Multi-pronged Approach to Reposition Drugs for Parkinson’s Disease

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The Michael J. Fox Foundation for Parkinson’s Research

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MJFF was founded in 2000 with clear objectives

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

- MJFF has funded over $304M in research since its founding in 2000
  - Over $55M was directed toward PD research in 2011
  - Estimate ~$55M in grants awarded in 2012
- In 2011, we received nearly 64,000 contributions and raised $68.4M
- Core values are efficiency and accountability: 88 cents of every $1 spent goes straight to research program efforts

Our in-house staff of 7 PhDs, 1 MD and 8 business strategists serve as portfolio managers, incorporating the advice and input of experts from academia and industry into their decision-making

We reviewed over 900 PD-specific grants in 2011 and currently have over 450 active grants in our portfolio
MJFF’s approach to funding

Craft an informed research agenda
- Understand patient needs
- View global field and identify most promising targets
- PhDs balance relevance and merit while business managers balance prioritization and risk

Map out critical research plans
- Infuse capital at underfunded, high-risk stages
- Develop and share essential research tools
- Pragmatically push research in a goal directed, milestone-driven fashion

Problem-Solve: lead and innovate
- Convene experts in non-competitive environment
- Facilitate handoffs and orchestrate connections
- Showcase top ideas to industry
Annual programs provide a constant flow of new ideas

The Edmond J. Safra Core Programs for PD Research

- **Rapid Response Innovation Awards (RRIA)** - Fast money for high-risk ideas
- **Target Validation (TV)** - Focused effort on early preclinical validation of new targets
- **Therapeutics Pipeline Program (TPP)** - Therapeutic development through clinical studies
Define PD/PD Progression

- Develop Biomarkers of PD Progression (PPMI, Taskforce)
- Improve PD Clinical/Pathological Understanding (APDC)

Alter Disease

- Validate Genetic Targets (α-synuclein, LRRK2)
- Develop Trophic Factor Therapies (GDNF, NTN)

Treat Symptoms & Side Effects

- Dyskinesias
- Untreated Symptoms (Cognitive/Mood, Posture/Gait)

Research Tools

- Animal Models
- Reagents/Assays
- Imaging ligands
- Data Sharing
Parkinson’s disease

**MOTOR**
- Rigidity, bradykinesia, tremor, postural instability
- Akinesia, gait disturbance, dyskinesia

**NON-MOTOR**
- Cognition, sleep disturbances, autonomic dysfunction, pain, hypomimia, hypophonia, anosmia, orthostatic hypotension

Current treatments can ameliorate symptoms for several years but progression is inevitable.
Parkinson’s disease - Market

- Current therapies effectively address mild/moderate motor symptoms, but have significant long-term side effects and do not address the numerous non-motor aspects of the disease, leaving significant unmet needs.
- A disease-modifying therapy that halts or slows underlying disease progression could generate from $2B to $3B in US revenues.
- A regenerative therapy targeted at later-stage patients could reach $500MM to $1B in US revenues.
- A therapy to address symptomatic dyskinesia, or involuntary jerking movements, could generate $360MM to $760MM in US revenues, while a mechanism treating motor symptoms without contributing to dyskinesias could garner $900MM to $1.2B in US revenues.
- A therapy to address major non-motor symptoms of PD such as cognitive dysfunction could achieve over $500MM in US revenues.
- PD is viewed as a particularly risky investment
  - Cause is unknown
  - No biomarkers exist to enable diagnosis and accurate measurement of progression
  - Poor pre-clinical models exist
MJFF’s research strategy

**Goal**
Make PD a more attractive investment opportunity

**How?**
Place bets on ideas and therapies that face obstacles

**Key Aspect**
De-risk PD
Drug Repositioning: Applying an existing compound (either an approved drug or a clinical candidate in testing) for one indication to another indication

- Advantages
  - Reduce cost
  - Mitigate risk
  - Decrease time to market
Repositioning Isradipine for PD – Disease Modifying

- **Efficacy/PK study in PD animal model**
  - L-type calcium channels regulate neuronal excitability
  - RRIA 2007 Funding

- **Open-label tolerability study in normotensive PD patients**

- **STEADY-PD Trial**
  - Phase 2, double-blind, safety, tolerability and efficacy
  - 10 mg dose well tolerated

- **Challenges**
  - BBB penetrability, patient characteristics
  - Future development

**Funding**
- CIA 2008 Funding
Repositioning Pioglitazone for PD – Disease Modifying

PPARgamma/Nrf2 system have antioxidant effects

CFT 2005 Funding

Efficacy study in non-human primate model

Supplemental Funding

PK/PD in monkey model

NINDS NET-PD Trial
Phase 2, double-blind, safety, tolerability and efficacy

Results to be announced 2013

Supplemental Funding

Biomarker study

Challenges
• BBB penetrability, NINDS consortium
• Future development
Repositioning Eltoprazine for PD - Dyskinesia

- **Target Validation**
  - 5-HT1A and 5-HT1B receptors suppress dyskinesia

- **Drug Discovery/Development**
  - Eltoprazine efficacy in two animal models

- **Phase I**
  - PK/Efficacy/tolerability study in PD patients – collaboration with Psychogenics

- **Phase II**
  - Significant reduction in LID at two doses without adverse effects on levodopa efficacy

- **Phase III**
  - CIA 2009 Funding

- **Challenges**
  - Compound ID, academia-industry partnership
  - Swedish regulatory requirements

**Funding**
- TDI 2008
- CIA 2009
Repositioning AVE 8112 for PD - Cognition

Target Validation

Drug Discovery/Development

Phase I

Phase II

Phase III

PDE-4 inhibition for cognitive dysfunction in AD

Sanofi

AVE 8112

MJFF-funded and run Phase 1B study in PD patients

MJFF

Sanofi

Challenges

• No regulatory path for PD cognition

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
Repositioning Drugs for PD 2011 - 2012

- RFA Intent – to support the repositioning of clinically safe compounds from other indications to PD research

<table>
<thead>
<tr>
<th>RFA</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Funding</td>
<td>$3 million</td>
</tr>
<tr>
<td>Applicants</td>
<td>Academic or industry</td>
</tr>
<tr>
<td>Project</td>
<td>Clinical or preclinical</td>
</tr>
<tr>
<td>Duration</td>
<td>Up to 3-years</td>
</tr>
</tbody>
</table>

- Publicity: Attract non-PD researchers
  - Email blast
  - Conference call
  - Personal communication
  - Nature online & FierceBiotech

- 2 phase application – Prepropsal and full proposal
  - Therapeutic scorecard
## Therapeutic Scorecard – Part 1

<table>
<thead>
<tr>
<th>Therapeutic Name</th>
<th>The current name/designation for the therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent/License Holder</td>
<td>Who owns the license/patent for the therapeutic being developed</td>
</tr>
</tbody>
</table>

### DRUG-TARGET RELATIONSHIP

<table>
<thead>
<tr>
<th>Selectivity</th>
<th>Untested/Unknown</th>
<th>Non-Selective; “hits” many targets</th>
<th>Non-Selective; “Hits” targets within general class</th>
<th>Selective for Target Family/isoforms</th>
<th>Selective for Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>Untested/Unknown</td>
<td>Micromolar (&gt;100 nM)</td>
<td>Nanomolar (&gt;10 nM)</td>
<td>Nanomolar (&lt;10 nM)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**

### THERAPEUTIC CHARACTERISTICS

<table>
<thead>
<tr>
<th>ADME/PK</th>
<th>Untested/Unknown</th>
<th>ICV dosing in animal models</th>
<th>IP dosing in animal models</th>
<th>SC dosing in animal models</th>
<th>Oral dosing in animal models</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBB Penetrability in Target Region</td>
<td>Untested/Unknown</td>
<td>Does Not Cross BBB</td>
<td>Limited (&lt;10% systemic exposure)</td>
<td>Moderate (&lt;50% systemic exposure)</td>
<td>Good (&lt;100% systemic exposure)</td>
</tr>
<tr>
<td>Target Engagement</td>
<td>Untested/Unknown</td>
<td>Not Possible to Determine</td>
<td>Suggested by PK</td>
<td>Confirmed; No Dose Relationship Established</td>
<td>Confirmed; Dose Dependent</td>
</tr>
</tbody>
</table>

**Note:**

### EFFICACY IN PRECLINICAL MODELS

<table>
<thead>
<tr>
<th>Experience in Parkinson’s Disease Model: INDICATE MODEL</th>
<th>Untested/Unknown</th>
<th>Negative</th>
<th>Positive, but high exposure required</th>
<th>Relevant Rodent Model</th>
<th>Relevant Primate Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience in Other CNS Disease Model: INDICATE MODEL</td>
<td>Untested/Unknown</td>
<td>Negative</td>
<td>Positive, but high exposure required</td>
<td>Relevant Rodent Model</td>
<td>Relevant Primate Model</td>
</tr>
<tr>
<td>Experience in Other Non-CNS Disease Model: INDICATE MODEL</td>
<td>Untested/Unknown</td>
<td>Negative</td>
<td>Positive, but high exposure required</td>
<td>Relevant Rodent Model</td>
<td>Relevant Primate Model</td>
</tr>
</tbody>
</table>

**Note:**
## Therapeutic Scorecard – Part 2

### IND ENABLING STUDIES

<table>
<thead>
<tr>
<th></th>
<th>Untested/Unknown</th>
<th>NOAEL known SR &lt; 1</th>
<th>NOAEL known SR &lt; 10</th>
<th>NOAEL known SR &lt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety Pharmacology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxicological Studies</strong></td>
<td></td>
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<tr>
<td><strong>Formulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADME/PK</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

### CLINICAL EXPERIENCE WITH THERAPEUTIC

<table>
<thead>
<tr>
<th>Phase 1: Dosing</th>
<th>Untested/Unknown</th>
<th>Currently Being Tested</th>
<th>Completed</th>
<th>Dose Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1: Safety And Tolerability</td>
<td>Untested/Unknown</td>
<td>Dose limiting safety/tolerability identified</td>
<td>MTD not yet Identified – further studies needed</td>
<td>MTD Identified</td>
</tr>
<tr>
<td>Pharmacodynamic Outcome</td>
<td>Untested/Unknown</td>
<td>Not Possible to Determine</td>
<td>Suggested by PK</td>
<td>Confirmed, No Dose Relationship Established</td>
</tr>
<tr>
<td>Phase 2: Dosing</td>
<td>Untested/Unknown</td>
<td>IV dosing for efficacy studies</td>
<td>SC dosing for efficacy studies</td>
<td>BID/TID oral dosing for efficacy studies</td>
</tr>
<tr>
<td>Phase 2: Safety And Tolerability</td>
<td>Untested/Unknown</td>
<td>Dose limiting safety/tolerability identified</td>
<td>Safety/Tolerability of significant concern</td>
<td>Safety/Tolerability of minor concern</td>
</tr>
<tr>
<td>Phase 2: Efficacy</td>
<td>Untested/Unknown</td>
<td>Not established</td>
<td></td>
<td></td>
</tr>
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</table>

**Experience in Humans: NON-PD (INDICATE DISEASE)**

| Untested | Tested; Safety Liability | Tested; Safe in Phase I Studies | Tested; Effective/Safe in Pivotal Phase 2/3 trials | FDA Approved |

**Experience in Humans: PD**

| Untested | Tested in Humans – Safety Liability | Tested in Humans – Safe in Phase I Studies | Tested in Humans-Effective/Safe in Pivotal Phase 2/3 trials |

**Note:**

The Michael J. Fox Foundation for Parkinson’s Research
RFA – Criteria for Funding

- Preclinical applications:
  - Clear and justified rationale for repurposing the therapeutic to PD
    - Target, mechanism of action
  - Is this therapeutic the right candidate for repositioning?
    - How far did the drug advance in clinical testing, safety profile, BBB penetrability
  - Research plan
    - Outcome measures, animal models, key milestones
  - Investigator/Environment
    - Team expertise, institutional resources
  - Budget
    - Timelines, feasibility
  - IP/drug development plan
    - Patent issues, development path

- Clinical applications:
  - Impact
    - Does the proposed trial address an area of critical need for PD patients?
  - Innovation
    - Does the proposed trial test a novel therapy or significantly improve existing therapies?
  - Study design
    - Hypothesis, trial objectives, endpoints, statistics, recruitment plan

- MJFF philosophy in grant review – “flexibility”
  - Novelty vs. critical next step
  - Fatal flaw vs. lack of information
  - Rewriting vs. restructuring
Repositioning PF-00734,200 for PD – Disease Modification

Target Validation

Drug Discovery/Development

Phase I

Phase II

Phase III

DPP-4 inhibition for diabetes mellitus

PF-00734,200

Pfizer

DPP-4 inhibition efficacy for neuroprotection in PD animal models

MJFF

NIH/NIA

Pfizer

Repositioning 2011 Funding

For Parkinson’s Disease

Challenges

- MTA agreement
- Pfizer’s Priorities

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON’S RESEARCH
Repositioning NH004 for PD – Symptomatic (Sialorrhea)

Target Validation

Drug Discovery/Development

Phase I

Phase II

Phase III

Tropicamide (anticholinergic) for ophthalmic use

NeuroHealing Pharmaceuticals

NH004 – Intraoral reformulation (thin strips)

Clinical Discovery Grant 2007

Phase 2a safety and efficacy in 19 PD patients – Doctors office study

Repositioning 2011

Phase 2 safety and efficacy study in 30 patients – Home setting

Challenges

• None
MJFF is Driving Repositioning Efforts in Parkinson’s disease

• Due to the significant challenges in CNS drug development in general and PD development in particular, innovative approaches such as drug repositioning allow for opportunistic strategy to reduce cost, mitigate risk and accelerate time to get the treatment to the market.

• The Michael J. Fox Foundation for Parkinson's Research (MJFF) has taken aggressive research initiatives in identifying and funding repositioning of clinically safe compounds from other indications to PD.
  - Working with and bringing together academia, industry and NIH to make it happen
  - Forging new and diverse partnerships to take compounds forward

• MJFF has funded pre-clinical and clinical projects at critical junctures, promoting research at key translational points, to "de-risk" PD research with the goal of developing improved treatments and ultimately a cure for PD.
MJFF Acknowledgements

- Todd Sherer
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- Maurizio Facheris
- Niketa Sheth
- Lona Vincent
- Patricia Schreiber
Repositioning in Parkinson’s Disease

• PD affects nearly 1 million Americans and is thought to affect approximately 5 million individuals worldwide
• Current therapies exist, but only target symptoms and lose effectiveness over time
• PD is viewed as a particularly risky investment
  – Cause is unknown
  – No biomarkers exist to enable diagnosis and accurate measurement of progression
  – Poor pre-clinical models exist
• There are multiple paths toward addressing PD opportunity*
  – Disease-modifying therapies: $2B to $3B
  – Regenerative therapy for late stage patients: $500MM to $1B
  – Treating dyskinesias: $350MM to $750MM
  – Improved management of motor symptoms: $900MM to $1.2B
  – Improved management of non-motor symptoms: $500MM to $900MM

Demand for new treatments exists, and financial payoff could be significant

*Market assessment report spearheaded by The Michael J. Fox Foundation and Health Advances
Overview of priority area activities

<table>
<thead>
<tr>
<th>Area</th>
<th>Activities</th>
</tr>
</thead>
</table>
| **LRRK2**             | • Roadmap prioritizing four activities: Biology Consortium, Clinical Cohort Consortium, Tool development and Therapeutic development  
                         • LRRK2 Industry Group informs MJFF’s activities                            |
| **Biomarkers**        | • PPMI: large scale clinical study to develop progression markers of PD  
                         • 2012: MJFF Resources program                                              |
| **Alpha-synuclein**   | • 2010-12: Collaborative network to develop alpha-synuclein imaging ligands  
                         • 2012: A-synuclein Biology program – 2-year grants to address critical issues in therapeutic development |
| **Trophic Factors**   | • MJFF is supporting two clinical programs: Ceregene (NTN) and MedGenesis (GDNF)  
                         • 2012: Neurotrophic Factor Challenge – 1-year grant on novel neurotrophic factors |
| **Untreated Symptoms**| • Past activities focused on cognition and PIGD  
                         • 2011: Cognition Scale Validation Study                                     |
| **Dyskinesia**        | • Clinical study to validate dyskinesia rating scales – results to be shared in summer 2012  
                         • 2012: Identification and testing of novel targets – Open rolling program  
                         • MJFF is supporting four trials: Addex (mGluR5), DepoMed and Neuroderm (improving ldopa delivery) and Bjorklund Lab/PsychoGenics (5-HT1A/B) |
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, dopaminergic improvements (NeuroDerm)
- Repurposing: Pioglitazone, Inosine, Isradipine
MJFF resources

Animal Models
- Transgenic mice, knockout rats
- Standardized characterization
- Open access and central repository

Reagents
- Novel LRRK2 antibodies
- Assay development and optimization
- Accessible to the research community

Human Tissue and Samples
- Arizona Brain Bank collaboration – PD and other tissue
- DATATOP (collaboration with PSG) – serum, urine, CSF and DNA
- PPMI and supporting studies – serum, plasma, whole blood, CSF, DNA, RNA and urine

Clinical Trial Tools
- Dyskinesia rating scale
- Cognitive scales
- Fox Trial Finder

Critical tools to accelerate drug development
 EVERY CLINICAL TRIAL NEEDS VOLUNTEERS. 
FOX TRIAL FINDER KNOWS WHICH TRIALS NEED YOU.

80 percent of clinical trial sites challenge finding the volunteers they need. Fox Trial Finder makes it easy to be part of the answer.

WHY ARE CLINICAL TRIALS IMPORTANT?

Clinical trial recruitment is a challenge across all diseases, and Parkinson’s disease is no exception. Thirty percent of all clinical trials fail to recruit a single subject and 65 percent of trials finish late due to recruitment challenges. Despite a willingness to participate, less than 10 percent of PD patients take part in trials. Patients pay the ultimate price for underenrollment in clinical research, as it means longer time horizons to treatment breakthroughs.

With an estimated 1 million people living with Parkinson’s in the U.S. alone, the PD community is poised to take shape to transform their willingness into action — and results. Fox Trial Finder is one solution to help patients and their loved ones get involved in research by making it easier to find trials that are right for them.

JOIN THE 4,303 CLINICAL TRIAL VOLUNTEERS WHO HAVE ALREADY STEPPED UP.

CLINICAL TRIAL RECRUITMENT COMMUNITY PARTNERS

Learn more about a global group of researchers, physicians and community organizations coming together to raise awareness and educate about the important trials. Learn More.

| as of March 21, 2012 |
PPMI funding partners

- PPMI is a $45-50M public-private partnership developed to identify progression markers of PD
- 11 industry partners are contributing to PPMI through financial and in-kind donations