



REQUEST FOR APPLICATIONS

Cognitive Deficits and Mood Disorders in Parkinson's Disease

Issued by:
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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Full Application Invitation: March 3, 2008

Application Receipt Date: April 15, 2008 – 6:00pm U.S. Eastern Time

****Application Narrative: 5 page maximum**

Anticipated Award Announcement: June 2008

Anticipated Funding: July 2008

BACKGROUND

Parkinson's disease has traditionally been considered a disorder affecting the motor system. However, more attention is being paid to the non-motor facets of PD including cognitive and psychiatric disturbances. Cognitive dysfunction and emotional or behavioral disorders are often the most disabling features of PD for patients and caregivers, and their development is closely associated with poor prognosis. While the importance of these conditions and their impact on patients' quality of life is recognized by patients and clinicians alike, research in this area, including the development of effective therapies, has been hindered by lack of a fundamental understanding of the phenomenology and pathophysiology of these symptoms, and a lack of validated clinical tools to assess these aspects of PD..

It is estimated that anywhere from 20-80% of PD patients experience cognitive dysfunction, many of whom develop subsequent dementia. Psychiatric disturbances are also common in PD. Some, such as depression or anxiety, may be part of the underlying disease process, while others, such as psychosis, emotional fluctuations and impulse control disorders may be related, at least in part, to antiparkinsonian medications. Cognitive and psychiatric symptoms often co-exist and some conditions, such as apathy, may be closely related to both aspects of mental functioning. While all patients with PD experience progressive motor dysfunction, not all patients experience cognitive and psychiatric disturbances. The presence of such heterogeneity within the illness underscores the need to better understand these conditions. For example, what renders some

patients vulnerable (or resistant) to certain cognitive and/or psychiatric disturbances? What factors influence the clinical presentation of cognitive and psychiatric symptoms, or predict the development of dementia?

There is a wealth of information resulting from the study of Alzheimer's disease (AD) and primary psychiatric disorders from which PD research may benefit. It would make sense to take advantage of developments in these areas and consider if and how they may pertain to patients with PD. However, findings from other illnesses cannot simply be extrapolated and applied directly to patients with PD. Cognitive and psychiatric symptoms manifest differently in patients with PD than in those without PD, perhaps due to the specific pathophysiology of PD and its treatments. The Michael J Fox Foundation for Parkinson's Research would like to encourage individuals who have experience in PD research to collaborate with researchers from other areas, including cognitive neuroscience, neuropsychology, and psychiatry, in order to capitalize on work already done within these disciplines, and to obtain different perspectives on cognitive and psychiatric disorders in Parkinson's disease.

The MJFF encourages innovative approaches to improve the understanding and development of treatments for these cognitive and psychiatric symptoms. Both pre-clinical and clinical research proposals are appropriate for this RFA.

PURPOSE

In the interest of facilitating development of treatments for the cognitive deficits and psychiatric disorders in Parkinson's disease patients, The Michael J. Fox Foundation for Parkinson's Research (MJFF) is issuing this Request for Applications (RFA) for investigator-initiated applications designed to promote pre-clinical and clinical research to understand the biological basis of, and facilitate the development of treatments for, the cognitive deficits and psychiatric disturbances associated with PD.

Topics appropriate for this RFA include but are not limited to:

- Novel approaches to understanding the pathophysiology of cognitive dysfunction and psychiatric disorders in PD - Studies to explore the neuropathological/neurochemical substrates of these symptoms. Studies examining non-dopaminergic lesions and non-nigrostriatal pathways in Parkinson's disease are of interest.
- Development and characterization of animal models for these symptoms.
- Examination of the role of cognitive dysfunction and psychiatric disorders in disease onset, progression and prognosis.
- Development and/or validation of clinical tools (screening tests, scales, or clinical markers) to predict or assess early development of cognitive dysfunction and psychiatric disorders in PD, or to predict or assess PD dementia.
- Detailed evaluation of the impact of existing PD treatments on these symptoms.
- Pre-clinical and clinical testing of available and/or experimental treatments for cognitive dysfunction and psychiatric disturbances in PD patients.

FUNDS AVAILABLE

MJFF will commit up to \$2 million to this Cognitive Deficits and Mood Disorders in Parkinson's Disease initiative. However, awards pursuant to the RFA are contingent upon the availability of

funds and the receipt of a sufficient number of applications of high scientific merit that meet the requirements of the RFA.

- MJFF intends to fund multiple proposals as part of this initiative.
- Applicants may request an annual budget of direct costs appropriate and justifiable for the work described, in addition to indirect costs of up to 25% of direct costs. Detailed budget justification should be provided and will be subject to review.
- It is anticipated that clinical research projects could require higher budget and longer duration than pre-clinical projects, however no application may exceed a project period greater than 3 years.
- Funds awarded under this RFA cannot be used for equipment purchases or travel expenses. For clinical projects, patient travel is accepted, if applicable.
- Each item and its cost must be clearly detailed in the budget and justified within the project narrative.

Applicants should propose time-dependent milestones to ensure completion of study objectives. The project budget should closely reflect the time-dependent milestones. Continuation of funding will be dependent upon the achievement of these milestones. Additionally, multi-year support is not automatic for any MJFF award and is contingent upon the grantee's submitted progress reports being favorably reviewed by an appointed MJFF Scientific Assessment Committee.

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, and eligible agencies of the federal government and for-profit entities. **Post-doctoral students or fellows are not eligible to apply as principal investigators for this RFA.** Responsibility for the planning, direction, and execution of the proposed project will be solely that of the principal investigator.

In addition to information required of all applicants, for-profit applicants are required to include audited financial statements (income statement and balance sheet) demonstrating the entity's cash position and overall financial health. 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 in accordance with the confidentiality requirements stated herein.

REVIEW CRITERIA

The intent of this research program is to support research that will increase the understanding of cognitive and behavior alterations in Parkinson's disease and promote the development of treatments for these changes. Each of the criteria listed below will be considered in assigning the overall score, weighting them as appropriate for each application. *Please note that clinical study design criteria are extremely important for clinical research proposals. Failure to include pertinent information requested below on study design may result in triage of the application.*

- Importance of the symptom to PD patients: Does the proposed work address a cognitive/behavioral change that is of high relevance to PD patients? What is the impact of the cognitive/behavioral symptoms on patient quality of life and caregiver burden? Could improved therapies for these symptoms result in significant improvement in the lives of PD patients?

- Impact on developing treatments for PD patients: Will the proposed work have significant impact on the development of treatments for PD patients? Are the models and experimental endpoints studied relevant to PD patients? Are the proposed clinical tools sensitive to, and relevant for, the specific signs and symptoms observed in PD?
- Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the goals of this RFA? Does the applicant acknowledge potential problem areas and consider alternative tactics?
- Investigator: Are the investigator and collaborators appropriately trained and well suited to carry out this work?
- Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support? Is the proposed protection and use of animals adequate?
- Budget and timeline: Is the proposed budget and duration reasonable and justified for the research proposed? Are the proposed time-dependent milestones realistic, yet aggressive? Budgets and timelines will be evaluated in detail to determine the feasibility of the proposed work.

Criteria specific to Clinical Research Projects:

- Clinical Study Design:
 - Is the study hypothesis clearly articulated? Is the study design appropriate to the stated aims? Is the relevance to PD well-described?
 - Does the proposed study design have adequate statistical power to address the hypothesis proposed? Pilot projects with appropriate power justification are acceptable.
 - Are the patient populations studied well defined and appropriate to address the study aims? Are the primary and secondary outcome measures appropriate for the proposed study?
 - Are provisions adequate for data management, monitoring and analysis? Is the analysis plan, including pre-specified outcome measures, well described?
 - Are the procedures appropriate for research participant ascertainment, recruitment, case-definition or inclusion/exclusion criteria, and enrollment? Are there adequate controls in the study? If appropriate, does the proposed study contain a plan for recruitment of research participants? Are the milestones for recruitment reasonable and attainable?
 - Are adequate protections for human subjects described in the proposal? What procedures and precautions are proposed to monitor safety and tolerability?

APPLICATION AND REVIEW PROCESS

****Please note that Pre-Proposals are mandatory and will be used to evaluate your proposal's fit with the stated aims and review criteria of the RFA****

There are two stages to the MJFF review process: Pre-proposals and the Application Process.

Pre-Proposal

Please note that Pre-proposals are required elements of the application process. **All Pre-proposals received in response to MJFF RFAs are subject 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 February 13, 2008, **Eastern Time**. Only Pre-proposals submitted online through the following link https://www.GrantRequest.com/SID_592?SA=SNA&FID=35039 will be accepted; MJFF will not accept Pre-proposals submitted by email or postal mail. This link will also be provided on the MJFF website (www.michaeljfox.org) under open programs. Applicants may at any time refer to the Pre-proposal Requirements posted on the MJFF website for information needed to submit online.

Pre-proposals will be reviewed by MJFF scientific staff in collaboration with the Chairs of the Grant Review Committee and assessed according to the following criteria:

- Responsiveness to the goals of the RFA
- Potential impact for Parkinson's disease patients
- Scientific rationale for the proposed study
- Experimental design described in the scientific aims

Each Pre-proposal will be screened by a minimum of two reviewers. Applicants whose Pre-proposals are determined to meet the criteria above will be invited to submit full application proposals. In order to expedite the review process, we do not provide written critiques for Pre-proposals. All Pre-proposals are treated with confidentiality by the MJFF and its reviewers in accordance with the principles set forth in this RFA

Full Application

Applicants will be notified by March 3, 2008, as to whether or not they are invited to submit full applications. At that time, application instructions and all information necessary for submitting online will be distributed. All applications are treated with confidentiality by MJFF and its reviewers. Upon receipt, all applications will be reviewed for completeness by MJFF. While it is recognized that potentially useful outcomes or results of research funded by this initiative may be commercialized, grant applications must contain sufficient specific information to allow adequate scientific review. Incomplete applications will not be reviewed.

Applications that are complete and responsive to the RFA will be further evaluated for relevance and scientific merit by a Grant Review Committee (GRC) composed of scientists familiar with the goals of this RFA and with the necessary expertise. Awards will be based on the outcome of this second scientific review and an administrative review which also considers overall funder priorities. All applications will receive brief written comments.

Due to administrative limitations, all GRC decisions are final and no appeals process is available at this time. Investigators are encouraged to use reviewer comments to improve applications for a subsequent round of funding through MJFF or another source.

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 RFA will be excluded from serving on the GRC that reviews their grant. However, non-applicants who are invited to serve on the GRC may still have a conflict of interest that arises during the grant review process. A GRC 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 GRC, (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 GRC 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 GRC 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. GRC 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.

SPECIAL REQUIREMENTS

Sharing Policy

As MJFF is a public charity, research conducted with funds from MJFF (the “Research”) must be conducted in the public interest. MJFF acknowledges that any discoveries and related regulatory approvals made by researchers through the Research are the property of those conducting and responsible for the Research and that unless otherwise agreed to by the parties, such researchers have the first opportunity to exploit the Research commercially or otherwise. Notwithstanding, each Applicant acknowledges that MJFF has the right, after reasonable consultation which will not be unreasonably denied, conditioned or delayed, to release a summary of findings of the Research within 3 months from the date of the grant program expiration.

Notwithstanding the foregoing, MJFF requires that all tools or reagents (i) funded by and (ii) that result from awarded projects (collectively, the “Results”) be made readily available to the community including MJFF for research purposes. You will be required to agree that you will cooperate and collaborate with MJFF and other researchers and share access to Results on fair and reasonable terms and conditions within 3 months of grant expiration. By submitting your application, you and your institution are confirming that you are not aware of any requirements that would prohibit, delay, or restrict your ability to share your Results from this initiative, including requirements of third-party collaborators or companies with which you are affiliated.

Intellectual Property Agreements among Collaborators

Although MJFF does not specify when intellectual property (IP) negotiations must take place among researchers funded under this program, MJFF does require that collaborators agree on any material IP issues prior to submission of final applications. Proposals that do not include a letter indicating that IP matters have been addressed will not be reviewed.

Publication

It is also required that the results of the Research will be published as rapidly as possible in the open scientific literature, consistent with high standards of scientific excellence and rigor, and include acknowledgement of the funding provided by The Michael J. Fox Foundation for Parkinson’s Research.

Requirements for multi-year grants

Multi-year support is not automatic for any award and is contingent upon several requirements:

- *Progress Reports.* Progress reports are due every year. Progress report forms will be provided by MJFF approximately two months before they are due.
- *Annual Meetings.* Principal investigators on funded grants are required to attend annual meetings at which they will report on the progress of their projects, exchange information with other investigators, explore possible collaborative efforts among grantees, and identify resources that would enhance the productivity of the grantees or the field-at-large.
- *Financial Accountability.* Grantees are expected to account for the moneys expended under any MJFF grant; any moneys spent either not in accordance with the approved

research project or prior to pre-approval of any material change in your project are both (i) recoverable by, and subject to restitution by you, to MJFF and (ii) may be cause for immediate termination of funding by MJFF.

Grantees are expected to meet scheduled milestones and deliver deliverables on time, and failure to meet milestones, furnish scheduled deliverables, including any reports, or to comply with the terms of the grant may serve as one or more bases for termination of funding by MJFF. Additionally, progress reports and annual meeting presentations must be favorably reviewed by an MJFF-appointed Assessment Committee against MJFF Assessment Criteria if funding is to continue. Other details of the meetings will be announced, but the first meeting will be approximately one year from the date of funding. Travel expenses will be provided by MJFF and should not be included in the application budget.

Supplemental Funding

While we encourage awardees to seek additional funds to further their work once the term of the initial award has expired, MJFF has no policy itself for continuation of grants. Awardees are eligible, however, to apply for funding under another MJFF RFA.

INQUIRIES

Inquiries concerning this RFA are encouraged, and the opportunity to clarify any issues or questions from potential applicants is welcome. To avoid submission complications, MJFF encourages questions well in advance of the deadline. Please direct inquiries regarding programmatic, fiscal and administrative issues to Patricia Schreiber at pschreiber@michaeljfox.org, or at (212) 509-0995 x254.