New Neuroprotective Therapeutic Targets in PD

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MULTIPLE SYSTEM ATROPHY | MULTIPLE SCLEROSIS

Disclosures

- Z. Mari is a full-time staff at Cleveland Clinic and is representing his own opinions and NOT that of CC
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- Z. Mari is founder and CMO for Neuraly, Inc & Z NeuroSciences, LLC

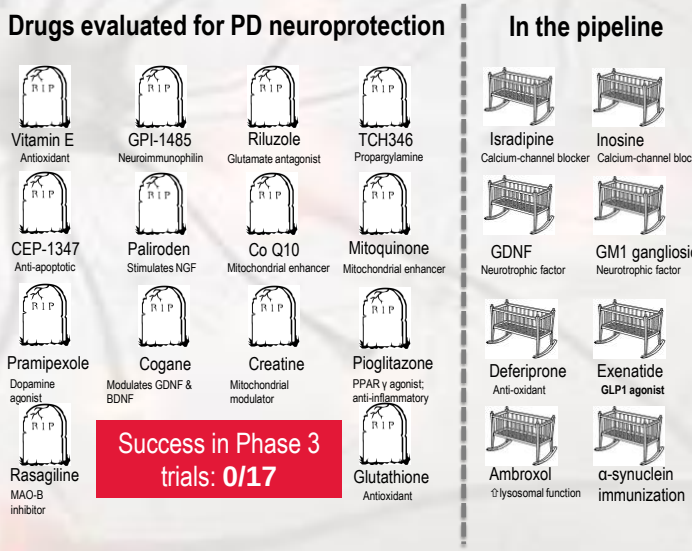
Outline

- Introduction and definitions
  - Symptomatic versus disease modifying
  - Disease modifying versus neuroprotective
  - Pathology versus etiology
- The possible reasons of failing trials in modifying PD
- Review of most promising disease modifying targets/trials:
  - Immune therapies
  - Gene therapies
  - Protein aggregation/small molecule therapies
  - c-Abl inhibitors
  - GLP1 analogues
  - Combination of multiple targets
  - Individualization of targets ("precision medicine") along with endpoints linked to target

Introduction & Definitions

- Symptomatic
  - All currently approved treatments for PD
  - Help improve symptoms: the appearance and impact – without affecting the underlying causes of disease
  - Symptomatic and disease modifying efficacy may not be exclusionary of each other
- "Disease modifying" (not a synonym of "neuroprotective")
  - There is no known proven or approved neuroprotective or disease modifying treatments – only symptomatic at this point
  - Disease modifying means altering any aspect of the disease in a lasting manner (e.g. after removing the intervention)
  - This may be through neuroprotection, but could be through a number of other mechanisms
  - Endpoints capturing disease modification technically more feasible than actual neuroprotection in human clinical trials
  - However, showing disease modification may imply underlying neuroprotection depending on the purported MoA

Lack of Tanslation to Human Trials



Why the Failures?

- The model and underpinning of decades of clinical trial testing (for symptomatic/dopaminergic therapies) not applicable for disease modification
- Animal models are imperfect – toxin based models may be useful for disease state (pathology) but not etiology
- Timing issue (perfect control in animal experiments – not so much in real life – "the horses are out of the barn")
- Lack of sensitive/specific disease progression markers – no good endpoint/poor clinical trial designs
- Heterogeneity of PD – it is a syndrome not a specific disease – particularly relevant in disease modification
- Our incomplete understanding of PD etio-pathogenesis
- Singled out targets maybe insufficient to carry significant impact on overall disease, which is multifactorial

Animal Modeling for PD

CHAPTER 9

MPTP-Induced Parkinsonian Syndrome in Humans and Animals: How Good is the Model?

ZOLTÁN MARI and IVÁN BÓDIS-WOLLNER

9.1 INTRODUCTION

It was shown more than a decade ago that MPTP (1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine), a meperidine analogue, caused a parkinsonian syndrome (PS) in humans (Davis et al., 1979; Langston et al., 1983). Subsequently, several studies demonstrated that MPTP, when injected intravenously, also causes a similar syndrome in the monkey (Burns et al., 1984; Langston et al., 1984). This was the first time that an animal model of a human neurodegenerative disease had been developed. Furthermore, this was also the first instance that a toxin-induced syndrome, which had been proposed as a model of a human disease, had been observed and could be studied longitudinally in the population.

The advantages of the MPTP model include (1) the monkey shows a behavior akin to human Parkinson's disease (PD) in respect to two or three cardinal symptoms; (2) these

Mari, Z. and Bódis-Wollner, I.: MPTP-induced parkinsonian syndrome in man and animals: how good is the model? In: M. Flint Beal MD, Iván Bódis-Wollner MD and Neil Howell PhD (Eds.) "Neurodegenerative Diseases: Mitochondria and Free Radicals in Pathogenesis", New York: John Wiley & Sons, pp 189-237, 1997

With Modern Animal Models the Tides are Changing?

Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yoshio Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greg, Susan Tebbs, Thomas Foltynie

Summary

Background Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in preclinical models of Parkinson's disease. We investigated whether these effects would be apparent in a clinical trial.

Methods In this single-centre, randomised, double-blind, placebo-controlled trial, patients with moderate Parkinson's disease were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. Eligible patients were aged 25–75 years, had idiopathic Parkinson's disease as measured by Queen Square Brain Bank criteria, were on dopaminergic treatment with wearing-off effects, and were at Hoehn and Yahr stage 2·5 or less when on treatment. Randomisation was by web-based randomisation with a two stratis block design according to disease severity. Patients and investigators were masked to treatment allocation. The primary outcome was the adjusted difference in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (part 3) in the practically defined off-medication state at 60 weeks. All efficacy analyses were based on a modified intention-to-treat principle, which included all patients who completed any post-randomisation follow-up assessments. The study is registered at ClinicalTrials.gov (NCT01971242) and is completed.

Findings Between June 18, 2014, and March 13, 2015, 62 patients were enrolled and randomly assigned, 32 to exenatide and 30 to placebo. Our primary analysis included 31 patients in the exenatide group and 29 patients in the placebo group. At 60 weeks, off-medication scores on part 3 of the MDS-UPDRS had improved by 1·0 points (95% CI −2·6 to 0·7) in the exenatide group and worsened by 2·1 points (−0·6 to 4·8) in the placebo group, an adjusted mean difference of −3·5 points (−6·7 to −0·3; p=0·0318). Injection site reactions and gastrointestinal symptoms were common adverse events in both groups. Six serious adverse events occurred in the exenatide group and two in the placebo group, although none in either group were judged to be related to the study interventions.

Interpretation Exenatide had positive effects on practically defined off-medication motor scores in Parkinson's disease, which were sustained beyond the period of exposure. Whether exenatide affects the underlying disease pathophysiology or simply induces long-lasting symptomatic effects is uncertain. Exenatide represents a major new avenue for investigation in Parkinson's disease, and effects on everyday symptoms should be examined in longer-term trials.

Funding Michael J Fox Foundation for Parkinson's Research.

Introduction

Perhaps the most important unmet need in Parkinson's disease is the development of a neuroprotective or disease-modifying therapy that can slow or halt disease progression. None of the compounds that had potential neuroprotective properties in invitro or animal models have shown any effects on disease progression in clinical trials.[1]

Glucagon-like peptide-1 (GLP-1) agonists are licensed for the treatment of type 2 diabetes. These drugs activate GLP-1 receptors to promote glucose-level-dependent insulin secretion, inhibit glucagon secretion, and slow gastric emptying.[2] Exenatide is a synthetic version of exendin-4, a naturally occurring analogue of human GLP-1 that was originally discovered in the saliva of the Gila monster (*Heloderma suspectum*) and is resistant to the normal metabolic processes that degrade endogenous human GLP-1.[3] In addition to effects on glucose homoeostasis, evidence from studies in toxin-based rodent models of Parkinson's disease show that exenatide crosses the blood–brain barrier and exerts neuroprotective and neurorestorative effects via GLP-1 receptors at doses similar to those used in type 2 diabetes, resulting in improvements in motor performance, behaviour, learning, and memory.[4–6]

We previously did a small, proof-of-concept, open-label trial[7] of exenatide in patients with Parkinson's disease of moderate severity, 12 months' exposure to exenatide led to improvements in motor and cognitive assessments in the intervention group compared with the control group, which persisted 12 months after drug withdrawal.[8] On the basis of these encouraging findings, we aimed to do a randomised, placebo-controlled trial (NCT01971242) to assess further the potential disease-modifying effects of 48 weeks' exposure to exenatide, followed by a 12-week washout, on the motor severity of Parkinson's disease.

Research in context

Evidence before this study

We searched PubMed with the terms "Parkinson's disease", "glucagon-like peptide-1", "exenatide", "trial", "neuroprotection", and "disease modification" for articles published in English on or before Dec 4, 2016 (the date of our final search), in any field. We identified several preclinical studies of exenatide, a glucagon-like peptide-1 agonist, which showed neuroprotective and neurorestorative effects in experimental animal-toxin models of Parkinson's disease. We also identified a proof-of-concept study of exenatide as a possible disease-modifying treatment in patients with Parkinson's disease. In this open-label trial, 21 patients who received 12 months of exenatide injections in addition to their regular drugs had a mean improvement of 2·7 points on the Movement Disorders Society Unified Parkinson's Disease Rating Scale part 3, compared with a deterioration of 2·2 points in 24 patients in the control group who received their regular drugs only (mean difference 4·9, 95% CI 0·3–9·4, p=0·037). Furthermore, patients treated with exenatide had a significant improvement on a cognitive assessment scale compared with those in the control group (mean difference 5·0, 95% CI 9·2–0·8, p=0·066). Persistent significant benefits were noted in the exenatide group compared with the control group in motor disability and cognitive function 12 months after the withdrawal of exenatide. However, because a placebo control was not used, these data could not be interpreted as proof of efficacy.

Added value of this study

To our knowledge, ours is the first randomised, placebo-controlled trial of exenatide as a potential disease-modifying drug in Parkinson's disease. After 48 weeks, patients given 2 mg exenatide weekly had a significant advantage in terms of the primary outcome, the Movement Disorders Society Unified Parkinson's Disease Rating Scale part 3, compared with those given placebo. This difference between groups was still significant after a 12-week drug washout period. Our study is also the first to show that exenatide, when given at licensed diabetes doses, crosses the blood–brain barrier and is detectable in cerebrospinal fluid in concentrations similar to those in preclinical models of Parkinson's disease, which are associated with advantageous outcomes. Exenatide was well tolerated, although injection site reactions and gastrointestinal symptoms were noted.

Implications of all the available evidence

We have replicated the results of our previous clinical study and shown that patients with Parkinson's disease who were given exenatide had improvements in the practically defined off-medication motor scores of Parkinson's disease compared with those given placebo. Whether exenatide affects the underlying pathophysiology of Parkinson's disease or simply induces long-lasting symptomatic effects remains uncertain. However, these results represent a major new avenue for investigation in the treatment of Parkinson's disease.

Methods

Study design and participants

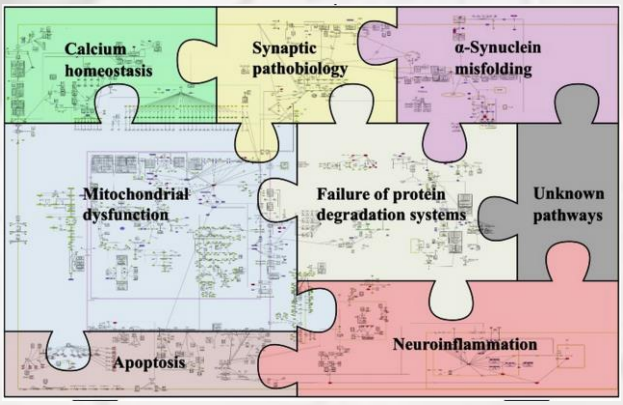
We did a randomised, double-blind, placebo-controlled, parallel-group, single-centre trial of exenatide once weekly in Parkinson's disease of moderate severity. The trial was done at the Leonard Wolfson Experimental Neuroscience Centre (London, UK), a dedicated clinical trial research facility and part of the University College London (UCL) Institute of Neurology and the National Hospital for Neurology & Neurosurgery. The study was coordinated by the UCL Comprehensive Clinical Trials Unit (London, UK). Clinical oversight was provided by a trial steering committee, and an independent data and safety monitoring board. Trial operations were supported by the Leonard Wolfson Experimental Neuroscience Centre and the National Institute for Health Research Biomedical Research Centre at the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery (London, UK).

Eligible men and women were aged 25–75 years, had idiopathic Parkinson's disease as measured by Queen Square Brain Bank criteria,[9] were on dopaminergic treatment with wearing-off effects, were judged able to administer the trial drug, and were at Hoehn and Yahr stage 2·5 or less when on treatment. We pre-screened patients over the phone against these criteria before formal in-person screening. Key exclusion criteria (see trial protocol for full list) included concurrent dementia (defined as a score <120 points on the Mattis-Dementia Rating scale), body-mass index (BMI) of less than 18·5, and diabetes (glycated haemoglobin [HbA_{1c}] ≥48 mmol/mol at screening). This trial was approved by the Brent NHS Research Ethics Committee, London. All patients provided written informed consent.

Randomisation and masking

Patients were recruited from the pool of patients attending the National Hospital for Neurology & Neurosurgery, or approached us as a result of hearing about the trial on ClinicalTrials.gov or Fox Trial Finder. We used SealedEnvelope, an independent, commerical, internet-based randomisation service that generated the online randomisation list on the basis of guidance from the trial IT manager (SH) and trial statistician (SSS). After extensive testing to ensure that the service worked perfectly, the trial recruiting team used it for randomisation, with a block design of two strata according to disease severity (Hoehn and Yahr stage 1·0–2·0 *vs* stage 2·5). Patients were randomly assigned (1:1) to subcutaneous exenatide once weekly or matched placebo injections, in addition to their regular drugs. The trial statistician (SSS) generated and uploaded unique

Neuroprotection: Biological systems involved in PD

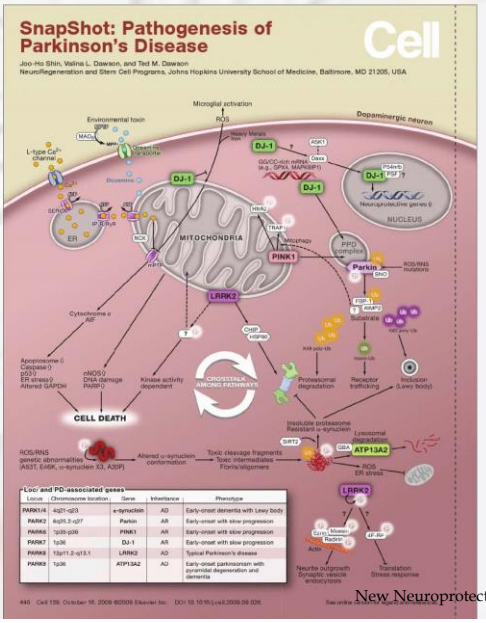


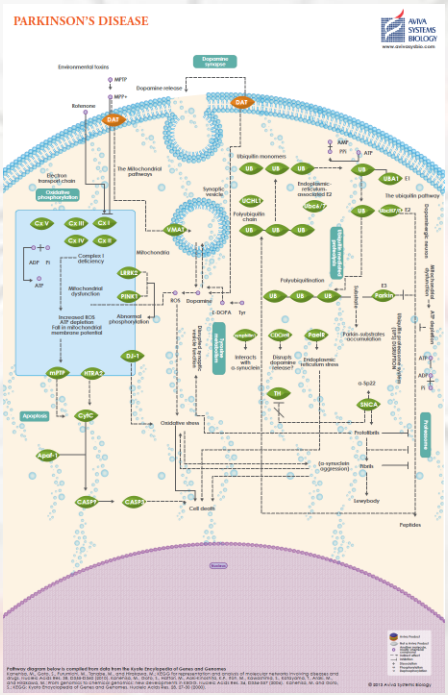
Fujita KA, Ostaszewski M, Matsuoka Y, Ghosh S, Glaab E, Trefois C, et al. Integrating pathways of parkinson's disease in a molecular interaction map. *Mol. Neurobiol.* 2014;49:88-102

The Many (potential) Targets of Disease Modification

- Overview of the molecular pathways
- Transplantation therapies – "stem cells" - popular topic, unlikely to go anywhere – abused worldwide to defraud patients – one issue is the apparent acquisition of synuclein pathology in graft – the "prion" hypothesis
- The LRRK2 story – genetic based therapies
- Immune based therapies – alpha-synuclein antibodies
- Small molecule therapies/aggregation inhibition
- c-Abl inhibition and the nilotinib story
- Microglia/neuroinflammation (HMGB1)/apoptosis
  - GLP1 Agonists

Risk genes and pathogenesis of PD: in 2009





PD Molecular Pathways (as of 2013)

- Oxidative phosphorylation
- Apoptosis
- Tyrosine metabolism
- Ubiquitin mediated proteolysis
- Proteasome system

Prion Hypothesis

- Recent reports demonstrate that a single intracerebral inoculation of misfolded a-synuclein can induce Lewy-like pathology in cells that can spread from affected to unaffected regions and can induce neurodegeneration with motor disturbances in both transgenic and normal mice.
- Further, inoculates derived from the brains of elderly a-synuclein–overexpressing transgenic mice have now been shown to accelerate the disease process when injected into the brains of young transgenic animals.

Evidence for α-synuclein prions causing multiple system atrophy in humans with parkinsonism

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Contributed by Stanley B. Prusiner, July 22, 2015 (sent for review May 19, 2015)

Prions are proteins that adopt alternative conformations that become self-propagating; the PrP^{Sc} prion causes the rare human disorder Creutzfeldt-Jakob disease (CJD). We report here that multiple system atrophy (MSA) is caused by a different human prion composed of the α-synuclein protein. MSA is a slowly evolving disorder characterized by progressive loss of autonomic nervous system function and often signs of parkinsonism; the neuropathological hallmark of MSA is glial cytoplasmic inclusions consisting of filaments of α-synuclein. To determine whether human α-synuclein forms prions, we examined 14 human brain homogenates for transmission to cultured human embryonic kidney (HEK) cells expressing full-length, mutant human α-synuclein fused to yellow fluorescent protein (α-syn140*A53T–YFP) and TgM83$^{+/-}$ mice expressing α-synuclein (A53T). The TgM83$^{+/-}$ mice that were hemizygous for the mutant transgene did not develop spontaneous illness; in contrast, the TgM83$^{+/+}$ mice that were homozygous developed neurological dysfunction. Brain extracts from 14 MSA cases all transmitted neurodegeneration to TgM83$^{+/+}$ mice after incubation periods of ∼120 d, which was accompanied by deposition of α-synuclein within neuronal cell bodies and axons. All of the MSA extracts also induced aggregation of α-syn*A53T–YFP in cultured cells, whereas none of six Parkinson's disease (PD) extracts or a control sample did so. Our findings argue that MSA is caused by a unique strain of α-synuclein prions, which is different from the putative prions causing PD and from those causing spontaneous neurodegeneration in TgM83$^{+/+}$ mice. Remarkably, α-synuclein is the first new human prion to be identified, to our knowledge, since the discovery a half century ago that CJD was transmissible.

neurodegeneration | Parkinson's disease | synucleinopathies | strains

Looking back almost 50 y ago, kuru was the first human prion disease to be transmitted to an experimental animal (1). Subsequently, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia were transmitted to nonhuman primates or transgenic (Tg) mice; all of these disorders were eventually found to be caused by PrP^{Sc} prions that were initially discovered in hamsters with experimental scrapie. Attempts to transmit other neurodegenerative diseases, including Alzheimer's and Parkinson's, to monkeys were disappointing; none of the animals developed signs of neurological dysfunction, and none showed recognizable neuropathological changes at autopsy (2).

In 1960, Milton Shy and Glenn Drager described two male patients suffering from orthostatic hypotension, additional forms of autonomic insufficiency, and a movement disorder resembling Parkinson's disease (PD). They also found an additional 40 cases of idiopathic hypotension in the literature, which shared many features with their patients. Nine years later, Graham and Oppenheimer suggested that Shy–Drager syndrome should be combined with striatonigral degeneration and olivopontocerebellar atrophy and that these three entities should be called multiple system atrophy (MSA) (3). They presciently argued that all three disorders were likely caused by a similar neurodegenerative process. Two decades passed before support for this hypothesis began to emerge when the brains of 11 MSA patients were reported to contain silver-positive accumulations or glial cytoplasmic inclusions (GCIs) primarily in oligodendrocytes (4). The nature of these GCIs remained elusive for another decade until three groups reported that GCIs exhibited positive immunostaining for α-synuclein (5–7). The discovery that MSA is a synucleinopathy followed a study reported 1 y earlier showing that Lewy bodies in PD contain α-synuclein by immunostaining (8). Such investigations were prompted by molecular genetic studies showing genetic linkage between the A53T point mutation in α-synuclein and inherited PD (9).

MSA is a sporadic, adult-onset, progressive neurodegenerative disorder with an annual incidence of ∼3 per 100,000 individuals over the age of 50 (10, 11). The duration of MSA is generally 5–10 y and is substantially shorter than most cases of PD, which

Significance

Prions are proteins that assume alternate shapes that become self-propagating, and while some prions perform normal physiological functions, others cause disease. Prions were discovered while studying the cause of rare neurodegenerative diseases of animals and humans called scrapie and Creutzfeldt-Jakob disease, respectively. We report here the discovery of α-synuclein prions that cause a more common neurodegenerative disease in humans called multiple system atrophy (MSA). In contrast to MSA, brain extracts from Parkinson's disease (PD) patients were not transmissible to genetically engineered cells or mice, although much evidence argues that PD is also caused by α-synucleín, suggesting that this strain (or variant) is different from those that cause MSA.

Author contributions: S.B.P., A.L.W., and K.G. designed research; A.L.W., J.C.W., R.R., D.B.B., S.P., A.O., and S.N.K. performed research; D.A.M., G.M.H., L.T.M., and S.M.G. contributed new reagents/analytic tools; S.B.P., A.L.W., J.C.W., R.R., D.B.B., J.K.L., D.H.G., D.V.G., L.T.G., and K.G. analyzed data; and S.B.P., A.L.W., R.R., and K.G. wrote the paper.

The authors declare no conflict of interest.

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Prion Hypothesis

- Fetal adrenal graft cells develop Lewy bodies

nature medicine

Brief Communication

Nature Medicine 14, 501 - 503 (2008)
Published online: 6 April 2008 | doi:10.1038/nm1746

Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation

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Two subjects with Parkinson's disease who had long-term survival of transplanted fetal mesencephalic dopaminergic neurons (11–16 years) developed α-synuclein–positive Lewy bodies in grafted neurons. Our observation has key implications for understanding Parkinson's pathogenesis by providing the first evidence, to our knowledge, that the disease can propagate from host to graft cells. However, available data suggest that the majority of grafted cells are functionally unimpaired after a decade, and recipients can still experience long-term symptomatic relief.

Two sham surgery–controlled trials of neural transplantation in Parkinson's disease did not reach their primary endpoints[1–3]. However, previous open-label trials with grafts of fetal ventral mesencephalic tissue reported long-lasting functional benefits in subjects with Parkinson's disease[3]. Positron emission tomography (PET) studies showed that grafted neurons were functionally integrated and released dopamine for more than 10 years after surgery[3]. In postmortem neuropathological studies performed 3–4 years after transplantation, large numbers of dopaminergic neurons were found in the grafts[1,2,3].

We now report that grafted cells can survive up to at least 16 years in subjects with Parkinson's disease. Large numbers of transplanted dopaminergic neurons were found in two subjects who had undergone bilateral implantation of fetal mesencephalic tissue into the putamen (subject 3 in the Lund series; left graft 16 years before death, right graft 12 years before death) or both putamen and caudate nucleus (subject 8; left graft 13 years before death, right graft 11 years before death)[4]. Graft survival was confirmed by clinical

Prion Hypothesis

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Spreading of pathology in neurodegenerative diseases: a focus on human studies

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Abstract

The progression of many neurodegenerative diseases is thought to be driven by the template-directed misfolding, seeded aggregation and cell–cell transmission of characteristic disease-related proteins, leading to the sequential dissemination of pathological protein aggregates. Recent evidence strongly suggests that the anatomical connections made by neurons — in addition to the intrinsic characteristics of neurons, such as morphology and gene expression profile — determine whether they are vulnerable to degeneration in these disorders. Notably, this common pathogenic principle opens up opportunities for pursuing novel targets for therapeutic interventions for these neurodegenerative disorders. We review recent evidence that supports the notion of neuron–neuron protein propagation, with a focus on neuropathological and positron emission tomography imaging studies in humans.

Neurodegenerative diseases are a major cause of disability and premature death among older people worldwide[1–3]. Although these diseases, for which there are currently no disease-modifying therapies, show a great diversity of clinical phenotypes, they share a common pathological hallmark — the accumulation of characteristic proteins into insoluble aggregates in or among selectively vulnerable neurons and glial cells.

Aggregates of the phosphorylated microtubule-associated protein tau in neurofibrillary tangles and neuropil threads, together with deposits of amyloid-β (Aβ), are characteristic of sporadic Alzheimer disease (AD). Tau pathology alone also characterizes a subgroup of

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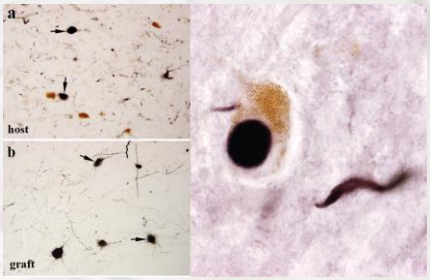
Competing interests statement
The authors declare no competing interests.



- **(Left)** Alpha-synuclein–stained Lewy bodies and Lewy neurites are shown in (a) host substantia nigra neurons and (b) embryonic dopamine neurons that had been implanted into the striatum of a PD patient 14 years earlier.
- **(Right)** This is a high-power view of an a-synuclein–stained Lewy body and a Lewy neurite in grafted mesencephalic dopamine neurons.

Immune-based Therapies

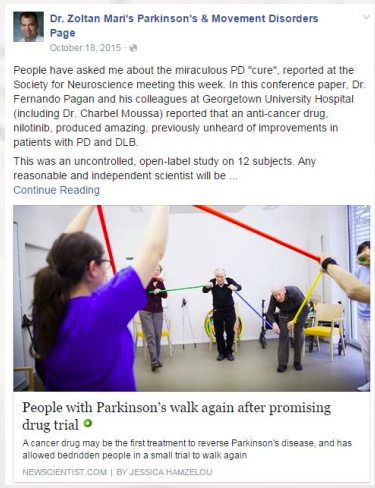
Immunotherapies in PD rely on 3 basic strategies:

1. Generation of antibodies against α-syn (primarily for removal of α-syn aggregates)
2. The induction of a particular T cell response to modulate the neuroinflammatory response
3. "Cool down" microglia and thus the neuroinflammatory response (e.g. GLP1 agonist peptides)

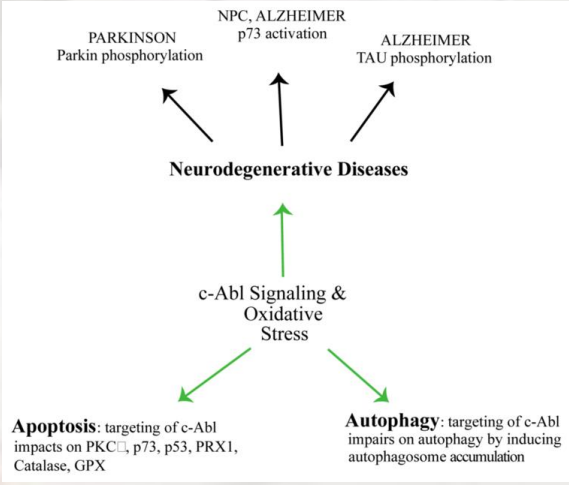
Immunization

- Immunization therapy with human a-synuclein has been shown to reduce a-synuclein aggregate formation and reduce neurodegeneration in human a-synuclein transgenic mice.
- A subsequent series of cell culture and animal experiments suggests that antibodies against a-synuclein reduce cell-to-cell transfer of the protein by directing extracellular a-synuclein to microglia, where it can be degraded.

The Georgetown Nilotinib Study



C-Abl



The Georgetown Nilotinib Study (cont.)

Should Patients and Families Be Considering Tasigna (Nilotinib) Therapy for Parkinson's Disease? The NPF Recommends Further Study but Not Clinical Use of this Investigational Drug

Tasigna (Nilotinib) is a leukemia drug that has recently been tested for safety in a small, phase I clinical trial on about a dozen Parkinson's disease patients. The study had positive results that certainly warrant the continuation to a phase II trial, however it is too early for patients to seek treatment outside the setting of a clinical trial. The study was very small, and it was not placebo controlled. The clinical trial process was designed primarily around patient safety, which is a critical issue with a chemotherapy drug, and this process should continue and more systematic evidence needs to be collected before we can truly understand the impact of this drug.

If you are interested in learning more about the results of this clinical trial, visit Georgetown University National Parkinson Foundation Center of Excellence. To learn about other clinical trials, check clinical trials.gov for trials taking place in your area.

The Georgetown Nilotinib Study (cont.)

- c-Abl inhibition is a promising avenue of research
- BUT:
  - Very small study
  - Open label
  - Advanced patients
  - Immediate effects
  - Non-standard outcome measures (videotaping)
  - Homeopathic dosing to avoid toxicity
  - Questionable choice of inhibitor (specificity)

To Correct the Nilotinib Story

- The MJFF has partnered with the PSG
- NILO-PD – multi-center, placebo controlled phase 2b
- First cohort to assess BBB passage – CSF measurements
- If successful – 2nd cohort to assess safety (further) and efficacy

LIFE • WELLBEING •

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World-first pill may stop Parkinson's

The therapy is partly under-written by the Michael J Fox Foundation. Photo: Getty

John Elder

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A new therapy that appears to stop Parkinson's disease "in its tracks" will begin phase-one clinical trials in humans next year.

The therapy, developed by researchers at the University of Queensland – and partly under-written by the Michael J Fox Foundation – is a world first because it stops the death of brain cells in Parkinson's sufferers rather than managing symptoms.

If human trials echo the stunning results in animal testing, the inflammation of the brain that causes so much of the progressive damage in Parkinson's disease (PD) could be halted by taking a single pill each day.

UQ Faculty of Medicine researcher Associate Professor Trent Woodruff said the key to the new therapy is a small molecule, MCC950 – a compound developed and abandoned 10 years ago by a big pharma company that didn't understand how it actually worked.

At that stage, though, inflammation in the Parkinson's brain was less well understood.

Parkinson's disease, said Dr Woodruff, is characterised by the loss of brain cells that produce dopamine, a chemical that co-ordinates motor control – and it's the loss of dopamine that has been the focus of treatment. But it is also accompanied by this chronic inflammation that occurs as an immune response gone haywire.

Neuroinflammation Targets HMGB1?

- High mobility group box 1 protein, also known as high-mobility group protein 1 (HMG-1)
- Like the histones, HMGB1 is among the most important chromatin proteins. In the nucleus HMGB1 interacts with nucleosomes, transcription factors, and histones.[5] This nuclear protein organizes the DNA and regulates transcription.[6] After binding, HMGB1 bends[7] DNA, which facilitates the binding of other proteins. HMGB1 supports transcription of many genes in interactions with many transcription factors. It also interacts with nucleosomes to loosen packed DNA and remodel the chromatin. Contact with core histones changes the structure of nucleosomes.
- The presence of HMGB1 in the nucleus depends on posttranslational modifications. When the protein is not acetylated, it stays in the nucleus, but hyperacetylation on lysine residues causes it to translocate into the cytosol.
- HMGB1 has been shown to play an important role in helping the RAG endonuclease form a paired complex during V(D)J recombination.

Gordon, Richard and Woodruff, Trent M. (2017). Neuroinflammation as a therapeutic target in neurodegenerative diseases. In Veerle Baekelandt and Evy Lobbestael (Ed.), Disease-modifying targets in neurodegenerative disorders: paving the way for disease-modifying therapies (pp. 49-80) London, United Kingdom: Academic Press. doi:10.1016/B978-0-12-805120-7.00003-8

Disease Modifying/Neuroprotective Trials

Sponsor	Therapeutic	Mechanism	Stage				Status
			I	II	III	Reg.	
GLP1							
University College London	Exenatide	GLP1 agonist					Trial pending
Neuraly	NLY01	GLP1 agonist					Phase I (cohort 2) ongoing
Peptron	PT320	GLP1 agonist					Trial pending
Cedars-Sinai	Liraglutide	GLP1 agonist					Results expected 2019
University Hospital, Toulouse	Lixisenatide	GLP1 agonist					Results expected 2021
Oslo Universitt	Semaglutide	GLP1 agonist					Trial pending
c-Abl							
SPARC	K0706	c-Abl kinase inhibitor					Results expected 2021
Inhibikase	IkT-148009	c-Abl kinase inhibitor					Trial pending
Georgetown University	nilotinib	c-Abl kinase inhibitor					Results expected 2019
Northwestern University (MJFF)	nilotinib	c-Abl kinase inhibitor					Results expected 2019

Disease Modifying/Neuroprotective Trials (Cont.)

Sponsor	Therapeutic	Mechanism	Stage	Status
			I II III Reg.	
ApoPharma	Deferiprone	Iron chelator		Results expected 2019
University of Plymouth	Simvastatin	Anti-inflammatory		Results expected 2020
University of Nebraska	Sargramoslim	Anti-inflammatory		Trial pending
University of Sheffield	Ursodiol (UDCA)	Mitochondrial enhancer		Results expected 2020
University of Minneosota	Ursodiol (UDCA)	Mitochondrial enhancer		Results available
BioElectron	EPI-589	Mitochondrial enhancer		Results pending
Kainos Medicine	KM-819	Cell death inhibitor		Trial pending
Io Therapeutics	IRX-4204	RXR agonist		Trial pending
University of Vermont	Nicotine patch	Acetylcholine receptor agonist		Results pending
University of Rochester	Isradipine	Calcium channel blocker		Results pending
Massachusetts General Hospital	Inosine	Urate precursor		Results pending

Cell Replacement and Repair

Sponsor	Therapeutic	Mechanism	Stage	Status
			I II III Reg.	
Trophic Factors				
Herantis	CDNF	CDNF protein infusion		Results expected 2019
NIH/NINDS	AAV2-GDNF	GDNF gene therapy		Results expected 2025
MedGenesis	GDNF	GDNF protein infusion		Results available
Cell-Based Therapy				
International Stemm Cell Corporation	ISC-hpNSC	Dopamine cell replacement		Trial pending
Kyoto University Hospital	iPSC-DA Transplants	Dopamine cell replacement		Results expected 2019
Celavie Biosciences	OK99	Dopamine cell replacement		Trial pending
Living Cell Technologies	NTCell	Pig choroid plexus cells/protection		Results pending

Alpha-Synuclein Therapies

Sponsor	Therapeutic	Mechanism	Stage	Status
			I II III Reg.	
AFFiRiS	AFFITOPE PD01A	Active immunotherapy		Trial pending
Biogen	BIIB054	Passive Immunotherapy		Results expected 2022
Prothena/Roche	Prasinezumab PRX002/RO794601	Passive Immunotherapy		Results expected 2020
AstraZeneca/Takeda	MEDI-1341	Passive Immunotherapy		Results expected 2019
Lundbeck	Lu-AF82422	Passive Immunotherapy		Results expected 2020
AbbVie/BioArctic	ABBV-0805	Passive Immunotherapy		Trial pending
Neuropore/UCB	NPT200-11 UCB0599	Small molecule disaggregator		Trial pending
Prana Bio	PBT434	Small molecule disaggregator		Trial pending
Proclara	NPT088	Small molecule disaggregator		AD trial results expected 2019
Yumanity	YTX-7739	Small molecule inhibitor of alpha-synuclein toxicity		Trial pending

Controversies: PD and Neuroprotection

- The profound lack of translation from basic science success to clinical trial results
- Exercise
- Is levodopa toxic?
- Is it proven that MAO-B inhibitors are neuroprotective
  - No, because even if disease modification is showed, that is not equivalent with neuroprotection
  - ADAGIO trial: inconclusive
  - "Conditioning" confound of symptomatic agents tested in the context of disease modification