



REQUEST FOR PROPOSALS
ISSUED BY
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

LEAPS
(Linked Efforts to Accelerate Parkinson's Solutions)

Release Date: December 11, 2006
Pre-Proposal Receipt Date: March 20, 2007 ****Required****
Invitation to Submit Full Proposal: By May 9, 2007
Final Application Receipt Date: June 21, 2007
Anticipated Award Announcement: Mid-August 2007
Anticipated Funding: December 2007

PROGRAM OVERVIEW

Purpose

The Michael J. Fox Foundation for Parkinson's Research (MJFF) invites investigators to apply for funding through a novel mechanism called LEAPS (Linked Efforts to Accelerate Parkinson's Solutions). LEAPS are multi-year, potentially multi-million dollar grant awards for collaborative, milestone-driven efforts to address questions that will have significant practical impact on the understanding and treatment of Parkinson's disease. MJFF believes the nature and scale of such research projects require coordinated, cross-disciplinary and multi-institution approaches. *MJFF expects that LEAPS is well-suited to projects that will translate into new treatments or otherwise have a tangible impact on Parkinson's disease.*

Background

Despite considerable progress in a number of important research areas, many questions about the cause, pathogenesis and treatment of Parkinson's disease remain unanswered. MJFF believes that the LEAPS research process paradigm will accelerate progress toward the development of new and improved interventions.

The core element of the LEAPS paradigm is a focus on a critical research question whose answering would result in major practical impact on the treatment of Parkinson's disease. LEAPS grants utilize a series of coordinated, linked projects and involve a variety of disciplines. In contrast to a sequential approach to multi-experiment projects, this process is designed to accelerate progress by establishing a multi-phase research blueprint, structuring simultaneous experiments, and collaboratively sharing information at every stage. In addition, by requiring that all work be focused on a single research question, MJFF seeks to ensure highly relevant and

measurable outcomes. Given the program's emphasis on translation, MJFF expects that academia and industry will be likely partners in these efforts.

What is the LEAPS program?

LEAPS grants are goal-oriented and focused on answering a research question, one whose answer would represent a major, practical step forward in Parkinson's disease – a solution to a Parkinson's problem. Proposals focused on repairing the PD brain, slowing or halting the disease's progression, and developing interventions to significantly improve management of symptoms are of particular interest to MJFF.

LEAPS are not intended to be conventional research grants. LEAPS investigators will be asked to interact regularly with MJFF staff and advisors to discuss elements of the project, research directions, progress against stated milestones, and possible ways (other than through additional financial resources) the MJFF may offer support or assistance. *In contrast to conventional 'Center Grants', which play to the strengths of a particular institution, it is expected that LEAPS questions will be addressed by "all-star" teams – the best people to address the question at hand – regardless of their geographical location or institutional affiliation.*

Critically important to the success of a LEAPS grant is a strong Coordinating Investigator who has primary responsibility for leading and managing the project. While it is anticipated that each LEAPS will have a number of Principal Investigators, each directing various pieces of the overall research, a strong lead Coordinating Investigator who oversees the team's research plan and manages team communication internally and with the MJFF is essential.

Funds Available

MJFF intends to commit up to \$10 million to fund multiple projects under this round of the LEAPS program. Applicants may request a project period of up to four years and a budget for all direct costs of the work proposed, in addition to indirect costs of up to 25% of the direct costs. Preliminary budgets are required for the pre-proposal. Detailed budget justifications are essential to the final evaluation of full LEAPS proposals.

Although the financial plans of MJFF provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of applications of high scientific merit.

Eligibility Requirements

Applications may be submitted by U.S. and non-U.S. entities, public and private non-profit entities, such as universities, colleges, hospitals, laboratories, units of state and local governments, eligible agencies of the federal government, and for-profit entities. Post-doctoral students or fellows are not eligible to apply as Coordinating or Principal Investigators for this RFP.

LEAPS will have multiple research components, each of which has its own Principal Investigator. The Coordinating Investigator for the LEAPS proposal should be the team member who submits the application.

In addition to information required of all applicants, for-profit applicants are required to include an audited statement of financial condition demonstrating the entity's cash position and overall financial health during the full application submission stage. This information is required to ensure the entity is a viable organization for the Foundation to contract with. All financial information will be kept strictly confidential.

Applicants who are resubmitting a pre-proposal that was originally submitted to a previous LEAPS program must have substantially modified that proposal since it was originally submitted.

Grant Contracting Requirement

Successful applicants will be notified in mid-August 2007 of their selection as awardees. Funding is contingent, however, on successful contracting between consortia members, member institutions and the MJFF. The content of contract discussions will vary on a case-by-case basis; however important elements will include intellectual property sharing, use, and return payment rights. While MJFF does not pursue ownership rights of intellectual property, it does seek to ensure the right to use outcomes of funded research as well as ensure that promising outcomes can be pursued by the MJFF or a designee of the MJFF if the funded team chooses not to pursue commercialization. If an applicant foresees his or her inability to comply with the above requirements, s/he should reconsider applying to this program.

Contracting must be completed within by December 15, 2007. If contracting is not completed at this point, the grant will not be funded. A key responsibility of the Coordinating Investigator is taking the lead role on managing the contract negotiation process for his/her team and their institutions.

LEAPS Review Process

The LEAPS Review Committee (LRC) and MJFF staff will oversee all LEAPS-related matters, including application review and progress assessment. The LRC is composed of scientists and lay people familiar with the subject matter and goals of the LEAPS program. Additional expertise will be added, as necessary, based on the number and content of the applications received.

Review Criteria

Proposals will be assessed against the four categories outlined below. Each criterion will be considered in assigning an overall score, weighing them as appropriate for each application.

Proposed Scientific Idea

- Would successful completion of the project have an immediate and relevant impact in improving the lives of patients affected by the disease? Would project results advance the development of new and future therapeutics?

Scientific Team

- Are the organizational responsibilities of the Coordinating Investigator appropriate and clearly defined? Does the Coordinating PI outline how s/he plans to coordinate, update and work with the Foundation and external assessors?
- Does the proposed research team have the experience and ability to coordinate the proposed project? Do the investigators have a track record of previous collaborative work? Are the investigators well-suited to fulfill their assigned roles?
- Is the proposed collaborative structure workable – does it enhance the chances of achieving the project aims? Where are the investigators located and how will they work together?

Proposed Research Plan

- Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the goals of this RFP? Does the applicant acknowledge potential problem areas and consider alternative approaches?
- Why does this need to be done in a LEAPS structure? Do the proposed research projects and components clearly attempt to resolve the stated hypothesis? Is the effort among the collaborating PIs well-conceived and tightly coordinated? Are the project milestones ambitious yet realistic?
- Are humans, animals, and the environment adequately protected to the extent that they may be adversely affected by the project proposed in the application?

Budget

- Is the proposed budget well-justified and reasonable given the work described?

APPLICATION PROCESS

There are two stages to the LEAPS review process: Pre-Proposal and Application.

Pre-Proposal

A pre-proposal is a mandatory part of the LEAPS RFP. **All pre-proposals received in response to MJFF RFPs will be subjected to a triage process and only those pre-proposals deemed to be of suitable scientific merit will be invited to submit a full application.**

Prospective applicants must submit a pre-proposal online by **6 p.m. Eastern Time, March 20, 2007**. MJFF will no longer accept pre-proposals submitted by email. Only pre-proposals submitted online through the following link https://www.GrantRequest.com/SID_592?SA=SNA&FID=35023 will be accepted; this link will also be provided on the research section of the MJFF website (www.michaeljfox.org). Applicants may at any time refer to the Pre-Proposal Instructions posted on the MJFF website for the information needed to submit a pre-proposal online.

Pre-proposals will be reviewed by the LRC and assessed according to the following criteria:

- Responsiveness to the goals of the RFP
- Scientific merit of the proposal
- Strength of the proposed research team
- Study workplan and collaborative model used by investigators

Following the pre-proposal review, selected applicants will be invited to submit a full application. We are unable to provide written feedback to applicants whose pre-proposals are not selected by the LRC. *Decisions of the LRC as to which pre-proposals may proceed to a full application will be final and may not be appealed.* For pre-proposals selected, it is anticipated that the LRC may provide specific feedback and suggestions or require certain modifications.

All pre-proposals are treated with confidentiality by the MJFF and its reviewers in accordance with the principles set forth in this RFP.

Final Application

By May 9th, a select number of pre-proposal applicants will be invited to submit full applications. Upon invitation to apply, LEAPS applicants will be provided with detailed information about final application guidelines. **All applications will be due by June 21, 2007 at 5pm, US Eastern Time.**

SPECIAL REQUIREMENTS

Requirements for MJFF Grants

Review of the progress of each awarded LEAPS project will be ongoing, and will involve regular interaction with MJFF staff and advisors. Continued funding will be contingent on successful completion of mutually agreed-upon milestones. Multi-year support is not automatic for any award and is contingent upon several requirements:

- *Progress Reports.* Grant recipients are required to submit progress reports every six months that must be favorably reviewed by an MJFF-appointed assessment committee if funding is to continue. Progress report forms will be provided by the MJFF in advance of the six-month deadline.
- *Assessment Meetings.* Grant recipients are also required to participate in regular assessment meetings, at which they will report on the progress and evaluation of their projects. Location and other details of the meetings will be announced, and frequency will vary based on project. It is anticipated that at least one meeting per year will be in person, with others held by phone or videoconference on a quarterly basis. Travel expenses will be provided by MJFF and should not be included in the application budget.

CONFIDENTIALITY

MJFF treats all Pre-Proposals, Applications, research projects and associated research information (collectively, the “Confidential Information”) in confidence using no less than reasonable care in protecting such Confidential Information from disclosure to third parties who do not participate in the grant review process and MJFF assessments. All Confidential Information will be used by MJFF and its grant reviewers only internally for the purposes of reviews and assessments, and will be shared only in accordance with its sharing policy stated herein. Notwithstanding MJFF’s and its reviewers’ obligations regarding such Confidential Information, such obligations cover any information retained in their unaided memories and may not be used without the permission of the disclosing party. Notwithstanding the foregoing, the obligations governing the disclosure and use of Confidential Information do not apply with respect to Confidential Information that it can be demonstrated:

- (a) was generally known to the public prior to the effective date of this RFP; or
- (b) becomes generally known to the public through no unlawful or unauthorized act of omission by any recipient of Confidential Information, or in violation of this RFP; or
- (c) was independently developed by any recipient prior to the effective date of this RFP; or
- (d) was disclosed to a recipient by a third party who has the right to make such disclosure.

If any recipient of Confidential Information is requested to produce any of the Confidential Information pursuant to a legal or governmental proceeding, such recipient shall give the applicant or other owner of such Confidential Information (the “Discloser”) as much prior notice of such requirement as is reasonably practicable under the circumstances and shall use its reasonable efforts to assist the Discloser of such Confidential Information in objecting to such request. If a recipient is compelled to disclose any of the Confidential Information pursuant to such legal or governmental proceeding, such recipient shall use its reasonable efforts to assist

Discloser in obtaining confidential treatment for such Confidential Information, will disclose only that portion of the Confidential Information which is responsive to the order, and will provide the Discloser with any copies of Confidential Information so disclosed; provided that such Confidential Information shall remain confidential until it falls into one of the categories specified in this Section entitled "CONFIDENTIALITY."

CONFLICTS OF INTEREST

Principal investigators and their paid collaborators submitting applications to the RFP will be excluded from serving on the LRC that reviews their grant. However, non-applicants who are invited to serve on the LRC may still have a conflict of interest that arises during the grant review process. A LRC member is judged to have a conflict of interest if (1) he or she is a collaborator, sub-contractor, and/or consultant with an investigator that has a grant application before the LRC, (2) the application is from the reviewer's own institution regardless of whether or not reviewer has had any involvement in preparing the application, (3) the member, his/her immediate family, or close professional associate(s) has a financial or vested interest in the outcome of the proposed research (even if no significant involvement is apparent in the proposal being considered), or (4) the LRC member has been involved in discussions regarding the application, is a provider of services, cell lines, reagents, or other materials, or writer of a letter of reference for the applicant.

When a conflict of interest is deemed to be present, the LRC member will be ineligible to review the proposal and will be asked to leave the room when the proposal is discussed during the review process, including when it is scored. Nor will the results of the review be made known to the conflicted reviewer until after the entire review process is complete. LRC members are also urged to avoid any actions that might give the appearance that a conflict of interest exists, even though he or she believes there may not be an actual conflict of interest.

INQUIRIES

Inquiries concerning this RFP are encouraged. To avoid submission complications, questions are encouraged well in advance of the deadline. Any direct inquiries regarding programmatic, fiscal, and administrative issues can be addressed to: research@michaeljfox.org or 212-509-0995 x 228.

Attachment – Sample LEAPS Project Overview

Project Title: Development of Alternative Neuroprotective Agents for PD
Coordinating Investigator: Professor White, University of Freedonia

Central Hypothesis/ Objective ('Deliverable'): We will identify potential 'alternative' or non-patentable neuroprotective compounds and, after appropriate preclinical testing and toxicology studies, bring them into early phase I controlled clinical trials for Parkinson's disease.

- **Why is this important?** In the absence of a cure, stopping or slowing disease progression is of critical importance. With early treatment, neuroprotective compounds may prevent or delay impairment of motor and cognitive function. Under the best circumstances, neuroprotective compounds might allow individuals with PD to live a normal lifespan without disability.
- **Why alternative or non-patentable compounds?** Although dietary supplements, other 'alternative' agents and non-patentable compounds may hold great potential as neuroprotective therapies, manufacturers do not typically have the resources or financial incentive to perform or fund research in this area. Moreover, there is no coordinated, focused research program in this area. Thus, this is a major unmet need and timely opportunity.

Proposed Approach: The requisite steps in this process are delineated below:

(1) Identification and creation of a library of apparently safe compounds (e.g., dietary supplements); (2) Identification of mechanistic targets; (3) Development and/or application of simple, cell-based or in vitro moderate-to high-throughput screening assays to assess for desired activities; (4) Evaluation of selected compounds in the most appropriate animal models; (5) Toxicology and pharmacokinetic studies of successful candidates; (6) Phase I safety studies in human subjects; (7) planning for Phase II safety and tolerability and early efficacy trials.

Investigators, Sites and Expertise:

1. ***Creation of a library of compounds.*** We have been fortunate to enlist the world-renowned expertise of Professor Black, of the Department of Weird and Exotic Medicinal Compounds at Gotham University for this project. Black has unsurpassed experience in weird medicines and his laboratory group can synthesize kilogram quantities of pure compound in their GMP facilities. Although he has not previously worked in the PD field, Black has worked effectively in similar consortia in the past and this has resulted in a cure for cancer.
2. ***Identification of mechanistic targets.*** Concurrent with identification of compounds and creation of a library, we will identify and prioritize potential mechanistic targets for therapeutic intervention. Dr. White is a senior investigator in PD research who, through his own work, grant review work and scientific advisory board work, is familiar with current and emerging targets in PD therapeutics. Dr. White will chair an advisory committee consisting of Drs. Raven (London), Crowe (Tübingen) and Hawkes (Los Angeles) – all recognized experts in PD pathogenesis – who will convene monthly conference calls to update each other on potential targets.
3. ***Development and/or application of moderate- to high-throughput screening assays.*** We have arranged with Screens-R-Us, Inc., a biotech startup company affiliated with Best Medical School, to develop or apply a variety of cell-based and in vitro screening assays to assess compounds that may act on the target mechanisms. Assays already available for immediate use include (i) a cell-based assay for mitochondrial re-vitalizers; (ii) an in vitro assay for proteasomal rejuvenators; and (iii) a Lewy-be-gone filtration assay. Dr. Greene, Chief Scientific Officer of Screens-R-Us, Inc., formerly of Best Medical School, will lead this effort, with input from Dr. White and the advisory committee. Additionally, we will make these assays available to other PD scientists who wish to have specific compounds

screened. After approval by the advisory committee, outside scientists will be able to send their compounds to SRU.

4. ***Evaluation of selected compounds in the most appropriate animal models.*** Promising compounds from the screening assays will be tested in the animal model that is most appropriate based on the target mechanism. For this purpose, we will focus exclusively on rodent models. Dr. Brown of the Saskatoon Animal Model Institute (Saskatoon, Canada) has extensive experience with the MPTP, paraquat and rotenone models of PD. In addition, he has large colonies of transgenic and knock-in mice expressing mutant and wild type alpha-synuclein, parkin, UCHL1 and DJ-1. His group is accomplished at behavioral, biochemical and neuropathological endpoints. Test compounds will be tested in the most appropriate animal models. For example, mitochondrial re-vitalizers will be tested in the MPTP and rotenone models, and Lewy-be-gone agents will be tested in the alpha-synuclein transgenics.
5. ***Toxicology and pharmacokinetic studies of successful candidates.*** Toxicological and pharmacokinetic studies of compounds that are successful in vivo will be performed by Contract Animal Testing Services, an experienced firm located in Chappaqua, NY, that works extensively with the pharmaceutical industry. Each compound tested will be subject to a standard fee (\$32,000).
6. ***Phase I safety studies in human subjects.*** Compounds with a favorable toxicological and pharmacokinetic profile will then be assessed in Phase I safety trials contracted to Human Assessment Technology Systems in Newark, NJ. Small, single-dose, dose-escalation and 6-week dosing studies will be performed.
7. ***Phase II safety and tolerability and early efficacy trials.*** This portion of the project will not be funded under the current LEAPS proposal; however, our ultimate goal is to create a pipeline of compounds that will be ready immediately for Phase II trials. We expect these trials will be funded separately, via NIH or foundation grants or with industry sponsorship. Promising candidates that pass Phase I testing will enter Phase II testing under the auspices of the Parkinson Trials Group. This is a multi-center academic consortium that has extensive experience designing, implementing and analyzing rigorous, controlled therapeutic trials in PD. Dr. Rouge, an experienced member of the PTG will coordinate this effort, including writing grant proposals to fund the phase II trials.

Shared resources: This LEAPS project will create two important new resources available to other investigators. First, we will develop a comprehensive, moderate throughput screening program aimed at the key targets in PD pathogenesis. Second, we will develop a centralized, standardized animal model testing program for in vivo screening of neuroprotective compounds in PD. Once these facilities are operational, they will be available for testing compounds suggested by other PD investigators on a fee-for-service basis.

Preliminary Budget:

Component	Year 1	Year 2	Year 3	Year 4	TOTAL
Coordination (White)	\$40,000	\$40,000	\$40,000	\$40,000	\$160,000
Accrual/Synthesis (Black)	\$150,000	\$75,000	\$40,000	\$0	\$265,000
Screens-R-Us	\$200,000	\$200,000	\$100,000	\$50,000	\$550,000
Animal Model Testing (Brown)	\$100,000	\$250,000	\$250,000	\$100,000	\$700,000
Toxicology & PK (CATS)	\$50,000	\$100,000	\$200,000	\$50,000	\$400,000
Phase I Trials (HATS)	\$0	\$0	\$250,000	\$250,000	\$500,000
Phase II planning (Rouge)	\$10,000	\$10,000	\$40,000	\$40,000	\$100,000
Advisors & Consultants	\$12,000	\$12,000	\$12,000	\$12,000	\$48,000
Total Direct Costs	\$562,000	\$687,000	\$932,000	\$542,000	\$2,723,000
Indirect Costs (@25%)	\$140,500	\$171,750	\$233,000	\$135,500	\$680,750
TOTAL COSTS	\$702,500	\$858,750	\$1,165,000	\$677,500	\$3,403,750

Structure of Collaboration: Dr. White will be the overall Director of the LEAPS project. He is an experienced PD clinician-scientist known for his laboratory and clinical research. He has appropriate organizational and administrative experience to coordinate this effort, having been Principal Investigator of both NIH Program Project Grants and multicenter clinical trials. He is a member of the Executive Committee of the PTG. Dr. White will be ultimately responsible for coordinating the proposed work and for making sure that milestones are met in a timely fashion. While he will be primarily responsible for interfacing with the MJFF, it is recognized that there may be reason for other component leaders to also interact directly with representatives of the MJFF. We have also established an international external advisory committee to regularly evaluate and critique our progress. Members of this distinguished committee are Drs. Nobel, Lasker and Erlich.

In the early phases of the project, Dr. White will speak every 2 weeks with Dr. Black to assess accrual of candidate compounds and Dr. Greene at SRU to follow up on development and implementation of screening assays. Dr. White will lead component #2 of this project and discuss therapeutic targets with the advisory committee (Drs. Raven, Crowe and Hawkes). As compounds become available for testing in animal models, Dr. White will work with Dr. Brown to ensure that this is accomplished expeditiously and efficiently. Results will be reviewed quarterly with the international external advisory committee. Dr. White, as overall Director, will determine which compounds enter the toxicology and phase I studies to be conducted by Contract Animal Testing Services and Human Assessment Technology Systems, respectively. Finally, Dr. White will interface with the PTG as phase II clinical trials are designed. In this regard, it is important to note that Dr. Rouge of the PTG will become involved with the project at an early stage so that as candidate compounds complete phase I testing, applications can be prepared immediately to fund phase II trials.

Timeline and Milestones: As suggested by the RFA, we will set an ambitious timeline and aggressive milestones. We propose to bring to Phase II trial, one mitochondrial re-vitalizer, one proteasomal rejuvenator and one Lewy-be-gone agent within about 3 years. (These studies will require separate funding.) Please note that the milestones we propose are not strictly sequential – to some extent, they can proceed concurrently – and the pipeline of compounds continues throughout the project. The following milestones are proposed:

- Accrual and/or synthesis of 100 pure ‘alternative’ compounds – 6 months
- Development and application of necessary screening assays – 12 months
- Screening of first 50 compounds – 18 months
- Testing of 15 compounds in animal models – 24 months
- Toxicology and pharmacokinetics of 10 compounds – 30 months
- Phase I studies of 6 compounds – 48 months
- Identification of at least 3 compounds for immediate Phase II studies – 36-48 months (to be funded separately)