Parkinson’s Advocates in Research Online Course

Part Two: What’s in the Parkinson’s Pipeline?

Presented By:

Claire Henchcliffe, M.D., D.Phil.

Director, Weill Cornell Parkinson’s Disease & Movement Disorders Institute

Associate Professor in Neurology & Neuroscience, New York Presbyterian Hospital/Weill Cornell Medical Center
Welcoming Remarks

Robin Elliott
Executive Director
Parkinson’s Disease Foundation
What’s in the Parkinson’s Pipeline?

Learning objectives:

• Understand the limitations of current Parkinson’s treatments
• Describe the difference between studies of symptomatic and neuroprotective treatments
• Understand how observational studies help move Parkinson’s research forward
What’s in the Parkinson’s Pipeline?

- Biomarkers for Improved Diagnosis and Monitoring
- Developing New Treatments to Tackle PD
- Advances in Surgical Treatment
What’s in the Parkinson’s Pipeline?

- Biomarkers for Improved Diagnosis and Monitoring
- Developing New Treatments to Tackle PD
- Advances in Surgical Treatment
What are biomarkers? And why do we need them?

• Translating promising treatments from the laboratory depends on clinical trials
  – Need accurate diagnosis of participants
  – Need objective measures of treatment
    • short term (symptom control)
    • long term (neuroprotection or disease modification)
    • understand if the treatments do what we predict
Diagnosis: How accurate are we?

• Currently we rely upon observation of asymmetric:
  – Rigidity
  – Tremor
  – Slowed movements
    • Also balance problems
  – Accuracy typically ranges from 75-95%
  – Often PD is diagnosed early when the correct diagnosis is a more aggressive, less treatable disorder
  – Diagnosis is often delayed

Dopaminergic Ligands for PET or SPECT

- Loss of dopamine can be measured by SPECT scans
  - Over half the dopamine-producing cells are lost before any motor symptoms are felt, so tests like DaTSCAN may be helpful early

Candidates for cerebrospinal fluid and blood biomarkers: α-synuclein, DJ-1, proteomic analysis, dopamine metabolites, chemicals in the purine pathway, inflammatory markers, many others...

Dauer and Przedborski Neuron 2003 39:889
Mollenhauer et al Exp Neurol 2008 213:315-25
What’s in the Parkinson’s Pipeline?

- Biomarkers for Improved Diagnosis and Monitoring
- Developing New Treatments to Tackle PD
- Advances in Surgical Treatment
Limitations of Current Treatments

• There is no proven means to slow progression or reverse the underlying disease
• Most current treatments are based upon dopamine replacement
  – Does not address imbalance, freezing, and falls, or problems with thought processing and memory
  – Levodopa, the most potent dopamine replacement, leads to long term motor complications including dyskinesias
The “Shaking Palsy”

- Early in the disease...” would perhaps think seldom of his being the subject of the disease, except when reminded of it by the unsteadiness of his hand whilst writing or employing”

- Late in the disease...” the fingers cannot be disposed of in the proposed direction and applied with certainty ..... the patient has recourse to walking, but as the disease progresses, the propensity to lean forwards becomes invincible ”

- An Essay on the Shaking Palsy (1817), James Parkinson.
  Whittingham and Rowland, London
How can we halt the spread of PD?

Braak et al J Neurol 2002 249 Suppl 3 1432--1459
Back to Basics! What leads to nerve cell loss in PD?

**PATHOGENESIS**

- GENES
  - abnormal protein processing
- TOXINS
  - oxidative stress
  - mitochondrial dysfunction
  - inflammation
  - transcriptional dysregulation

Cell death

**PARKINSON’S DISEASE**
Will antioxidants or mitochondrial therapy help?

- Diets rich in antioxidants are associated with lower risk of Parkinson’s disease
- Mediterranean-style diets lower the risk of Parkinson’s and Alzheimer’s
- Antioxidants and compounds promoting antioxidant pathways are protective in the laboratory
- Trials including Vitamin E, Vitamin C, Coenzyme Q10 have now all failed!
Could any of the known PD drugs help?

- Large phase III clinical trials testing neuroprotection in PD:
  - selegiline
  - rasagiline
  - levodopa
  - pramipexole
- Update: FDA rejected claim for rasagiline on Monday, October 17, 2011

Pipeline Efforts in Neuroprotection...

- Calcium channel blockade
  - Isradipine
- Modulating uric acid levels
  - Inosine
- Regulating high energy stores and antioxidants
  - Creatine
  - N-acetyl cysteine
- Alpha-synuclein clearance
  - Antibodies, small molecules
...and Improving Symptom Control

- Need for smoother dopamine stimulation
  - Extended release carbidopa/levodopa (IPX066)
  - Levodopa/carbidopa intestinal gel (Duodopa)
  - Apomorphine infusion

- Non-dopaminergic drugs
  - Adenosine A2A antagonists (SYN115, others)
  - Long acting amantadine
  - Metabotropic glutamate receptor antagonists (ADQ056, ADX48621)
  - Dextromethorphan/quinididine
  - Safinamide (reversible MAO-B inhibitor, antiglutamatergic, reduces dopamine reuptake)
  - And many others
Exercise, exercise, exercise...

- Tango improves mobility and balance in Parkinson’s disease
- Tandem biking improves Parkinson’s disease symptoms
- Tai Chi decreases risk of falls in Parkinson’s disease and healthy older individuals

- Do any of these delay disease progression?

Dance for PD: http://danceforparkinsons.org/
What’s in the Parkinson’s Pipeline?

• Biomarkers for Improved Diagnosis and Monitoring

• Developing New Treatments to Tackle PD

• Advances in Surgical Treatment
New Perspectives in DBS

• When?
  – traditionally considered for disabling motor complications that cannot be medically managed

• EARLYSTIM trial
  – DBS of bilateral subthalamic nucleus (STN)
  – “early” motor complications of ≤ 3 years’ duration
  – preserved social and occupational function
  – randomised, observational, 2 years follow up
  – DBS was superior to best medical therapy (primary outcome – quality of life)

Gene Therapy Testing for Parkinson’s Disease

“Before the operation I was a quivering mass of flesh. With my medications I am like 80 or 90% better. I am at a point right now where if you didn’t know I had Parkinson’s disease you couldn’t tell.”

– Nathan Klein to MSNBC

June 2003: New York Presbyterian Hospital/Weill Cornell Medical Center
How does gene therapy work?

• Use the adeno-associated virus - “AAV” with the gene of your choice contained within...
What is the GAD gene used? Why should it work?

- A nucleus called the STN is hyperactive in Parkinson’s
- It releases excess glutamic acid = slowed movements
- GAD (glutamic acid decarboxyase) ensures the STN releases less glutamic acid and more GABA = faster movement

Similar principle to DBS surgery
Sham Surgery Controlled GAD Gene Therapy Trial

LeWitt et al. (2011) Lancet Neurology 10, 309-319
MR-guided Focused Ultrasound

- Focused ultrasound signals can provide precise lesion of a small area of tissue
  - used in cancer, fibroid treatment
- Initial study of transcranial MR-guided focused ultrasound (ExAblate) in essential tremor provided relief in a small number of patients
- Testing has started in PD
Are there hopes for stem cell therapy?

• Stem cell properties

• *Self-renewal* - the ability to go through numerous **cycles** of **cell division** while maintaining the undifferentiated state

• *Potency* - the capacity to differentiate into specialized cell types
  – **totipotent**
  – **pluripotent**
Historical Timeline

1908 Term coined by Maximov

1963 Self-renewing cells found in marrow

Bone marrow transplant 1968

1981 Mouse ES cells Evans/Martin/Kaufman

1998 human ES cells

1998 ES-like cells derived by electroporation

2006 Rat iPS

2007 human iPS Takahashi/Yamanaka

2009 ES-like cells derived by electroporation

Bush’s restrictions of Federal Funding for Stem Cell Research
Fetal Mesencephalic Cell Transplants: Initial Success

• Basic principle: to replace striatal dopamine
• Numerous early open label studies reported benefit in PD from 1990 onwards
• One study reported benefit in MPTP-induced parkinsonism (n=2)
• Nuclear neuroimaging demonstrated long term graft survival and functionality (dopamine release)
A Controlled Cell Transplant Trial

- Randomised, double-blinded, sham surgery-controlled clinical trial in 40 people with severe PD
- Cultured mesencephalic tissue (4 embryos per side) grafted into the bilateral putamen
- Primary endpoint was not achieved, but a subset of younger patients derived mild clinical benefit
- Some developed “runaway dyskinesias”

Freed et al 2001, NEJM 344: 710-719
Do stem cells not work in PD? Or are we just doing it wrong?

• Problems to the “traditional” transplant approach include:
  – Lack of reliable sources
  – Variability in cells transplanted
  – Lack of control once cells are transplanted
  – Do we need to give immunosuppression treatment?
  – New questions over possible spread of disease from PD cells to transplanted “healthy” cells!
Advances in Stem Cell Biology

- Ability to generate dopaminergic neurons from cultured embryonic stem cells
- Ability to produce inducible pluripotent stem cells from skin biopsies

Research Advocacy: Working with Researchers

Help to identify funding.

Help to identify funding.

Review the informed consent form.

Develop plan for sharing study results with participants and the public.

Advocate for monitoring and making information available to the public.

Identify the needs of people with PD.

Assess how easy or difficult it would be to participate in the study.

Discuss and fine-tune recruitment efforts.

Provide input through written public comments or as member of FDA Advisory Committee.

Post approval studies

Ideas | Funding | Protocol | Implementation | Monitoring | Analysis and Results | FDA Review and Approval | Post approval studies

Parkinson’s Disease Foundation