Critical Targets in Parkinson’s Disease Research

Sonal S. Das, PhD
The Michael J. Fox Foundation for Parkinson’s Research

August 20, 2012
What is Parkinson’s disease?

**Parkinson’s Disease**
- Chronic, degenerative neurological disorder that results when dopaminergic neurons projecting from the substantia nigra to the striatum degenerate
- Affects 1 in 100 people over age 60
- Average age at onset is 60, though people have been diagnosed as young as 18

**Symptoms**
- **Motor**: Resting tremor, bradykinesia, muscle rigidity, loss of balance
- **Non-motor**: Cognitive impairment, loss of smell, constipation, sleep disorders (quality of life problem)

**Causes**
- Idiopathic, Genetic, Environmental
MJFF was founded in 2000 with clear objectives

- Drive the best Parkinson’s research
- Deliver improved therapies and a cure
MJFF’s research strategy

Key Aspect
De-risk PD

How?
Place bets on ideas and therapies that face obstacles

Goal
Make PD a more attractive investment opportunity
MJFF Identifies Field Needs Through Two Strategic Efforts

**Pipeline Strategy**

- Address Critical Gaps in Pipeline
- Maintain Field View

**Priority Area Strategy**

- Defining PD/Markers of Progression
- Altering Disease
- Treating Symptoms & Side Effects

**Tools**

- Focus on top priority areas
- Proactive MJFF management
What is in the MJFF pipeline?

Promising targets

• Disease-modification: genetics (α-synuclein, LRRK2), inflammation, Nrf2, Nurr1, GDNF, CDNF, antioxidants
• Symptomatic: mGluR5, mGluR4, nicotinic, mu opioid

Preclinical development

• Over 100 industry led projects moving to the clinic
• Dyskinesia therapies
• Translational research tools: animal models, antibodies, biomarkers

Clinical Trials

• 20 ongoing MJFF funded intervention trials
• NTN gene therapy (Ceregene), α-synuclein (AFFiRiS)
• mGluR5 (Addex), Eltopazine, L-DOPA delivery improvements (Civitas)
• Repurposing: Pioglitazone, Inosine, Isradipine

PD pipeline shows promise
Predominant Pathways in MJFF Portfolio

- Neurotransmitters: 29%
- Neurodegeneration: 21%
- Protein Handling: 17%
- Inflammation: 10%
- Antioxidant: 9%
- Trophic Factors: 7%
- Mitochondrial Dysfunction: 5%
- Excitotoxicity: 1%
- Cell Replacement: 1%
PD Drugs in Clinical Trials – By Target

Number of Drugs

Target

- Dopamine Receptors: 40
- Other: 15
- Serotonin Receptors: 14
- Cholinergic Signaling: 9
- Adenosine A2A Receptors: 7
- MAO B: 6
- Catechol O-Methyltransferase: 6
- Alpha Adrenoreceptors: 5
- Antioxidant: 5
- Trophic Factors: 4
- Muscarinic Receptors: 4
- GABA Receptors: 3
- Amyloid beta: 3
- Mitochondria: 3
- Sodium Channels: 3
- Calcium Channels: 2
- mGluR5: 2
- GSK-3: 2
- Tyrosine Hydroxylase: 2

Source: www.thomson-pharma.com
SYMPTOMATIC THERAPIES
Critical Targets in PD – Symptomatic Benefit

A2A Antagonists

Merck

Target Validation

Drug Delivery Development

Phase I

Phase II

Phase III

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON’S RESEARCH
Clinical Targets – Disease Modification/Symptomatic Benefit – **Adenosine Receptors**

- **Strong epidemiological link to PD**
  - Caffeine consumption inversely associated with PD onset

- **Compelling molecular target for therapy**
  - Highly selective localization on striato-pallidal neurons
  - A2A antagonists have been found to provide neuroprotection and motor improvement in preclinical models

- **Stage of Development**
  - Several industry players have moved their compounds into late-stage clinical trials
    - Merck -- Preladenant

Critical Targets in PD – Symptomatic Benefit

Target Validation

Drug /Delivery Development

Phase I

Phase II

Phase III

Serotonin Receptors

Lund University, PsychoGenics, Inc.
Clinical Targets – Symptomatic Benefit – **Serotonin Receptors**

- **The link to PD**
  - Preclinical studies have demonstrated a reduction in dyskinesias using combinations of selective 5-HT receptor agonists/antagonists

- **Compelling molecular target for therapy**
  - Uptake of L-DOPA/Dopamine into serotonergic presynaptic terminals followed by aberrant dopamine release may be to blame

- **Stage of Development**
  - Investigators at Lund University and PsychoGenics are examining selective targeting of auto-receptors (5-HT1a/5-HT2)
    - Phase I clinical trials have thus far reported positive results

Critical Targets in PD – Symptomatic Benefit

- Target Validation
- Drug/Delivery Development
- Phase I
- Phase II
- Phase III

mGluR5 NAM

Addex Pharmaceuticals

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON’S RESEARCH
Clinical Targets – Symptomatic Benefit – mGluR5

• The link to PD
  – Loss of dopaminergic neurons in PD results in aberrant signaling

• Compelling molecular target for therapy
  – Targeting postsynaptic mGluR5 receptors may provide benefits at both direct and indirect pathways

• Stage of Development
  – Investigators at Addex Pharmaceuticals have tested Dipraglurant and shown it to be safe and efficacious.

Critical Targets in PD – Symptomatic Benefit

- Target Validation
- Drug /Delivery Development
- Phase I
- Phase II
- Phase III

Vanderbilt University/Addex Pharmaceuticals

mGluR4 PAMs
Preclinical Targets – Symptomatic Benefit – mGluR4

- **The link to PD**
  - Loss of dopaminergic neurons in PD results in aberrant signaling

- **Compelling molecular target for therapy**
  - Selective targeting of D2-positive neurons -- at presynaptic mGluR4

- **Stage of Development**
  - Investigators at Vanderbilt University and Addex Pharmaceuticals are currently looking to move forward lead mGluR4 PAMs for PD, having demonstrated efficacy in preclinical PD models

Critical Targets in PD – Symptomatic Benefit

- **A2A Antagonists**
  - Merck

- **mGluR5 NAM**
  - Addex Pharmaceuticals

- **Serotonin Receptors**
  - Lund University, PsychoGenics, Inc.

- **mGluR4 PAMs**
  - Vanderbilt University/Addex Pharmaceuticals

- **Nicotinic Receptors**
  - Targacept
DISEASE MODIFYING THERAPIES
Critical Targets in PD – Disease Modification

- Target Validation
- Drug/Delivery Development
- Phase I
- Phase II
- Phase III

Trophic Factors

Ceregene
Clinical Targets – Disease Modification – Trophic Factors

• **Compelling molecular target for therapy**
  – Regardless of the cause of neurodegeneration, trophic factors can promote the development, survival and function of neurons

• **Stage of Development**
  – Ceregene has focused on AAV2-Neurturin delivery
  – Current Considerations
    • Site(s) of delivery
    • Time points at which outcomes measures are assessed
    • Patient population
    • Dose

[www.macalester.edu/psychology/whathap/ubnrp/parkinsons/GDNF.html]
Critical Targets in PD – Disease Modification

Target Validation

Drug /Delivery Development

Phase I

Phase II

Phase III

Northwestern University

Calcium Channels
Clinical Targets – Disease Modification – **CaV1.3 Channels**

- **Strong link to PD**
  - Mature dopamine neurons utilize calcium to maintain their function as pacemakers

- **Compelling molecular target for therapy**
  - Excess calcium can promote neurodegeneration
  - Inhibition of calcium channels results in dopamine neurons reverting to utilizing sodium to maintain activity

- **Stage of Development**
  - Investigators at Northwestern University have repositioned the compound Isradipine and are examining its ability to provide neuroprotection

Critical Targets in PD – Disease Modification

Target Validation / Delivery Development

Phase I

Phase II

Phase III

Alpha-Synuclein

AFFiRiS
Clinical Targets – Disease Modification – **Alpha-Synuclein**

- **Strong link to PD**
  - Pathological presence in Lewy bodies of familial and sporadic PD
  - Genetic association in familial cases of PD

- **Compelling molecular target for therapy**
  - It is not clear if alpha-synuclein aggregation plays a causative role in PD pathogenesis or if aggregation is protective mechanism
  - Given the effect of multiple copies of alpha-synuclein and the genetic tie to PD, therapeutics directed focused on decreasing alpha-synuclein protein levels (formation or clearance) are key

- **Stage of Development**
  - Affiris has initiated the first-in-human clinical trial of a vaccine against alpha-synuclein

Critical Targets in PD – Disease Modification

- Target Validation
- Drug /Delivery Development
- Phase I
- Phase II
- Phase III

Industry/Harvard/Dundee

LRRK2
Emerging Targets: **LRRK2**

- **Strong genetic link to PD**
  - Predominant genetic cause of PD (1-2% of cases), and up to 40% in certain ethnic groups
  - Common mutations include G20129S and R1441G; Asian risk variant G2385R

- **Compelling molecular target for therapy**
  - PD-associated mutation appears to enhance LRRK2 enzymatic (kinase) activity suggesting that a kinase inhibitor drug would be therapeutic

- **Stage of Development**
  - Pharma/Academia working have identified kinase inhibitor tools and lead compound for testing in *in vitro* and *in vivo* models
  - Identification of appropriate models has been difficult
    - Key Activity: Determination of biomarker of kinase activity
    - Concerted effort around structure determination to inform SAR

*Cookson (2010). Nature Reviews Neuroscience 11, 791-797*
### Other Genetic Targets

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Notes</th>
<th>Mode of Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1</td>
<td>EOPD</td>
<td>AD</td>
<td>SNCA</td>
<td>Confirmed</td>
<td>Linkage Analysis</td>
</tr>
<tr>
<td>PARK2</td>
<td>EOPD</td>
<td>AR</td>
<td>Parkin</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK6</td>
<td>EOPD</td>
<td>AR</td>
<td>PINK1</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK7</td>
<td>EOPD</td>
<td>AR</td>
<td>DJ-1</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK8</td>
<td>Classical PD</td>
<td>AD</td>
<td>LRRK2</td>
<td>Confirmed; variations in LRRK2 gene include risk-conferring variants and disease-causing mutations</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK9</td>
<td>Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy</td>
<td>AR</td>
<td>ATP13A2</td>
<td>Confirmed; complex phenotype that would not be mistaken for early-onset or classical parkinsonism</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK14</td>
<td>Early-onset dystonia-parkinsonism</td>
<td>AR</td>
<td>PLA2G6</td>
<td>Confirmed</td>
<td>Linkage analysis (homozygosity mapping)</td>
</tr>
<tr>
<td>PARK15</td>
<td>Early-onset parkinsonian-pyramidal syndrome</td>
<td>AR</td>
<td>FBX07</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK17</td>
<td>Classical PD</td>
<td>AD</td>
<td>VPS35</td>
<td>Confirmed</td>
<td>Exome sequencing</td>
</tr>
<tr>
<td>PARK18</td>
<td>Classical PD</td>
<td>AD</td>
<td>EIF4G1</td>
<td>Unconfirmed; recently published (Chartier-Harlin et al. 2011)</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>?</td>
<td>Late-onset PD</td>
<td>AD</td>
<td>DNAJC13</td>
<td>Unconfirmed? Mennonite community</td>
<td>Exome sequencing</td>
</tr>
</tbody>
</table>
Critical Targets in PD – Disease Modification

- Target Validation
- Drug/Delivery Development
- Phase I
- Phase II
- Phase III

Nrf-2

Industry/Academia
Emerging Targets: Nrf-2

- **Link to PD**
  - Increased oxidative stress is associated with neuronal cell death during the pathogenesis of Parkinson’s disease

- **Compelling molecular target for therapy**
  - Nrf2 upregulates a number of antioxidant enzymes

- **Stage of Development**
  - A number of investigators have validated Nrf2 as providing neuroprotection in PD toxin models *in vitro* and *in vivo*
  - Currently, investigators in industry and academia are working to screen and optimize compounds to identify small molecules that may promote the upregulation of antioxidants in vivo to modify the course of Parkinson’s disease

Critical Targets in PD – Disease Modification

- **Trophic Factors**
  - Ceregene

- **Calcium Channels**
  - Northwestern University

- **Alpha-Synuclein**
  - AFFiRiS

- **Nrf-2**
  - Xenoport

- **LRRK2**
  - Industry/Harvard/Dundee

**Phase I**

**Phase II**

**Phase III**

**Drug /Delivery Development**

**Target Validation**

**Phase I**

**Phase II**

**Phase III**

**Drug /Delivery Development**

**Target Validation**
Conclusions

• Since the 1960’s, PD patients have had to rely on dopamine-based therapies

• Now, over 50 years later, there is a robust pipeline for novel targets, many of which are close to or even in the clinic:
  – Non-dopaminergic
  – Genetic

• Ongoing Challenges
  – Clinical Testing
    • Patient population
  – Understanding the right measures
    • Biomarkers
    • Clinical scales
Thank You

• The American Chemical Society
  – John Macor, PhD

• The Michael J. Fox Foundation for Parkinson’s Research
  – Research Programs Staff