PD ExpertBriefing: The Parkinson's Pipeline: Treating Your Parkinson's

Presented By:

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University of Ottawa, Ottawa, Ontario
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Welcoming Remarks

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PD ExpertBriefing: The Parkinson's Pipeline: Treating Your Parkinson's

Presented By:

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As of 2011, Alzheimer’s, Parkinson’s and stroke are understood as COMPLEX diseases, i.e., they have environmental and genetic contributors.
As of 2011, Alzheimer’s, Parkinson’s and stroke are understood as complex diseases ... 

... but so are diabetes, heart disease and asthma.

Klein C & Schlossmacher MG, Neurology 2007
Typical Parkinson’s Cases Grouped by Cause

ENVIRONMENTAL DISEASE:

One or possibly, more than one contributor, for example accidental ingestion of a toxin.

*Klein C et al., Arch Neurol 2011*
Ingestion of a toxin, such as manganese, in subjects that used a new drug, methcathinone; however, other drugs and environmental triggers are likely to play a role in PD.

(In the MRI image, arrows point to areas of cell death and inflammation as a result).
GENETIC DISEASE:

Likely, more than one genetic risk factor; or,
Single genetic risk factors.
Since 1997, geneticists have identified many genetic clues to PD.

**Early-onset PD (≤15%)**

- Probability of **monogenic** cause: range, very high to low

**Late-onset PD (≥85%)**

Distribution of age-at-disease onset: range: <20 to >60 years

**Familial PD**

- Parkin (~10–20%)
- PINK1 (~2–7%)
- DJ1 (~1–2%)
- LRRK2 (~5–10%)
- SNCA (<0.5%)

**Sporadic PD**

- GBA (>8%)
- LRRK2 (~2%)
- Parkin (rare, but very limited data)
- PINK1
- DJ1

*Klein and Schlossmacher, Nat Clin Pract Neurol, 2006*
GROUPED BY CAUSE

COMPLEX DISEASE:
Several environmental events combined with one or more genetic susceptibility (risk) factor

Klein C & Schlossmacher MG, Neurology 2007
All 100 have typical PD!

ENVIRONMENTAL DISEASE:
One or more contributor(s)

COMPLEX DISEASE
Environmental factors (one or more) combined with one or more genetic risk factors

GENETIC DISEASE:
Multiple genetic risk factors
Single genetic risk factor
However, ~70 out of the 100 patients share the same pathology in the brain, ie, the accumulation of α-synuclein inside nerve cells (“like bad cholesterol”)

Spillantini MG et al., Nature 1997
Why Haven’t We Fixed Parkinson’s Yet?

Three reasons among several:

• Because there are multiple look-alikes of typical Parkinson disease, as mentioned;
• Because we have not yet unmasked the key environmental contributors other than a few toxins (eg, manganese shown above);
• We have not yet developed drugs that are specific for the individual variants for PD.
How does a COMPLEX DISEASE develop?
(we inherit two copies of each gene, one from our mother, one from our father)
Then we encounter environmental risk factors (such as through our diet, or exposure to toxins) during the process of getting older...
The beginning of neurodegeneration (pink triangle) is usually clinically unrecognized = pre-symptomatic. The motor phase starts decades later (red asterisk)
The progression of Parkinson disease - >25 years !!!

<table>
<thead>
<tr>
<th>Braak Classification Stage I - VI</th>
<th>Principal Site of α-Synuclein Pathology</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>Nervous system of the gut</td>
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<tr>
<td>Stage 1</td>
<td>Medulla = lowest part of brainstem</td>
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<tr>
<td>Stage 2</td>
<td>Pons = middle part of brainstem (light blue)</td>
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<tr>
<td>Stage 3</td>
<td>S.nigra in Midbrain = upper part of brainstem</td>
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<tr>
<td>Stage 4</td>
<td>Hippocampus = memory center of brain</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Association cortices = thinking parts of brain</td>
</tr>
<tr>
<td>Stage 6</td>
<td>Sensory and motor cortices = center for feeling touches and moving limbs</td>
</tr>
</tbody>
</table>

Braak H et al., 2003; Jellinger K, 2004; Braak H et al., 2004; Hawkes C et al., 2007
Three challenges remain as relevant today in Alzheimer’s disease and Parkinson’s research: Pathogenesis, Biomarkers and Causal Therapy.
Our goal is to develop cause-specific, individualized treatment for each of the typical PD variants that we can identify to then stop or at least, slow the disease process.

*Klein C et al., Arch Neurol 2011*
Imaging PD subjects measuring their brain DAT activity is not informative as to the cause of their ‘typical PD’.

A PET scan showing reduced striatal fluorodopa uptake.

Pursuing α-synuclein (and Alzheimer’s linked tau and amyloid beta-protein and others) as suitable biomarker candidates in human cerebrospinal fluid
Testing α-synuclein and Alzheimer’s linked tau and other proteins as suitable biomarker candidates in human fluids. We are getting closer to establishing laboratory tests that help make the diagnosis (in addition to the doctor’s exam), eg spinal fluid, blood, urine, smell test etc.

Hong et al., 2010; Tokuda et al., 2010; Mollenhauer et al., 2011
We may not be so fortunate as to accidentally discover the ‘magic bullet’ for PD. The solution lies in finding specific causes (genetic and environmental), in using biological tests to track their effects in living subjects, in “target identification”, and in specific drug development – as we did successfully in other disorders (heart disease, cancer, asthma,..)
Finding targets that are specific: Because 70% of typical PD patients share its accumulation in the brain, α-synuclein has become such a target.
The rise of α-synuclein from 100% in normal subjects to >125% puts us at great risk to develop Parkinson disease – graphic summary of all the genetic evidence that supports this conclusion.

Spillantini MG et al., 1997; Farrer M et al., 2006; Tomlinson JJ et al., 2010; Cullen V et al., 2011
The Life Cycle of α-Synuclein in the Brain: How Can we Lower It in Living Patients?

Tomlinson J et al., 2010
The RED ARROW indicates the “translational road map”: Find and develop drugs for your pipeline that lower α-synuclein by ~50%!

Tomlinson JJ et al., 2010; Cullen V et al., 2011
We received an exciting clue!

IN COMPLEX DISEASE CASES:

Between 8 percent and 20 percent of people carry a mutation in one of their two copies for the GBA gene as an important risk factor – how can we use this piece of information?

Sidransky E et al., NEJM 2009
This genetic clue is now well established around the world; we may not fully understand it yet, but it has implications for future trials in the near future.
Mutant GBA proteins elevate α-synuclein in cells and mice

Cullen V et al., 2011
Why is this important? Because it might be possible to reverse this effect by new – or old – drugs.
Mutant GBA effect on α-synuclein can be reversed by pharmacological treatment in cells

Cullen V, Sardi P, Ng J et al., 2011
The Life Cycle of α-Synuclein in the Brain Offers Many Potential Targets – Drug Companies Show Interest

SYNUCLEIN IN HEALTH AND DISEASE
SiHD 2010 • November 11-12, 2010 • San Diego, CA

Tomlinson J et al., 2010
If we select our patients better ("stratification") future clinical trials are more likely to succeed.
Guest Editors:
Schlossmacher M & Mollenhauer B.
Oct. 14\textsuperscript{th}, 2010
Questions and Answers
Closing Remarks

Robin Elliott
Executive Director
Parkinson’s Disease Foundation