JR Jr. (2008) Human neural stem cells migrate along the nigrostriatal pathway in a primate model of Parkinson's disease Exp Neurol 211:362–369 doi:10.1016/j.expneurol.2008.01.025 [PubMed: 18394605]

Blackburn J, Curry D, Thomsen A, Roth R, Elsworth J (2020) Pioglitazone activates paraoxonase-2 in the brain: a novel neuroprotective mechanism Exp Neurol in press

Brakedal B, Flones I, Reiter SF, Torkildsen O, Dolle C, Assmus J, Haugarvoll K, Tzoulis C (2017) Glitazone use associated with reduced risk of Parkinson's disease Mov Disord 32:1594–1599 doi:10.1002/mds.27128 [PubMed: 28861893]

Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, Horak FB, Okun MS, Foote KD, Krack P, Pahwa R, Henderson JM, Hariz MI, Bakay RA, Rezai A, Marks WJ Jr., Moro E, Vitek JL, Weaver FM, Gross RE, DeLong MR (2011) Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues Arch Neurol 68:165 doi:10.1001/archneurol.2010.260 [PubMed: 20937936]

Bullich C, Keshavarzian A, Garssen J, Kraneveld A, Perez-Pardo P (2019) Gut Vibes in Parkinson's Disease: The Microbiota-Gut-Brain Axis Mov Disord Clin Pract 6:639–651 doi:10.1002/mdc3.12840 [PubMed: 31745471]

Cai W, Yang T, Liu H, Han L, Zhang K, Hu X, Zhang X, Yin KJ, Gao Y, Bennett MVL, Leak RK, Chen J (2018) Peroxisome proliferator-activated receptor gamma (PPARgamma): A master gatekeeper in CNS injury and repair Prog Neurobiol 163-164:27–58 doi:10.1016/j.pneurobio.2017.10.002 [PubMed: 29032144]

Carney BJ, Shah K (2011) Migration and fate of therapeutic stem cells in different brain disease models Neuroscience 197:37–47 doi:10.1016/j.neuroscience.2011.08.063 [PubMed: 21946010]

Cassell K, Shaw K, Stern G (1973) A computerised tracking technique for the assessment of Parkinsonian motor disabilities Brain 96:815–826 doi:10.1093/brain/96.4.815 [PubMed: 4589948]

Chen H, Ritz B (2018) The Search for Environmental Causes of Parkinson's Disease: Moving Forward J Parkinsons Dis 8:S9–S17 doi:10.3233/JPD-181493 [PubMed: 30584168]

Chen Y, Zhu G, Shi L, Liu D, Zhang X, Liu Y, Yuan T, Du T, Zhang J (2019) Establishment of a novel mesial temporal lobe epilepsy rhesus monkey model via intra-hippocampal and intra-amygdala kainic acid injection assisted by neurosurgical robot system Brain Res Bull 149:32–41 doi:10.1016/j.brainresbull.2019.04.002 [PubMed: 30954527]

Chiueh CC, Markey SP, Burns RS, Johannessen JN, Pert A, Kopin IJ (1984) Neurochemical and behavioral effects of systemic and intranigral administration of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the rat Eur J Pharmacol 100:189–194 doi:10.1016/0014-2999(84)90221-8 [PubMed: 6203759]

Choi-Lundberg DL, Lin Q, Chang YN, Chiang YL, Hay CM, Mohajeri H, Davidson BL, Bohn MC (1997) Dopaminergic neurons protected from degeneration by GDNF gene therapy Science 275:838–841 doi:10.1126/science.275.5301.838 [PubMed: 9012352]

Christine CW, Bankiewicz KS, Van Laar AD, Richardson RM, Ravina B, Kells AP, Boot B, Martin AJ, Nutt J, Thompson ME, Larson PS (2019) Magnetic resonance imaging-guided phase 1 trial of putaminal AADC gene therapy for Parkinson's disease Ann Neurol 85:704–714 doi:10.1002/ana.25450 [PubMed: 30802998]

Costa LG, de Laat R, Dao K, Pellacani C, Cole TB, Furlong CE (2014) Paraoxonase-2 (PON2) in brain and its potential role in neuroprotection Neurotoxicology 43:3–9 doi:10.1016/j.neuro.2013.08.011 [PubMed: 24012887]

Danielyan L, Schafer R, von Ameln-Mayerhofer A, Bernhard F, Verleysdonk S, Buadze M, Lourhmati A, Klopfer T, Schaumann F, Schmid B, Koehle C, Proksch B, Weissert R, Reichardt HM, van den Brandt J, Buniatian GH, Schwab M, Gleiter CH, Frey WH 2nd (2011) Therapeutic efficacy of

intranasally delivered mesenchymal stem cells in a rat model of Parkinson disease Rejuvenation Res 14:3–16 doi:10.1089/rej.2010.1130 [PubMed: 21291297]

De Los Angeles A, Hyun I, Latham SR, Elsworth JD, Redmond DE Jr. (2019) Human-Monkey Chimeras for Modeling Human Disease: Opportunities and Challenges Methods Mol Biol 2005:221–231 doi:10.1007/978-1-4939-9524-0_15 [PubMed: 31175656]

Desikan RS, Schork AJ, Wang Y, Witoelar A, Sharma M, McEvoy LK, Holland D, Brewer JB, Chen CH, Thompson WK, Harold D, Williams J, Owen MJ, O'Donovan MC, Pericak-Vance MA, Mayeux R, Haines JL, Farrer LA, Schellenberg GD, Heutink P, Singleton AB, Brice A, Wood NW, Hardy J, Martinez M, Choi SH, DeStefano A, Ikram MA, Bis JC, Smith A, Fitzpatrick AL, Launer L, van Duijn C, Seshadri S, Ulstein ID, Aarsland D, Fladby T, Djurovic S, Hyman BT, Snaedal J, Stefansson H, Stefansson K, Gasser T, Andreassen OA, Dale AM, Adni AGC, Investigators I (2015) Genetic overlap between Alzheimer's disease and Parkinson's disease at the MAPT locus Mol Psychiatry 20:1588–1595 doi:10.1038/mp.2015.6 [PubMed: 25687773]

Devarajan A, Bourquard N, Hama S, Navab M, Grijalva VR, Morvardi S, Clarke CF, Vergnes L, Reue K, Teiber JF, Reddy ST (2011) Paraoxonase 2 deficiency alters mitochondrial function and exacerbates the development of atherosclerosis Antioxid Redox Signal 14:341–351 doi:10.1089/ars.2010.3430 [PubMed: 20578959]

Duda J, Potschke C, Liss B (2016) Converging roles of ion channels, calcium, metabolic stress, and activity pattern of Substantia nigra dopaminergic neurons in health and Parkinson's disease J Neurochem 139 Suppl 1:156–178 doi:10.1111/jnc.13572 [PubMed: 26865375]

Elsworth JD, Glover V, Reynolds GP, Sandler M, Lees AJ, Phuapradit P, Shaw KM, Stern GM, Kumar P (1978) Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the 'cheese effect' Psychopharmacology (Berl) 57:33–38 doi:10.1007/bf00426954 [PubMed: 96466]

Faggiani E, Benazzouz A (2017) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: From history to the interaction with the monoaminergic systems Prog Neurobiol 151:139–156 doi:10.1016/j.pneurobio.2016.07.003 [PubMed: 27412110]

Frankel JP, Hughes A, Lees AJ, Stern GM (1990) Marijuana for parkinsonian tremor J Neurol Neurosurg Psychiatry 53:436 doi:10.1136/jnnp.53.5.436

Garrick JM, Dao K, de Laat R, Elsworth J, Cole TB, Marsillach J, Furlong CE, Costa LG (2016) Developmental expression of paraoxonase 2 Chem Biol Interact 259:168–174 doi:10.1016/j.cbi.2016.04.001 [PubMed: 27062895]

Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, Trojanowski JQ, Lee VM (2003) Initiation and synergistic fibrillization of tau and alpha-synuclein Science 300:636–640 doi:10.1126/science.1082324 [PubMed: 12714745]

Grenier K, Kao J, Diamandis P (2020) Three-dimensional modeling of human neurodegeneration: brain organoids coming of age Mol Psychiatry 25:254–274 doi:10.1038/s41380-019-0500-7 [PubMed: 31444473]

Herrero MT, Hirsch EC, Kastner A, Ruberg M, Luquin MR, Laguna J, Javoy-Agid F, Obeso JA, Agid Y (1993) Does neuromelanin contribute to the vulnerability of catecholaminergic neurons in monkeys intoxicated with MPTP? Neuroscience 56:499–511 doi:10.1016/0306-4522(93)90349-k [PubMed: 8247275]

Hunter KR, Stern GM, Laurence DR, Armitage P (1970) Combined treatment of parkinsonism with L-dopa and amantadine Lancet 2:566 doi:10.1016/s0140-6736(70)91365-6

Investigators NETiPDF-Z (2015) Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial Lancet Neurol 14:795–803 doi:10.1016/S1474-4422(15)00144-1 [PubMed: 26116315]

Jellinger KA (2011) Interaction between alpha-synuclein and other proteins in neurodegenerative disorders ScientificWorldJournal 11:1893–1907 doi:10.1100/2011/371893 [PubMed: 22125446]

Kaplitt MG (2019) Gene-targeting approaches for movement disorders: recent advances Curr Opin Neurol 32:566–570 doi:10.1097/WCO.0000000000000719 [PubMed: 31232714]

Kirik D, Cederfjall E, Halliday G, Petersen A (2017) Gene therapy for Parkinson's disease: Disease modification by GDNF family of ligands Neurobiol Dis 97:179–188 doi:10.1016/j.nbd.2016.09.008 [PubMed: 27616425]

Kleedorfer B, Turjanski N, Ryan R, Lees AJ, Milroy C, Stern GM (1991) Intranasal apomorphine in Parkinson's disease Neurology 41:761–762 doi:10.1212/wnl.41.5.761-a

Lees AJ, Shaw KM, Kohout LJ, Stern GM, Elsworth JD, Sandler M, Youdim MB (1977) Deprenyl in Parkinson's disease Lancet 2:791–795 doi:10.1016/s0140-6736(77)90725-5 [PubMed: 71602]

Lees AJ, Shaw KM, Stern GM (1978) Baclofen in Parkinson's disease J Neurol Neurosurg Psychiatry 41:707–708 doi:10.1136/jnnp.41.8.707 [PubMed: 355602]

Li YI, Wong G, Humphrey J, Raj T (2019) Prioritizing Parkinson's disease genes using population-scale transcriptomic data Nat Commun 10:994 doi:10.1038/s41467-019-08912-9 [PubMed: 30824768]

Liang CL, Nelson O, Yazdani U, Pasbakhsh P, German DC (2004) Inverse relationship between the contents of neuromelanin pigment and the vesicular monoamine transporter-2: human midbrain dopamine neurons J Comp Neurol 473:97–106 doi:10.1002/cne.20098 [PubMed: 15067721]

Lindholm D, Eriksson O, Makela J, Belluardo N, Korhonen L (2012) PGC-1alpha: a master gene that is hard to master Cell Mol Life Sci 69:2465–2468 doi:10.1007/s00018-012-1043-0 [PubMed: 22678664]

Lindvall O (2015) Treatment of Parkinson's disease using cell transplantation Philos Trans R Soc Lond B Biol Sci 370:20140370 doi:10.1098/rstb.2014.0370 [PubMed: 26416681]

Lu CH, Yang CY, Li CY, Hsieh CY, Ou HT (2018) Lower risk of dementia with pioglitazone, compared with other second-line treatments, in metformin-based dual therapy: a population-based longitudinal study Diabetologia 61:562–573 doi:10.1007/s00125-017-4499-5 [PubMed: 29138876]

Machado MMF, Bassani TB, Coppola-Segovia V, Moura ELR, Zanata SM, Andreatini R, Vital M (2019) PPAR-gamma agonist pioglitazone reduces microglial proliferation and NF-kappaB activation in the substantia nigra in the 6-hydroxydopamine model of Parkinson's disease Pharmacol Rep 71:556–564 doi:10.1016/j.pharep.2018.11.005 [PubMed: 31132685]

Marotta N, Kim S, Krainc D (2020) Organoid and pluripotent stem cells in Parkinson's disease modeling: an expert view on their value to drug discovery Expert Opin Drug Discov:1–15 doi:10.1080/17460441.2020.1703671

Marsden CD (1983) Neuromelanin and Parkinson's disease J Neural Transm Suppl 19:121–141 [PubMed: 6321645]

McCaul JA, Cassell KJ, Stern GM (1974) Letter: Intravenous thyrotrophin-releasing hormone in Parkinson's disease Lancet 1:735 doi:10.1016/s0140-6736(74)92939-0

McCaul JA, Stern GM (1974) Letter: Lithium in Parkinson's disease Lancet 1:1117 doi:10.1016/s0140-6736(74)90602-3

Morizane A, Kikuchi T, Hayashi T, Mizuma H, Takara S, Doi H, Mawatari A, Glasser MF, Shiina T, Ishigaki H, Itoh Y, Okita K, Yamasaki E, Doi D, Onoe H, Ogasawara K, Yamanaka S, Takahashi J (2017) MHC matching improves engraftment of iPSC-derived neurons in non-human primates Nat Commun 8:385 doi:10.1038/s41467-017-00926-5 [PubMed: 28855509]

Morrow BA, Roth RH, Redmond DE, Elsworth JD (2011) Impact of methamphetamine on dopamine neurons in primates is dependent on age: implications for development of Parkinson's disease Neuroscience 189:277–285 doi:10.1016/j.neuroscience.2011.05.046 [PubMed: 21640165]

Morrow BA, Roth RH, Redmond DE Jr., Diano S, Elsworth JD (2012) Susceptibility to a parkinsonian toxin varies during primate development Exp Neurol 235:273–281 doi:10.1016/j.expneurol.2012.02.005 [PubMed: 22366325]

Pacelli C, Giguere N, Bourque MJ, Levesque M, Slack RS, Trudeau LE (2015) Elevated Mitochondrial Bioenergetics and Axonal Arborization Size Are Key Contributors to the Vulnerability of Dopamine Neurons Curr Biol 25:2349–2360 doi:10.1016/j.cub.2015.07.050 [PubMed: 26320949]

Parmar M (2018) Towards stem cell based therapies for Parkinson's disease Development 145 doi:10.1242/dev.156117

Parsanejad M, Bourquard N, Qu D, Zhang Y, Huang E, Rousseaux MW, Aleyasin H, Irrcher I, Callaghan S, Vaillant DC, Kim RH, Slack RS, Mak TW, Reddy ST, Figeys D, Park DS (2014) DJ-1 interacts with and regulates paraoxonase-2, an enzyme critical for neuronal survival in response to oxidative stress PLoS One 9:e106601 doi:10.1371/journal.pone.0106601 [PubMed: 25210784]

Pissadaki EK, Bolam JP (2013) The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease Front Comput Neurosci 7:13 doi:10.3389/fncom.2013.00013 [PubMed: 23515615]

Pozo Devoto VM, Falzone TL (2017) Mitochondrial dynamics in Parkinson's disease: a role for alpha-synuclein? Dis Model Mech 10:1075–1087 doi:10.1242/dmm.026294 [PubMed: 28883016]

Riederer P, Berg D, Casadei N, Cheng F, Classen J, Dresel C, Jost W, Kruger R, Muller T, Reichmann H, Riess O, Storch A, Strobel S, van Eimeren T, Volker HU, Winkler J, Winklhofer KF, Wullner U, Zunke F, Monoranu CM (2019) alpha-Synuclein in Parkinson's disease: causal or bystander? J Neural Transm (Vienna) 126:815–840 doi:10.1007/s00702-019-02025-9 [PubMed: 31240402]

Sandler M, Corne SJ, Stephens R, Shaw DM, Hunter DR, Stern GM (1972) Metatyrosine in the treatment of parkinsonism Lancet 2:605 doi:10.1016/s0140-6736(72)92006-5

Scaduto CM (2016) Methods for creating transgenic primates Lab Anim (NY) 45:291–292 doi:10.1038/laban.1068 [PubMed: 27439097]

Sharma A, Osato N, Liu H, Asthana S, Dakal TC, Ambrosini G, Bucher P, Schmitt I, Wullner U (2019) Common genetic variants associated with Parkinson's disease display widespread signature of epigenetic plasticity Sci Rep 9:18464 doi:10.1038/s41598-019-54865-w [PubMed: 31804560]

Shaw KM, Stern GM, Sandler M (1973) Melatonin and parkinsonism Lancet 1:271 doi:10.1016/s0140-6736(73)90118-9

Stefanis L (2012) alpha-Synuclein in Parkinson's disease Cold Spring Harb Perspect Med 2:a009399 doi:10.1101/cshperspect.a009399 [PubMed: 22355802]

Stern G (1966) The effects of lesions in the substantia nigra Brain 89:449–478 doi:10.1093/brain/89.3.449 [PubMed: 4958587]

Stern G (1969) Parkinsonism Br Med J 4:541–542 doi:10.1136/bmj.4.5682.541 [PubMed: 5354854]

Stern G (2012a) Genetics and the neurodegenerations: musings of a gadfly J Parkinsons Dis 2:1–5 doi:10.3233/JPD-2012-11065 [PubMed: 23939402]

Stern G (2012b) The horse that wouldn't run Pract Neurol 12:63–67 doi:10.1136/practneurol-2011-000113 [PubMed: 22258176]

Stern GM (1987) Vitamin E and Parkinson's disease Lancet 1:508 doi:10.1016/s0140-6736(87)92120-9

Stibe CM, Lees AJ, Kempster PA, Stern GM (1988) Subcutaneous apomorphine in parkinsonian on-off oscillations Lancet 1:403–406 doi:10.1016/s0140-6736(88)91193-2 [PubMed: 2893200]

Surmeier DJ, Schumacker PT, Guzman JD, Ilijic E, Yang B, Zampese E (2017) Calcium and Parkinson's disease Biochem Biophys Res Commun 483:1013–1019 doi:10.1016/j.bbrc.2016.08.168 [PubMed: 27590583]

Swanson CR, Joers V, Bondarenko V, Brunner K, Simmons HA, Ziegler TE, Kemnitz JW, Johnson JA, Emborg ME (2011) The PPAR-gamma agonist pioglitazone modulates inflammation and induces neuroprotection in parkinsonian monkeys J Neuroinflammation 8:91 doi:10.1186/1742-2094-8-91 [PubMed: 21819568]

Tseng CH (2018) Pioglitazone Reduces Dementia Risk in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Analysis J Clin Med 7 doi:10.3390/jcm7100306

Ur Rasheed MS, Mishra AK, Singh MP (2017) Cytochrome P450 2D6 and Parkinson's Disease: Polymorphism, Metabolic Role, Risk and Protection Neurochem Res 42:3353–3361 doi:10.1007/s11064-017-2384-8 [PubMed: 28871472]

van Heesbeen HJ, Smidt MP (2019) Entanglement of Genetics and Epigenetics in Parkinson's Disease Front Neurosci 13:277 doi:10.3389/fnins.2019.00277 [PubMed: 30983962]

Vila M (2019) Neuromelanin, aging, and neuronal vulnerability in Parkinson's disease Mov Disord 34:1440–1451 doi:10.1002/mds.27776 [PubMed: 31251435]

Wang D, Li S, Gessler DJ, Xie J, Zhong L, Li J, Tran K, Van Vliet K, Ren L, Su Q, He R, Goetzmann JE, Flotte TR, Agbandje McKenna M, Gao G (2018) A Rationally Engineered Capsid Variant of AAV9 for Systemic CNS-Directed and Peripheral Tissue-Detargeted Gene Delivery in Neonates Mol Ther Methods Clin Dev 9:234–246 doi:10.1016/j.omtm.2018.03.004 [PubMed: 29766031]

Ward C, Stern GM, Pratt RT, McKenna P (1980) Electroconvulsive therapy in Parkinsonian patients with the "on-off" syndrome J Neural Transm 49:133–135 doi:10.1007/bf01249195 [PubMed: 7441236]

Wolf DP, Morey R, Kang E, Ma H, Hayama T, Laurent LC, Mitalipov S (2017) Concise Review: Embryonic Stem Cells Derived by Somatic Cell Nuclear Transfer: A Horse in the Race? Stem Cells 35:26–34 doi:10.1002/stem.2496 [PubMed: 27612640]

Wu HF, Kao LT, Shih JH, Kao HH, Chou YC, Li IH, Kao S (2018) Pioglitazone use and Parkinson's disease: a retrospective cohort study in Taiwan BMJ Open 8:e023302 doi:10.1136/bmjopen-2018-023302

Youle RJ, van der Bliek AM (2012) Mitochondrial fission, fusion, and stress Science 337:1062–1065 doi:10.1126/science.1219855 [PubMed: 22936770]

Zecca L, Youdim MB, Riederer P, Connor JR, Crichton RR (2004) Iron, brain ageing and neurodegenerative disorders Nat Rev Neurosci 5:863–873 doi:10.1038/nrn1537 [PubMed: 15496864]

Zhang PL, Chen Y, Zhang CH, Wang YX, Fernandez-Funez P (2018) Genetics of Parkinson's disease and related disorders J Med Genet 55:73–80 doi:10.1136/jmedgenet-2017-105047 [PubMed: 29151060]

Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, Eklund AC, Zhang-James Y, Kim PD, Hauser MA, Grunblatt E, Moran LB, Mandel SA, Riederer P, Miller RM, Federoff HJ, Wullner U, Papapetropoulos S, Youdim MB, Cantuti-Castelvetri I, Young AB, Vance JM, Davis RL, Hedreen JC, Adler CH, Beach TG, Graeber MB, Middleton FA, Rochet JC, Scherzer CR, Global PDGEC (2010) PGC-1alpha, a potential therapeutic target for early intervention in Parkinson's disease Sci Transl Med 2:52ra73 doi:10.1126/scitranslmed.3001059

Zhou J, Bradford HF, Stern GM (1997) Influence of BDNF on the expression of the dopaminergic phenotype of tissue used for brain transplants Brain Res Dev Brain Res 100:43–51 doi:10.1016/s0165-3806(97)00019-9 [PubMed: 9174245]