MARK SELIGER

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

ACCELERATING THE CURE

The newsletter for friends and supporters of
The Michael J.Fox Foundation for Parkinson's Research

WINTER 2010

Building Momentum in the Search for a Cure

The Michael J. Fox Foundation has crossed the $200-million mark in research funded and anticipates ending 2010 with over $220 million in funding to help speed patient-relevant breakthroughs.

The funding represents nearly 10 years of Foundation investments in research targeted at translating early-stage discoveries into life-transforming treatments for Parkinson's disease.

"We have built a reputation in the scientific and patient communities for identifying the research critical to moving the dial, then doing whatever it takes to push those approaches forward toward relevance to patients' everyday lives," said Katie Hood, CEO. "While there's still a great deal of work to do, we are heartened by the progress we've made in our short history and optimistic about what the future holds."

A game plan to build momentum

Since its launch in 2000, the Foundation's financial and intellectual leadership has galvanized the Parkinson's research field. Assembling an in-house staff of scientific PhDs and business-trained project managers, the Foundation continuously monitors research developments, setbacks and challenges facing Parkinson's drug development, then works to take action that can help catalyze progress — making critical introductions, creating new funding streams, holding workshops and summit meetings that bring the community together to identify and prioritize critical opportunities.

The Foundation has created consortium models and innovative vehicles for scientific collaboration and data sharing, driven work on over 100 therapeutic targets, brought hundreds of new labs into Parkinson's therapeutic development, mobilized state-of-the-art tools and technologies in PD research, and significantly deepened industry involvement in pre-clinical and clinical studies of Parkinson's disease.

The Foundation's pioneering approach to medical research has enabled major strides on the path to breakthrough treatments patients can feel in their everyday lives. These include:

■ Leading the development of a Parkinson's biomarker, critical to the development of breakthrough treatments. In September, the Foundation launched the Parkinson's Progression Markers Initiative (PPMI) (www.michaeljfox.org/PPMI), a landmark $40-million clinical study seeking to identify consistent and reliable biomarkers of PD within five years.

■ Recognizing dyskinesia, the disabling side effect of long-term dopamine replacement, as a top priority for therapeutic development. The Foundation has provided consistent and significant funding for researchers developing novel dyskinesia targets. Thanks to the Foundation's leadership, several novel dyskinesia treatments are in clinical trials today, and a major study is under way to establish benchmarks for measuring dyskinesia severity — critical to testing future drug candidates.

■ Proactively orchestrating the development of treatments targeting LRRK2 (the most common genetic contributor to Parkinson's disease) rather than allowing science to take its course. The strategic goal: speed up the process of identifying and vetting molecular agents that can successfully target LRRK2, while simultaneously laying the groundwork for conclusive clinical trials to test candidate treatments once they are found.

■ Keeping neurotrophic factors (specialized proteins that protect the dopamine neurons that die in Parkinson's disease) in clinical testing despite disappointing results from earlier trials. Patients have told us they care deeply about the continuing development of trophic factors because these agents have shown potential in pre-clinical studies to slow or stop the progression of Parkinson's disease.

■ Providing consistent funding to develop alpha-synuclein (whose protein clumps form Lewy bodies, the pathological hallmark of PD) as a therapeutic target for Parkinson's. The Foundation has pushed forward both small-molecule and alternative, such as RNA-interference/gene silencing, approaches to alpha-synuclein.

■ Driving development of the research tools required for drug development, including better pre-clinical models of Parkinson's disease. Traditional drug development stakeholders have no financial interest in developing pre-competitive research tools, yet without them, the field faces intractable hurdles to the development of breakthrough treatments. With its sole interest in speeding progress to benefit patients' interests, the Foundation is uniquely poised to provide the financial and intellectual resources required to create and distribute high-quality tools that speed progress toward practical new treatments.

"There is no doubt that far more progress has been made than would be the case if The Michael J. Fox Foundation didn't exist," the *New York Times* wrote.

Flip the page to hear straight from the world's leading researchers about how the Foundation's work is driving progress. To learn more about how the Foundation is building momentum in the search for a Parkinson's cure, and how you can play a part in Parkinson's research, please visit www.michaeljfox.org/momentum.

ELENA OLIVO

NEWS FROM THE CEO

At this year-end, The Michael J. Fox Foundation is reflecting on the remarkable momentum we've built toward our ultimate goal — a cure for Parkinson's — thanks to you, our dedicated supporters.

In 2010, we continued working to tackle the toughest challenges standing in the way of research progress. While much work remains to be done, we are heartened by the real strides we've made toward breakthrough treatments patients can feel in their everyday lives. Turn the page to read "Priorities and Progress" — MJFF-funded scientists, in their own words, on promising results achieved this year and how we will build on those outcomes together in 2011.

If there's one thing we know for sure, it's that we'll never get where we need to go without the committed involvement of a wide range of stakeholders — researchers, academic and industry experts, service providers, patients and their loved ones. In short: you. Your willingness to play a personal role in our work is indispensable to progress. Whether you choose to join a clinical study, set up a monthly donation or planned gift in support of our research programs, or join Team Fox and rally your entire community around the need to speed up Parkinson's drug development, you are making an invaluable contribution to our shared mission to find the cure. (To learn more about Team Fox, our inspirational grassroots network of fundraisers all over the world, take a look at the special insert we've tucked into this newsletter or visit www.teamfox.org.)

Our Foundation was launched in the unfailing belief that our vision of a world without Parkinson's disease was possible. Today we believe it more strongly than ever. With your help, we are coming closer every day to making that vision a reality. Thank you.

Katie Hood

Katie Hood, CEO

Priorities + Progress

As 2010 draws to a close, researchers funded by MJFF reflect on the progress made by their labs this year — and envision how they'll partner with the Foundation in 2011 to build on these results and help bring the cure closer.

On the hunt for "a treatment that would mean everything to patients":
Raymond T. Bartus, Executive Vice President and Chief Scientific Officer, Ceregene, Inc.

In June, MJFF announced funding for Ceregene Inc.'s second Phase 2 clinical trial of CERE-120, a gene therapy product that aims to deliver the neurotrophic factor neurturin to dying dopamine neurons in the brain. MJFF has partnered with Ceregene on the development of CERE-120 since 2005.

The potential power generally recognized to exist in neurotrophic factors has yet to be successfully translated into treatments for human Parkinson's. But decades of pre-clinical work have shown us the promise of a treatment that can stimulate sickened neurons in models of PD to repair themselves, becoming stronger, healthier and better functioning. A treatment like that would mean everything to patients.

We're excited about our second Phase 2 study of CERE-120, which launched in October at clinical sites around the country. The accumulated data on CERE-120 is compelling, both in pre-clinical models of PD and now in PD patients, and for this reason we believe our chances of success are respectably good. We've made several rational changes in our trial design and dosing methods to optimize the likelihood of inducing a robust restorative, biological response. However, no one really knows how effective these changes might be. Minimally, we hope to gain a clear answer as to whether applying the most innovative, currently available technology can allow the power of neurotrophic factors to significantly improve the status of PD patients.

The Foundation's decision to contribute support for the trial significantly aided our efforts to secure the remaining funds required to move forward. This speaks both to the Foundation's leadership in this field and to the enormous potential of neurotrophic factors to positively change the lives of PD patients. It's why we've worked so hard on this program for over eight years and continue to search for the means to demonstrate that CERE-120 can provide real benefit in patients' lives.

"As close to a Eureka! moment as it gets" leads to a multi-million-dollar development deal targeting alpha-synuclein:
Gerard Griffioen, Chief Scientific Officer, reMYND

In Parkinson's disease the alpha-synuclein protein aggregates to form Lewy bodies, microscopic clumps that are the pathological hallmark of PD. Alpha-synuclein is a high-priority research area for MJFF because growing evidence supports the idea that decreasing its levels in the brain, or inhibiting its toxic properties, could be a way to slow or stop Parkinson's progression.

When reMynd discovered potential compounds to inhibit noxious alpha-synuclein aggregation linked to Parkinson's disease, one in particular, ReS9-S7, was a standout. As it turned out, the compound harnessed a previously unknown molecular mechanism clearing alpha-synuclein. We were excited by its elegant mode of action, which removes specifically the toxic forms of alpha-synuclein that cause brain cells to die in PD.

In 2009, MJFF funded us to perform dose-response studies in our pre-clinical model showing that ReS9-S7 was worthy of further investigation. When we found that our compound had potent and robust therapeutic effect at a very low dose, it was as close to a Eureka! moment as it gets. We knew we had found a promising effect in pre-clinical models and we wanted to bring this to patients as rapidly as possible.

Thankfully, our findings didn't go unnoticed. In September 2010 Roche Pharmaceuticals partnered with us, committing up to $637 million for the continued development of disease-modifying drugs for PD and Alzheimer's disease, including ReS9-S7. Roche has the experience, expertise and resources in clinical development that we don't have, so this partnership is critical in speeding the results of our work to patients.

I am certain that without MJFF funding we would not have garnered this attention. My relationship with the Foundation is a very constructive and positive one. MJFF is not only a funder but also a thought leader for Parkinson's research; its staff is constantly monitoring developments, finding new opportunities for translation and applying the resources to push the science forward. It's a source of inspiration to me — and I know many other researchers feel the same way.

Making biomarkers a reality sooner rather than later:
David Vaillancourt, University of Illinois at Chicago

The discovery of consistent and reliable biomarkers of Parkinson's disease holds promise to transform PD diagnosis and drug development. This year, The Michael J. Fox Foundation launched the Parkinson's Progression Markers Initiative (PPMI), a landmark $40-million study to identify and validate PD biomarkers. Diffusion tensor imaging (DTI), a special form of MRI scanning, is one of the sophisticated neuroimaging techniques that will be tested as a potential PD biomarker through PPMI.

PPMI is looking for biomarkers in three areas: biological samples (such as blood and spinal fluid), clinical and behavioral assessments, and neuroimaging tests, including DTI. Our laboratory has already showed that DTI is capable of distinguishing newly diagnosed PD patients from people who do not have the disease. Through PPMI, we'll have a larger dataset to test our algorithms for determining if DTI can accurately predict a diagnosis — that is, serve as a biomarker — of Parkinson's disease.

DTI tracks the directional flow of water molecules in the brain and has been shown to reflect changes in the number of dopaminergic neurons. Many medical institutions have access to a DTI scanner, and we've found that people with movement disorders can undergo this type of brain scan comfortably and successfully to deliver high-definition images. DTI doesn't require as much infrastructure as some other imaging techniques, and it is quick. DTI also has the potential for differentiating between movement disorders, which is the focus of other work we are doing with funding from the Foundation.

It is amazing to me that with all that science has to offer, PD is still diagnosed by clinical judgment. A low-cost, noninvasive, highly sensitive and specific diagnostic toolkit that allows for an objective diagnosis is critical not only to lessen the impact of misdiagnosis on individual lives, but also to speed and streamline drug development-particularly when it comes to disease-modifying treatments, the kind patients need most. By leading PPMI, The Michael J. Fox Foundation has galvanized PD researchers and clinicians to make this vision a reality sooner rather than later.

Priorities + Progress

Working to eliminate a "terrible tradeoff" in the management of Parkinson's disease:
Charlotte Keywood, Chief Medical Officer, Addex Pharmaceuticals

One promising approach to dyskinesia (the excessive, uncontrollable movement that is a complication of long-term dopamine replacement therapy to control the symptoms of Parkinson's disease) could lie in a specific glutamate receptor known as mGluR5 (Metabotropic Glutamate Receptor Type 5). MJFF has been shepherding mGluR5 through development with different research teams since 2005. In August, Swiss biotech Addex Pharmaceuticals received Foundation funding for a Phase 2 clinical trial testing their mGluR5-targeting agent known as ADX 48621.

One of the paradoxical consequences of dopamine replacement to control PD symptoms is the disabling dyskinesias that typically occur after years of levodopa use. Patients often delay or reduce the optimal dose of levodopa in an effort to avoid this complication. It is a terrible tradeoff.

Our drug has been shown to successfully inhibit the mGluR5 receptor in pre-clinical models, dampening excessive signaling activity caused by glutamate, which may be responsible for levodopa-induced dyskinesias.

The MJFF funding gives us an opportunity to see if we can replicate these positive pre-clinical results in a small group of people with PD. In the next phase of our study we will monitor the antidyskinesia effect our drug has on morning, midday and evening doses of levodopa. We will also collect data from patient diaries to monitor the amount of on- and off-time they experience. This will allow us to track our drug's impact on overall Parkinsonian disability and quality-of-life factors.

Financial support from The Michael J. Fox Foundation is tremendous for a small company like Addex. But it's the recognition and validation the Foundation has bestowed on our research that gives us the impetus to carry on what we are doing. To know that we will contribute to a therapeutic strategy for the treatment and prevention of dyskinesia is an amazing feeling because it will be a great leap forward in the care of people with PD.

Homing in on the underlying cause of PIGD:
Chantal Francois, Researcher First Class, Hôpital de la Salpètriére

Evidence suggests that PIGD (postural instability and gait disturbances) stems in part from a region of the brain called the pedopontine nucleus (PPN) that is not responsive to dopamine replacement. Studying the specific neurons involved in PIGD will allow researchers to develop therapies that target this region — and offer hope for patients who suffer from this troubling constellation of symptoms that include freezing of gait, shuffling, and falling.

Current PD therapies such as dopamine replacement and deep brain stimulation do not address the troubling and often disabling postural and balance problems that affect many patients with advanced Parkinson's disease (along with the "classic" symptoms such as tremor and rigidity). In fact, there are no approved treatments for these problems.

To develop effective therapeutic strategies for advanced PD, we need to first identify the underlying causes of symptoms. This past year, our lab developed a pre-clinical model that clearly demonstrates that cholinergic neurons in the PPN are involved in the onset of PIGD symptoms. This finding is extremely important because we now have a basis from which to study all of the anatomic structures involved in PIGD and advanced Parkinson's, and to develop a targeted therapeutic approach.

Our model offers a natural representation of the spectrum of symptoms found in advanced PD. Going forward, it will allow us to identify areas of dysfunction within and related to the PPN that specifically affect balance and posture. Homing in on these anatomical regions will enable us to define therapeutic targets and develop pharmacologic or surgical interventions that address all of these symptoms.

MJFF funding was crucial to help us validate the hypothesis that the PPN is implicated in PIGD, and develop a more comprehensive, realistic model of advanced Parkinson's. With the Foundation's support, we can use what we have learned to discover areas of the brain that will serve as viable therapeutic targets — a critical step in moving our research out of the lab and into the clinic.

Answering the "make-or-break questions" about LRRK2:
Andrew West, University of Alabama at Birmingham

The LRRK2 gene holds tremendous promise as a therapeutic target for PD. Not only is it the single most common known genetic cause of the disease, but it encodes a protein kinase — a type of cellular enzyme that is often highly 'druggable' (modified by orally administered, small-molecule drugs). Development of LRRK2-targeted drugs may lead to highly potent therapies capable of blocking disease progression in many people with Parkinson's disease (not necessarily just in people with relatively rare LRRK2 mutations).

We know, primarily from extensive learnings out of cancer research, that kinase activities such as that seen in LRRK2 are relatively easily modified with small-molecule drugs in the clinic — treatments that pharmaceutical companies have a great deal of experience developing. This year, our lab was part of a team that demonstrated that the kinase activity of LRRK2 is specifically implicated in the cell death characterizing PD. This has been suspected, but we now have some initial evidence to build on, which is very important in pushing research forward. The work has helped to validate LRRK2 kinase activity as a target for new drugs, created a strong new model for studying the cell death seen in PD, and enhanced the field's understanding of the relationship between LRRK2 and cell death. These are all major factors in lessening the risk for industry to invest in LRRK2-based therapeutics.

LRRK2 researchers also made strides this year in the area of research tools. Led by The Michael J. Fox Foundation, the PD research community came together to validate high-quality LRRK2 antibodies — a laboratory "ingredient" required to carry out LRRK2 experiments. Those antibodies had eluded us for years, and thanks to the Foundation's leadership, they can now be freely ordered by any laboratory from a lab supply catalog at low cost.

The Foundation is working strategically to seed the therapeutic development pipeline with new LRRK2-based drug candidates while at the same time prioritizing the development of better research tools that will push these candidates forward to conclusive clinical testing faster. The goal is to help the field identify and answer the make-or-break questions that will move next-generation therapies out of the lab and into the hands of patients as rapidly as possible.

special insert

Celebrating Five Years of TEAMFOX

Launched in 2006, Team Fox is the grassroots fundraising network for The Michael J. Fox Foundation — thousands of people using their unique talents and passions to help speed a cure for Parkinson's disease. In five short years, this incredible group has raised a jaw-dropping $10.5 million to support the Foundation's aggressive research agenda. Read on or visit **www.teamfox.org** to learn more about the phenomenon that is Team Fox!

By the Numbers...

Total funds raised to date: $10.5 million

2006: $1.2M	2007: $1.7M	2008: $2.1M	2009: $2.9M	2010: $3.5M projected

Events held in 2010: 300*

Team Fox wristbands shipped by the FoxShop in 2010: 6,728*
Get yours today: shop.michaeljfox.org

Active memberships to date: 2,686

2006-07: 400	2008: 550 (Challenge Year!)	2009: 736	2010: 1000*

Where you'll find us:
United States United Kingdom Australia Austria Bermuda Brazil Canada China Denmark Finland France Germany Great Britain Ireland Japan Mexico Puerto Rico Slovakia South Africa Spain Turkey Netherlands

Northeast: 1,040	South: 355	West: 360	Midwest: 220	International: 136

35,000: Miles run by all Team Fox marathoners combined.
(One trip around the equator in miles: 25,000)

Flowers sniffed in four years of Mary Anne Ostrenga's **Garden Walk: 3,000****

Bartenders who have mixed drinks in five years of Susan Bilotta's **Tips for Parkinson's: 80**

Mountains climbed by **The Regulars** so far: **11** (160,556 vertical feet!)

Divots stomped in three years of Bill and Daniel Wilkins' **Polo for Parkinson's: 414****

65: **Pancakes for Parkinson's** events hosted to date
(including Denny's Pancakes for Parkinson's at over 35 restaurants in spring 2010!)

Total pancakes flipped for PD to date: **30,000****

* and counting!

** (our best guess)

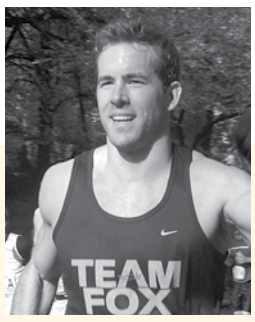
Celebrating Five Years of TEAMFOX

www.teamfox.org

Photo Contest Winners

In July, Team Fox launched its first-ever Team Fox Photo Competition. Over 120 photos were submitted on Facebook, and five winners were chosen by Team Fox Celebrity Chair and MJFF Board member Ryan Reynolds.

"A picture is worth a thousand words, and one glance at these photos reveals how much creativity and passion Team Fox members bring to the pursuit of a cure for Parkinson's disease," said Ryan. "I was inspired by every shot I looked at — it was difficult to select just five winning entries! My deepest thanks to everyone who took part in the contest and, of course, to everyone working to raise funds and awareness for Parkinson's research. It's an honor to be part of this group."

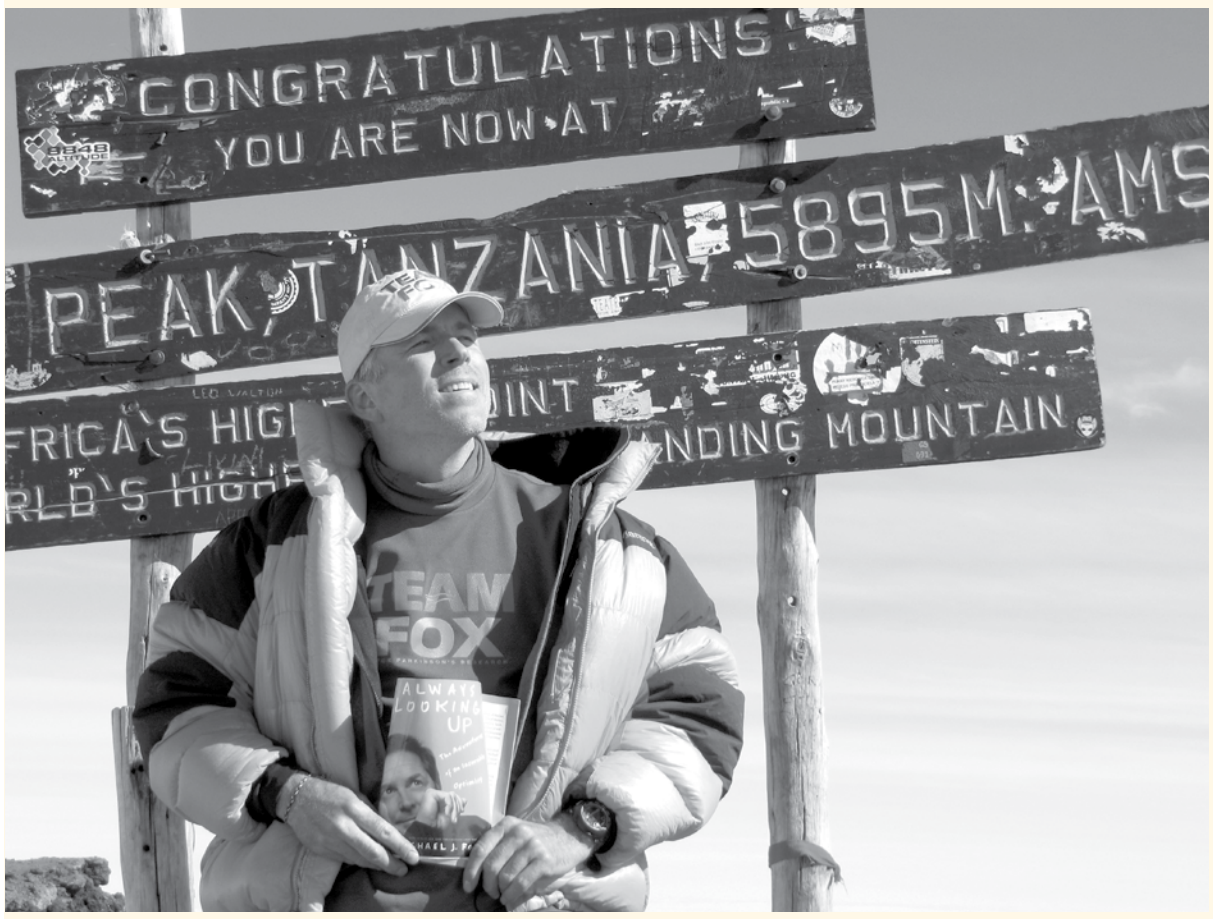


Ryan ran his own Team Fox marathon in 2008, raising over $100,000.

Skip Bailey of Wellington, Florida, biked from Coast to Coast to raise funds and awareness for MJFF in honor of his dad, Arch, who has PD. Here, his dog wears a Team Fox singlet and gives him a high five!

Oliver and Terry Holler of Myrtle Beach, South Carolina, drive their DeLorean all over the country to make a difference in the fight against Parkinson's.

Melanie Camp hosted Yoga for Parkinson's on the beach in Ft. Lauderdale, Florida. Om!



Tom Sabourin of Milwaukee, Wisconsin, climbed Mt. Kilimanjaro in 2009 to raise funds and awareness for MJFF. Here he poses with Michael J. Fox's second book, Always Looking Up*, at the peak of the mountain.*

Judy Binder's son sold lemonade at their fundraiser, "Pour for Parkinson's," in San Antonio, Texas.

Meet Our Mentors

The Team Fox Mentor Network, launched in May 2009, was created to strengthen the Team Fox community and to ensure that every member receives the highest level of support in their fundraising efforts. Each Team Fox member who joins the Mentor Network is assigned to one of our mentors — Barry Cohen, Gail Oliver, Gene Gurkoff, Katie Clark, Mary Anne Ostrenga, Mary Yonkman, Mike Dubin, Sharon Greif or Susan Bilotta. All are seasoned Team Fox fundraisers who are generously donating their time, knowledge and enthusiasm to encourage Team Fox members and assist them in reaching their goals.

L to R: Team Fox Mentors Susan Bilotta, Mike Dubin, Sharon Greif, Barry Cohen and Gene Gurkoff with Michael J. Fox at the 2010 MVP Awards.

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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WINTER 2010 NEWSLETTER

CREATE A LEGACY OF HOPE.

The Legacy Circle is The Michael J. Fox Foundation's planned giving society honoring friends who have provided for the Foundation in their wills or through other planned gifts. A thoughtful planned gift enables charitable donations at a level that you might not have thought possible, while maximizing tax benefits for you and your family.

"I am proud to be one of the original members of The Legacy Circle, a special group of donors who have discovered that planned giving is a wonderful and flexible philanthropic tool. I feel blessed to be in a position to help continue the Foundation's critical work when I can no longer write checks." — Larry Davis

Learn more about how planned gifts can help the Foundation find the cure for Parkinson's disease. Visit www.michaeljfox.org/legacy today.

Three ways you can help us tomorrow (even when budgets are tight today):

Give through your will or revocable living trust. Known as a bequest, this is accomplished simply by including a few sentences in your will or living trust.

Give a percentage of retirement plan assets. One of the most tax-wise planned gift options is to name MJFF as the primary or contingent beneficiary of a portion of your qualified retirement plan. Often, a retirement plan is a pre-tax asset and, when transferred to a beneficiary, is subject to estate tax as well as income tax. Naming the Foundation as the beneficiary can be advantageous and financially judicious.

Give a percentage of life insurance death benefits. You can name MJFF as a partial beneficiary of the policy, while retaining ownership of the policy (and thus the right to change the beneficiary designation at any time during your life). For example, consider designating 90 to 98 percent of the death benefit to your family and the remaining percentage to MJFF.

ACCELERATING THE CURE is published three times a year by The Michael J. Fox Foundation. Two issues are mailed to donors who have given $25 or more within 12 months. The year-end issue is mailed to friends and supporters who have given $25 or more within three years. Past issues are available at www.michaeljfox.org. Submit questions, comments and feedback to the editor at the address at right. To subscribe or unsubscribe, please e-mail Lorri Stamile at lstamile@michaeljfox.org.

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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 THERAPIES FOR THOSE LIVING WITH PARKINSON'S TODAY.