THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Progress

ANNUAL REPORT 2008

“The Michael J. Fox Foundation has managed to become, in its short life, the most credible voice on Parkinson’s research in the world.”

— *The New York Times*

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.

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON’S RESEARCH

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ANNUAL REPORT 2008

LETTER FROM THE CEO, FOUNDER AND CO-FOUNDER

The Michael J. Fox Foundation has set one clear and simple measure of success: accelerating the delivery of life-changing treatments — and ultimately, a cure — to people with Parkinson's disease.

In 2008 we funded $32.8 million in Parkinson's research, bringing our total investments since inception to over $140 million. But in our short history we have come to appreciate that ending Parkinson's disease is not only about spending more money, it is about how we spend it. MJFF targets underfunded, high-risk, translational science, stepping in where government and industry players can't or won't, to drive PD therapies and address what's broken in the broader medical research enterprise.

Our singular focus on developing new therapies requires a strategic approach. We review more Parkinson's-specific grant proposals than any other private funder (nearly 800 in 2008), covering every phase of drug discovery and development through clinical studies. We strive to identify the most compelling ideas, then shepherd them through the vagaries of the therapeutic development process and toward the clinic. For most diseases, this purposeful view of how to drive research progress is absent. No one stakeholder exists to align the efforts of disparate players. No one is in charge of finding cures.

At MJFF, we're shooting for nothing less than the cure for Parkinson's. Our leadership, drawn from the worlds of both science and business, works tirelessly to increase impact by blending the best of those two worldviews. We proactively manage the largest PD portfolio in the world. We prioritize key studies, insist that researchers share their results early, and tee up academic/industry partnerships. We keep the most promising ideas on a strategic course forward. Our eye is on patients' needs, clinical studies and better treatments.

The researchers we work with around the globe quickly come to appreciate how we streamline the research process by challenging them to overcome the "language barrier" common among biologists working in different disciplines — even if they study the same disease. Scientists will tell you that we are bridgers and connectors, bringing together highly specialized researchers and clinicians who might not otherwise interact, let alone collaborate. In 2008 alone, we brought together more than 460 of them for meetings and workshops to set strategy and future direction. Never before have we had this level of discourse and enthusiasm, nor this much optimism that new, transformative treatments are within reach.

While we can never be satisfied until we've achieved a cure, we've named this report for the tangible progress we're proud to have driven since we've come on the scene: More researchers working on Parkinson's (in 2008 alone we funded nearly $6 million in research undertaken by 25 teams new to PD). More focus on relevance for patients. Industry getting involved earlier. And more scientific hits successfully passing to their next stage of development, whatever that might be.

Your generosity and support make this possible. Thank you for your commitment to ending Parkinson's disease. Together we are speeding transformational therapies for PD — and in the process changing the paradigm for how medical research funders can impact the pace and nature of progress.

With gratitude,

Katie Hood
CEO

Michael J. Fox
Founder

Deborah W. Brooks
Co-Founder

MJFF WORKS TO SPEED PROGRESS ALONG THE THERAPEUTIC DEVELOPMENT PIPELINE The federal government annually funds millions in PD research, the vast majority directed at early-stage discovery research. At the opposite end of the pipeline, the pharmaceutical industry spends even more, primarily for late-stage drug development. MJFF works to bridge the "valley of death" between these major pools of capital, prioritizing investments to transform basic discoveries into therapeutic targets and speed clinical testing of new interventions. Our single-minded goal: Shorten the time required for Parkinson's disease treatments to advance from discovery to FDA approval (currently 10 to 20 years for a symptomatic treatment and likely even longer for a neuroprotective one). *Dollar figures for 2007.*

*Source: Research!America, *Investment in U.S. Health Research 2007*

TRANSFORMING BASIC DISCOVERIES INTO THERAPEUTIC TARGETS

Discoveries about the cellular and molecular causes and effects of Parkinson's disease are published in scientific journals every week, but only a tiny fraction stand a chance of resulting in breakthrough therapeutics. Filtering through hits (some already decades old) and systematically evaluating their potential to impact patients' lives — sooner, rather than later — is a job The Michael J. Fox Foundation tackles each day.

Reviewing as many as 800 grant applications a year, our staff PhDs and in-house research team, extensively trained in neuroscience and project management, continuously monitor and troubleshoot PD research developments. Then we aggressively apply financial and intellectual resources to push critical findings forward on the pipeline, assuring their steady advancement toward the clinic and patients.

In our short history, we've funded work on approximately 100 therapeutic targets for neuroprotective and symptomatic approaches to PD, and driven novel treatments to address complications of current therapies. Some targets have been validated, and work on them continues. But even when outcomes do not meet our hopes, taking ideas off the table allows us to redirect limited resources where they are more likely to lead to practical treatments.

The stories on these pages illustrate the MJFF impact: how we prioritize the projects where we believe our funding and expertise can make the greatest difference, then partner with researchers to speed their work toward relevance for patients.

$6.9 million

Research funded by MJFF in international labs in 2008

$25.9 million

Research funded by MJFF in U.S. labs in 2008

When Proteins Misfold: Driving Validation of a Novel Neuroprotective Target

In 2005, scientists working in tiny worms known as *C.elegans* demonstrated that the protein TorsinA, which occurs naturally in the brain, can protect dopamine neurons from death. While TorsinA's normal function is not entirely understood, it is thought to be a "chaperone" — a molecule that helps cells repair damaged or misfolded proteins. Increasing TorsinA activity, researchers hypothesize, may improve cells' ability to repair themselves.

Now MJFF is funding an academic-industry collaboration to validate the *C.elegans* results in a second pre-clinical model of Parkinson's disease. The goal: establish enough evidence to compel an industry partner to launch a program that would fully flesh out the therapeutic potential of compounds targeting TorsinA function.

"The modulation of TorsinA points to a new direction for treating PD at what may be one of its root causes — the toxic effects of misfolded proteins that accumulate in critical brain cells," says lead investigator David Standaert, MD, PhD, of the University of Alabama at Birmingham. "If the protective effect of TorsinA seen in *C.elegans* is also found in mammalian pre-clinical models of the disease, our work could spark meaningful investment in this promising new target."

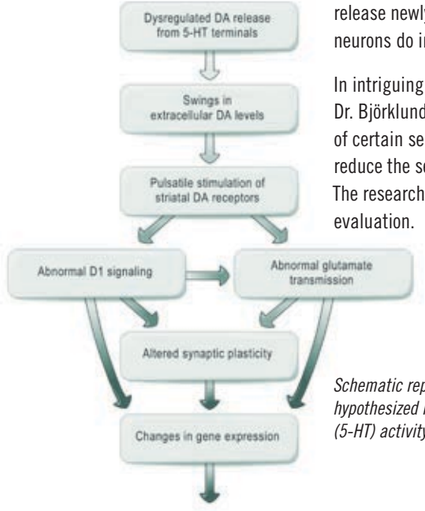
TARGETING THE SEROTONIN SYSTEM FOR TREATMENT OF LEVODOPA-INDUCED DYSKINESIAS

Anders Björklund, MD, PhD, of Lund University in Sweden and his colleagues are working to target the brain's serotonin system as a way to lessen levodopa-induced dyskinesias. Dyskinesias are the uncontrollable, wavy or jerky disruptive movements that are a side effect of long-term dopamine replacement therapy. For many patients, they are among the most debilitating aspects of living with PD. The prospect of dyskinesias leads many patients to delay starting on levodopa, the gold-standard treatment for PD, or refuse it altogether.

Dr. Björklund hypothesizes that serotonin neurons, best known for their role in clinical depression and other mood disorders, also play a role in Parkinson's. Over three years, with support from the Bachmann-Strauss Dystonia & Parkinson Foundation, MJFF has invested $725,000 in the Björklund team's development of a serotonin-based treatment for dyskinesias, moving it several steps closer to the clinic than would otherwise be possible.

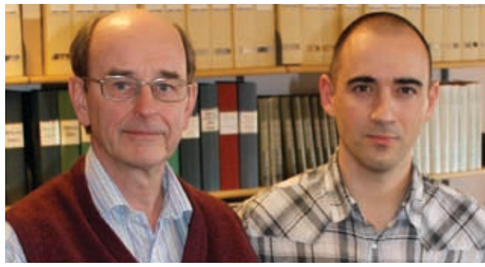
"We think that as Parkinson's disease progresses and the dopamine system becomes more impaired, the serotonin system is called on to assist," says Dr. Björklund. "Serotonin neurons are capable of converting levodopa to dopamine, and can store and release newly synthesized dopamine, as dopamine neurons do in a healthy brain."

In intriguing pilot experiments in pre-clinical models, Dr. Björklund observed that manipulating the activity of certain serotonin neurons had a profound ability to reduce the severity of levodopa-induced dyskinesias. The researchers brought the data to MJFF for evaluation.



Schematic representation of the hypothesized role of altered serotonin (5-HT) activity leading to dyskinesia

"It was apparent to us right away that these findings could be important," says Todd Sherer, PhD, vice president of research programs at MJFF. "The scientific evidence for a serotonin role in dyskinesia was compelling. And because clinical depression affects an estimated 15 million people in the United States alone, the serotonin system was already the subject of intense investigation outside of Parkinson's. If a serotonin role in PD were borne out, we could marry that to what's already known about the serotonin system, and potentially accelerate the development and clinical testing of a new Parkinson's therapeutic."



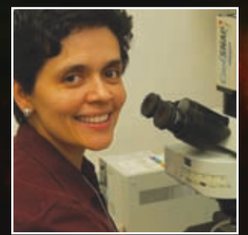
Anders Björklund and Manolo Carta

MJFF quickly approved Community Fast Track 2005 funding to validate the results in a larger study. When that study confirmed the pilot findings, MJFF sent more money to drive additional experiments. Within another year the scientists had identified two specific serotonin receptors, 5-HT1A and 5-HT1B, whose activation produced a near-complete suppression of levodopa-induced dyskinesia in pre-clinical Parkinson's models. At the same time, they screened the scientific literature to identify known candidate drugs that activate both receptors and may be suitable for clinical use. In December 2008, Manolo Carta, PhD, a member of the Björklund lab, received funding for another round of experiments, which could be the final pre-clinical work required before a Phase 1 clinical trial.

"We'll pay particular attention to the long-term effects of these drug candidate compounds," says Dr. Carta. "The results will be highly relevant for the design of a proof-of-concept clinical study investigating the efficacy of this approach to treat dyskinesia in people with PD."

"I'm enthusiastic about partnering with The Michael J. Fox Foundation because they share my team's **commitment to push promising therapeutics toward the clinic and patients.** MJFF understands and provides the kind of support — financial and intellectual — required to speed the translation of research discoveries into new treatments."

— Jeff Conn



Malú Tansey

Targeting Inflammation in PD

For decades researchers have worked to understand the role of chronic inflammation in the death of dopamine neurons in PD. MJFF is exploring multiple approaches to characterize the relationship between inflammation and Parkinson's, and to validate therapeutic targets that could slow or reverse inflammation-related pathology.

In 2003 Kalipada Pahan, PhD (then a faculty member at the University of Nebraska Medical Center), received funding to study the role of naturally occurring protein NF-kB in the production of various inflammatory molecules. Working in pre-clinical PD models, Dr. Pahan's team demonstrated that chains of amino acids known as NBD peptides, which control inflammation and protect neurons, can rescue dopamine neurons from death. In 2008 MJFF brought Dr. Pahan (now at the Rush University Medical Center) one step closer to the clinic by funding him to test the efficacy of NBD peptides in more predictive models of PD. If the results show promise at this stage, NBD peptides could enter the clinic and become the basis of a novel drug to modify the progression of PD.

Malú Tansey, PhD, of the UT Southwestern Medical Center at Dallas is pioneering a separate inflammation-based therapeutic approach to PD. Dr. Tansey was first funded in 2003 to investigate a pro-inflammatory protein called Tumor Necrosis Factor (TNF). Based on exciting progress from that project, MJFF staff elected to provide supplemental funding to Dr. Tansey in 2004 and 2005. She went on to demonstrate in pre-clinical models of PD that dopamine neurons can be rescued from death by inhibiting the activity of TNF. In 2008 the Foundation funded Dr. Tansey's current investigation of a gene therapy approach selectively targeted at soluble TNF that could inhibit inflammation, potentially slowing or stopping the progressive loss of dopamine neurons in Parkinson's disease.

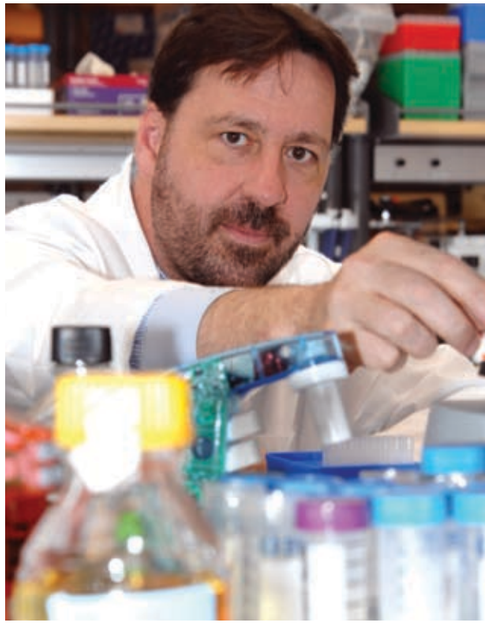
Midbrain cells expressing potentially therapeutic dominant/ negative TNF (green)

Targeting Glutamate Receptors for Sustained Symptomatic Relief

MJFF is partnering with P. Jeffrey Conn, PhD, to jump-start a new class of symptomatic PD treatment targeting the glutamate system. (To learn more about glutamate's potential therapeutic role in PD, see "Anatomy of a Novel Target" below.)

Dr. Conn, Vanderbilt University's Lee E. Limbird Professor of Pharmacology and Director of the Program in Drug Discovery, came to MJFF with evidence that increasing the activity of certain glutamate receptors could alleviate symptoms in pre-clinical models of PD. He received Target Validation 2005 funding to home in on the right receptors for further study, and to identify molecules capable of boosting the activity of those receptors. That work substantiated the mGluR4 receptor as an especially promising target for a new symptomatic therapy.

Typically, once promising drug leads are identified, they must be engineered into a compound suitable for clinical testing. This phase of work requires an interdisciplinary team with expertise spanning medicinal chemistry, molecular biology and in vivo studies. Late in 2007, with support from The Edmond J. Safra Foundation, MJFF granted Dr. Conn a $4.4 million *LEAPS (Linked Efforts to Accelerate Parkinson's Solutions)* award to assemble and lead such a team for further work on the mGluR4 receptor. The LEAPS team spent 2008 more thoroughly characterizing mGluR4's therapeutic potential while simultaneously generating a viable drug candidate to target it. Further optimization is ongoing in the first half of 2009, with pre-clinical testing of the most promising candidate on deck for the latter part of the year.



Jeff Conn

Stephen Traynelis

Electron micrograph image of glutamate receptor immunoreactivity

Anatomy of a Novel Target: Exploring Glutamate

While the dopamine system has long been the primary interest of PD researchers, recent evidence supports the potential of glutamate, another neurotransmitter, as a therapeutic target for PD.

Like dopamine, glutamate is a signaling molecule that plays a role in transporting brain messages and controlling body functions. Early findings suggest that manipulating specific parts of the glutamate system could alleviate Parkinson's symptoms and complications while bypassing the dopamine system altogether. Alternatively, it may be possible to develop a dual or complementary treatment approach, in which glutamate-based therapies lessen patients' needs for dopamine-based therapies — in turn reducing the debilitating side effects of long-term dopamine replacement.

"Dopamine replacement therapies lose effectiveness over time and bring serious side effects. And many disruptive symptoms of Parkinson's don't respond to dopamine replacement at all," says MJFF awardee Stephen Traynelis, PhD, of Emory University. "My lab is exploring whether decreasing the activity of a particular glutamate receptor may lower the known overactivation of three different sets of neurons in Parkinson's."

MJFF has funded 11 researchers in six separate labs, including Dr. Traynelis's, to advance novel treatment paradigms based on glutamate.

"A great deal of Parkinson's disease research, including the validation of glutamate as a therapeutic target, is at a stage where scientists have not yet identified the precise tactic that will yield the greatest therapeutic benefit," says Katie Hood, CEO. "Throughout our portfolio, MJFF identifies multiple promising approaches and funds them simultaneously. Even if one strategy fails, another may still be making strides toward practical relevance for patients."

SPEEDING CLINICAL TESTING OF NEW INTERVENTIONS

Clinical research for any disease is expensive and requires unique and distinct expertise. No matter how promising a new treatment strategy, shepherding it through trials and regulatory approval is a lengthy and costly process. An entire team must be assembled with the skill and experience to conduct research in humans. Individuals who fit the study's needs must be found and agree to enroll. Once the intervention begins, tests must be performed at regular intervals, often requiring multiple visits to a clinical center. Results must be scrupulously assessed and reported to the appropriate regulatory bureau with compelling evidence that the new treatment represents a marked improvement over existing ones.

In addition to these standard hurdles, Parkinson's disease trial sponsors lack objective tools and scales for measuring the effects of disease-modifying interventions. This represents a serious challenge in PD clinical research: Biotech and pharmaceutical companies, whose resources are needed to carry new therapeutics over the finish line, are unlikely to risk investing in trials where the likelihood of clear and marketable outcomes is low.

MJFF shares patients' urgency to overcome these challenges and bring new therapies to market as fast as possible. In prioritizing clinical trials, we emphasize proof-of-principle and first-in-human studies that can alter the risk profile of a given treatment. We also step in as needed to help assemble and organize the right teams, lend expertise to biotech and pharmaceutical companies testing the PD waters, vet the Parkinson's potential of drugs approved for other diseases, and sponsor trials where intellectual property or patent issues reduce companies' incentive to get involved.

Why Test Other Diseases' Drugs for Parkinson's?

Iwona Strycharska-Orzyk

Over the 10 to 15 years it takes to turn a target into a marketable drug, a pharmaceutical company typically spends $800 million or more. One reason it takes so long and costs so much is that the safety of every new candidate drug for human use must be carefully established.

That's why MJFF pays close attention when a drug already approved by a regulatory body shows potential to benefit Parkinson's. If MJFF funding can help demonstrate efficacy against PD, the drug can advance much more rapidly to clinical testing in Parkinson's patients.

In addition to the projects described on these pages, the Foundation is funding Erwan Bezard, PhD, of the University of Bordeaux, France, to investigate statin (high cholesterol) drugs to alleviate levodopa-induced dyskinesias. And Marina Emborg, MD, PhD, of the University of Wisconsin, Madison, is exploring the diabetes drug pioglitazone as a neuroprotective treatment for Parkinson's disease. Her work, funded by MJFF since 2005, has demonstrated that pioglitazone causes functional benefits in pre-clinical models of PD. "Pioglitazone already has FDA approval and a well-established safety profile," says Dr. Emborg. "With further promising pre-clinical outcomes, it could be ready for clinical studies in Parkinson's patients as soon as 2010."

COULD A HIGH-BLOOD-PRESSURE DRUG SLOW THE PROGRESSION OF PD?

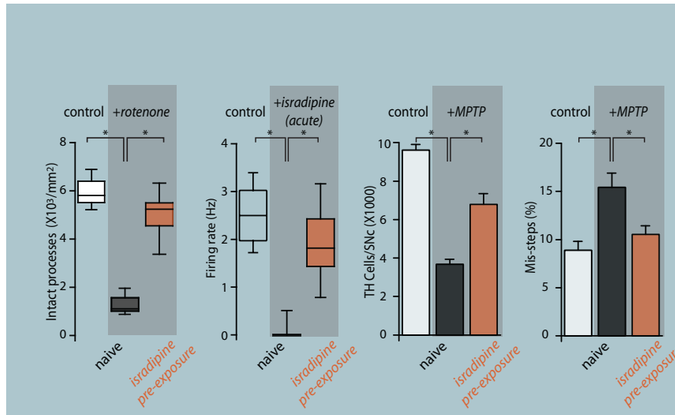
In December 2008 MJFF announced a three-year award of $2 million to fund a Phase 2 clinical trial investigating isradipine, an FDA-approved high blood pressure drug. Isradipine is in a class of high-blood pressure medications that work by blocking the activity of calcium channels, which help cells fire electrically. D. James Surmeier, PhD, a noted Parkinson's researcher at Northwestern University in Chicago, developed a theory that hyperactive calcium channels may stress dopamine neurons, leading them to shut down or die. He hypothesized that drugs like isradipine might reduce this stress, thereby slowing or stopping the progression of Parkinson's disease. In 2007 he published this hypothesis in the prestigious scientific journal *Nature*.

No current Parkinson's treatment has been definitively proven to modify the progression of PD. Available therapies mask symptoms while the underlying pathology continues to worsen. A neuroprotective treatment is the ultimate goal of Parkinson's research. Dr. Surmeier's article suggested a potential new research path to such a treatment. MJFF research staff encouraged him to apply for immediate Foundation funding. Within weeks of his first conversation with MJFF, Dr. Surmeier had a $75,000 *Rapid Response Innovation Award* in hand to expand pre-clinical testing of his hypothesis.

Dr. Surmeier's experiments quickly demonstrated considerable promise for isradipine in slowing Parkinson's progression. In October 2008 the results were met with excitement at the Foundation's second PD Therapeutics Conference in Chicago.

The next steps were clear: determine requirements to take these findings to a clinical trial and see whether the promising pre-clinical data carried through to people with PD. Safety would be a particular concern: Many people with Parkinson's already have low blood pressure, so lowering blood pressure further could prove dangerous. Working closely with Dr. Surmeier and his Northwestern colleague Tanya Simuni, MD, the Foundation mapped the route to a pilot Phase 2 clinical trial to establish optimal dosage and possible side effects.

Following enthusiastic peer review, and with support from the Mann Family Foundation in memory of its founder, Fred Mann, MJFF awarded the investigators a $2-million *Clinical Investigation Award.* The award allowed the researchers to begin the trial in 2009 in 100 patients with early idiopathic PD. If the trial yields a critical mass of data on isradipine's efficacy in Parkinson's disease, other funders will have a strong incentive to expand the Phase 2 trial and continue into Phase 3 — helping speed this potential breakthrough to PD patients.



Potential disease-modifying effects of isradipine in a pre-clinical model of PD

An important cautionary note: While MJFF is funding clinical trials on supplements and drugs already available for purchase or prescription, people with Parkinson's (other than those who ultimately enroll in these trials) should not begin taking these agents as part of a Parkinson's disease treatment regimen without the explicit recommendation of their doctor. Evidence to date has not yet definitively proved a benefit in PD, and these substances carry potential health risks, which doctors will carefully monitor in trial participants. It is crucial that all care and treatment decisions related to Parkinson's disease and any other medical condition be made in consultation with a physician or other qualified medical professional.

CERE-120 AND THE FUTURE OF TROPHIC-BASED APPROACHES TO PD

In November 2008 the Parkinson's community was disappointed to learn that Ceregene Inc.'s CERE-120, a gene therapy approach to treat Parkinson's patients with trophic factor neurturin, had not demonstrated greater benefit than a placebo in a double-blind, controlled Phase 2 clinical trial. Trophic factors (also known as neurotrophic factors or growth factors) are specialized proteins that protect and nurture neurons, including the dopamine neurons that die in Parkinson's disease. Ceregene's Phase 2 trial of neurturin was partially supported by The Michael J. Fox Foundation with leadership funding from the family of Board member Daniel E. Spitzer, MD. A successful Phase 1 trial also was funded by MJFF with principal support from The Pioneer Fund, a private family foundation that supports endeavors including medical research.

Phase 2 trial participants, all Parkinson's patients, were split into two groups — one group received active CERE-120 and one received inactive placebo. In both groups, 70 percent of participants showed a five-point or greater improvement in their UPDRS motor off scores. This made it a challenge to demonstrate that CERE-120 had exerted a therapeutic effect. The problem was exacerbated, as always in PD clinical trials, by the lack of a biomarker that could objectively measure treatment effects.

Nonetheless, The Michael J. Fox Foundation continues to see real promise in trophic-based approaches to treating PD — even, potentially, in CERE-120 itself. Lessons learned from this trial will be of great value in refining future attempts to treat PD with trophic factors, noted Todd Sherer, PhD, vice president of research programs at MJFF. "Going forward, the data from the Phase 2 CERE-120 trial will help researchers make critical adjustments in how and where they attempt to deliver trophic factors to the Parkinson's brain. This could be the key to future trials' success."

"There's no question that outcomes of trophic-based trials have been frustrating so far," added Katie Hood. "Our Foundation shares that frustration with patients. But far from giving up, we're working aggressively to learn from past outcomes in order to solve the problems that have hindered these treatments to date. MJFF believes it is possible to obtain the same beneficial response in PD patients that has been observed time and again in pre-clinical studies."

Exercise and PD: Getting to the Bottom of the Connection

Lisa Shulman

There is some scientific evidence that exercise holds specific benefits for people with Parkinson's disease.

"Personally, I believe it's quite likely that exercise may prove to be more beneficial than some of the pharmaceutical agents available to PD patients," says Lisa Shulman, MD, of the University of Maryland. "With MJFF funding, my team is working to definitively show that exercise can be a beneficial addition to overall management of the disease. And exercise is something that can restore a sense of control and reduce feelings of helplessness. Having a chronic disorder doesn't mean you need to be a 'passive patient'; you don't have to throw in the towel."

MJFF has invested over $2.7 million in exercise studies to date. Our priorities: establishing concrete evidence of how exercise may alleviate PD symptoms, or even slow or stop disease progression; and accelerating identification of the most effective forms of exercise for people with PD.

"Only MJFF would have the incentive and flexibility to fund a trial like ours in a matter of months." — *Michael Schwarzschild*

Michael Schwarzschild

INVESTIGATING INOSINE

In April 2008 the journal *Archives of Neurology* published an epidemiological study showing that people with early PD who had elevated blood levels of urate — a natural antioxidant in the blood — were able to forgo dopamine replacement therapy longer than people with lower urate levels. Those with higher urate levels also showed less severe changes on brain scans.

"Our findings, combined with prior knowledge of urate's protective properties in laboratory studies, raised the possibility that urate-elevating strategies could be used to slow the neurodegeneration of Parkinson's disease," says the study's lead author, Michael Schwarzschild, MD, PhD, of Harvard Medical School.

Epidemiological findings are intriguing, but must be tested clinically. Dr. Schwarzschild and his colleagues wanted to take the next logical step: determining whether raising urate levels in PD patients might slow the progression of Parkinson's. They immediately began designing a Phase 2 clinical trial to investigate the potential of a naturally occurring chemical, inosine, which is converted by our bodies into urate.

As inosine is widely available to consumers at health food and vitamin stores, no corporate entity had the incentive to sponsor clinical research to definitively assess its potential in Parkinson's. "When we thought about potential funders, it was clear that finding funding for this trial might take years," Dr. Schwarzschild said. "Only MJFF would have the incentive and flexibility to fund a trial like ours in a matter of months." He and his colleagues decided to approach the Foundation.

"Dr. Schwarzschild and his team brought their results to us knowing that we were the only organization likely to jump on inosine as a strategy for PD because of its promise as a new treatment, regardless of IP value or profit margin considerations," says Katie Hood. "This is just the kind of gap between the bench and the clinic that our Foundation exists to bridge."

With support from The Edmond J. Safra Foundation, MJFF awarded the team a *LEAPS* award of up to $5.6 million to undertake the Phase 2 study. The goals are to assess the safety of using inosine to raise blood urate levels, and to determine optimal dosage. The researchers plan to begin patient enrollment in mid-2009 and are applying for NIH funding for a larger trial.

Despite the promising findings so far, Dr. Schwarzschild cautioned, people with Parkinson's (other than those who enroll in this trial) should not start taking inosine.

"The potential benefits of urate must be tempered against the risks of elevated urate levels, which include gout and kidney stones. From what we know now, urate elevation should be attempted only in the context of a closely monitored clinical trial, in which potential benefits and risks are carefully balanced."

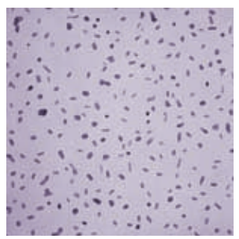
MOBILIZING NEW TECHNOLOGIES AND TOOLS IN PD THERAPEUTIC DEVELOPMENT

While new genetic and cellular targets have invigorated pre-clinical and clinical Parkinson's research over the last 10 years, converting these discoveries into practical treatments requires deliberate and strategic investment in the development of new research technologies and tools.

In 2008 MJFF worked to apply novel concepts to PD at every stage of development. RNAi technology could bring relief by silencing molecules whose overexpression is implicated in PD. New methods ranging from a nasal spray to gene therapy might allow for practical and non-invasive delivery of therapies that do not naturally cross the blood-brain barrier.

Acceleration also requires that we facilitate and lead the development of research tools that could shift paradigms across the board for pre-clinical and clinical research. Since 2002 MJFF has led the hunt for biomarkers to diagnose and measure the progression of Parkinson's disease, vital tools for the development of disease-modifying therapies. And in our quest to create pre-clinical tools that can help researchers better understand PD as well as screen new therapies, our portfolio includes the development of new genetic models and an exploration of induced pluripotent stem cell technology to develop personalized models of Parkinson's disease. We are also exploring how the Internet may change the way research gets done — as it has changed so much else in the past decade.

Nanotechnology for Parkinson's Disease

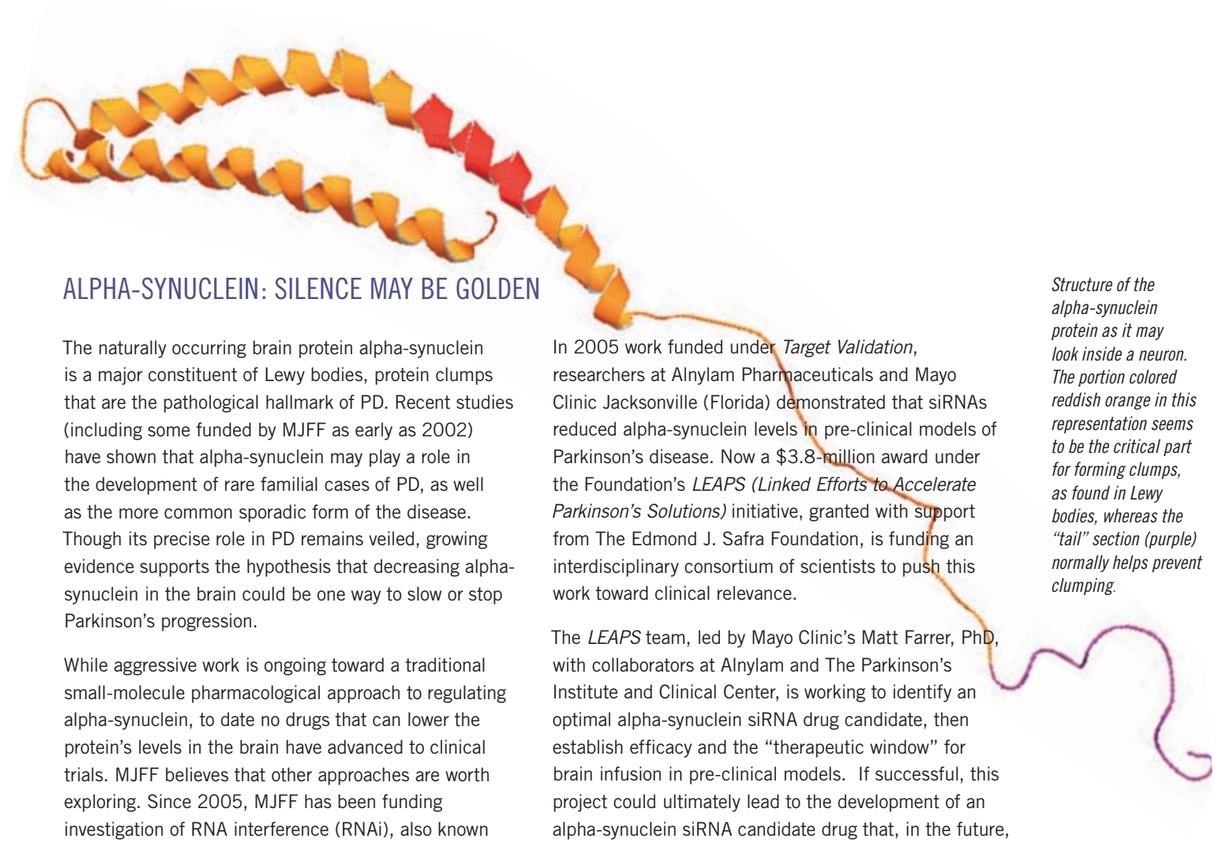


Molecules of condensed DNA that could be used in gene therapy to treat PD

In December 2004 Copernicus Therapeutics, Inc., of Cleveland, Ohio, first published results of a human clinical trial for cystic fibrosis showing that nanotechnology — condensing molecules of DNA into particles tiny enough to penetrate the membrane surrounding a cell's nucleus — can be used as a nonviral approach to gene therapy. Now, MJFF is working to determine the feasibility of a nanotechnology gene therapy approach for Parkinson's disease.

Under the Foundation's 2007 *Rapid Response Innovation Awards*, which provide fast funding for high-risk, high-reward concepts that could kick-start new treatment approaches to Parkinson's, David Yurek, PhD, successfully introduced condensed DNA coding for trophic factor GDNF; these nanoparticles are small enough to enter brain cells. These particles were safely injected into the brains of pre-clinical models of PD and successfully caused the cells of interest to begin manufacturing GDNF.

In 2008 MJFF approved supplemental funding for Dr. Yurek, a faculty member at the University of Kentucky, to partner with Copernicus Therapeutics, the provider of condensed DNA, to compare several different formulations of DNA coding GDNF. The goal is to optimize a particular formulation for long-term expression in pre-clinical models and determine whether the treatment results in improved motor function. If the project is successful, it could help give rise to an entirely new strategy for treating PD.



Structure of the alpha-synuclein protein as it may look inside a neuron. The portion colored reddish orange in this representation seems to be the critical part for forming clumps, as found in Lewy bodies, whereas the "tail" section (purple) normally helps prevent clumping.

ALPHA-SYNUCLEIN: SILENCE MAY BE GOLDEN

The naturally occurring brain protein alpha-synuclein is a major constituent of Lewy bodies, protein clumps that are the pathological hallmark of PD. Recent studies (including some funded by MJFF as early as 2002) have shown that alpha-synuclein may play a role in the development of rare familial cases of PD, as well as the more common sporadic form of the disease. Though its precise role in PD remains veiled, growing evidence supports the hypothesis that decreasing alpha-synuclein in the brain could be one way to slow or stop Parkinson's progression.

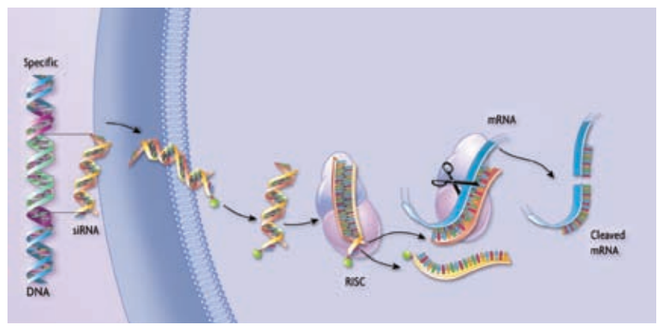
While aggressive work is ongoing toward a traditional small-molecule pharmacological approach to regulating alpha-synuclein, to date no drugs that can lower the protein's levels in the brain have advanced to clinical trials. MJFF believes that other approaches are worth exploring. Since 2005, MJFF has been funding investigation of RNA interference (RNAi), also known as gene silencing, as a strategy for reducing alpha-synuclein in the Parkinson's brain.

RNAi is a mechanism naturally present in all body cells. "Small interfering RNA" (siRNA) molecules are able to silence a gene's expression of a particular protein through the destruction of messenger RNA, the molecule that contains the instructions for protein synthesis. Since the discovery of RNAi in the 1990s, researchers have worked to harness this natural capability of small RNA molecules to silence genes' expression of proteins linked to disease — such as alpha-synuclein in PD.

"The Michael J. Fox Foundation is optimistic about aggressively pursuing RNAi therapeutics for PD," says CEO Katie Hood. "It's a completely novel approach, but one that could lead to a major scientific leap forward in terms of improving patients' quality of life."

In 2005 work funded under *Target Validation*, researchers at Alnylam Pharmaceuticals and Mayo Clinic Jacksonville (Florida) demonstrated that siRNAs reduced alpha-synuclein levels in pre-clinical models of Parkinson's disease. Now a $3.8-million award under the Foundation's *LEAPS (Linked Efforts to Accelerate Parkinson's Solutions)* initiative, granted with support from The Edmond J. Safra Foundation, is funding an interdisciplinary consortium of scientists to push this work toward clinical relevance.

The *LEAPS* team, led by Mayo Clinic's Matt Farrer, PhD, with collaborators at Alnylam and The Parkinson's Institute and Clinical Center, is working to identify an optimal alpha-synuclein siRNA drug candidate, then establish efficacy and the "therapeutic window" for brain infusion in pre-clinical models. If successful, this project could ultimately lead to the development of an alpha-synuclein siRNA candidate drug that, in the future, could be tested in PD patients in Phase 1 clinical trials.



Schematic representation of the therapeutic mechanism of RNAi. Left to right: A short interfering RNA (siRNA) is designed to correspond to a gene target of interest. The siRNA is then synthesized with drug-like properties. The modified siRNA penetrates the cell membrane and harnesses the RNAi mechanism for gene silencing to achieve a therapeutic effect.

Outsmarting the Blood-Brain Barrier

The blood-brain barrier (BBB) is critical to human health. It surrounds the brain and keeps out agents that could do us harm. Unfortunately, this thin membrane of tightly packed cells is an overachiever. In addition to putting up a velvet rope for viruses and other pathogens, it prevents many potentially beneficial therapies for neurodegenerative diseases, including Parkinson's, from entering as well.

So-called large- and small-molecule treatments work by causing therapeutic molecules to enter the bloodstream. From the blood, these molecules are taken up by the appropriate body cells to bring about the desired beneficial effect. Small-molecule treatments make up the majority of orally administered treatments on today's market. Large-molecule treatments typically involve the use of specialized proteins. To rescue dopamine neurons from death, small or large therapeutic molecules must find their way into the brain. But the BBB prevents them from doing so.

The Foundation is committed to driving new and novel approaches to drug delivery throughout its portfolio of PD research investments. And in 2008 MJFF and The Kinetics Foundation co-launched a $2-million initiative, *Improving Delivery of Parkinson's Disease Therapeutics to the Brain*, dedicated to improving therapeutics delivery across the BBB as well as refining surgical approaches that today represent the only option for getting many therapeutics of interest into the brain.

Ancient History Meets Science Fiction: A "Trojan Horse" That Can Sneak GDNF across the Blood-Brain Barrier

In 2006 William M. Pardridge, MD, of the University of California, Los Angeles, was funded by MJFF to vet the potential of "Trojan Horse" technology to overcome the challenge of getting trophic factors across the blood-brain barrier (BBB). Trojan Horse technology aims to fuse a large molecule, which normally cannot cross the BBB, to an antibody that naturally can. The antibody hides the large molecule from the BBB sentry — as the Trojan horse of Homer's Iliad hid Greek soldiers, allowing them to enter Troy — and ferries the attached protein from the blood to the target site in brain.

"Prior attempts to treat PD may have failed because of problems with drug delivery," says Dr. Pardridge. "Trojan Horse technology provides a new approach to target therapeutic agents of interest to the proper areas of the Parkinson's brain."

Dr. Pardridge demonstrated in pre-clinical models that a single intravenous injection transported the GDNF gene to the desired areas of the brain, resulting in lasting improvement in motor function and brain biochemistry.

Building on these promising early results, in 2008 MJFF awarded $1 million to Santa Monica-based biotech ArmaGen Technologies, Inc., for a project using Trojan horse technology to re-engineer the GDNF protein to cross the blood-brain barrier. The end goal is to create a safe and effective treatment in which the GDNF protein, fused to a genetically engineered antibody naturally capable of crossing the blood-brain barrier, can simply be injected into the blood.

"Trojan horse technology has intrigued PD researchers for years," says Gene Johnson, PhD, chief scientific advisor to MJFF. "The Foundation's goal is to speed the timetable for determining just how real the potential here is."

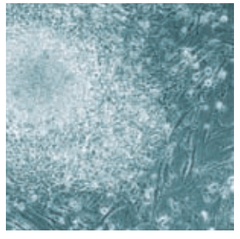
"Intranasal delivery is widely used to treat many diseases. If proven safe in PD, it could be **a practical intervention to benefit millions of people with Parkinson's** worldwide." *— Barbara Waszczak*

Nasal Spray: An On-the-Nose Approach to Delivering GDNF?

Barbara Waszczak, PhD, a professor at Northeastern University, is focusing on the potential of a nasal spray to treat much more than the common cold. In 2007 Dr. Waszczak approached MJFF with her idea to use an intranasal method to deliver GDNF to the brain and quickly received a Rapid Response Innovation Award to investigate the efficacy of delivering the protein through the nose. She found that when given intranasally, GDNF reached the brains of pre-clinical models in sufficient quantities to protect dopamine neurons from an experimental neurotoxin.

Now, with funding under the Foundation's 2008 *Improving Delivery of Parkinson's Disease Therapeutics to the Brain*, Dr. Waszczak's team is using GDNF provided by Amgen to determine if this delivery method results in nasal toxicity and how much GDNF actually reaches the target area of the brain.

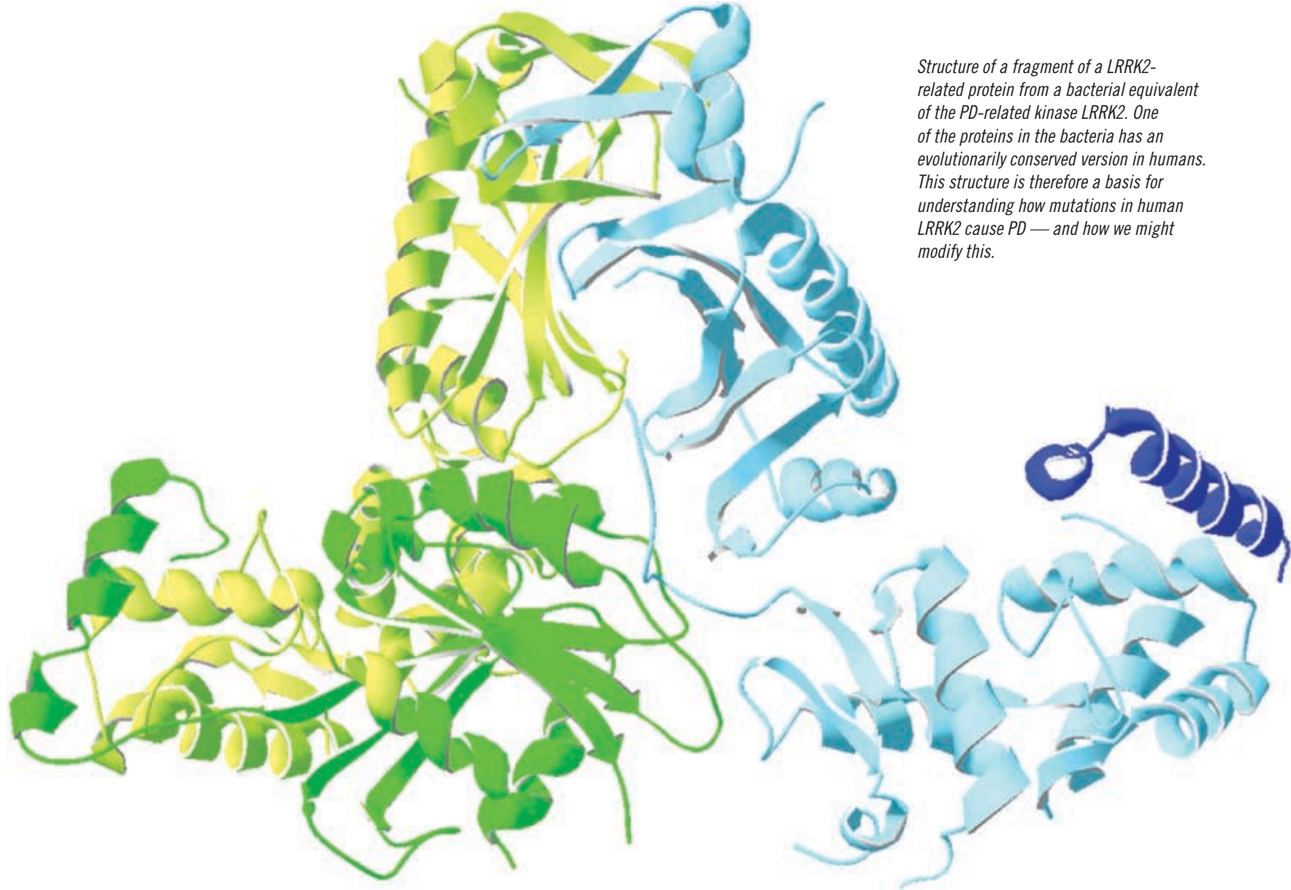
Using Reprogrammed Cells to Develop a New Model of LRRK2-associated PD



Induced pluripotent stem cells (iPS cells) generated from a patient carrying a mutation in LRRK2

U.K. researchers Patrick A. Lewis, PhD, of the Institute of Neurology and John Hardy, PhD, of University College London have received MJFF funding to use induced pluripotent stem cells (iPS cells) to develop an entirely new cellular model of Parkinson's disease. IPS cells are created when scientists "reprogram" skin cells into an embryonic-like state. Dr. Lewis will engineer iPS cells from the skin cells of people with a form of Parkinson's linked to a mutation in the LRRK2 gene. The cells will then be converted into the specific dopamine-producing cells within the substantia nigra that die in PD. By comparing these engineered cells to those from individuals who do not have a genetic disposition to Parkinson's disease, the investigators hope to discover what makes the LRRK2 cells different and more susceptible to a premature demise. This, in turn, could help uncover new molecular and cellular pathways involved in PD as well as new targets for drug treatment.

"If this project succeeds, we will have developed a new PD model from which we can learn more about the mechanisms underlying the disease — knowledge essential to developing better treatments," says Dr. Lewis. "In addition to providing a valuable resource for basic discovery research into Parkinson's, such a model would also provide an important testing ground for therapies to reverse any deficits that we uncover."



Structure of a fragment of a LRRK2-related protein from a bacterial equivalent of the PD-related kinase LRRK2. One of the proteins in the bacteria has an evolutionarily conserved version in humans. This structure is therefore a basis for understanding how mutations in human LRRK2 cause PD — and how we might modify this.

"Our partnership with MJFF has allowed us to upgrade the infrastructure of our Brain and Body Donation Program and collect data that will **identify new predictors of cognitive dysfunction, early parkinsonian pathology in non-symptomatic subjects, and PD-like pathology in body tissue not previously implicated** in PD." *— Charles H. Adler, MD, PhD, Professor of Neurology, Mayo Clinic College of Medicine, and Co-Principal Investigator of MJFF's* Prescott Family Initiative at The Arizona Parkinson's Disease Consortium

Could the Internet Change the Way Research Gets Done?

62:
Number of 2008 meetings between MJFF and industry to discuss funding and strategic partnership possibilities

769:
Number of grant applications reviewed by MJFF in 2008

What if it were possible for any interested individual to switch on their personal computer and participate in clinical research — without ever needing to leave their home? The Michael J. Fox Foundation thinks such a development would lead to increased participation in clinical research at lower cost; amplification of patients' voices in the research process; more data for researchers to work with; and, ultimately, faster progress toward a cure.

With acceleration of new treatments MJFF's chief goal, the appeal of technology-enabled approaches to PD research is clear. In 2008 the Foundation funded five projects to develop Web-based tools — such as online questionnaires, or motion-sensor devices — that could enable scientifically valid PD research to be conducted outside the confines of the clinic.

In May MJFF announced that it would support a partnership between personal genetics company 23andMe and The Parkinson's Institute and Clinical Center to develop Web-based tools and surveys to gather information from people with Parkinson's in a scientifically meaningful way. That project is still in progress, with validation studies under way for the use of Web technologies to gather epidemiological data. Additionally, in September four research teams were awarded $1 million under the Foundation's *Developing and Validating Web-based Clinical Assessments for Parkinson's Disease* initiative. Teams will test different methods of remotely gathering data on aspects of Parkinson's ranging from cognitive and motor function to visual and spatial symptoms, as well as develop Spanish-language Web-based assessments.

"The Internet has changed so much of what we do in our lives over the last 10 years — how we buy, how we communicate, how we find information, how we do business," says CEO Katie Hood. "It's hard to believe it can't have a similar impact on how we do research."

SELECTED LIST OF 2008 MJFF MEETINGS

The Power to Convene

Driving research toward transformative treatments requires not only better communication, but also cooperation and multidisciplinary thinking. In 2008 MJFF brought together more than 460 top researchers from academic and industry labs all over the world for formal and informal face-to-face conferences, summit meetings and workshops. These activities are not ends in themselves, but rather catalysts for concrete action steps — new grant programs, funding for critical tools and resources, novel collaborations and other tactical interventions to move promising ideas forward faster.

Following are highlights of approximately 60 scientific sessions, grant reviews and assessments that we sponsored or co-sponsored in 2008 to help set strategy and future direction for the entire field. In addition to these meetings, our full Scientific Advisory Board convened in Fort Lauderdale in March, and our Executive Scientific Advisory Board met in June and November.

Drug Delivery Workshop, *January 16*
(Co-convened with The Kinetics Foundation)
Experts in drug delivery worked to improve understanding of challenges in delivering therapeutics to the brain.

Demonstrating Disease-modifying Effects for the Treatment of Parkinson's Disease: Drug Development and Regulatory Issues, *April 28-29*
(Co-convened with the United States Food and Drug Administration, the American Association of Pharmacological Scientists and the Parkinson Study Group)
Experts in Parkinson's disease, drug development, quantitative clinical pharmacology and statistics worked toward a consensus on objective endpoints for clinical trials of neuroprotective therapies.

MJFF Research Strategy Assessment, *August 6*
External experts objectively assessed MJFF activities to date and provided recommendations for future programmatic activities.

Fetal Tissue Transplants and PD Pathology Summit, *September 4*
Experts discussed new findings on long-term survival and status of fetal transplant tissue in Parkinson's patients and implications for cell replacement strategies in PD.

Second Annual PD Therapeutics Conference, *September 15*
More than 120 academic and industry researchers and business development professionals attended the only major scientific symposium exclusively focused on speeding PD therapeutics development.

LRRK2 Biology, *November 5*
Leading experts set priorities for investigation into the biology and pathology of the Parkinson's disease-associated gene LRRK2.

LRRK2 Cohort Meetings, *December 4 and 12*
PD scientists discussed the unique data or information that could be provided by cohorts of Ashkenazi Jewish and North African Arab-Berber individuals with PD-implicated LRRK2 mutations.

"The topics and attendees, format and fast pace make the PD Therapeutics Conference a wonderful venue for **understanding clinical implications of the most current PD research.**"
— Lisa McConlogue, PhD, Elan Pharmaceuticals, Inc.

ORGANIZATIONS WITH ACTIVE MJFF AWARDS IN 2008

25
Number of labs funded by MJFF in 2008 that had never worked in PD before

$5.9 million
Amount of 2008 research funded by MJFF in those labs

The most promising projects, undertaken by the best teams, at the right times.

Each year The Michael J. Fox Foundation receives hundreds of grant proposals from scientists based at medical research institutes, universities and biotech and pharmaceutical companies all over the world. In reviewing these applications, our research staff and expert advisors are always seeking the same thing — ideas ready to be translated into new treatments, teams with the expertise to execute those ideas, thoughtful and realistic work plans, and outcomes that will take us closer to breakthrough treatments and a cure for PD. MJFF had active research projects with the following institutions and companies in 2008.

United States

23&Me, Inc.
Acadia Pharmaceuticals
Amicus Therapeutics
ArmaGen Technologies, Inc.
Beth Israel Deaconess Medical Center (Harvard Medical School)
Beth Israel Medical Center
Biodesy, LLC
Boston University
Brandeis University
C2N Diagnostics
California Institute of Technology
Caliper Life Sciences (Xenogen)
Case Western Reserve University
Ceregene, Inc.
Clemson University
Cleveland Clinic
Columbia University
Copernicus Therapeutics, Inc.
Covance
Depomed, Inc.
Emory University
FoldRx Pharmaceuticals, Inc.
Harvard University
The Institute for Neurodegenerative Disorders
Intra-Cellular Therapies, Inc.
Intrexon Corporation
Johns Hopkins University
Kaiser Permanente
Link Medicine Corporation
Massachusetts General Hospital (Harvard Medical School)
Massachusetts Institute of Technology
Mayo Clinic
McLean Hospital (Harvard Medical School)
Memorial Hospital of Rhode Island
MIGENIX Corporation
Mount Sinai School of Medicine
National Institute of Neurodegenerative Disease and Stroke, NIH
Nebraska Health and Human Services System
Neurocrine Biosciences
NeuroHealing Pharmaceuticals, Inc.
Northeastern University
Northern California Institute for Research and Education
Northwestern University
Omeros Corporation
Oregon Health and Science University
P2D, Inc.
Parkinson's and Movement Disorders Center of Maryland
The Parkinson's Institute and Clinical Center
Philadelphia VA Medical Center
ProteoTech, Inc.
Purdue University
Rush University
Sangamo BioSciences, Inc.
ShanaRx, Inc.
Spaulding Rehabilitation Hospital
State University of New York at Buffalo
Sun Health Research Institute
SUNY Downstate Medical Center
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The Salk Institute for Biological Studies
TheraLogics, Inc.
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University of Texas Southwestern Medical Center at Dallas
University of Virginia
University of Washington
University of Wisconsin, Madison
Vanderbilt University
Washington University in St. Louis
Weill Medical College of Cornell University
Wyeth Pharmaceuticals
Yale University
Zenobia Therapeutics, Inc

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University of Melbourne

Canada

Allon Therapeutics
Molecular Biometrics
Toronto Western Hospital
University of Ottawa

Chile

University of Chile

China

Capital University of Medical Sciences

Denmark

Lundbeck A/S

Finland

University of Helsinki
University of Aarhus

France

École Normale Superieur
INSERM
Salpêtrière Hospital
Joseph Fourier University
University of Bordeaux
Trophos

Germany

Johann Wolfgang Goethe University
Paracelsus Elena Klinik
Philipps University Marburg
Rentschler Biotechnologie GmbH
University of Innsbruck
University of Ulm
University of Tuebingen
University Hospital Goettingen

Greece

Biomedical Research Foundation Academy of Athens

Iceland

deCode

Israel

CellCure Neurosciences Ltd.
Hebrew University of Jerusalem
NeuroDerm Ltd.
ProNeuron Biotechnologies
Tel Aviv Sourasky Medical Center

Italy

San Raffaelle Institute

Netherlands

Academic Medical Center
Leiden University Medical Center
Maastricht University Hospital
Nijmegen University Medical Center
University of Aarhus

New Zealand

University of Auckland (New)

Norway

DiaGenic U.S./Int'l

Portugal

Institute for Molecular Medicine

Spain

Hospital General Yague

Sweden

Karolinska Institute
Lund University Sweden

Switzerland

Swiss Federal Institute of Technology Lausanne

United Arab Emirates

United Arab Emirates University

United Kingdom

Imperial College London
The Institute of Neurology
Phytopharm
Proximagen Neuroscience Ltd.
ReNeuron Group Plc
University of Cambridge
University of Glasgow
University of London

2008 IN PHOTOS

Top Row, clockwise from left:
MJFF Board Chair George Prescott (left) and a member of his foursome get ready to hit the green at Breaking PARkinson's, which in 2008 raised over $830,000 for Parkinson's research.

MJFF staffers Alison Urkowitz (left) and Veronique Enos at the Parkinson's Unity Walk.

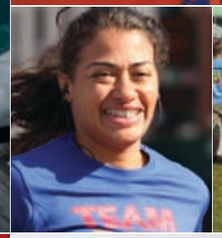
Veronique Koch cycles for Team Fox.

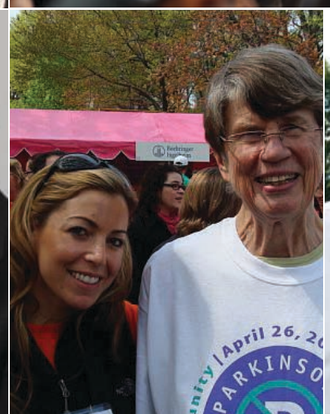
Anthanette Fields, one of 130 Team Fox 2008 ING NYC Marathon runners who together raised $570,000 for MJFF.

Middle Row (l–r):
MJFF Co-Founder Debi Brooks and CEO Katie Hood address 870 "Funny Thing" guests.

Michael J. Fox and Tracy Pollan.

Bottom Row:
The 2008 Team Fox ING NYC Marathon runners visit The Rachael Ray Show *with Board member Woody Shackleton and his wife, Denise.*





Top Row:
Actor Ryan Reynolds, Celebrity Chair of Team Fox, high-fives Michael J. Fox at Mile 23 of Ryan's $108,000 ING NYC Marathon run.

Middle Row, clockwise from left:
Board member Al Glickman and wife Judy.

Michael J. Fox rocks out with The Who on the "Funny Thing" stage.

Board member Curtis Schenker and New York Yankees shortstop Derek Jeter at "Funny Thing."

Bottom Row (l–r):
Lily Safra, chairwoman of The Edmond J. Safra Foundation and MJFF Board member, with Michael J. Fox.

MJFF staffer Jennifer Hagel with former attorney general Janet Reno at the Parkinson's Unity Walk.

Board member Ed Levy, son Matt Levy and grandson Danny Levy at Breaking PARkinson's.

2008 DONOR LISTING

The Michael J. Fox Foundation is humbled by, and deeply grateful for, the incredible dedication of our friends and supporters. Your generosity allows us to continue doing whatever it takes to make Parkinson's a thing of the past.

This report lists those who supported us with significant contributions in 2008. Also listed are the many friends and family members they honored or memorialized through their donations. Their names remind us that finding a cure has never been more urgent.

THE EDMOND J. SAFRA CORE PROGRAMS FOR PD RESEARCH In 2008, recognizing The Edmond J. Safra Foundation's extraordinary commitment to our shared search for revolutionary treatments for Parkinson's disease, MJFF named its core scientific programs in honor of the late philanthropist and humanitarian Edmond J. Safra. Mr. Safra's devotion to this cause lives on with his beloved wife, Lily, a member of the Board of The Michael J. Fox Foundation and, since her husband's passing, Chairwoman of The Edmond J. Safra Foundation.

The Edmond J. Safra Core Programs for PD Research, focusing on historically under-funded stages of drug development, are:

Rapid Response Innovation Awards — supporting groundbreaking Parkinson's disease research in real-time.

Target Validation — supporting rigorous testing of early-stage discoveries to determine whether they are true targets for PD therapeutic development.

Clinical Intervention Awards — supporting clinical research toward new neuroprotective treatments, improvements on existing therapies and treatments for unmet symptoms.

$20,000,000 or more
The Brin Foundation

$10,000,000 or more
Chris Sullivan*

$2,000,000 or more
EMD Serono
Judith and George Prescott and Family*

$1,000,000 or more
Becky and Jack Benaroya
Elan Pharmaceuticals, Inc.**
Anne and Burt Kaplan*
Edmond J. Safra Foundation**
Kinetics Foundation**
Carolyn and Curtis Schenker**
Shackleton Family*
Anne and Bernard Spitzer*

$500,000 or more
Donny Deutsch*
Einhorn Family Charitable Trust
Tracy Pollan and Michael J. Fox*
Breaking PARkinson's/Edwin A. Levy
Great Investors' Best Ideas Foundation/Michele and Shad Rowe

Donor listing continues on page 24

*recognizes existing multi-year commitment
**recognizes new multi-year commitment

MJFF BOARD APPEAL: CATALYZING INDUSTRY INVESTMENT IN PARKINSON'S DISEASE Speeding transformative treatments requires a creative strategy that goes beyond funding isolated projects in academic research labs. Increasing industry engagement in pre-clinical therapeutic development is essential to bridging the gap between discovery and the clinic. In 2006 the Foundation launched a three-year targeted initiative to deepen industry involvement in our efforts.

MJFF is grateful for the remarkable dedication of our Board of Directors in helping us achieve this goal. With characteristic generosity and enthusiasm, members of the Board pledged over $10 million in seed funding. MJFF extends its heartfelt thanks to the following Board members, whose personal leadership, both financial and intellectual, continued to be vital to our success in 2008 industry efforts:

Holly Andersen, MD, and Douglas Hirsch
Shanna and Jon Brooks
Joyce and Barry Cohen
Donny Deutsch
Einhorn Family Charitable Trust
Karen Finerman and Lawrence Golub
Nelle and John Fortenberry
Judy and Al Glickman
Lisa Piazza and David B. Golub
John and Amy Griffin Foundation
Ann and Skip Irving
Marguerite and Morton M. Kondracke
Carolyne and Edwin A. Levy
Julie and Doug Ostrover
Tracy Pollan and Michael J. Fox
Judith and George Prescott and Family
Michele and Shad Rowe
Edmond J. Safra Foundation
Carolyn and Curtis Schenker
The Shackleton Family Fund
Heidi and Daniel Spitzer
Amy and Fred Weiss

Donor listing continued from page 23

$250,000 or more
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The Adams Foundation
Judy and Al Glickman
Lisa Piazza and David B. Golub*
Amy and John Griffin
Julie and Doug Ostrover*
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Robert Pritzker
R.B. Sellars Foundation, Inc.
Sutherland Family Estate
Karen Pritzker and Michael Vlock

$100,000 or more
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Cantor Fitzgerald
Patricia and Jimmy Cayne
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Consolidated Anti-Aging Foundation
Karen Finerman and Lawrence Golub
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Holly Andersen, MD, and Douglas Hirsch
David and Barbara Hirschhorn Foundation*
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Ronald O. Perelman
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Heidi and Daniel Spitzer

$50,000 or more
Anonymous (3)
Anonymous Fund at The Silicon Valley Community Foundation
Bachman-Strauss Dystonia and Parkinson Foundation, Inc.
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CJM Foundation
Close To A Cure
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Ashley and Charles Holzer
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Patricia Jehle
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Kathy and Michael J. Lewis
Mrs. Wendy Gimbel and Mr. Douglas S. Liebhafsky
The Litwin Foundation
The Lobster House on Fisherman's Wharf
Amalia and Peter H. Lucas
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In Team Fox's first three years, members raised an astounding $5 million and this diverse community of changemakers continues to grow and inspire us every day. There is no limit to the creativity and optimism of Team Fox members who have made it their personal mission to make Parkinson's disease nobody's disease.

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Skykings for Leonard Cyphers
39th Annual Peachtree Road Race - 10K
Rik Spier
Mini Marathon 5K Walk/Run
Matt, Angie and Kristin Sremba
1/2 Ironman, Marathon and 25K
The Tjader Family
Tjader Family Fundraiser
Lisa Unger
Jarden Westchester Triathlon
Nanette VanAlstyne
Mailing Event
Stewart Wallace
Students Give Back
Morag Webster
London Marathon
Eileen Werndorfer
Brookfield Parkinson's Walk/Run
Kat Milly West
Friends of Kat 5K
Diana Wiesner
Disneyland 1/2 Marathon

$1,000 or more

Sara Adland
Baltimore Running Festival - CareFirst BlueCross BlueShield Half-Marathon
Jonathan Artz
Boston Marathon
James Beattie
Team Fox Fundraiser
Jan Bogner
Put the Fire Out for Parkinsons
Dennie Bridges
Book Sales
Beth Buzza
Scott Tinley's Adventures Road Triathlon
Tamra Cantore
Team Cantore Fundraisers
Lisa Clark
2009 Boston Marathon
Vicky Clark
Team Fox Fundraiser
Cherie Crowningshield
Paddle for a Cure
Jen and Bob Davis
Dallas White Rock Marathon
Taylor Dewey
Pedal and Paddle for Parkinson's
The Dorsey Family
Gumball Guessing Challenge
Tim Egan
Chicago Irish Brotherhood Event
John Fitzmaurice
Marine Corps Marathon
Sarah Gerk
Marathon Runner
Lev Gershman
Team Fox Fundraiser
Mark Gherty
American Birkebeiner
Hunter Hall
Chicago Marathon
Jon Halle
Car Wash
Hal Halvorsen
Boston Marathon
Oliver Holler
ToTheFuture.org
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PDHope
Carol Kennelly
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Peter and Brooke Kotsonis
Disney Marathon
Jeffrey LaGrange
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Heavenly PeaceMadison
Anne Maglia
Show-Me State Games
Andrew Maguire
Big Lake Half Marathon
Barbra Sue Miller
Long Beach Marathon
Greg Myers
Chickamauga Battlefield Marathon
Leah Nitishin
PF Chang Rock and Roll Half Marathon
Brendan O'Connell
Team Fox Fundraiser
Mitsuko Ogawa
Chicago Half Marathon
Michala Kinney
Pubbin' 4 Parkinson's
Cyrus Rajabi
Birthday Party
Larissa Raze
Team Fox Fundraiser
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2007 ING NYC Marathon
Susie Rosenthal
Team Fox Fundraiser
Martha Ruest
2007 ING NYC Marathon
Jill Sabatine
Berlin Marathon
Thomas Sabourin
Team Fox Runner
Roy Schifilliti
Cape Cod Marathon
Shawna Schueller
Twin Cities Walk for Parkinson's Disease
Joan Shepp
60s and 70s Fashion Show
The Regulars
10 Mountains - 10 Years (A Quest for the Cure)
Benjamin Terry
Monument Ave 10K

ING NYC MARATHON In 2008 Team Fox was proud to be selected once again as an official charity partner in the ING New York City Marathon. 130 runners from four countries and 20 U.S. states teamed up to raise $570,000 and bring us all 26.2 miles closer to a cure.

$100,000 or more

Ryan Reynolds
Team Fox Celebrity Chair

$25,000 or more

Alyssa Johnson and Barry Cohen
Andrew Fitzgerald and Richard Fitzgerald

$10,000 or more

Sheila Brand
Edward Casey
Veronique Enos
John Houston
Ken Kubota
Amy Lee
Kenneth Olson

$5,000 or more

Maureen Ashdown
Beth Baker
Seanna Bruno
Lisa DeLusignan
Dan Dreiling/Pocket Change 4 Parkinson's
Jeremiah Driansky
Jordan Goldwarg
Alexis Howard
Anita Johnson
Terry McCarty
Andrew McLean
Peggy Pichi
Winthrop Smith

$2,500 or more

Katie Barker
Loren Berger
Jeroen Cammeraat
Ron Carlson
Galia Clemens
Thomas Clifford
Tim Crowley
Patrick Culligan
Adam Cummings
Nicholle Davis
Dayna De Simone
Timothy Diamond
Bob DiSabato
Christina DiSabato
James Driscoll
Jacob Elberg
Jessica Ernst
Dan Fagin
Michael Fagin
Jamie Forman
Mark Frasier
Marisa Friedman
Kate Gannon
Ashley Gilbertson
Lori Gillen
Jim Goldenziel
Howard Goldstein
Matthew Goldstein
Katie Griffith
Tammy Hoblak
Danielle Jacobs-Erwin
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Lauren Rich
Susan Rubino
Sara Runnels
Jeremy Ryerson
Emily Sarokhan
Adam Shepherd
Lara Spagnuolo
Marie Spodek
Robert Stanlake
Simon Stanlake
Elizabeth Stevens
Jacquelyn Strycker
Sabrina Tamraz
Susie Teal
Tricia Tinney
Lindsay Totams
Danielle Vasak
Ed Werner

$1,000 or more

Amy Albright
Jason Bennett
Jenny-Brooke Condon
Anthanette Fields
Bradford Kear
Mary Kelly
Shawn Kingsley
Michele Kustera
Frank and Diane LaDore
Kevin Levine
Liesl Lilly
Erin Loebner
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Melissa Shaw
Andrew Vale
Lee Vartan
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We are grateful to these companies for their generosity in matching employee gifts to MJFF.

Abbott Laboratories, Employee Giving Campaign
Adobe Systems, Incorporated Matching Gift Program
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The Brown Foundation
The Capital Group Companies Charitable Foundation
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Chubb & Son
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Grainger Matching Charitable Gifts Program
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NIKE Employee Matching Gift
Oracle Corporation
Pfizer United Way Campaign
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XL Reinsurance America, Inc.

2008 COMMUNITY FUNDRAISERS

The Foundation is grateful to the following donors for their generous efforts to raise funds and awareness for MJFF and Parkinson's research through community fundraising events.

$50,000 or more
Anne-Cecilie and Rob Speyer

$25,000 or more
Vintage Rallies, Inc.

$10,000 or more
Apple Optical
Michael Cotoia
Firstgiving, Inc.
ITSource Technology
Rosemary Beach Foundation, Inc.

$5,000 or more
Samantha Kitchen
Parkinson's Support Group of Rochester NY Inc.
Scars Into Stars Charity

$2,500 or more
Federal Aviation Administration
GVI Property Management
Bruce Levitt
Sundance Running Club

$1,000 or more
Anchorage Parkinson's Disease Support Group
Adriana Avitia
Michael Brodnax
Cambridge Area Parkinson Support Organization
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Pamela Cundall
Entertainment Industry Foundation
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Lydia Hires
I Do Foundation
Andrea Konsky
Lincoln Elementary School
MissionFish
Kerry M. Mitchell/NorthWest Indiana PD Support Group
Monterey Peninsula Foundation
Mark O'Donnell
Stuart Rothstein
Ralph Silwa
Lindsay Spring
Wachovia

FINANCIAL HIGHLIGHTS

Efficiency. Accountability. Impact.

We demand the same accountability and transparency of ourselves as of our awardees, and we keep a tight rein on expenses. Fiscal accountability and transparency are core elements of our organizational values, particularly in how we spend supporters' contributions. While we believe that a quality enterprise requires investment, we are proud that, since inception, 85 percent of our funds have gone directly to research program efforts.

We deliberately have no endowment, instead seeking to deploy funds raised as quickly and wisely as possible. This is an unusual strategic position for a nonprofit. But we believe that to find a cure for PD as quickly as possible, our capital needs to push research forward today — not sit in an endowment or reserve. In 2008 this philosophy proved especially prescient. With no investment portfolio, MJFF suffered no investment losses.

We are outcomes-focused, incorporating milestones and tying grant payments to achievement of those milestones. We fund promising, high-potential research projects as long as they remain on track. We work with awardees to troubleshoot and tackle problems as they arise, but if the science stalls, we halt funding so that limited resources can be reallocated to other efforts.

We proactively measure the impact of our dollars on the pace of Parkinson's research progress. Our in-house research team scores the outcomes of every grant we make, in the interest of assessing impact and maximizing learning to inform future efforts. In 2008 we also conducted an external audit of our research program, asking unbiased advisors to help evaluate our efforts.

We measure our impact not by input — dollars raised — but by output — scientific advances achieved. We're proud of what we've accomplished to date. But ultimately we have only one definition of success: Scientific solutions that produce tangible improvements in patients' lives.

2008 financial highlights follow. Full audited financials and our most recent IRS Form 990s are available at www. michaeljfox.org.

The Michael J. Fox Foundation for Parkinson's Research

STATEMENT OF FINANCIAL POSITION

Year Ended December 31,	2008	2007
ASSETS		
Cash, cash equivalents and investments	$ 30,962,536	$ 32,185,002
Contributions receivable, net	26,762,424	15,566,497
Prepaid expenses and other current assets	162,958	37,015
Security deposits	33,061	33,061
Property and equipment, net	388,610	518,718
Total assets	**$ 58,309,589**	**$ 48,340,293**
LIABILITIES AND NET ASSETS		
Liabilities:		
Accounts payable and accrued expenses	$ 1,066,594	$ 957,787
Grants payable, net	38,882,706	31,331,041
Deferred rent	367,192	376,270
Loan payable	1,013,285	—
Total liabilities	$ 41,329,777	$ 32,665,098
Net Assets:		
Unrestricted (deficit)	(5,516,236)	6,766,811
Temporarily restricted	22,496,048	8,908,384
Total net assets:	16,979,812	15,675,195
Total liabilities and net assets	**$ 58,309,589**	**$ 48,340,293**

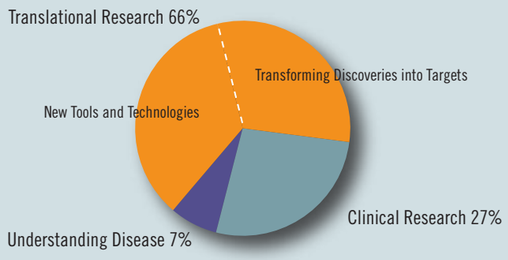
Note: Investments are in highly liquid U.S. government securities.

The Michael J. Fox Foundation for Parkinson's Research

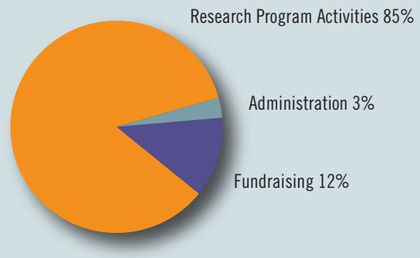
STATEMENT OF ACTIVITIES

Year Ended December 31,	2008	2007
Public support and revenue:		
Contributions	$ 35,335,877	$ 30,613,241
Special events	6,741,990	7,087,215
Investment income	662,655	748,194
Miscellaneous income	25,682	117
Total public support and revenue	42,766,204	38,448,767
Expenses:		
Program services	36,236,785	26,270,247
Management and general	1,093,996	1,017,356
Fund-raising	4,130,806	3,947,418
Total expenses	41,461,587	31,235,021
Change in net assets	**1,304,617**	**7,213,746**
Net assets, beginning of year	15,675,195	8,461,449
Net assets, end of year	**$ 16,979,812**	**$ 15,675,195**

RESEARCH PRIORITIZATION 2008



OUR OBSESSION WITH EFFICIENCY 2000-2008



GROWING INVESTMENTS IN PD RESEARCH 2001-2008

Dollar amounts in millions. Does not include 2001 R21 awards in partnership with NIH.

Photo and Illustration Credits

On the Cover
Midbrain cells expressing potentially therapeutic dominant/negative TNF. Image courtesy of Malú Tansey, PhD, University of Texas Southwest Medical Center at Dallas. Dr. Tansey is funded by The Michael J. Fox Foundation to study the role of TNF and inflammation in the death of dopamine neurons in Parkinson's disease. To learn more about her work, see page 6.

Page 3
Photo of Katie Hood by Elena Olivo.

Photos of Michael J. Fox and Debi Brooks by Mark Seliger courtesy of Seliger Studio.

Page 5
Photo of Anders Björklund and Manolo Carta courtesy of Manolo Carta.

Schematic courtesy of Anders Björklund.

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Cells expressing TNF image courtesy of Malú Tansey.

Photo of Malú Tansey courtesy of UT Southwestern Medical Center at Dallas.

Photo of Jeff Conn courtesy of Vanderbilt Medical Center.

Photo of Stephen Traynelis courtesy of Emory University/Jack Kearse.

Electron micrograph image of glutamate receptor immunoreactivity (unpublished data, Y. Smith) courtesy of Stephen Traynelis.

Pages 8–9
Photo of Lisa Shulman courtesy of University of Maryland.

Schematic showing effects of isradipine, Chan et al., courtesy of D. James Surmeier.

Pages 10–11
File photo of Iwona Strycharska-Orzyk provided by The Parkinson's Institute and Clinical Center.

Photo of Michael Schwarzschild courtesy of Massachusetts General Hospital.

Pages 12–13
Nanoparticles of condensed DNA image courtesy of Copernicus Therapeutics, Inc.

Structure of alpha-synuclein courtesy of Mark R. Cookson, PhD. Redrawn from publicly available data (protein databank ID 1XQ8), derived from experiments described by Ulmer et al. in *J Biol Chem.* 2005 Mar 11:280(10):9595-603.

Schematic of RNAi therapeutic process by Jennifer Fairman/Fairman Studios courtesy of Alnylam Pharmaceuticals, Inc.

Page 15
iPS cell image courtesy of Patrick Lewis.

Structure of the largest fragment of a LRRK2-related protein available to date courtesy of Mark Cookson. Redrawn from protein databank deposition 3DPU.

Page 20
Top row, clockwise from left:
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Ann Billingsley
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Bottom row, left–right:
Ann Billingsley
The Michael J. Fox Foundation
Elena Olivo

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Progress: *The 2008 Annual Report of The Michael J. Fox Foundation for Parkinson's Research* was published in June 2009. It is available in PDF format at www.michaeljfox.org.

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Susan Shaw Design

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