PD Research Update: Hope for the future

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Why don’t we have a disease delaying treatment or a cure yet?

Clinical Trials: A brief definition of Phase I, II, III, IV trials

Why do we need placebo controlled trials?

Can we slow the rate of disease progression?

Gene transfer trials and PD.
Why isn’t there a cure yet?
PD is a bit more complicated than we thought....

Dopamine (DA) and Acetylcholine (ACH) Imbalance.

Loss of pigmented cells in the substantia nigra
Braak Staging

Yellow represents a likely origin of Parkinson's pathology.
Pink/purple represent Stages 1 and 2.
Blue represents Stages 3 and 4.
Orange represents Stage 5.
Yellow represents full neocortex engagement and Stage 6.

Sfayre and Vissel, 2014
Clinical Trials: A brief definition of Phase I, II, III, IV trials
Clinical Trial Stages

• **Phase 1**
  – Safety and tolerability.
  – Usually done in healthy volunteers (~20-100). No placebo control.

• **Phase 2**
  – Safety, tolerability and hints of efficacy.
  – Usually 100-300 individuals with disease compared to placebo.
  – Usually ~ 6-12 months long.

• **Phase 3**
  – Primary outcome is effectiveness and efficacy. Safety and tolerability monitored. Compared to Placebo.
  – Larger number of participants. Often 300-3,000 patients.
  – Trial may last 2-5 years.

• **Phase 4**
  – Post FDA marketing surveillance.
  – Verifying long term effects. Documenting effectiveness for other indications.
Why are placebo controls so important?

The “placebo effect” and Parkinson’s Disease.
“High expectations that a new research product will work may make dopamine levels in the brain increase, thereby improving motor function.”

- Fuente-Fernandez et al., Science, 293, 1164-1666, 2001

Fuente-Fernandez et al., Trends in Neurosci. 2002
“Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery treatment”

McRae et al. Archives of General Psychiatry. April 2004

- Individuals were asked right after receiving either a fetal cell transplant or sham procedure which they thought that they had gotten.
- **Those who believed** that they had gotten the cell transplant scored better on self assessment of function questionnaires.
- The experienced **blinded medical raters also consistently** rated those who believe that they got the transplant as doing better on UPDRS motor exam.
- **The placebo effect persisted over a year.**
Figure 3. Mean changes in Unified Parkinson’s Disease Rating Scale (UPDRS) motor “off” scores (baseline to 12 months) for the total group in the parent study (n=39). Increased scores indicate improvement. Error bars represent SEM.
Can we delay disease progression at disease onset?
Some recent phase 3 clinical research trials

- Disease modifying/neuroprotective treatments

  - **QE3 PD (CoEnzyme Q10)**
    - “The QE3 trial is a large multicenter clinical trial designed to determine whether the nutritional supplement coenzyme Q10, which traps a potentially dangerous type of chemical in the brain called free radicals, will slow the progression of PD.” (MJFF)

  - **STEADY PD (Isradipine)**
    - “Calcium channel blocker prescribed to treat high blood pressure. Data from large studies showed lower risk of PD among people who took the drug for hypertension. Scientists believe isradipine works to prevent the death of dopamine-producing cells and therefore may slow PD progression.” (MJFF)

  - **SURE PD (Inosine)**
    - “Urate – a natural metabolite and major antioxidant – is emerging as a predictor of both the risk and the progression of typical Parkinson’s disease (PD). Studies of healthy individuals have linked urate levels in the upper normal range to a reduced risk of developing PD. Similarly, studies of individuals recently diagnosed with PD have found that the disease tends to progress more slowly in those with higher urate levels in their blood and cerebrospinal fluid, the fluid that surrounds the brain. The findings raise the possibility that boosting brain urate by treatment with the urate precursor inosine could slow the brain cell degeneration of PD.” (MJFF)
There's always failure. And there's always disappointment. And there's always loss. But the secret is learning from the loss, and realizing that none of those holes are vacuums.

------ Michael J. Fox

**PROSEEK TRIAL – starting soon**

- A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF K0706 IN SUBJECTS WITH EARLY PARKINSON’S DISEASE

- Sponsored by: Sun Pharma Advanced Research Company (SPARC)

- For newly diagnosed individuals not yet on PD medications.

- Two doses of K0706 vs Placebo once daily for 40 weeks.

- Primary outcome: Change in UPDRS II and III scores.

- Mechanism of study drug: cAbl Tyrosine Kinase Inhibition (Activated c-Abl can lead to neurodegeneration through its phosphorylation of parkin and alpha-synuclein)
Gene transfer trials in PD

AAV-GAD
AAV-AADC
Several thers in the pipeline
Gene therapy using an adenovirus vector
Motor cortex circuitry activity changes in Parkinson disease

(Associative) motor cortex

Striatum

Direct pathway

Indirect pathway

Thalamus

Substantia nigra pars compacta

Globus pallidus externus

Subthalamic nucleus

Globus pallidus internus

Substantia nigra pars reticulata

Mesencephalic motor regions

Increased excitatory activity

Reduced excitatory activity

Increased inhibitory activity

Reduced inhibitory activity

AADC

GAD

Nature Reviews | Disease Primers
Poewe, W. et al. (2017) Parkinson disease
Parkinson's disease gene therapy: GAD Zooks!
Excitement to inhibition in one easy step?

“In a recent issue of Science, Matt During's group presents intriguing results that highlight an imaginative new gene therapy approach for treating Parkinson's disease.”

GAD: Glutamic Acid Dehydrogenase. When injected into the STN, using a viral vector, overactive excitatory glutaminergic cells switch to making GABA, an inhibitory transmitter instead, helping to balance circuits.
AAV2-GAD gene STN infusion
AAV2-GAD Gene Therapy for Advanced Parkinson’s Disease: a double-blind, sham-surgery controlled, randomized trial


Lancet Neurology. Published online March 17, 2011
Primary Endpoint: Mean Change in off-medication UPDRS motor scores
AAV2-GAD  Gene Therapy for Advanced Parkinson’s Disease: a double-blind, sham-surgery controlled, randomized trial.

• This was the **first ever positive** result for a double-blinded **gene treatment** study for Parkinson’s disease.

• Previous therapy trials with GDNF and neurturin gene transfer into the putamen failed in phase 2 trials.

• **OSU** participation included basic scientists, neurosurgeons, neurologists, coordinators and patients.

• (Participating national sites: Ohio State University, Massachusetts General Hospital, Wake Forest, Henry Ford, University of Colorado, University of Rochester, Stanford University)
2011 Neurologix Stock Value Price Chart
The search must go on....

AAV-AADC gene transfer therapy for PD
AADC
Aromatic L-amino acid decarboxylase

Figure 7 Dopaminergic drug targets in Parkinson disease

Poewe, W. et al. (2017) Parkinson disease
Voyager Therapeutics. Trials PD-1101, 1102, 1104, 1105

• **PHASE 1b.** PD-1101 and 1102 (1104 is long term follow up) Safety, tolerability and efficacy of ascending doses of AAV-AADC infused into the putamen.
  - Degree of coverage of putamen with AADC correlated with F-DOPA PET scan Signal.
  - Increased coverage achieved using posterior surgical approach.
  - Decreased off-time. Decrease daily oral medications.
  - Four sites: OSU, Emory, USCF and U Pittsburg.

• **Phase 2a:** Restore-1 A Randomized, Placebo Surgery Controlled, Double-blinded, Multi-center, Phase 2 Clinical Trial, Evaluating the Efficacy and Safety of VY-AADC02 in Advanced Parkinson’s Disease with Motor Fluctuations
AADC

Aromatic L-amino acid decarboxylase

Voyager’s VY-AADC02
Voyager Therapeutics’ experimental gene therapy is intended to put the AADC gene into the brain where the AADC enzyme is needed to convert levodopa to dopamine.
You may be eligible to participate if you:

- Are 40 to 75 years of age (inclusive)
- Have been diagnosed with Parkinson’s disease for at least four years
- Are able and willing to travel and take part in extended study visits, including off-medication visits
- Have noticed your motor symptoms are unpredictable despite medication
- Agree to defer any neurological surgery, including deep brain stimulation (DBS), other invasive treatments for Parkinson’s disease including Duodopa, or the addition of new dopaminergic formulations until after completing the 12-month study visit
Thank You For Your Attention

Wexnermedical.osu.edu
George W. Paulson  
July 27, 1930 – July 25, 2019

• Joined OSU in 1967  
  Department of Medicine, Division of Neurology

• In 1983 he became the  
  first chairman of the  
  newly created  
  Department of Neurology at OSU.

• Founder of OSU  
  Movement Disorder  
  Division.