1. GENE THERAPY FOR PARKINSON’S

INTRODUCTION
A cardinal feature of Parkinson’s disease (PD) is the loss of dopaminergic neurons in the substantia nigra, leading to a decrease in axonal connections to the striatum. The resulting loss of dopamine causes the motor, and some non-motor symptoms. Increasing the presence of dopamine in the target areas of the putamen is one way to restore some of the lost function.

This restoration can be achieved in several ways, by reintroduction of dopaminergic neurons via implanted stem cells; stimulation of neuron regrowth and/or awakening via infusion of exogenous molecules, e.g. Glial Cell-Derived Neurotrophic Factor (GDNF); or gene therapy, the introduction of engineered DNA sequences able to code for in situ production of the relevant molecule. This article will briefly summarize the current approach to gene therapy for Parkinson’s and then describe the projects currently in the clinic.

The feasibility of gene therapy has been proven clinically, in indications such as Spinal Muscular Atrophy (SMA) [1], lysosomal storage diseases [2] and hereditary leukodystrophy [2]. As unprotected DNA or RNA sequences are rapidly degraded and are thus not feasible, these therapies use a delivery vehicle which in most cases is a viral vector, usually Adeno-Associated Virus (AAV) or Lentivirus (LV).

An excellent review of the therapeutic use of AAV in the nervous system was recently published by Huidry and Vandenberghe [2]. Many years of pre-clinical and now clinical experience have demonstrated the safety and efficacy of AAV. It is easily manipulated to insert the desired sequence with little residual viral DNA. It has rarely been shown to integrate into the host genome, primarily existing as episomal DNA, with the viral particles unable to replicate and devoid of viral genes. Lentivirus-delivered sequences can integrate into the host genome, but only in non-dividing cells.

The highest technical hurdle for any gene therapy is delivering the engineered virus to the target tissue. In the context of Parkinson’s, where the targets lie either deep inside the brain or widely located in the periphery,
intravenous, intranasal and intrathecal delivery are not currently feasible. The only remaining option is direct administration, in the case of the CNS usually to the putamen, in a complicated surgical procedure.

The advantage of gene therapy over infusion of molecules such as GDNF is that, in practice thus far and in theory in the future, only one administration of drug product is needed for long-term biological activity. The addition of a double-blind placebo arm is also easier as simple sham surgery without dura penetration is possible. Whilst it may be easier, it is still not easy and the logistics of surgical delivery bring complications to the design, conduct and funding of clinical trials.

The therapeutic benefits of gene therapy for Parkinson’s must also be assessed in the context of the symptom relief provided by Deep Brain Stimulation (DBS), for both efficacy and safety. While gene delivery still requires a surgical intervention, it offers a potentially attractive alternative to DBS as there is no requirement for an implantable device or postoperative programming.

Finally, it must be stressed that none of the gene therapy projects currently in trial can be classified as a “cure”. They are highly unlikely to influence disease pathology, whether that is a-synuclein aggregation, LRRK2 malfunction or another route. Dysfunction in other neurotransmitter routes will continue with residual motor and continued non-motor symptoms.

This is not to underplay the importance and potential of gene therapy in Parkinson’s. The potential to deliver long-term motor (and some non-motor) symptom relief with greater ON time, reduced dyskinesia and significantly improved quality of life from a single surgical procedure will be extremely attractive. After all, if People with Parkinson’s (PwP) retain the pathology but can’t feel it, why should we care?

GENE THERAPIES IN THE CLINIC
There are five gene therapy programmes currently in the clinic, in phase 1 or 2, designed to deliver either biosynthetic enzymes or growth factors. Three projects aim to induce synthesis of dopamine, one to make gamma-aminobutyric acid (GABA) and one to introduce GDNF.

Voyager Therapeutics in the USA and Jichi Medical University with Takara in Japan use AAV to deliver the gene for amino acid decarboxylase (AADC), the enzyme that converts levodopa to dopamine. Axovant’s Axo-Lenti-PD, licensed from Oxford Biomedica, codes for two enzymes that synthesize dopamine - AADC and tyrosine hydroxylase (TH) – and GTP cyclohydrolase 1 (GCH1), coding for production of an essential enzyme cofactor.

Axovant’s phase 2 trial of Axo-Lenti-PD, SUNRISE-PD, is in phase 2, building on successful safety trials conducted by Oxford Biomedica on a previous version, ProSavin®. Jichi’s AAV-HAADC-2 is in phase 1/2, following on from a successful phase 1 trial in inherited AADC deficiency.

MeiraGTx are developing AAV-GAD, which codes for glutamic acid decarboxylase (GAD), an essential enzyme for GABA synthesis. Neurologix had previously taken this potential therapy to a Phase 2 trial prior to the company folding. MeiraGTx acquired the rights from Vector Neurosciences and plan to continue phase 2 studies.

The National Institutes of Neurological Disorders and Stroke (NINDS) in the USA are developing AAV-GDNF, currently in Phase 1, involving a smaller open-label cohort primarily testing safety. Finally, Prevail Therapeutics are investigating AAV vectors to correct lysosomal malfunction in Parkinson’s, although the date of entry to clinical trials is as yet unknown.
The site of delivery is the striatum, primarily the putamen, in all of the projects except one; AAV-GAD is targeted at the sub-thalamic nucleus (STN) in an effort to reduce the overactivity seen in Parkinson’s. All of the therapies have a single surgical procedure with no further infusions.

The duration of treatment and observation varies. Axovant will assess safety at 3 months and efficacy (as a secondary outcome) at 6 months. Jichi will assess both at 6 months and Voyager at 12 months post-operation. NINDS will assess both at regular intervals over 12 years. The details of MeiraGTx’s next study are not yet available.

Primary outcomes are all on safety measures, with one exception. Voyager’s AAV2-hAADC has an additional assessment of efficacy, measuring the patient-rated change in ON time without dyskinesia. UPDRS and PDQ-39 are both secondary outcome measures. The Axovant study has only three secondary outcomes, all on efficacy.

The more advanced a patient is in the course of their condition, the greater the therapeutic range over which improvement may be detected. All the studies are looking for moderately advanced patients, with a minimum duration of disease of 5 years (4 years in the Voyager study). In addition, Axovant are actively seeking patients with motor fluctuations and dyskinesia.

The time to study end is highly variable. Voyager’s RESTORE-1 started in 2018 and will finish in 2020, with a separately listed follow up trial ending in 2026. The NINDS trial started in 2012 and is targeted to complete in 2026. Axovant’s follow up is to 2031, with primary reporting in 2022. From the perspective of PwP, the time taken to complete these phase 2 studies with phase 3 still to come is highly frustrating, although the prospect exists for phase 3 to run in parallel with the follow up stage of phase 2.

In summary, the number of gene therapies in the clinic for Parkinson’s is relatively small but builds on a generation of technical and clinical feasibility in this and other indications. The complexity of drug administration limits the numbers of patients that can be included in clinical trials. The direct delivery to the anatomy of choice holds great potential for significant therapeutic benefit and symptom relief with reduced motor complications.

References
[1] Mendell, JR., Al-Zaidy S., Shell R., et al., (2017) N Engl J Med, 377, 1713-1722.
[2] Huidry, E and Vandenberghe, L (2019) Neuron, 101, 839-862.

**AAV-hAADC – Jichi Medical University**

**BACKGROUND:** Aromatic amino acid decarboxylase (AADC) converts both endogenous and exogenous levodopa to dopamine in the nigro-striatal region. AADC activity is reduced along with reduced production of dopamine as a function of a progressive nigrostriatal degeneration with advancing disease. This in turn reduces conversion of exogenous levodopa to dopamine leading to increased dose requirement which can be limited due to potential complications. Gene therapy transducing production of AADC alone in the striatum may help restore the enzymatic activity and may be able to reduce the dose of exogenous levodopa but cannot restore the endogenous levodopa production. There are two programs, Jichi University in Japan and Voyager Therapeutics in the USA currently conducting early phase studies of AADC gene delivery in PD.

A small Phase I study was conducted in Japan demonstrating acceptable safety/tolerability and trends for efficacy [1]. The group has since then launched a phase 1/2 dose escalation study.

**TITLE:** A Phase 1/2 Study of Intra-putaminal Infusion of Adeno-Associated Virus Encoding Human Aromatic L-Amino Acid Decarboxylase in Subjects with Parkinson’s Disease.
**OBJECTIVE:** To evaluate the safety and efficacy of intra-puaminal infusion of AAV-hAADC-2 (adeno-associated virus encoding human aromatic L-amino acid decarboxylase) delivered via stereotaxic surgery in advanced PD patients.

**STATUS:** Recruiting.

**CLINICALTRIALS.GOV IDENTIFIER:** NCT02418598.

**SPONSOR:** Jichi Medical University.

**COLLABORATOR:**
- Takara Bio Inc.
- Gene Therapy Research Institution, Co., Ltd.

**ESTIMATED ENROLMENT:** 6 (Phase 1 cohort).

**ESTIMATED PRIMARY COMPLETION DATE:** October 2018 according to clinicaltrials.gov though no results have yet been posted.

**STUDY DESIGN:** This study is a phase 1/2 non-randomized, single center, open label, interventional, safety and dose evaluation study of the active agent AAV-hAADC-2 being delivered intra-puaminal via stereotaxic surgery. It is being conducted at the Jichi Medical University in Japan. The target putamen is identified on the pre-operative MRI brain and then bilateral putamina are infused with the active drug at a total of 4 spots (2 on each putamen). AAV-hAADC-2 is administered via bilateral intra-puaminal infusion in either low or high dose.

There are two sequential study arms. Cohort 1 receives low dose (3x10^11 vector genome/subject) and is infused with a total volume of 200 µl of the drug (50 µl per site). If there are no safety concerns at 6 months, then the study moves to cohort 2. Cohort 2 will receive high dose (9x10^11 vector genome/subject) with 600 µl of total infusion volume (150 µl per site).

The study includes patients with clinical diagnosis of idiopathic PD aged between 35 to 75 years of age with no other known or suspected cause of parkinsonism. Patients should be levodopa responsive and should have been on it for at least 5 years. An OFF state MDS-UPDRS score between 30 – 100 and Hoehn and Yahr stage IV is required. Patients with a history of 3 hours or more of intensive or violent dyskinesia are excluded from the study. Standard surgical exclusionary criteria are applied.

**OUTCOME:** Primary outcome measures include assessment of safety of intra-puaminal infusion of AAV-hAADC-2 as measured by adverse events.

Secondary outcomes include two measures:

1. The treatment effect of the drug at the end of 6 months. This is assessed by improvement in PD symptoms as recorded in subject diaries, clinical assessment and change in levodopa dosage.
2. The amount of intra-puaminal expression of AAV-hAADC-2 after 6 months, as measured by FMT-PET imaging.

Investigators will continue to assess the safety for 5 years after baseline examination and long term follow up will continue for 10 years.

**COMMENTS:** This is a phase 1/2 dose escalation safety and efficacy study. No results have been published yet. Voyager Therapeutics is further ahead in their development program that is reviewed below.
VY-AADC02 - VOYAGER THERAPEUTICS

BACKGROUND: Voyager Therapeutics are developing VY-AADC02, an AAV-2 vector coding for aromatic L-amino acid decarboxylase (AADC). It is delivered surgically to the putamen where, once expressed, AADC converts levodopa to dopamine.

Two phase 1 studies (NCT01973543 and NCT03065192) evaluated the safety of escalating doses of VY-AADC01, a precursor of VY-AADC02. The Phase 1b, open-label, three dose-escalation trial included 15 patients with advanced Parkinson’s Disease (an average of 10 years post-diagnosis) and disabling motor fluctuations, despite treatment with optimal anti-parkinsonian medications.

Putaminal coverage (as measured by co-administration of the MRI contrast agent, gadoteridol) was up to 42%. AADC activity increased by up to 79% as measured by 18F fluoro-L-DOPA PET. After 18 months, results showed an increase in ON time without troublesome dyskinesia of 2.4 hours in the combination of cohorts 2 and 3. These results were achieved with clinically meaningful and sustained reductions in daily oral levodopa and related medications of up to 42% [1]. Infusions of VY-AADC have been well-tolerated in all 15 patients treated in these cohorts, with no reported vector-related serious adverse events (SAEs).

This progress enabled Voyager to start the phase 2 RESTORE-1 study summarized below. Patients from the earlier phase 1 studies and RESTORE-1 will be invited to participate in a long-term follow up observational safety study (NCT03733496).

Voyager have now agreed with the FDA to increase the number of patients in RESTORE-1 to 75-100 and to commence another trial of similar size and design, RESTORE-2, to act as a staggered-parallel phase 3 study. Together with the granting of RMAT (Regenerative Medicine Advanced Therapy) status, this will hopefully be sufficient to enable regulatory submission of the full package [2].

TITLE: VY-AADC02 for Parkinson’s Disease with motor fluctuations.

STATUS: Recruiting. More information is available at https://restore1study.com

CLINICALTRIALS.GOV ID: NCT03562494.

SPONSOR: Voyager Therapeutics.

ENROLMENT: 42 patients (now revised to 75-100).

COMPLETION: December 2020.

STUDY DESIGN: Voyager’s phase 2 study is randomized, placebo-controlled and double-blind, comparing one active dose of VY-AADC02 with a placebo of sham surgery involving a partial burr/twist hole without dura penetration.

OUTCOME MEASURES: Primary outcomes will measure both efficacy and safety. The safety criteria will be evaluated at 12 months and 30 day follow up. The efficacy measures will be taken at 12 months, with enzyme activity also assessed at 45 days. The outcome measures are:

References
[1] S. Muramatsu, K. Fujimoto, S. Kato, H. Mizukami, S. Asari, K. Ikeguchi, T. Kawakami, M. Urabe, A. Kume, T. Sato, E. Watanabe, K. Ozawa, I. Nakano, A phase I study of aromatic L-amino acid decarboxylase gene therapy for Parkinson’s disease., Mol. Ther. 18 (2010) 1731–5. doi:10.1038/mt.2010.135.
a. change in patient rated motor fluctuations.
b. percent coverage within the putamen at time of administration of VY-AADC02.
c. change in AADC enzyme activity (distribution).
d. safety of VY-AADC02 as measured by:
   i. number of treatment emergent adverse events.
   ii. changes in vital signs.
   iii. physical examinations and routine clinical laboratory analysis, (hematology and clinical chemistry).
   iv. changes in findings on brain images.
   v. the Columbia-Suicide Severity Rating Scale (C-SSRS).
   vi. change in impulse control disorders.

Secondary outcomes are all related to efficacy, as measured at the twelve-month timepoint by changes in:
   a. activities of daily living (UPDRS II).
   b. PD related quality of life (PDQ-39).
   c. time course response to levodopa (UPDRS III).
   d. clinical global function (CGI).
   e. overall non-motor symptoms (NMSS).

 COMMENTS: Voyager are recruiting patients at least four years since diagnosis, although there is no explicit requirement for the presence of motor complications, despite the study title. The choice of primary and secondary outcome measures has some interesting features. The primary efficacy outcome is a patient rating of motor fluctuations, with UPDRS measures only as secondary outcomes. The assessment of coverage of the putamen on administration and distribution of enzyme activity, both already validated in the phase 1b trial, will give a good indication of target engagement and change in biological activity. The combination of a good safety profile thus far; the change in biological activity leading to significant clinical change; and a favourable regulatory review, give cause for optimism with VY-AADC02.

References
[1] Christine, CW et al, (2019) Ann Neurol 00 1-11
[2] http://ir.voyagertherapeutics.com/phoenix.zhtml?c=254026&p=irol-newsArticle&ID=2382295

MeiraGTx - AAV-GAD

BACKGROUND: Loss of substantia nigra pars compacta dopaminergic modulation of the basal ganglia circuitry results in reduction of inhibitory activity of the external globus pallidus (GP) via reduced GABAergic output. That translates into disinhibition of the subthalamic nucleus (STN), increasing its excitatory glutaminergic output to the internal GP which, coupled with over activity of the direct pathway, leads to over activity of the GPi and results in the motor symptoms of parkinsonism. Increasing inhibitory flow to the glutaminergic neurons in the STN may normalize its function and thereby lead to clinical benefits. Since glutamic acid decarboxylase (GAD) is the rate limiting step in the synthesis of GABA, the major inhibitory neurotransmitter, preclinical studies have explored injections of vectors containing GAD into the STN with promising results that lead to early phase human studies. Phase 1 and phase 2 studies have been completed.

NCT00195143 was a phase 1 open label trial assessing the safety and tolerability of AAV-GAD injections into unilateral STN in patients with PD. Three cohorts with 4 patients each received either low, medium or high dose AAV-GAD. There were no safety concerns and clinical benefits were noted in reduced motor UPDRS scores beginning at 3 months after the surgery and maintained at the 12 months assessment. PET scans revealed reduced thalamic metabolism on the implanted side which correlated with reduced pallidal activity [1].
A subsequent phase 2, double-blind, randomized, sham surgery-controlled trial with bilateral STN injection of high dose (1x10^{12} viral genomes) AAV-GAD was completed in 2010 and analysed data from 37 patients (NCT00643890). At the end of 6 months the AAV-GAD group showed significant improvement in motor scores as compared to the sham group (23% reduction in the active group vs 13% in the sham, p< 0.003) with no treatment or surgery related adverse events. A 12-month analysis showed reduction of levodopa induced dyskinesias in the treated group. Furthermore, reduced metabolic activities on FDG-PET in the thalamus, striatum, prefrontal, anterior cingulate and orbitofrontal cortices were noted in AAV-GAD treated patients [2,3]. A phase 3 trial was planned but was terminated by the sponsoring company Neurologix due to financial reasons.

A recent analysis used the FDG-PET data from the phase 2 study to understand the metabolic brain network involved. The included patients had completed imaging visits at baseline, 6 and 12 months. The data suggested that the clinical improvement was not exerted via suppressing the abnormal PD related networks, but by developing new polysynaptic networks connecting STN to the cortices [4].

In October 2018, MeiraGTx acquired the vector company (Vector Neurosciences Inc.) and as a result acquired clinical development of the AAV-GAD therapy [5]. According to the company website, a phase 1/2 trial of AAV-GAD in PD patients is in the pipeline. No further information is available at this time and no trial is posted on clinicaltrials.gov.

**COMMENTS:** The phase 1 and phase 2 clinical trials of AAV-GAD gene therapy have shown promising results. Both studies demonstrated an acceptable safety profile of the drug and significant efficacy over sham-controlled arm in the phase 2 trial though the effect size compared to sham was modest, a relative reduction of 10% in motor scores. The drug has now been acquired by MeiraGTx and a phase 1/2 study is in the pipeline.

**References**

1. M.G. Kaplitt, A. Feigin, C. Tang, H.L. Fitzsimons, P. Mattis, P.A. Lawlor, R.J. Bland, D. Young, K. Strybing, D. Eidelberg, M.J. During, Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson’s disease: an open label, phase I trial, Lancet. 369 (2007) 2097–2105. doi:10.1016/S0140-6736(07)60982-9.

2. P.A. LeWitt, A.R. Rezai, M.A. Leehey, S.G. Ojemann, A.W. Flaherty, E.N. Eskandar, S.K. Kostyk, K. Thomas, A. Sarkar, M.S. Siddiqui, S.B. Tatter, J.M. Schwab, K.L. Poston, J.M. Henderson, R.M. Kurlan, I.H. Richard, L. Van Meter, C. V Sapan, M.J. During, M.G. Kaplitt, A. Feigin, AAV2-GAD gene therapy for advanced Parkinson’s disease: a double-blind, sham-surgery controlled, randomised trial, Lancet Neurol. 10 (2011) 309–319. doi:10.1016/S1474-4422(11)70039-4.

3. M. Niethammer, C.C. Tang, P.A. LeWitt, A.R. Rezai, M.A. Leehey, S.G. Ojemann, A.W. Flaherty, E.N. Eskandar, S.K. Kostyk, A. Sarkar, M.S. Siddiqui, S.B. Tatter, J.M. Schwab, K.L. Poston, J.M. Henderson, R.M. Kurlan, I.H. Richard, C. V Sapan, D. Eidelberg, M.J. During, M.G. Kaplitt, A. Feigin, Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson’s disease, JCI Insight. 2 (2017) e90133. doi:10.1172/jci.insight.90133.

4. M. Niethammer, C.C. Tang, A. Vo, N. Nguyen, P. Spetsieris, V. Dhawan, Y. Ma, M. Small, A. Feigin, M.J. During, M.G. Kaplitt, D. Eidelberg, Gene therapy reduces Parkinson’s disease symptoms by reorganizing functional brain connectivity, Sci. Transl. Med. 10 (2018) 713.

5. https://investors.meiragtx.com/news-releases/news-release-details/meiragtx-announces-acquisition-vector-neurosciences-gains-phase
AXO-Lenti-PD - AXOVANT

BACKGROUND: Axovant are developing AXO-Lenti-PD, previously known as OXB-102 when under development by Oxford Biomedica. OXB-102 was, in turn, a successor to ProSavin®. AXO-Lenti-PD uses a lentivirus vector to deliver three genes to the striatum in a single surgical procedure. The genes codes for three enzymes essential to the dopamine production cascade: amino acid decarboxylase (AADC), tyrosine hydroxylase (TH) and GTP-cyclohydrolase 1(GCH1). The latter was shown to convert transduced non-dopaminergic neurons into dopamine producing cells. The rationale for the treatment is to provide a cocktail of exogenously delivered enzymes to maximize endogenous dopamine production.

Oxford BioMedica successfully completed a phase 1/2 study for ProSavin®, which met its primary endpoint. The design was an open label dose escalation (NCT00627588), followed by a long-term observation study (NCT01856439). The results showed favourable safety and tolerability, with a statistically significant improvement of motor function as measured by the UPDRS part III score at 6 and 12 months [1]. This improvement was sustained in most patients for up to six years [2].

The FDA have confirmed that the previous studies of ProSavin® can be considered as part of a single development program for AXO-Lenti-PD.

TITLE: Study of OXB-102 (AXO-Lenti-PD) in patients with idiopathic Parkinson’s Disease (SUNRISE-PD).

STATUS: Recruiting.

CLINICALTRIALS.GOV ID: NCT03720418.

SPONSOR: Axovant.

ENROLMENT: 32 patients.

COMPLETION: The primary completion target is June 2022, with full completion in December 2031.

STUDY DESIGN: There are two parts to this phase 1/2 study. The first is an open-label phase where three escalating dose levels will be tested. The second phase will take the optimal dose from part one into a randomized, double-blind phase in which patients will receive either active AXO-Lenti-PD or an imitation surgical procedure (ISP).

OUTCOME MEASURES: Primary outcomes are all related to safety at the three-month time point, as measured by:
   a. incidence of treatment emergent adverse events and serious adverse events.
   b. changes in clinical laboratory analysis.
   c. changes in vital signs.
   d. changes in brain MRI findings.
   e. changes in physical examination.

Secondary outcomes are all related to efficacy, as measured at the six-month timepoint by changes in:
   a. the Unified Parkinson’s Disease Rating Scale (UPDRS) scores compared to baseline in defined “OFF” and “ON” medication states.
   b. motor fluctuations compared to baseline as assessed by patient diaries.
   c. the dyskinesia rating scale from baseline.

COMMENTS: Axovant are recruiting patients at a relatively advanced stage of Parkinson’s, with at least five years since diagnosis and a Hoehn and Yahr stage of 3 or 4 in the OFF state. The patients must also be experiencing motor complications.
Results from the first cohort using the lowest dose of AXO-Lenti-PD in two patients, were announced in March 2019 [3], showing efficacy greater than the highest dose of ProSavin® used in previous studies. No serious adverse events were reported. Clearly, caution must be applied given the number of patients and further results are awaited.

References
[1] Palfi, S, et al., Lancet (2014) 383, 1138-46.
[2] http://investors.axovant.com/news-releases/news-release-details/axovant-announces-feedback-fda-meeting-regarding-axo-lenti-pd
[3] http://investors.axovant.com/news-releases/news-release-details/axovant-reports-positive-interim-results-first-cohort-sunrise-pd

AAV2-GDNF

BACKGROUND: Glial cell derived neurotrophic factors (GDNF) have been studied for more than a decade as potential neuroprotective interventions in PD. In preclinical models GDNF was shown to support the development of embryonic dopamine neurons (DA) and also to protect and restore mature DA of the substantia nigra in animal models. Though conflicting results exist, the weight of preclinical data is on the side of increased GDNF expression in the striatum during the late stages of PD with marked loss of DA and striatal connections [1].

Further exploring the neuroprotective aspect of GDNF in PD, preclinical data in rat and primate models have positively shown the ability of transduced GDNF to induce sprouting from the lesioned axons or axon terminals. However, the positive meaningful effects were dependent on the location and timing of injection. Injecting the striatum during the early stage of disease process when the dopaminergic innervation of the striatum, particularly the putamen, is still relatively preserved was shown to have meaningful impact [2]. The promising neuroprotective benefits in the animal models supported the assessment of GDNF in human trials.

A number of studies explored the efficacy of direct infusion of GDNF into the putamen and while open label studies were promising, not a single randomized study demonstrated efficacy [3,4]. One potential reason for failure was attributed to limitations of the direct putaminal delivery.

Gene vector delivery of GDNF is considered as a potentially more efficient alternative. Another growth factor, neurturin, was studied with vector delivery into the putamen and substantia nigra but the studies were negative [5]. Sangamo therapeutics were conducting a phase 1/2 study of AAV- neurturin in PD (https://clinicaltrials.gov/show/NCT00985517) but the company has terminated the project.

A single on-going study is exploring gene delivery GDNF in PD:

NINDS - AAV2-GDNF

TITLE: A Phase 1 Open-Label Dose Escalation Safety Study of Convection Enhanced Delivery (CED) of Adeno-Associated Virus Encoding Glial Cell Line-Derived Neurotrophic Factor (AAV2-GDNF) in Subjects with Advanced Parkinson’s Disease.

OBJECTIVE: To assess the safety, tolerability and potential clinical effects of active drug AAV2-GDNF delivered by convection-enhanced delivery in advanced PD patients.

STATUS: Active, not recruiting.

CLINICALTRIALS.GOV IDENTIFIER: NCT01621581.
SPONSOR: National Institute of Neurological Disorders and Stroke (NINDS).

ACTUAL ENROLMENT: 25.

ESTIMATED PRIMARY COMPLETION DATE: January 2022.

STUDY DESIGN: This is a phase 1 single center, open-label, dose escalation, safety and tolerability study of the AAV2-GDNF (adeno-associated virus, serotype 2 containing the human GDNF complementary DNA). The active drug will be delivered surgically by convection-enhanced delivery to bilateral putamina. The study includes 4 cohorts to evaluate the four escalating dose levels. Each cohort will have 6 subjects. The drug level for each cohort is as follows:

- Cohort 1: $9 \times 10^{10}$ vg
- Cohort 2: $3 \times 10^{11}$ vg
- Cohort 3: $9 \times 10^{11}$ vg
- Cohort 4: $3 \times 10^{12}$ vg

The study includes individuals 18 years and above with clinical idiopathic PD of at least 5 years disease duration with no other known or suspected cause for parkinsonism. An Off state UPDRS score of more than or equal to 30 and Hoehn and Yahr stage of III and IV are required for inclusion. The study also requires a 30% or greater improvement in the UPDRS total motor score on sinemet study according to the CAPSIT guidelines.

The participants in the study will be followed for 5 years with 18 outpatient study visits and a 3-day stay in the hospital post-surgery. Lumbar puncture for CSF analysis will be done at the time of surgery, 6 months and 18 months after surgery.

OUTCOME: Primary outcome measure: To assess the safety and tolerability of 4 different dose levels of AAV2-GDNF over a period of 12 years.

Secondary outcome measures: To obtain preliminary data regarding the potential for clinical responses of the 4 dose levels testing by assessing the magnitude and variability of any treatment effects including clinical, laboratory and neuroimaging studies.

CURRENT STATUS: This is a phase 1 study looking at the safety, tolerability and potential clinical efficacy of the drug. The group presented preliminary data at the American Association of Neurological Surgeons in April 2019 [6]. The data shows tolerability of the drug based on short and long term clinical and radiological assessment in the three cohorts (6, 6 and 1 patients in cohort 1, 2 and 3 respectively). The motor scores remained stable during the study period and PET imaging showed increased F-DOPA uptake in the infused areas at 6 and 18 months in 10/13 and 12/13 patients respectively. Data, as expected given it is a phase 1 study, are not sufficient to suggest clinical efficacy but supports the tolerability in the first 3 escalating doses. Further trial is planned with intention to increase the putaminal coverage as preliminary data shows average coverage of 22% in the putamen.

COMMENTS: GDNF and neurturin have been studied extensively as potential neuroprotective interventions in PD so far with disappointing results despite reproducibly positive data in preclinical models. It remains to be determined if lack of success in PD clinical trials reflects a lack of biological effect of intervention, limitations of the technical delivery modes (insufficient coverage of putamen, dose, etc) or failure to reverse the course of the advanced disease at the time of intervention. The ongoing study will be closely followed.

References
[1] C.M. Bäckman, L. Shan, Y.J. Zhang, B.J. Hoffer, S. Leonard, J.C. Troncoso, P. Vonsatel, A.C. Tomac, Gene expression patterns for GDNF and its receptors in the human putamen affected by Parkinson’s disease: A real-time PCR study, Mol. Cell. Endocrinol. 252 (2006) 160–166. doi:10.1016/J.MCE.2006.03.013.
Clinical Trial Highlights

[2] A. Björklund, D.Kirik, C. Rosenblad, B. Georgievska, C. Lundberg, R.J. Mandel, Towards a neuroprotective gene therapy for Parkinson’s disease: use of adenovirus, AAV and lentivirus vectors for gene transfer of GDNF to the nigrostriatal system in the rat Parkinson model, Brain Res. 886 (2000) 82–98. doi:10.1016/S0006-8993(00)02915-2.

[3] A. Whone, M. Luz, M. Boca, M. Woolley, L. Mooney, S. Dharia, J. Broadfoot, D. Cronin, C. Schroers, N.U. Barua, L. Longpre, C.L. Barclay, C. Boiko, G.A. Johnson, H.C. Fibiger, R. Harrison, O. Lewis, G. Pritchard, M. Howell, C. Irving, D. Johnson, S. Kinch, C. Marshall, A.D. Lawrence, S. Blinder, V. Sossi, A.J. Stoessl, P. Skinner, E. Mohr, S.S. Gill, Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson’s disease, Brain. 142 (2019) 512–525. doi:10.1093/brain/awz023.

[4] A.E. Lang, S. Gill, N.K. Patel, A. Lozano, J.G. Nutt, R. Penn, D.J. Brooks, G. Hutton, E. Moro, P. Heywood, M.A. Brodsky, K. Burchiel, P. Kelly, A. Dalvi, B. Scott, M. Stacy, D. Turner, V.G.F. Wooten, W.J. Elias, E.R. Laws, V. Dhawan, A.J. Stoessl, J. Matcham, R.J. Coffey, M. Traub, Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease, Ann. Neurol. 59 (2006) 459–466. doi:10.1002/ana.20737.

[5] C. Warren Olanow, R.T. Bartus, T.L. Baumann, S. Factor, N. Boulis, M. Stacy, D.A. Turner, W. Marks, P. Larson, P.A. Starr, J. Jankovic, R. Simpson, R. Watts, B. Guthrie, K. Poston, J.M. Henderson, M. Stern, G. Baltuch, C.G. Goetz, C. Herzog, J.H. Kordower, R. Alterman, A.M. Lozano, A.E. Lang, Gene delivery of neurturin to putamen and substantia nigra in Parkinson disease: A double-blind, randomized, controlled trial, Ann. Neurol. 78 (2015) 248–257. doi:10.1002/ana.24436.

[6] D. Davis Palmer Argersinger, B.S.; Codrin Lungu, MD; Dima Hammoud, MD; Peter Herscovitch, MD; Debra Ehrlich, MD; Gretchen Scott; Krystof Bankiewicz, MD, PhD; Kareem Zaghoul, MD, PhD; Mark Hallett, MD; Russell Lonser, MD; John Heiss, MD (Washington, Phase 1 Trial of Convection-Enhanced Delivery of Adeno-Associated Virus Encoding Glial Cell Line-Derived Neurotrophic Factor in Patients With Advanced Parkinson’s Disease, (n.d.). https://www.aans.org/Annual-Scientific-Meeting/2019/Online-Program/Eposter?eventid=48888&itemid=SSIII&propid=45733&fbclid=IwAR2pqhDXYvm_gmsI34suPwELe0WyexMndU2U59rZFaDkqmHw6wx3-avguuo. https://www.aans.org/Annual-Scientific-Meeting/2019/Eposter
2. PHASE 3 STUDY IN FOCUS – INTEC PHARMA’S ACCORDION PILL

TITLE: A Study to Assess the Safety and Efficacy of the Gastric-retentive AP-CD/LD in Advanced Parkinson’s Patients (Accordance).

STATUS: Active, not recruiting.

CLINICALTRIALS.GOV ID: NCT02605434.

SPONSOR: Intec Pharma.

ENROLMENT: 420.

ESTIMATED COMPLETION DATE: The primary completion date is August 2019.

OBJECTIVE: The purpose of this study is to determine whether the gastric retentive Accordion Pill™ Carbidopa/Levodopa (AP-CD/LD) is more effective than immediate release Carbidopa/Levodopa in reducing motor fluctuations such as “off time” in advanced Parkinson’s Disease patients.

BACKGROUND: Levodopa remains the most potent symptomatic therapy for PD. One of the major limitations of levodopa therapy is the risk of development of motor fluctuations and dyskinesia related to the short half life of the drug, coupled with progressive decline of neuronal dopamine storage capacity. Current formulations of levodopa are generally taken every few hours, leading to a pulsatile profile of peaks and troughs. The peaks can induce troublesome dyskinesia while the troughs can lead to OFF time with significant symptom breakthrough. A steadier and more consistent plasma profile should reduce the incidence of both types of motor fluctuation as well as reducing the number of tablets patients need to take.

Intec Pharma have developed the Accordion Pill, a gastric-retentive capsule containing multiple layers of both immediate release and controlled release levodopa and carbidopa. The pill remains in the stomach for up to 12 hours [1].

In two phase 1 trials conducted in healthy adults, a single dose of Intec Pharma’s AP-CD/LD provided more consistent levodopa plasma levels and less peak-trough fluctuation than immediate release carbidopa/levodopa (IR-CD/LD) [2]. The safety of AP-CD/LD was similar to the known safety of CD/LD. AP-CD/LD should be taken with meals as it gives a more favorable pharmacokinetic profile.

A phase 2 study (NCT00918177) in Parkinson’s patients showed that peak-to-trough fluctuations (mean Cmax – mean Cmin) with the AP CD-LD formulation were half of those with the reference product [1]. The levodopa morning plasma levels (pre-first dose) were significantly higher than those achieved with the IR-CD/LD (522ng/µl vs. 68ng/µl). The high bioavailability of levodopa was preserved.

STUDY DESIGN and OUTCOMES

The phase 3 Accordance study is a multi-center (97 study locations), global, randomized, double-blind, double-dummy, active-controlled, parallel-group study in adult subjects with fluctuating PD. The study will have 2 open label titration periods of 6 weeks each prior to the double-blind maintenance period. In the open label periods, all patients will be stabilized on the active comparator, IR-CD/LD and then on AP-CD/LD. The double-blind maintenance period will be 13 weeks long.

The primary outcome is change from baseline through to study completion, an average of 27 weeks, in the percentage of daily “Off time” during waking hours, based on Hauser Home Diary assessments.

Secondary outcomes, all measured on the same timescale as the primary outcome, are:
1. Change in “On time” without troublesome dyskinesia during waking hours.
2. Change in the number of total daily LD doses.
3. Clinical Global Impression Improvement (CGI-I), as recorded by physician & patient.
4. Change in total UPDRS Score (sum of Parts I-III).

**CURRENT STUDY STATUS:** Enrolment was started in November 2015. Recruitment is closed and while the official primary completion date is August 2019, Intec expects to release top-line data in mid-2019 [3].

**COMMENTS:** Until disease-modifying therapies are available, people with Parkinson’s will welcome any therapy that extends the duration of symptom relief and reduces motor fluctuations. The novel design of the Accordion Pill and the promising safety and efficacy data generated in phases 1 and 2, hold out great hope for the achievement of these benefits.

**References**
[1] https://www.intecpharma.com/wp-content/uploads/2018/06/AP-CDLD-Phase-II-Poster-.pdf
[2] https://www.intecpharma.com/wp-content/uploads/2018/06/AP-CD_LD_Comp-PK-and-Safety_AAN-2018_Pos_FINAL.pdf
[3] https://ir.intecpharma.com/static-files/13933a14-add2-4fee-b361-3a50a9300335
3. CLINICAL TRIAL RESOURCES

PARKINSON’S THERAPIES IN DEVELOPMENT

The Hope List - http://bit.ly/ParkinsonsHopeList

FINDING A CLINICAL TRIAL

ClinicalTrials.gov from the US National Library of Medicine - https://clinicaltrials.gov
PD Trial Tracker; analysing ClinicalTrials.gov for Parkinson’s specific trials - http://www.pdtrialtracker.info
Fox Trial Finder - https://foxtrialfinder.michaeljfox.org
European Parkinson’s Disease Association - https://www.epda.eu.com/about-parkinsons/treatments/clinical-trials/
Parkinson’s UK - https://www.parkinsons.org.uk/research/take-part-research
UK NHS Clinical Trials Gateway - https://www.ukctg.nihr.ac.uk
Cure Parkinson’s Trust - https://www.parkinsonsmovement.com/clinical-trials/
Parkinson’s Study Group - http://www.parkinson-study-group.org/clinical-trials
American Parkinson Disease Association - https://www.apdaparkinson.org/resources-support/living-with-parkinsons-disease/clinical-trials/
CenterWatch - https://www.centerwatch.com/clinical-trials/listings/condition/117/parkinsons-disease/

WHAT DOES IT MEAN TO PARTICIPATE IN A PARKINSON’S CLINICAL TRIAL?

Michael J Fox Foundation, Clinical Trial Companion – https://www.michaeljfox.org/pdcompanion.html
Parkinson’s Foundation - https://www.parkinson.org/Understanding-Parkinsons/Treatment/Clinical-Trials