Future Treatment Landscape: Unmet Needs and Emerging Therapies

Anthony E. Lang
University of Toronto
The Complexity of Parkinson’s Disease

- Hyposmia
- Depression
- Constipation
- Bradykinesia
- Rigidity
- Tremor
- Dysphagia
- Postural instability
- Freezing of gait
- Falls
- Pain
- Fatigue
- MCI
- Urinary symptoms
- Orthostatic hypotension
- Dementia

Motor:
- Bradykinesia
- Rigidity
- Tremor
- Dysphagia
- Postural instability
- Freezing of gait
- Falls

Non-Motor:
- Hyposmia
- Depression
- Constipation
- Pain
- Fatigue
- MCI
- Urinary symptoms
- Orthostatic hypotension
- Dementia

Pre-Motor/Prodromal Period
- Constipation
- RBD
- EDS
- Depression

Parkinson’s Disease Diagnosis
- Early
- Advanced/Late

Complications
- Fluctuations
- Dyskinesia
- Psychosis

Time (years)
- Degree of Disability
- Non-Motor
- Motor
- Advanced/Late
- Early
Sydney Multicentre Study of PD
Non-L-dopa-responsive problems dominate at 15 years
Hely et al, 2005

- 52/136 patients survived – SMR: 1.86
- 94% dyskinesias, 96% “end-of-dose failure”:
  - non-disabling in the majority
- Falls – 81%; fractures 23%
- Cognitive decline 84%; 48% demented
- Hallucinations 50% (21% @ 15 yr visit)
- Depression 50%; most mild
- Choking 50%; Severe speech impediment 27%
  symptomatic postural hypotension 50%, urinary incontinence 35%; EDS 79%
- 40% living in aged care facilities
Stage 1:
Dorsal IX/X motor nucleus
Anterior olfactory nucleus

Stage 2:
Caudal raphe nucleus
Locus ceruleous

Stage 3:
Substantia nigra pars compacta
Basal forebrain – Meynert, amygdala

Stage 4:
Anteromedial temporal mesocortex

Stage 5:
Neocortex: prefrontal, sensory association
Anterior cingulate

Stage 6:
Neocortex: Premotor, Primary motor & sensory areas, primary auditory area

Braak et al, 2003
Sydney Multicentre Study of PD

Increasing L-dopa-Resistant Problems

15 → 20 years
Hely et al, 2005 → 2008

• 52 → 36/136 patients survived – SMR: 1.86 → 3.1
• **Falls** – 81% → 87%; fractures 23% → 35%
• **Dementia** 48% → 83%
• **Hallucinations** 50% → 74%
• **Choking** 50% → 48%;
• Mod-Severe **Speech** impediment 27% → 81%
• Symptomatic **Postural hypotension** 50% → 48%
• **Urinary** **Incontinence** 35% → 71%
• EDS 79% → 70%
• Living in aged care facilities 40% → 48%
PD at 30 years in DBS Patients

Merola et al, 2011
Outcome-Specific Hazard Rates for Motor and Non-Motor Complications

Patients aged 65 yrs at Diagnosis

Prange et al, 2019
Treatment of Parkinson’s Disease

- **Protective / Disease Modifying / Compensatory**

- **Symptomatic – Medical**
  - Restore dopamine levels to normal
  - Non-dopaminergic therapies
    - Primary motor features
    - Secondary motor features – motor fluctuations, dyskinesia
    - Non-motor features

- **Symptomatic - Surgical**
  - Alter abnormal motor system physiology
  - Improve striatal dopamine availability/metabolism

- **Restorative**
  - Increase neuronal cell growth
  - Replace degenerated neurons
Cellular Pathways Involved in Pathogenesis of PD

- Impairment of cellular clearance systems
  - The ubiquitin–proteasome pathway
  - Autophagy
  - Mitophagy
- Alterations in mitochondrial homeostasis and dynamics
- ER-mitochondria interplay and Ca^{++} homeostasis
- Endoplasmic reticulum stress
- Inflammation

Independent of / Secondary to α SYN
Cell death

- Calcium homeostasis
- Synaptic pathobiology
- Mitochondrial dysfunction
- Failure of protein degradation
- Apoptosis
- Neuro-inflammation

α SYN

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Cell death
Therapeutics Targeting α-SYN

Revised from Wong & Krainc, 2017
Targeting α-Synuclein

- Stabilizing agents
  - Passive immunization with protofibril-selective Ab
  - Small molecules inhibiting aggregation

- siRNAs
  - Antisense oligonucleotides
  - β-adrenergic agonists

- Active immunization:
  - AP01A & PD03A (AFFiRiS)

- Passive immunization
  - Monoclonal α-SYN Abs
    - PRX002 (Prothena/Roche)
    - BIIB054 (Biogen)
    - AF82422 (Lundbeck)

Active immunization:
- • Inhibit cellular uptake

↑ Lysosomal / Autophagic Degradation
- Passive immunization → ↑ lysosomal clearance
  - microglial targeting

↑ GCase activity (modulators, enzyme replacement)

Revised from Wong & Krainc, 2017
# Agents in Study for Disease Modification

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism of Action</th>
<th>Examples</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-synuclein</td>
<td>Monoclonal antibodies</td>
<td>Prasinezumab (Roche), Cinpanemab (Biogen), others (AbbVie, Lundbeck, others)</td>
<td>Phase 2 (Roche, Biogen); Phase 1 and earlier others</td>
</tr>
<tr>
<td></td>
<td>Active immunization</td>
<td>AP01A &amp; PD03A (AFFiRis), UB-312 (United Neurosci)</td>
<td>Phase 1 (AFFiRis)</td>
</tr>
<tr>
<td></td>
<td>ASOs</td>
<td>Biogen, others</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibitors of pathological aggregation</td>
<td>ENT-01 (Enterin), PBT434 (Alterity), NPT200-11 (Neuropore), Mannitol, others</td>
<td>Phase 1</td>
</tr>
<tr>
<td>C-Abl kinase</td>
<td>C-Abl kinase inhibitors (c-Abl has multiple effects incl. via α-synuclein)</td>
<td>Nilotinib, K076 (SPARC), FB101 (1ST Biotherapeutics)</td>
<td>Phase 2 (Nilotinib; K076)</td>
</tr>
<tr>
<td>LRRK2</td>
<td>LRRK2 kinase inhibitors</td>
<td>DNL-151, DNL 201 (Denali)</td>
<td>Phase 1b</td>
</tr>
<tr>
<td>Glucocerebroside</td>
<td>Chaperone – translocates mutant enzyme from ER to lysosomes</td>
<td>Ambroxol, others (Allergan)</td>
<td>Phase 2 (Ambroxol)</td>
</tr>
<tr>
<td></td>
<td>Glucosylceramide synthase inhibitor</td>
<td>Ibiglustat (Genzyme/Sanofi)</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Gene therapy – GBA1</td>
<td>PR001</td>
<td></td>
</tr>
<tr>
<td>GLP-1 Receptor</td>
<td>GLP-1R inhibitors – multiple potential effects (inflammation, apoptosis, other)</td>
<td>Exenatide, Liraglutide, Lixisenatide, others</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Iron</td>
<td>Iron chelation</td>
<td>Deferiprone</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Others</td>
<td>Mixed</td>
<td>Pro-mitochondria (Ursodeoxycholic acid); Sigma-1 receptor (Pridopidine); anti-inflammatory (AZD3241, NPT520-34); others</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of Parkinson’s Disease

• Protective / Disease Modifying / Compensatory

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Pharmacological Strategies For Extending / Improving the Effects of Levodopa

• Microtablet – “cluster bomb” preparation to release a mixture of pharmacokinetic profiles:
  – Rytary (1:4 rapid:slower release)

• Gastro-retentive formulation:
  – Madopar HBS; Accordion pill

• L-dopa prodrug absorbed over an extended GI territory:
  – XP21279

• Intestinal gel LD/CD for continuous administration:
  – LCIG/Duodopa

• Subcutaneous administration of LC/CD:
  – ND0612; ABBV-951

• Inhaled LD preparation
Review

Dopamine and Levodopa Prodrugs for the Treatment of Parkinson’s Disease

Fatma Haddad, Maryam Sawalha, Yahya Khawaja, Anas Najjar and Rafik Karaman *

Department of Bioorganic & Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Quds University, Jerusalem P.O. Box 20002, Palestine; ianfromhebron@hotmail.com (F.H.); maryam_khaled2@yahoo.com (M.S.); yahya.khawaja@hotmail.com (Y.K.); nash.najjar@gmail.com (A.N.)

* Correspondence: dr_karaman@yahoo.com or rkaraman@staff.alquds.edu

Received: 4 December 2017; Accepted: 20 December 2017; Published: 25 December 2017

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REVIEW

Advances in prodrug design for Parkinson’s disease

Ivana Cacciatore, Michele Giulla, Lisa Marinelli, Piera Eusepi and Antonio Di Stefano

Department of Pharmacy, University ‘G. D’Annunzio’ Chieti-Pescara, Chieti, Italy
Medical Management of Motor Fluctuations

• Newer treatments / Under development
  – Newer formulations: levodopa (inhaled, transdermal), apomorphine (sublingual)
  – Increased DA release (+ other?): Zonisamide
  – Safinamide – MAOB-I +
  – Newer COMT-I: Opicapone
  – $A_{2A}$ adenosine receptor antagonists (e.g., Istradefylline)
  – Alpha2 antagonists: Fipamezole
  – Others – noradrenergic, serotonergic
Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations
A Randomized Clinical Trial

Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci; Susan H. Fox, MBChB, MRCP(UK), PhD; Robert A. Hauser, MD, MBA; Joseph Jankovic, MD; Wolfgang H. Jost, MD, PhD; Christopher Kenney, MD; Jaime Kulisevsky, MD; Rajesh Pahwa, MD; Werner Poewe, MD; Ravi Anand, MD
RESULTS A total of 427 patients (258 men [60.4%] and 169 women [39.6%]; mean [SD] age, 63.1 [8.8] years) were randomized to a 25-mg/d (n = 129) or a 50-mg/d (n = 154) dosage of opicapone or to placebo (n = 144). Of these, 376 patients completed the double-blind phase and entered the open-label phase, of whom 286 completed 1 year of open-label treatment. At the end of the double-blind phase, the least squares mean change (SE) in off-time was $-64.5 \ (14.4)$ minutes for the placebo group, $-101.7 \ (14.9)$ minutes for the 25-mg/d opicapone group, and $-118.8 \ (13.8)$ minutes for the 50-mg/d opicapone group. The adjusted treatment difference vs placebo was significant for the 50-mg/d opicapone group (treatment effect, $-54.3 \ [95\% \ CI, -96.2 \ to \ -12.4]$ minutes; $P = .008$), but not for the 25-mg/d opicapone group (treatment effect, $-37.2 \ [95\% \ CI, -80.8 \ to \ 6.4]$ minutes; $P = .11$). The off-time reduction was sustained throughout the open-label phase ($-126.3$ minutes at 1-year open-label end point). The most common adverse events in the opicapone vs placebo groups were dyskinesia, constipation, and dry mouth. Fifty-one patients (11.9%) discontinued from the study during the double-blind phase.
Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson’s disease: a randomised, double-blind, placebo-controlled phase 3 trial

Peter A LeWitt, Robert A Hauser, Rajesh Pahwa, Stuart H Isaacson, Hubert H Fernandez, Mark Lew, Marie Saint-Hilaire, Emmanuelle Pourcher, Lydia Lopez-Manzanares, Cheryl Waters, Monika Rudzinska, Alexander Sedkov, Richard Batycky, Charles Oh, on behalf of the SPAN-PD Study Investigators

Week 12 Results

Proportion of patients in an ON state at 60 min postdose *p=0·0027

UPDRS motor score changes postdose
* Primary efficacy endpoint comparing CVT-301 84 mg versus placebo at 30 min (p=0·0088).
Change from predose (time 0) at wk 12

Change from predose to 30 min post-dose
Ads-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia (EASE LID Study): A randomized clinical trial

Rajesh Pahwa, MD; Caroline M. Tanner, MD, PhD; Robert A. Hauser, MD; Paul A. Nasredda, MD; Daniel D. Truong, MD; Pinky Agarwal, MD; Keith Reed Johnson, BS; Mary Jean Stempien, MD

Table 3. Adverse events in patients receiving ADS-5102 and placebo (safety population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 60)</th>
<th>ADS-5102 (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any AEs</td>
<td>36 (60.0)</td>
<td>56 (88.9)</td>
</tr>
<tr>
<td>Patients with any study drug-related AEs</td>
<td>7 (11.7)</td>
<td>40 (63.5)</td>
</tr>
<tr>
<td>Patients with any serious AEs</td>
<td>3 (5.0)</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Patients with any study drug-related serious AEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients who permanently discontinued treatment owing to any AEs</td>
<td>4 (6.7)</td>
<td>13 (20.6)</td>
</tr>
<tr>
<td>Patients who permanently discontinued treatment owing to any study drug-related AEs</td>
<td>4 (6.7)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Most common AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>1 (1.7)</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>14 (22.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>11 (17.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (5.0)</td>
<td>10 (15.9)</td>
</tr>
<tr>
<td>Fall</td>
<td>5 (8.3)</td>
<td>10 (15.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1.7)</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>0</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>0</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>2 (3.3)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (1.7)</td>
<td>4 (6.3)</td>
</tr>
</tbody>
</table>

Change in UDSysRS over time

[Graph showing change in UDSysRS total score (mean ± SD) least squares over weeks]

-7.9 (-12.5 to -3.1) at primary end point

P < .001
Neurotransmitters and Terminals Implicated in LID

Espay et al, 2018
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dyskinesia Endpoint/Duration</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADS-5102 (amantadine extended release; GOCOVRI)</td>
<td>Glutamate antagonist (NMDA receptor antagonist)</td>
<td>UDysRS/12 weeks</td>
<td>Dose-dependent decrease in dyskinesia with secondary benefit of reduced OFF time(^{1-3}); approved by FDA in 2017</td>
</tr>
<tr>
<td>Amantadine HCl extended release (OSMOLEX ER)</td>
<td>Glutamate antagonist (NMDA receptor antagonist)</td>
<td>UDysRS/98 days</td>
<td>Phase III studies, NCT02153645 (ALLAY-LID I)/NCT02153632 (ALLAY-LID II) have been terminated; approved for symptoms of parkinsonism by FDA in 2018 based on PK equivalence with amantadine</td>
</tr>
<tr>
<td>Dextromethorphan/quinidine (AVP-923-45)</td>
<td>Sigma-1 receptor agonist and glutamatergic/monoaminergic modulator</td>
<td>UDysRS/2 weeks</td>
<td>Phase II crossover study, minimal clinical benefit (n = 13); well tolerated(^{109})</td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism of Action</td>
<td>Dyskinesia Endpoint/Duration</td>
<td>Clinical Relevance</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Eltoprazine</td>
<td>Serotonin agonist mixed 5-HT1A/1B receptor agonist</td>
<td>Clinical Dyskinesia Rating Scale; acute dose</td>
<td>Phase IIa; acute dosing reduced peak-dose dyskinesia (n=22) compared with placebo; no worsening of PD motor scores; AEs: nausea and dizziness&lt;sup&gt;83&lt;/sup&gt;</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5-HT1A receptor agonist</td>
<td>UDysRS/84 days</td>
<td>Phase IIb, double-blind, randomized, controlled trial; 2.5–7.5mg/day; NCT02439125; results pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIMS/acute dose</td>
<td>Subgroup from PET imaging study; acute dosing reduced LID during a L-dopa challenge vs placebo (n = 24); more effective in subjects with milder LID than with severe LID; no worsening of PD motor scores; AEs: drowsiness and dizziness&lt;sup&gt;82&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UDysRS/12 weeks</td>
<td>Phase III study; NCT02617017 (BUSPARK), evaluating efficacy of buspirone in PD-LID; results pending</td>
</tr>
<tr>
<td></td>
<td>Force plate measurements/6-h LD dose cycle</td>
<td></td>
<td>Phase II study; NCT02589340 (BUS-PD); evaluating the efficacy of buspirone in combination with amantadine in reducing PD-LID</td>
</tr>
</tbody>
</table>
## Therapies in Clinical Research Development for L-dopa–Induced Dyskinesia III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dyskinesia Endpoint/Duration</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foliglurax (PXT002331)</td>
<td>Positive allosteric modulator of mGluR4</td>
<td>Dyskinesia rating not defined; Hauser diary/28 days</td>
<td>Phase IIa study; NCT03162874 (AMBLED), for LID-PD and end-of-dose wearing off; results pending</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Channel modulator</td>
<td>UDysRS/12 weeks</td>
<td>Phase IV open-label study; NCT03034538, evaluating 2 doses for tolerability and efficacy for PD dyskinesias; results pending</td>
</tr>
<tr>
<td>NLX-112 (befiradol or F13640)</td>
<td>5-HT1A receptor full agonist</td>
<td>No information available</td>
<td>Inhibits LID in rodent models of PD(^{58}); phase II study results pending</td>
</tr>
<tr>
<td>IRL790</td>
<td>Dopamine D3 receptor agonist</td>
<td>UDysRS/4 weeks</td>
<td>Phase IIa study; NCT03368170, evaluating IRL790 as an adjunctive treatment for PD-LID; results pending</td>
</tr>
</tbody>
</table>
Therapies Under Development

• “Physical therapies”:
  – physiotherapy and exercise programs (+ addition of low dose of methylphenidate or atomoxetine), kickboxing, dancing, acupuncture, rTMS, tDCS (fatigue, cognitive slowing)

• Therapies targeting the microbiome (influence on PD Sx including clinical phenotype, L-dopa response):
  – e.g., PRIM-DJ2727 (filtered fecal microbiota product from three screened healthy donors lyophilized and encapsulated in enteric-coated capsules); a dietary fiber, resistant maltodextrin
Pharmacological Treatments Under Development
Dopaminergic Agents

• Older DA agonists:
  – P2B001 (pramipexole ER + rasagiline) – early untreated PD (Phase III)
  – Rotigotine Extended Release Microspheres for injection (LY03003) – Weekly IM injections
  – Ropinirole implant - ProNeura subdermal drug delivery technology (? 3-6 mo) - on hold
• Tavapadon (PF 06412562) – selective D1/D5 agonist – Phase 2 positive
• KDT-3594 – DA with improved D2/3 balance (? Less sedation)
• XC130-A10H – DA
• IRL790 - D3 receptor antagonist – Dyskinesia ; PD Psychosis
• LY3154207 - D1 positive allosteric modulator (PAM) – motor, cognition (PDD)
Pharmacological Treatments Under Development

Motor Indications

• Idebenone - synthetic analogue of ubiquinone (Coenzyme Q10) – clinical features of PD
• KW-6356 - Adenosine A2A receptor antagonist – Phase II
• BTRX-246040 - antagonist of the nociceptin receptor (NOPR) – Phase 2 – motor fluctuations
• Cannabidiol – motor Sx especially tremor
• CX-8998 - potent, selective T-type calcium channel antagonist – tremor (Phase II)
• PXT002331 (Foliglurax) - glutamate mGluR4 positive allosteric modulator – dyskinesia, motor complications
• Varenicline (Chantix) - novel partial nicotinic cholinergic α4β2 agonist and full α7 agonist – gait and balance
• CVN424 – selectively targets striatal D2R (indirect) pathway
• Brumetanide – diuretic, antagonist of Cl importer – gait and freezing
Pharmacological Treatments Under Development Non-Motor Indications I

- Parkinson’s Disease Dementia (PDD)
  - Anavex 2-73 - mixed ligand for sigma1/muscarinic receptors
  - IRL752 - 5HT7 and cortical Alpha receptor agonist
  - Ambroxol - Increases glucosylceramidase activity → lowers alpha-synuclein levels
  - Ceftriaxone - reducing glutamatergic hyperactivity and excitotoxicity and may exhibit neuro-protective functions
  - NYX-458 – NMDA antagonist for PD-MCI

- PD psychosis
  - SEP-363856 - agonism at 5-HT1A and TAAR1 (trace amine-associated receptor 1)

- “Non-motor symptoms”
  - Nabilone - analogue of tetrahydrocannabinol (THC)
Pharmacological Treatments Under Development
Non-Motor Indications II

• Excessive Daytime Sleepiness
  – THN102 (combination of modafinil and flecainide) - excessive daytime sleepiness
  – Bavisant (BEN 2001) - H3 antagonist

• Insomnia
  – Suvorexant - selective, dual orexin receptor antagonist

• Erectile dysfunction
  – Selegiline + tadalafil (generic for Cialis®)

• Orthostatic hypotension
  – Ampreloxetine (TD-9855) – noradrenaline reuptake inhibitor
Other Treatments Under Development 1

- Zolpidem (sub-hypnotic doses) – motor and cognitive effects (but – suggestion that zolpidem increases the risk of PD)
- Droxidopa (L-Dihydroxyphenylserine (L-DOPS)) – influence on falls with and without OH; freezing, fatigue, cognition, motor
- N-acetylcysteine (NAC) – for ICDs
- Near Infrared Stimulation / Bright Light therapy – improves circadian function, sleep and alertness - mood, cognition, non-motor Sx
Other Treatments Under Development II

• OnabotulinumtoxinA – facial (corrugator and procerus) injections – *depression*
• IPT803 - ? mechanism of action – Phase I/II
• Kenterin (ENT-01) - dislodging αSyn from gut neurons; indications – *constipation*; ? impact on *PD progression*
• GRF6021 (Alkhest) – IV plasma derived product (young plasma replacing “chronokines”) - initially testing in *PD with cognitive impairment*
• Umbilical cord derived mesenchymal stem cells - administered intrathecally and IV
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Functional Surgery: Newer Developments

• DBS
  – Newer devices
    • Newer IPGs - different programming capabilities
    • Newer electrodes – sizes, directional stimulation, steering current
    • Potential for Closed-Loop / Adaptive Stimulation in the future
  – ? New / Revised targets (including Spinal Cord Stimulation, Vagal N. Stim)

• MR-Guided Focused Ultrasound
  – Lesions - role in PD remains to be defined (thalamic, STN, other)
  – ? Opening the BBB as an adjunct to other therapies

• Other
  – Gene therapy, cell-based therapies
Potential “Disease Modifying” Surgery for Parkinson’s Disease

Cell-based (reinnervation): Fetal Mesencephalic, Stem Cells

Trophic: GDNF, CDNFR

Increase and enhance striatal dopamine: AAV-AADC, Lenti-TH/AADC/GTPCH1

STN DBS
- ↓ GLU excitotoxicity
- BDNF signaling
- Direct anti-αSYN effect

AAV2-GDNF

AAV-GAD

? AAV-Parkin
Surgery for Parkinson’s Disease: Gene therapy

AAV2-GDNF

AAV-Neurturin (CERE-120)
AAV-AADC
Lenti-TH/AADC/GTPCH1
(ProSavin)

AAV2-GAD

AAV-Parkin
AAV2-GAD gene therapy for advanced Parkinson’s disease: a double-blind, sham-surgery controlled, randomisedised trial

Magnetic Resonance Imaging–Guided Phase 1 Trial of Putaminal AADC Gene Therapy for Parkinson’s Disease

Chadwick W. Christine, MD,1 Krystof S. Bankiewicz, MD,2 Amber D. Van Laar, MD,3 R. Mark Richardson, MD,4 Bernard Ravina, MD,5a Adrian P. Kells, PhD,5b Brendon Boot, MBBS,5c Alastair J. Martin, PhD,6 John Nutt, MD,7 Marin E. Thompson, MS,2 and Paul S. Larson, MD2

F-dopa

![Graph of F-dopa showing percentage increase in AADC activity by FDOPA PET.]

LED

Diary

![Graph showing change in UPDRS III score over time.]

UPDRS On-med

UPDRS Off-med

![Graph showing change in LEDD over time.]

ANN NEUROL 2019;85:704–714
Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson’s disease: a dose escalation, open-label, phase 1/2 trial


Lancet 2014; 383: 1138-46
Cell loss with normal aging

Loss of DA neurons in SNc in PD

Loss of non-DA neurons in PD

Level of cell loss associated with development of symptoms

? Successful nigrostriatal restoration

Sydney Multicentre Study of PD: 15 → 20 yr
(Hely et al, 2005 → 2008)

Natural History of PD:
Increasing L-dopa-Resistant Problems
- SMR: 1.86 → 3.1 (52 → 36/136 patients survived)
- Falls: 81% → 87%; fractures 23% → 35%
- Dementia: 48% → 83%
- Hallucinations: 50% → 74%
- Choking: 50% → 48%
- Speech Impediment (Mod-Severe): 27% → 81%
- Postural hypotension (Symptomatic): 50% → 48%
- Urinary Incontinence: 35% → 71%
- EDS: 79% → 70%
- Living in aged care facilities: 40% → 48%
Late-Stage Problems
Increasing “Non-Dopaminergic” Symptoms

• Walking – freezing and falls
• Cognitive dysfunction and dementia
• Psychiatric problems
• Daytime sleepiness
• Speech and swallowing
• Orthostatic hypotension (blood pressure)
• Urinary bladder
PD – Major Unmet Needs
The Next 20 Years

- Fluctuations and Dyskinesias
- Progression of disease
- Cognitive dysfunction
- Non-dopaminergic motor features
- Other non-motor features
Thank you!