The Brin Wojcicki Challenge: **MAKING PARKINSON’S DISEASE HISTORY**

The Michael J. Fox Foundation for Parkinson’s Research
THE MICHAEL J. FOX FOUNDATION IS DEDICATED TO FINDING A CURE FOR PARKINSON’S DISEASE THROUGH AN AGGRESSIVELY FUNDED RESEARCH AGENDA AND TO ENSURING THE DEVELOPMENT OF IMPROVED THERAPIES FOR THOSE LIVING WITH PARKINSON’S TODAY.
From the earliest days of The Michael J. Fox Foundation for Parkinson’s Research (MJFF), we knew that developing new treatments for Parkinson’s disease (PD) would be challenging. The deeper we’ve gone, the more we have come to understand the nature of that challenge.

Today we view the disease as a series of layered problems. Illuminating the biology of the disease is only part of our work — to shepherd ideas and findings from concept to clinic, we also must expertly navigate the maze of drug development and approval. Each aspect of this puzzle requires its own strategic plan.

We see the roadblocks on our path to finding a cure for Parkinson’s but look past them. We are working ceaselessly to unite the very best minds around the world and create a movement filled with optimism and passion — a movement that will ultimately make finding the cure inevitable.

Changing the Paradigm for Parkinson’s Patients: What We’ve Accomplished So Far

When we launched the Foundation in 2000, nearly every PD therapy on the market or in development focused on replacing lost dopamine — the dominant treatment paradigm for over 40 years, in spite of its inadequacy to meet patients’ medical needs. Due in no small part to MJFF’s risk-taking investments in novel research targets, that status quo has yielded. Today’s Parkinson’s scientists are pursuing avenues undreamed of only a decade ago. Thanks to an increased understanding of PD genetics, researchers are exploring new pathways that target the underlying cause of the disease. Our work is paying off with dozens of new therapies now approaching the clinic — and providing the spark that could bring Big Pharma to the table, and give them something to do when they get there.

We’re working to transform the medical research enterprise and shape a system that fosters, rather than inhibits, the development of cures. We have become a trusted ally and partner to the Parkinson’s research community, speeding financial and intellectual resources to the scientists who can help realize ideas with the greatest promise to impact patients’ lives. We have ignited collaboration among academic and industry players by requiring researchers to share information in real time. We have stepped up to meet scientists’ need for research tools that enable them to move toward breakthroughs faster. We have funded work on over 100 therapeutic targets, and are supporting over 20 clinical trials. Along the way, we have proven not only that a new kind of stakeholder can accelerate drug development — but that it is what was missing all along.

Much has changed in the past decade, but one thing remains constant: our commitment to Parkinson’s patients. Everything we do is with patients in mind, at all stages of PD, which informs our investments in disease-modifying therapies, better symptomatic treatments and new approaches to the symptoms entirely unaddressed by today’s generation of drugs.
The Opportunity to Transform: Our Vision for the Future

Supporters of MJFF believe in the model we’ve built to rapidly, wisely and effectively deploy resources to tackle challenges and jumpstart new opportunities. Among these supporters are Sergey Brin, co-founder of Google, and his wife, Anne Wojcicki, co-founder of personal genetics company 23andMe. Our largest donors for five years running, Sergey and Anne have partnered with us to chart an unprecedented course to develop treatments targeting LRRK2, a Parkinson’s-implicated gene, with possible outcomes for all PD patients.

Obsessed with efficiency, we always strive to do more with less. Yet we also keep a keen eye toward what we could do with greater resources. Meeting the Brin Wojcicki Challenge will expand our ability to streamline and fund targeted research toward breakthrough treatments for Parkinson’s disease. It will allow us to bring our out-of-the-box strategies into critical areas that remain underfunded. It will aid our continuing efforts to drive pre-clinical research, leading groundbreaking public-private partnerships that speed results to patients, and attracting broad expertise to address the unmet needs of the Parkinson’s patient community.

While it is exciting to see Parkinson’s drug development as a whole advancing toward the clinic, this also poses new challenges. As resource-intensive as pre-clinical research is, the clinical projects on the horizon come with exponentially steeper price tags. Our average pre-clinical grant is $250,000; our average clinical grant could start at $1 million. And, as if dollars alone weren’t enough of a hurdle, we must also innovate tools and strategies that can rally the patient community to volunteer for these clinical studies — or all the investment will have been for naught.

In the Brin Wojcicki Challenge, we have a tremendous opportunity to inspire new and current donors, and to transform Parkinson’s research for the benefit of patients — that much sooner. This is a unique moment in our Foundation’s history, and in millions of patients’ futures. We hope you will join us. People with PD can’t wait for a cure; neither can we. The time is now. As always, thank you for being part of the answer.

Sincerely,

Todd Sherer, PhD
CEO

Deborah W. Brooks
Co-Founder and Executive Vice Chairman

About The Brin Wojcicki Challenge

The $50-million Brin Wojcicki Challenge, announced in 2011, aims to increase The Michael J. Fox Foundation’s capacity to speed breakthrough treatments and a cure for Parkinson’s disease. The Challenge, launched by Sergey Brin, co-founder of Google, and his wife, Anne Wojcicki, co-founder of personal genetics company 23andMe, matches all new and increased giving to MJFF, as well as gifts from donors who have not given since 2010 or earlier, on a dollar-for-dollar basis through December 31, 2012.

Become a part of the Challenge by making a contribution at any level! Here’s how your gift will be matched:

New Donors’ Gifts
Entire Gift Will Be Matched. If this is your first contribution to MJFF, your gift will be doubled.

Returning Donors’ Gifts
Entire Gift Will Be Matched. If this is your first gift to MJFF since 2010 or earlier, your entire gift will be matched.

Current Donors’ Increased Gifts
Increase Amount Will Be Matched. If you are a current donor to MJFF and you raise your giving level, the increase over your total giving in 2011 will be matched dollar-for-dollar.

For more information about the Challenge, or to make a gift online, please visit www.michaeljfox.org/challenge.

“This is a unique moment in our Foundation’s history, and in millions of patients’ futures.”
Breaking Down Barriers

“MJFF has the ability to take a broad view, anticipate research needs and develop straightforward and sensible plans to provide all researchers with tools and information needed to accelerate progress. In a few short years, this model has yielded major wins in the ongoing development of LRRK2 and of critical research tools. Future successes, in Parkinson’s disease and beyond, will be based on scaling and replicating this model.”

Jennifer Johnston, PhD, Elan Pharmaceuticals

Strategies in LRRK2 Development

Recent research supports the emerging belief that genetics plays a much greater role in Parkinson’s than was previously thought. Genetic research holds critical potential to help all people living with PD, whether or not they carry mutations linked to the disease. By studying the biological processes underlying genetic forms of Parkinson’s, scientists can elucidate mechanisms that play a role in the more common sporadic form of the disease, opening new avenues for therapeutic development.

With leadership support from the Brin Wojcicki Foundation, The Michael J. Fox Foundation is pioneering a new approach to streamline drug development targeting LRRK2, the single greatest genetic contributor to Parkinson’s disease. The goal is to shed light on the biology of the gene and its underlying role in PD while simultaneously laying the foundation for conclusive clinical trials once drug candidates are found. What sets this approach apart — and what has defined its success — is a four-pronged design that speeds progress toward LRRK2-based treatments by tackling multiple scientific questions and challenges concurrently.

The Foundation is leading a consortium of more than 30 investigators testing critical hypotheses about normal and mutated LRRK2; establishing cohorts of genetic carriers who can help us understand LRRK2 Parkinson’s; spearheading development and distribution of research tools required to effectively study LRRK2; and ensuring that the pharmaceutical industry’s expertise is leveraged in the pursuit of LRRK2-based treatments.

Our coordinated LRRK2 strategy answers the need for a paradigm shift in the traditional approach to drug development, where different research teams study a drug target independently and from discrete angles — often at the expense of collaboration, cost efficiencies and speed. By orchestrating efforts to encourage data- and resource-sharing in real time, MJFF aims to accelerate a practical drug therapy that will benefit everyone living with Parkinson’s.
## MJFF’s LRRK2 Approach Answers the Need for a Paradigm Shift in Drug Development

<table>
<thead>
<tr>
<th>PROJECT</th>
<th>STRATEGY</th>
<th>MJFF INVESTMENT</th>
<th>OUTCOMES</th>
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<tbody>
<tr>
<td>LRRK2 Biology Consortium</td>
<td>Develop collaborative network to test critical hypotheses about LRRK2’s structure and function and identify drug candidates that can modify its activity in the body and brain</td>
<td>Convene group of more than 30 investigator teams; $14.5M invested</td>
<td>Discovery of potential biomarker for LRRK2 function to be used in clinical testing; evidence for new understanding of LRRK2’s role in the immune system potentially linking genetic and environmental causes of PD</td>
</tr>
<tr>
<td>LRRK2 Tools</td>
<td>Provide researchers with critical tools to study LRRK2 biology and pathology</td>
<td>Generate, characterize and distribute tools; $6.7M invested</td>
<td>Development of biological maps and 13 pre-clinical tools to date, distributed over 1,800 times to scientists</td>
</tr>
<tr>
<td>LRRK2 Cohort Consortium</td>
<td>Bring together individuals with LRRK2 mutations to contribute biological samples and undergo clinical assessments to establish a resource for continued study of LRRK2-linked parkinsonism</td>
<td>Facilitate collaboration between 8 cohorts of 3,000 individuals at 20 clinical sites globally; $18.7M invested</td>
<td>Identification of potential early markers of PD (prior to diagnosis) including smell, neuroimaging and gait markers; identification of potential genetic modifiers; possible link between LRRK2 and cancer</td>
</tr>
<tr>
<td>LRRK2 Industry Advisory Group (IAG)</td>
<td>Convene IAG members to discuss how to best create and share resources to speed LRRK2-based drug development</td>
<td>Connect more than 10 industry partners actively engaged in LRRK2 drug development</td>
<td>Quarterly meetings guide investment in tools, clinical trial strategy and ways to accelerate LRRK2 pipeline</td>
</tr>
</tbody>
</table>
Potential Benefit for All

“With cohorts in Tel Aviv, Israel, Tunis, Tunisia, and at 18 other sites worldwide, MJFF’s LRRK2 Cohort Consortium is helping researchers understand the role LRRK2 plays in global populations of people with Parkinson’s disease. This could provide critical new leads for speeding therapies that will benefit everyone with PD — not just those who carry a LRRK2 mutation.”

Susan Bressman, MD, Albert Einstein College of Medicine (left) with Maurizio Facheris, MD, MSc, of MJFF
Your generous support can help MJFF expand its multi-faceted approach to LRRK2, and apply it to other priority areas, for patients’ benefit.

Some opportunities:

- MJFF is expanding partnerships and infrastructure for identifying people with PD-implicated genetic mutations. Larger and more geographically diverse cohorts offer greater opportunity to link clinical features of PD to underlying biological and genetic processes. This will help provide a basis for the design of future clinical trials.

- Expanding these cohorts to include more family members of patients would allow researchers to study asymptomatic people with LRRK2 mutations who may later develop PD, an unprecedented opportunity to see disease in its earliest stages. This is critical to earlier diagnosis and treatment strategies tied to stages of disease progression.

- To greater leverage MJFF-owned LRRK2 pre-clinical models, funding streams can be earmarked for promising research using these resources.

- LRRK2 imaging agents allow scientists to visualize the presence of genetic mutations and their interactions with potential drugs in the living brain. With further development these agents will enable swifter and more effective evaluation of LRRK2-based treatments for Parkinson’s disease.

- MJFF can apply its multi-pronged approach, a game-changer in LRRK2, to other top priority areas, such as alpha-synuclein.
Research Tools — Practical Solutions to Speed Progress

Laboratory tools are required to develop and test potential drugs. Too often, these tools are prohibitively expensive or altogether unavailable to the research community at large — which forces scientists to either do without or devote time to creating their own — thus slowing progress for all.

Stepping into this void, The Michael J. Fox Foundation has forged new paths for developing critical research tools and distributing them at low or no cost to academic and industry researchers. These include pre-clinical models and basic laboratory reagents (such as antibodies, viruses and cell lines) that allow scientists to efficiently study cellular functions at work in Parkinson’s pathology and test new treatment approaches.

The Foundation’s successful initiative to generate high-quality LRRK2 antibodies (molecular “ingredients” that allow researchers to look at LRRK2 proteins in cells, tissues and brain regions) served as a case study for the journal *BioTechniques* in out-of-the-box thinking that led to vastly increased scientific opportunity in an emerging field. Our common-sense approach to generating and distributing high-quality pre-clinical models has similarly solved a longstanding problem for the Parkinson’s research community.

Today, seven MJFF-owned pre-clinical models are available at low or no cost to researchers who need them for promising PD drug development studies — and this number will more than double by May 2013.

In addition to an absence of key tools in the laboratory, certain tools are missing in the clinic. Alongside its groundbreaking achievements in reagents and models, MJFF is playing a vital role in the development of clinical scales to effectively test treatments for dyskinesia and cognitive impairment, among the greatest unmet medical needs for Parkinson’s patients. Because researchers currently lack a unified system of measuring either symptom, they are unable to accurately evaluate progression or improvement in these areas, which slows the delivery of new treatments.

Together, these tools and scales form the necessary building blocks that will yield results in the lab and the clinic — and ultimately, for patients.

### MJFF Has Forged New Paths for Developing and Distributing Necessary Tools for Researchers

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>STRATEGY</th>
<th>MJFF INVESTMENT</th>
<th>OUTCOMES</th>
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<tbody>
<tr>
<td>Pre-clinical models and reagents are expensive or inaccessible; researchers spend valuable time developing these tools instead of developing new treatments</td>
<td>Develop, characterize and distribute models and reagents at little or no cost to researchers</td>
<td>$8M for development of pre-clinical models and $2.5M for development of reagents to date</td>
<td>Seven pre-clinical models currently available, and 17 more to be made available to the research community by May 2013; 10 antibodies currently available and 20 antibodies to be made available by the end of 2012; combined models and antibodies distributed over 2,400 times to scientists</td>
</tr>
<tr>
<td>No unified way of measuring cognitive symptoms and dyskinesia in PD; establishing such scales will allow future treatments to be evaluated more effectively</td>
<td>Fund and support cognitive and dyskinesia scales trials</td>
<td>$1.5M for cognitive scales clinical trial and $1M for dyskinesia scales trial</td>
<td>Cognition clinical trial expected to begin in 2012; final enrollment of subjects for dyskinesia clinical trial completed in 2011, with results expected this year — which will inform design of dyskinesia trials waiting to begin</td>
</tr>
</tbody>
</table>
Your generous support can help MJFF expand its portfolio of critical research tools and keep researchers focused on developing new treatments. Some opportunities:

- Based on the success of its LRRK2 antibodies effort and feedback from the research community on the pressing need, MJFF is creating additional antibodies against proteins implicated in PD. The Foundation is also launching a new effort to develop viral vectors and cell lines specific to alpha-synuclein and LRRK2 — critical tools that enable investigators to better understand the biological function of these proteins, leading to new therapeutic approaches.

- With greater resources, the Foundation could create funding streams to specifically encourage novel studies leveraging MJFF-driven tools.

- The explosion of Big Data is touching all aspects of scientific discovery. With increased capacity for data collection and analysis, MJFF will continue leading the field in identifying the most effective tools quickly as well as highlighting areas of emerging need.

- Standardization across multiple labs remains challenging. The Foundation is investigating how best to establish a standardized process for testing new drugs in MJFF-developed models so that results of studies conducted by different teams can be efficiently and reliably compared.

- Establishment of scales for cognitive symptoms of PD and dyskinesia will help MJFF and other sponsors inform trial design and patient selection strategies.

“Funding organizations that focus on other diseases can and should mirror the Fox Foundation’s direct and involved approach in generating critical research tools. I would really like to see this being done on a very large scale — more of the same, and in the public domain as much as possible, that’s the next step.”

Mark Cookson, PhD, National Institute on Aging
Championing Creative Solutions for Patients

MJFF shares patients’ sense of urgency about the need for improved treatments for Parkinson’s disease. The Foundation takes no intellectual property or royalty position on its investments; the only return on investment we care about is potential to produce therapies that will make a meaningful difference in the lives of people with PD.

Our determination to meet patients’ needs first and foremost compels us to explore less conventional paths to accelerate the development of new PD treatments. For example, MJFF funds research to develop promising therapies based on non-patentable compounds, such as inosine, which traditional drugmakers are not incentivized to pursue, and non-drug interventions, such as exercise, which often lack champions as they don’t lead to a sellable product.

Research sometimes reveals that a medication approved for a condition unrelated to Parkinson’s disease, such as depression and high blood pressure, may have unexpected benefits for PD patients. We avidly pursue such leads, known in the field as “repositioning” an existing therapy. Why? Because these drugs have already been proven safe in large populations, we can shave years off the time it takes to push these treatments to the clinic. Pursuit of these creative, out-of-the-box approaches moves us toward our goal of eradicating PD as quickly and expeditiously as possible.

MJFF Funds Non-traditional Therapies to Address Patients’ Unmet Needs

<table>
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<tr>
<th>PATIENTS’ UNMET NEED</th>
<th>THERAPY</th>
<th>MJFF INVESTMENT</th>
<th>OUTCOMES</th>
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</thead>
<tbody>
<tr>
<td>Treat PD-related fatigue</td>
<td>Acupuncture</td>
<td>$477K to fund clinical study led by Benzi Kluger, MD, MS, to test effects of acupuncture on fatigue in patients</td>
<td>Study recruiting up to 100 PD patients, who will receive acupuncture treatment or a placebo</td>
</tr>
<tr>
<td>Treat dysphagia (difficulty swallowing)</td>
<td>Strength training</td>
<td>$277K to fund clinical study led by Christine Sapienza, PhD, with PD patients to determine if strength training improves swallow function</td>
<td>Strength training successful; ongoing work to leverage finding as practical treatment option</td>
</tr>
<tr>
<td>Overall symptomatic improvement</td>
<td>Exercise</td>
<td>$750K to fund clinical study to test effectiveness of treadmill training and stretching and resistance exercise to improve gait-related impairment, led by Lisa Shulman, MD, and Richard Macko, MD $840K to fund ParkFit clinical trial with unique program to promote physical activity among patients and assess health benefits, led by Bastiaan R. Bloem, MD, PhD, and Marten Munneke, PhD</td>
<td>Treadmill study showed different types of exercise can improve gait ParkFit’s initial results identified interventions that could increase patients’ physical activity levels</td>
</tr>
</tbody>
</table>
A Life-changing Gift

“My wife Felicia and I admire MJFF’s strategic approach to funding research and their collaboration with drug companies to speed new treatments to patients. We decided to double our intended contribution to MJFF. When we heard that the Brin Wojcicki Challenge would double our gift again, we knew we’d made the right decision at the right time.”

Patient Council member, Challenge donor and Fox Trial Finder volunteer Christopher Chadbourne (left) with MJFF-funded researcher Clemens Scherzer, MD, of Harvard Medical School/Brigham and Women’s Hospital
### MJFF Avidly Pursues Repositioning Leads

<table>
<thead>
<tr>
<th>PATIENTS’ UNMET NEED</th>
<th>THERAPY</th>
<th>ORIGINAL USE</th>
<th>MJFF INVESTMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow or halt disease progression</td>
<td>Isradipine (Dynacirc)</td>
<td>Hypertension</td>
<td>$75K to fund pre-clinical work of D. James Surmeier, PhD, followed by $2.1M to fund a Phase II trial, led by Tanya Simuni, MD; resulting data informed application to NIH for Phase III trial</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Duloxetine (Cymbalta)</td>
<td>Depression</td>
<td>$225K award to Ole Isacson, MD, and Penelope Hallett, PhD, to test Cymbalta as neuroprotective treatment in pre-clinical models</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Nicotine skin patch</td>
<td>Smoking cessation</td>
<td>$1M to fund a clinical trial (NIC-PD) evaluating the potential of a nicotine patch to slow PD progression in newly diagnosed patients; led by Wolfgang H. Oertel, MD, Karl Kieburtz, MD, MPH, and Marcus M. Unger, MD</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Inosine</td>
<td>Fitness supplement</td>
<td>$250K to fund pre-clinical work, followed by $5.6M to fund Phase II trial in newly diagnosed patients to test if inosine slows disease progression; led by Michael A. Schwarzschild, MD, PhD, Alberto Ascherio, MD, DrPH, and Karl Kieburtz, MD, MPH</td>
</tr>
<tr>
<td>Reduce dyskinesia</td>
<td>Citalopram (Celexa) and Paroxetine (Paxil) (SSRIs)</td>
<td>Depression</td>
<td>$249K to fund pre-clinical work of Christopher Bishop, PhD, assessing the capability of SSRIs to treat dyskinesia</td>
</tr>
<tr>
<td>Reduce dyskinesia</td>
<td>Nalbuphine</td>
<td>Pain</td>
<td>$275K to fund pre-clinical work of M. Maral Mouradian, MD, and Stella Papa, MD, to determine if nalbuphine represses dyskinesia</td>
</tr>
<tr>
<td>Treat sialorrhea (uncontrolled drooling)</td>
<td>NH004 Films</td>
<td>Pupil dilation</td>
<td>$500K for clinical trial led by Elkan Gamzu, PhD, to test if NH004 Films provide relief to PD patients with sialorrhea</td>
</tr>
</tbody>
</table>
Championing Solutions

Q MJFF has expanded its Repositioning Drugs for PD program into an annually recurring funding stream. Allocating greater resources to this initiative would allow the Foundation to reach greater numbers of multidisciplinary scientists who may not have considered the potential Parkinson’s applicability of their compounds in development.

Q In 2012, MJFF anticipates launching its first partnership with a major pharmaceutical company to resuscitate a shelved compound for clinical testing in Parkinson’s patients. Enhanced resources would allow us to leverage the credibility we have built with industry to take on additional such trials and bring potential breakthroughs back into development for patients’ benefit.

We’re grateful to The Michael J. Fox Foundation for enabling our work on the ParkFit study, which is focused on optimizing Parkinson’s patients’ quality of life and ability to contribute to society and family, rather than what they cannot do anymore. We’ve already shown that the right kind of intervention can significantly increase PD patients’ level of activity, and we’re excited to study the health benefits of this change in lifestyle in the second part of the trial.”

Bastiaan R. Bloem, MD, PhD, Radboud University Nijmegen Medical Centre, Netherlands

Your generous support can help MJFF expand its efforts to champion creative solutions to address patients’ unmet needs.

Some opportunities:

■ MJFF has expanded its Repositioning Drugs for PD program into an annually recurring funding stream. Allocating greater resources to this initiative would allow the Foundation to reach greater numbers of multidisciplinary scientists who may not have considered the potential Parkinson’s applicability of their compounds in development.

■ In 2012, MJFF anticipates launching its first partnership with a major pharmaceutical company to resuscitate a shelved compound for clinical testing in Parkinson’s patients. Enhanced resources would allow us to leverage the credibility we have built with industry to take on additional such trials and bring potential breakthroughs back into development for patients’ benefit.

■ The Foundation holds a vision of singlehandedly sponsoring multiple clinical trials of non-patentable compounds (where traditional funders are not incentivized to invest) to assess benefit in PD — something we aren’t realistically positioned to do today.

■ Because MJFF sees the business challenges that prevent pharmaceutical and biotech companies from investing in opportunities, it is imperative that we continue and expand our contributions to policy incentives that drive industry innovation and investment in the face of potentially limited or minimal financial return.
Seizing the Risk

“MJFF is widely recognized as the model for how patient-driven research should be conducted and fostered.”

Anders Björklund, MD, PhD, Lund University

Great leaps forward toward treatment breakthroughs require taking risks on novel approaches and discoveries. The current medical research enterprise, however, rewards incremental advances and prioritizes funding for well-trodden ideas.

At MJFF, our definition of success is the same as patients’ — improved treatments and a cure — so our assessment of risk is different from that of government or industry funders. We have made a substantial investment in high-risk/high-reward targets, and have provided funding for more than 100 novel targets. We believe it is our responsibility to step in where other funders can’t or won’t — when little to no preliminary data exists, the probability of payoff is unknown, and the investment stakes are high.

MJFF also takes calculated risks in our relentless pursuit of translational science. We collaborate with scientists to convert molecular advances into real therapeutic opportunities — an area of research that requires targeted funding and proactive management. To date, MJFF’s Target Validation program has funded over 75 grants totaling more than $15 million. We support the most promising work to keep it moving toward clinical testing; we push for definitive answers where an approach is not looking successful, in order to divert funds to greener pastures as quickly as possible.

We possess the vision, the determination and the scientific expertise to seize risk and act on opportunity. For MJFF, the potential to improve the lives of those with Parkinson’s is worth the risk of investing in a promising new idea.
Taking Flight for a Cure

“I heard Michael J. Fox explain once that he considered his Parkinson’s to be a ‘gift,’ but as he put it, ‘a gift that keeps on taking.’ I had enjoyed the experience of being a private pilot for 20 years. When I realized that my Parkinson’s was going to take that ability from me, I decided to follow Michael’s lead and turn that event into something positive. When I learned about the Brin Wojcicki Challenge I decided to sell my airplane and donate the proceeds to be matched by the Challenge. Through the incredible generosity of Sergey and Anne, more than $3 million from this single contribution was put toward the fight against Parkinson’s disease. It is truly incredible.”

MJFF Board member and Challenge donor Sonny Whelen (left) with Kim Barry of Civitas Therapeutics, an MJFF-funded biotech
**MJFF Has Made a Substantial Investment in High-Risk/High-Reward Targets**

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<th>PATIENTS’ UNMET NEED</th>
<th>TARGET</th>
<th>HIGH-RISK MJFF INVESTMENT</th>
<th>EARLY SUCCESS PROMPTS ADDITIONAL MJFF INVESTMENT</th>
<th>OUTCOMES</th>
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<tbody>
<tr>
<td>Symptomatic treatment</td>
<td>mGluR4 (glutamate receptor)</td>
<td>$250K award to Jeff Conn, PhD, to identify new class of drug targets that bypass dopamine replacement altogether</td>
<td>$4.7M</td>
<td>New drug candidate identified, could enter clinic as soon as 2013</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>GDNF (trophic factor)</td>
<td>$75K award to Barbara Waszczak, PhD, to test novel nasal delivery of GDNF, a potential therapy in which brain delivery has not been optimized</td>
<td>$563K</td>
<td>Method delivers GDNF to brain and protects dopamine neurons in pre-clinical models</td>
</tr>
<tr>
<td>Reduce dyskinesia</td>
<td>Serotonin (neurotransmitter known for role in depression)</td>
<td>$150K award to Anders Björklund, MD, PhD, for assessment of role of serotonin receptors in dyskinesia</td>
<td>$884K</td>
<td>Success in pre-clinical models leads to 24-patient clinical trial</td>
</tr>
<tr>
<td>Reduce dyskinesia</td>
<td>mGluR5 (glutamate receptor)</td>
<td>$173K to M. Angela Cenci-Nilsson, MD, PhD, to test new theory that blocking mGluR5 receptors could prevent dyskinesia</td>
<td>$250K</td>
<td>Two active clinical programs (Novartis and MJFF-funded Addex) testing mGluR5 drugs for dyskinesia in PD patients</td>
</tr>
<tr>
<td>Reduce dyskinesia</td>
<td>Mu-opioid receptors (receptors in brain and spinal cord known to regulate pain)</td>
<td>$265K to Adolor Corporation to identify compounds that block mu-opioid receptors — a new approach to treating dyskinesia</td>
<td>$363K</td>
<td>New class of drug identified and now testing best candidates in pre-clinical models</td>
</tr>
</tbody>
</table>
Seizing the Risk

Your generous support can help MJFF to expand its efforts to take risks with patients in mind.

Some opportunities:

- To allow for increased exploration of more novel biology, MJFF is stepping up its investment in early-stage therapies.

- The Foundation is expanding early translational programs to facilitate more rapid conversion to therapeutic molecules, and ultimately into patients’ hands.

- As new discoveries emerge, MJFF applies its streamlined process to compare and prioritize these developments — helping to determine in which ones to invest.

- The Foundation continues its ongoing investment in promising therapies across its broad portfolio as they move closer to the clinic.

“Although there is significant risk that our approach might not work, there is also incredible potential if it does.”

Barbara Waszczak, PhD, Northeastern University
Catalyzing Investment in Parkinson’s Drug Development

“The neuroscience pharmaceuticals sector faces some major challenges at the moment. External partnerships between academia and industry are vital to address fundamental issues in this area, and the network and support that The Michael J. Fox Foundation provides is helping to keep PD-related drug discovery efforts moving forward.”

Alastair Reith, PhD, GlaxoSmithKline

A key aspect of the Foundation’s strategy is to catalyze PD research by placing bets on ideas and therapies that face scientific or business obstacles. By funding research to overcome these obstacles, MJFF aims to make PD a more attractive investment to pharmaceutical companies and follow-on funders alike.

MJFF deploys financial and scientific resources at every stage of the PD therapeutic development pipeline. We share the risk of investment in promising drug targets, funding work that builds the case to advance them toward the clinic. Our on-staff PhDs and business-trained project managers work closely with both industry and academic research teams to generate and support ideas with the greatest promise to speed potential treatments toward pharmacy shelves.

The Foundation goes well beyond investing dollars, building and supporting teams and consortia with the specific expertise required to keep high-impact research moving. Serving as an information broker, we share the best information about the best ideas for new drugs in PD to better position the field for investment. Each year our staff, supported by an extensive network of scientific advisors, reviews up to 900 grant proposals; talks formally and informally with hundreds of the world’s top PD experts; and convenes dozens of conferences, meetings and workshops. By combining scientific expertise with a comprehensive view of the field, the Foundation facilitates key introductions and fosters critical collaborations to move the dial on new treatments.

Today we can say with confidence that the model we have built is speeding progress. Numerous Foundation awardees have scored follow-on funding deals with Big Pharma and venture capital firms; others have garnered major investment from government funding agencies at the state or federal level. With your help, we can continue to identify and invest in collaborations that better our chances at finding new therapies to improve the lives of those living with PD today and in the future.
“Going into a five-year study, it was important for me to get a good feeling about the PPMI staff who would be working with me. It became clear very quickly how much they cared about me and my well-being.”

Parkinson’s Progression Markers Initiative (PPMI) participant Denise Dvorak (right) with Ole Isacson, MD, an MJFF-funded researcher at McLean Hospital, Harvard Medical School
## Early MJFF Investment Leads to Follow-on Funding

<table>
<thead>
<tr>
<th>PATIENTS’ UNMET NEED</th>
<th>TARGET/PROJECT</th>
<th>MJFF INVESTMENT</th>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow or halt disease progression</td>
<td>Trophic Factors</td>
<td>$1.6M for Ceregene’s Phase II clinical study</td>
<td>$28.1M in venture capital investment</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Alpha-Synuclein</td>
<td>$1.5M to AFFiRiS for the first-ever clinical trial testing a Parkinson’s vaccine</td>
<td>€30M venture capital investment to advance work on PD and Alzheimer’s vaccines</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Alpha-Synuclein</td>
<td>$300K to reMYND to fund pre-clinical work</td>
<td>Up to $637M deal with Roche to advance four drugs in PD (including MJFF-funded one) and Alzheimer’s</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Alpha-Synuclein</td>
<td>Nearly $300K for Signum Biosciences’ new compound targeting alpha-synuclein</td>
<td>Follow-on deal with GSK to advance drug toward clinic</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Alpha-Synuclein</td>
<td>$3.1M to Proteotech for pre-clinical work on compound to reduce alpha-synuclein</td>
<td>Follow-on deal with GSK to advance drug toward clinic</td>
</tr>
<tr>
<td>Slow or halt disease progression</td>
<td>Pioglitazone</td>
<td>Shepherded repositioned diabetes drug from pre-clinical stage to early clinical studies; partners include University of Wisconsin and Parkinson Study Group</td>
<td>Along with MJFF support, NIH funding clinical trial to test drug potential as disease-modifying</td>
</tr>
<tr>
<td>Reduce dyskinesia</td>
<td>mGluR5</td>
<td>$2.4M to chaperone target from pre-clinical stage to Phase II clinical trial; partners include Lund University, University of Bordeaux, Institute for Neurodegenerative Disorders and Addex Pharmaceuticals</td>
<td>mGluR5 in clinic at Novartis; Phase II clinical trial under way at Addex Pharmaceuticals</td>
</tr>
<tr>
<td>Understand cause of PD and its progression</td>
<td>Arizona Parkinson’s Disease Consortium (APDC)</td>
<td>Over $5M to Banner Sun Health Research Institute for brain/body donation program to build comprehensive data resource</td>
<td>$8M funding from NIH; MJFF funding available for research leveraging APDC samples/data</td>
</tr>
</tbody>
</table>
Your generous support now can help to catalyze future investment in PD research.

New therapies in development typically have low success rates. By continuing to de-risk novel targets, MJFF can seed the pipeline and improve clinical research infrastructure, making investment more attractive for Big Pharma and other late-stage funders. With your help we can:

Seed The Pipeline
- Increase funding allocation to new ideas and new drug development programs.
- Expand projects in which MJFF makes a greater investment and takes larger risk on initiatives that bring together all-star research teams.
- Expand our Partnering Program, a pilot initiative for formally connecting MJFF awardees and industry to foster potential collaborations.
- Add a second annual PD Therapeutics Conference in a different location, providing more academic and industry scientists the opportunity to learn of MJFF-funded advances ripe for follow-on funding toward the development of improved therapies for PD.

Create expanded role for industry via establishment of new advisory groups, meetings and partnerships.

Adopt “virtual biotech” model in which MJFF directs, manages and monitors applied drug development research conducted by contract research organizations.

Improve Clinical Research
- Expand Fox Trial Finder, the Foundation’s Web-based tool to connect willing volunteers with the clinical trials that need them, into Western Europe.
- Expand MJFF-led infrastructure for strategic clinical research management, network and support to maximize opportunities for cost and workflow efficiencies.
- Leverage knowledge gained from PPMI, MJFF’s comprehensive biomarker study.
Charting a New Course

“...MJFF recognized early on the need for a biomarker for Parkinson’s disease, a critical and missing tool in the development of disease-modifying treatments. Reliable and consistent biomarkers for PD would allow scientists to predict, objectively diagnose and monitor the disease, and to determine which medications work and which do not.

But an effort of this magnitude would require MJFF to chart an entirely new course — stepping in to take the lead where no one else would.

In 2010, MJFF launched the Parkinson’s Progression Markers Initiative (PPMI), a landmark five-year clinical study to establish a comprehensive set of clinical, imaging and biological data that would define biomarkers of PD progression. To make PPMI a reality, in addition to committing up to $45 million, the Foundation brought together a who’s-who of Parkinson’s leadership from both academia and industry to conceive, spearhead and fund the study. As the sponsor of PPMI, the Foundation also holds ultimate responsibility for raising awareness of the study and ensuring that its ambitious enrollment goals are met. It is an unprecedented role for a private research funder.

In under two years, PPMI has recruited more than half of the 600 participants required, and this year the study will expand to 24 sites around the globe. The study’s open-source model means that well-characterized biosamples and robust clinical data are available to the research community in real time — to speed biomarker validation studies and bring therapeutic breakthroughs closer. Almost 10,000 data downloads have been made and shared by scientists across the world, all of whom now have access to PPMI’s repository of PD data and biological samples — the largest collected to date. Bringing together the research community at large with a groundbreaking data-driven scientific resource, PPMI is driving progress toward biomarker discovery with the end goal of finding better treatments and a cure for PD.

“The role of The Michael J. Fox Foundation in conceiving PPMI and shaping its course has been extremely innovative... It’s truly impressive how the Foundation has brought the community together on this study and Pfizer is proud to be part of it.”

Tom Comery, PhD, Pfizer Neuroscience
Making PPMI a Reality

“The role that MJFF plays in the PD community is unique — they have brought together divergent groups to collaborate on a large-scale study to find a biomarker for the disease. Without the Foundation’s foresight, resources, intellectual capital and convening presence, PPMI would never have gotten off the ground.”

Kenneth Marek, MD, Institute for Neurodegenerative Disorders, Principal Investigator of PPMI (left) with MJFF Patient Council member Steven D. DeWitte
**MJFF’s Role as the Sponsor of PPMI Is Unprecedented for a Private Research Funder**

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>MJFF INVESTMENT</th>
<th>PARTNERS</th>
<th>OUTCOMES</th>
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<tbody>
<tr>
<td>There is a critical need for PD biomarkers to objectively measure disease progression, toward the development of disease-modifying therapies — the most significant unmet need</td>
<td>From 2002–2011, MJFF invests $38 million in biomarkers, and in 2010 launches PPMI, a landmark $45-million, five-year study of 600 participants across 24 sites worldwide, establishing open-source access to data and well-characterized biosamples for the PD research community at large</td>
<td>Ten industry partners, a who’s-who of Parkinson’s research, are contributing to PPMI through financial and in-kind donations and are playing a lead role in providing feedback on study parameters; through close interaction with study leaders, they inform the selection and review of potential progression markers that could make the greatest impact on PD clinical trials</td>
<td>Almost 10,000 downloads of data 24 sites and 300+ participants enrolled Industry/academia collaboration Open-source model speeds new studies from early results Infrastructure created to develop crucial tool</td>
</tr>
</tbody>
</table>
Your generous support can help to catalyze future investment in PPMI.

Some opportunities:

- In 2012, MJFF is adding a cohort of individuals who are at-risk for PD, either genetically or clinically, to compare their data alongside that of PPMI participants who have PD. The goal is to be able to identify the disease at an earlier stage — and to ultimately prevent it.

- To build on new and encouraging results, MJFF may extend the timeline of PPMI beyond the initial five years.

- The Foundation is creating specific funding streams to enable future work that efficiently analyzes and optimizes PPMI data.

- MJFF is leading the development and distribution of lab tests that scientists can use to further their work to identify biomarkers.

“... My participation in PPMI means a lot to me, because I want to do what I can to help in the fight against this disease. I can be a proactive part of the solution. I don’t want to be defined by PD, I want to help define it."

Jon Surine, PPMI participant
The Answer’s in All of Us

“My husband and I were impressed with the passion and expertise of the scientists working with MJFF, and the level of research that’s being done. We were relieved to know that someone is on this, and is devoted to finding a cure. It inspired us to step up for the Brin Wojcicki Challenge.”

Claudia Revilla, Fox Trial Finder Volunteer, Challenge Donor

The Michael J. Fox Foundation has developed a strategic roadmap to orchestrate and streamline Parkinson’s therapeutic development, providing both financial and intellectual leadership that has galvanized the scientific field and moved us tangibly closer to definitive clinical trials and breakthrough treatments.

This is exciting. Yet even out of solutions arise new challenges for our problem-solving. We are committed to meeting each obstacle head-on with the same dedication and fresh, collaborative platforms designed to inspire the Parkinson’s community — and the general public — to act in greater numbers than ever. We are eager to help like-minded people join with us in our mission, which enables us to grow stronger.

Underenrollment in clinical research, by people with and without Parkinson’s, slows research progress — and patients pay the price in terms of higher costs and longer time horizons to treatment breakthroughs. The Foundation has stepped up to answer this challenge with the development of a next-generation Web tool, Fox Trial Finder, a user-friendly solution to connect willing volunteers with the specific trials that need them. So far thousands have raised their hands to participate, but more are needed.

Our grassroots fundraising network, Team Fox, has grown dramatically since its founding in 2006. With more than $15 million raised, this group remains the collective voice for our message of can-do optimism and action across the country and around the world — and its numbers continue to increase.

Helping to guide our progress is our 20-member Patient Council, which advises MJFF on a range of programmatic fronts. We bring MJFF’s knowledge and expertise directly to patients and families and engage with them through educational offerings such as Research Roundtables, a Seminar Call Series and support group presentations.

We’re also leveraging the growing sense of community among patients in the digital realm, with more than 100,000 Facebook fans, 10,000 Twitter followers, a podcast series and a Foundation blog.
“At first I thought he was nuts,” says Lucy Fox (no relation to Michael J. Fox), recalling the day her son, Sam, informed her of his plan to run the 2,650-mile Pacific Crest Trail in two months — averaging 43 miles a day — to raise money for Team Fox. “Now I’m tremendously proud.” Sam (pictured opposite page, left, with Brian Fiske, PhD, of MJFF), completed the run and raised $150,000, which was doubled by the Brin Wojcicki Challenge. His inspiration: Lucy’s grace and fortitude in the face of Parkinson’s disease. “On the trail, I thought about my mother and what she goes through,” he says. “She lives with the symptoms of Parkinson’s every day with a smile and with strength — I tried to emulate that.” He has since joined the Foundation’s staff as Outreach and Engagement Officer, helping inspire others to get involved to speed a cure.

Lucy Fox (left) with MJFF-funded researcher Sarah Coon
### MJFF Is Eager to Help Like-minded People Join Us in our Mission to Eradicate Parkinson’s Disease

<table>
<thead>
<tr>
<th>OPPORTUNITY</th>
<th>STRATEGY</th>
<th>MJFF INVESTMENT</th>
<th>OUTCOMES</th>
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</thead>
<tbody>
<tr>
<td>People want to raise dollars and awareness in their communities</td>
<td>Provide guidance, peer-to-peer support, and branding tools to maximize individuals’ efforts to speed a cure</td>
<td>Team Fox, MJFF's grassroots fundraising arm, launches in 2006</td>
<td>1,500 active Team Fox members</td>
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<td>Over $15 million raised to date</td>
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<td>In 2011, over 1,200 Team Fox events</td>
</tr>
<tr>
<td>Patients want to step up to speed research progress, but aren’t sure how to help</td>
<td>Educate PD community on need to participate and make it easy to act on intention</td>
<td>Fox Trial Finder launches in 2011 to connect willing volunteers with the trials that need them</td>
<td>3,000+ volunteers registered</td>
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<td></td>
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<td>140+ trial team members registered</td>
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<td></td>
<td></td>
<td></td>
<td>180+ trials recruiting</td>
</tr>
<tr>
<td>Patients want to hear from MJFF on state of science and research progress</td>
<td>Connect patients with experts on current research most critical to speeding treatment breakthroughs</td>
<td>Research Roundtable Series Seminar Call Series on Hot Topics in PD Support Group Engagement</td>
<td>44 Research Roundtables</td>
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<td></td>
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<td>10 Hot Topics Calls</td>
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<td></td>
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<td>35 support group presentations in 2011</td>
</tr>
<tr>
<td>Patients need real-time analysis and unbiased interpretation of breaking research news</td>
<td>Disseminate MJFF’s expert perspective on breaking research news across digital channels</td>
<td>Podcast series Social media engagement News in Context Q&amp;A series MJFF Blog</td>
<td>Over 30 podcasts 100,000+ Facebook fans 10,000+ Twitter followers 30+ News in Context Q&amp;As</td>
</tr>
<tr>
<td>Strategic direction must be informed by PD patients’ voice and experience</td>
<td>Establish formal channel for patients to provide input to MJFF</td>
<td>Patient Council launches in 2009 and expands in 2012 to advise MJFF on programmatic fronts</td>
<td>Critical insights into program direction, research participation strategy, and prioritization of educational messages to patients, caregivers and physicians</td>
</tr>
</tbody>
</table>

In September 2011, Nike announced the limited-edition release of the 2011 Nike MAG sneakers to benefit MJFF. An exact replica of the *Back to the Future II* shoes worn by Michael J. Fox as Marty McFly, 1,500 pairs were auctioned on eBay over 10 days, with net proceeds totaling over $4.7 million — doubled to more than $9.4 million through the Brin Wojcicki Challenge. “We wanted to translate the excitement people have for the ‘greatest shoe never made’ and for *Back to the Future* into positive action,” said Mark Parker, Nike CEO. “But the long-term objective is to raise awareness to help the Foundation achieve their goal of eradicating Parkinson’s disease.”
Your generous support can help MJFF to expand its efforts to engage the PD community, as everyone is a part of the solution on the road to better treatments — and a cure. Some opportunities:

■ MJFF is expanding Fox Trial Finder to the U.K., Australia and Canada this year, followed by Western Europe.

■ The Foundation continues to grow its Research Roundtable Series, by bringing it to additional cities in the U.S. and abroad.

■ In 2012, MJFF is connecting the PD community more frequently with leading experts in the field. The Quarterly Hot Topics calls have been relaunched as a Seminar Call Series on Hot Topics in PD, which will be hosted monthly.

■ MJFF is expanding its podcast series, which provides patients and their loved ones with insight on relevant and timely news in PD research.

■ The Foundation is widening its interaction with support groups around the country and beyond, through presentations and participation in local events.

■ MJFF recognizes the need to increase its programmatic education to the physician community, which has direct implications for the patients they treat.

■ The importance of seeking specialist care cannot be overemphasized and is a critical educational message the Foundation brings to patients.

■ MJFF shares its can-do optimism by building awareness about the therapeutic benefits of active engagement — for patients and their loved ones.

■ With the goal of enabling patients and their loved ones to make strategic choices about how to get involved in the quest for a cure, the Foundation is dedicated to helping more patients access credible and authoritative information to de-mystify Parkinson’s biology and drug development.
Dear Friend,

It’s a rare day that passes for me without a reminder of the incredible commitment and radical generosity we at the Foundation have been so fortunate to attract to our cause. The Brin Wojcicki Challenge is a truly awe-inspiring example. I’m immensely grateful for the dedication of our friends and supporters — Sergey and Anne who had the vision to launch this Challenge, and you who are helping us meet it.

Because above all, the Brin Wojcicki Challenge recognizes that making Parkinson’s a thing of the past requires all of us, working together. No matter how you choose to get involved, you are central to our success.

We stand at an inflection point on our journey to the cure. I celebrate how far we’ve already come, dream big about what the future still holds, and pay tribute to you whose commitment makes everything possible.

With gratitude,

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Inset photos, left to right:
Sonny Whelen, MJFF Board member and Challenge donor
Lucy Fox, mother of Team Fox member
Steven D. DeWitte, Patient Council member
Denise Dvorak,* PPMI participant
Christopher Chadbourne, Patient Council member, Challenge donor and Fox Trial Finder volunteer

For more information on each individual pictured above, visit www.michaeljfox.org/challenge
Photos by Sam Ogden

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Elena Olivo

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