THE MF CHALLENGE A GRANT PROGRAM SUPPORTED JOINTLY BY THE MPN RESEARCH FOUNDATION AND THE LEUKEMIA & LYMPHOMA SOCIETY

Call for Proposals: 01/24/13

The MPN Research Foundation (MPNRF) and The Leukemia & Lymphoma Society (LLS) are proud to announce a second round of **The MF Challenge**, a grant program whose objective is to change the trajectory and ultimate prognosis for patients with myelofibrosis, a rare and often fatal blood neoplasm. This program represents an important partnership between MPNRF and LLS, who share a mission to advance the scientific understanding of MF and the other myeloproliferative neoplasms and bring new treatments and the hope for a cure to patients with these rare diseases.

BACKGROUND

Myelofibrosis (MF) is a chronic malignant hematological disorder, one of a family of blood diseases classified as myeloproliferative neoplasms, or MPNs, by the World Health Organization. MF is characterized by an enlarged spleen, varying degrees of anemia and low platelet counts, red cells in the peripheral blood that resemble tear drops, the appearance of small numbers of immature nucleated red cells and white cells in the blood, varying degrees of fibrosis of the marrow cavity (myelofibrosis) and the presence of marrow cells outside the marrow cavity. In some patients MF terminates in conversion to acute leukemia (particularly AML).

In recent years, the MPN community was encouraged by the discovery of the JAK2 V617F mutation found in almost all polycythemia vera (PV) patients, and about 50% of essential thrombocythemia (ET) and MF patients. This first discovery of a genetic mutation that relates to the MPNs ignited a quantum leap in the level of discourse and inquiry into the genetic causes of these diseases. Many resources were directed towards inhibiting the constitutive activity of this mutant JAK2, with the expectation that a successful drug would provide an important new treatment option.

As a consequence of this research, a number of JAK2 inhibitors are currently in clinical trial(s) and are beginning to receive FDA approval. To date these drugs have demonstrated significant benefits in reducing many constitutional issues (such as enlarged spleen), and with longitudinal studies now underway, may in the future demonstrate a positive impact on disease survival. Additional genetic mutations have been found in some MPN patients, and are contributing further to our understanding of the genetic complexity of the MPNs.

The Underlying Cause of Fibrosis Remains a Critical Concern

Myelosuppression resulting from fibrosis in the bone marrow remains one of the most critical consequences of MF. Although considerable research continues to be done on the pathogenesis and treatment of MF, scientists have not been able to identify the specific mechanisms that induce fibrosis.

The prevailing hypothesis has been that the bone marrow stromal changes (i.e. fibrosis) in MF are secondary to the abnormal proliferation of hematopoietic cells, particularly megakaryocytes. This hypothesis suggests that inflammatory and "fibrogenic" growth factors (such as TGF-beta) are produced in excess by the dysplastic and necrotic megakaryocytes that characterize MF. However, recent studies indicate that stromal cells also contribute to the abnormal hematopoietic clone development through specific and mutually dependent interactions with the pathologic hematopoietic cells. Fundamental questions about the cause of MF now need to be answered in order to develop rational and targeted therapies for this disease. These questions include identification of (a) the specific mediator(s) of fibrosis, (b) the specific cell types (and cell-cell interactions) that lead to the production of such mediator(s) of fibrosis, and (c) the signal transduction pathways (and/or their suppressors) that directly lead to the stromal reactions that define this disease.

Importance to MPN Patients

As patient advocacy organizations, MPNRF and LLS receive many calls and emails from MPN patients, and over many years we recognize common threads. Patients with ET, PV or MF have concerns about symptoms, treatment options, and quality of life, but their most pressing concern is prognosis – will my disease progress, will I get MF, will I transform to AML? Our most harrowing calls are with MF patients, who face the bleakest prognosis and the greatest fears.

The emergence of new treatments for MF patients is encouraging, but until there is proof that these emerging treatments actually change the course of the disease, these fears will remain. MF will kill many of our patients, and bone marrow fibrosis will be its weapon. We at MPNRF and LLS seek to change this future, and we believe a focus on MF and fibrosis can change the trajectory of this disease. We seek the help of independent researchers who can join us in an attempt to achieve that goal.

THE MF CHALLENGE: PROGRAM APPROACH

The goal of The MF Challenge is to discover the factor(s) that induce(s) fibrosis in bone marrow, and to identify opportunities to arrest and reverse this fibrosis. We believe that such a campaign will be a game-changing opportunity for MF science and a life-changing opportunity for MF patients.

Why this Approach is Appropriate Now

MPNRF and LLS believe that a focus on MF and fibrosis is particularly appropriate now. New high throughput techniques for screening molecules have been developed in recent years that have been successful in identifying secreted proteins; these techniques have not yet been applied to research in MF. MPNRF and LLS believe that "paradigm-shifting" strategies that would use these technologies and bring a multi-disciplinary approach to identifying the cause of fibrosis could attack this riddle from an entirely new direction. Identification of the agent(s) which causes fibrosis could provide completely new targets for drug development. Agents that inhibit these targets-alone, or in combination with currently emerging MF drugs, could truly change the course of this disease.

Use Concept Grants to Stimulate New Avenues of Research

MPNRF and LLS also believe that the best way to encourage innovative research on MF and fibrosis is to encourage new ideas and potentially new researchers. We therefore propose to solicit proposals for **concept grants** designed to allow initial exploration of untested but potentially transformative research ideas and approaches. In order to receive such a concept grant, applicants must describe an innovative idea or approach and a method for testing that idea/approach within a one-year grant period. Particular attention will be given to proposals which engage novel disciplinary or interdisciplinary perspectives.

Upon completion of the one-year period, applicants will be evaluated on the extent to which their concept has been substantiated by initial testing, and selected projects would be eligible for expanded funding. The overall goal of **The MF Challenge** would be to deliver through this future funding new mechanisms for stopping and potentially reversing fibrosis, and, ultimately, saving the lives of MF patients.

MF Concept Grants will be awarded in the amount of up to \$100,000 for a one-year grant period. Depending on the response to this RFP (i.e., if multiple proposals of sufficient potential to merit an award are received), we anticipate funding up to 4 concept awards in calendar year 2013.

2012 MF Challenge Concept Grants Currently Underway

In the first round of the MF Challenge, we received 23 proposals from new and established researchers around the world. After an intensive review process, grants were awarded to:

- Ann Mullaly & Benjamin L. Ebert (Brigham and Women's Hospital
- Amit Verma and Zhizhuang Joe Zhao (Albert Einstein College of Medicine & University of Health Sciences Center)
- Pearlie Epling-Burnette and Adam Mailloux (H. Lee Moffitt Cancer Center)
- C. Arnold Spek (Center for Experimental and Molecular Medicine, Austria)

Funding for these grants began on October 1, 2012, and results of the projects will be reviewed in 4th quarter 2013 to evaluate the success of the applicants' hypotheses and to determine next steps for successful projects.

CRITERIA FOR EVALUATION

Proposals will be evaluated against the following criteria:

- Relevance to Primary Objective. As described above, the goal of The MF Challenge is to discover the factor(s) that induce(s) fibrosis in bone marrow, and to identify opportunities to arrest and potentially reverse this fibrosis. Areas of interest/relevance include but are not limited to the following:
 - Myelofibrosis caused by abnormal megakaryopoiesis and platelet production, including abnormal growth factor release
 - Myelofibrosis caused by inflammation; role of cytokines
 - > Myelofibrosis caused by disordered extracellular matrix formation
 - ➤ Myelofibrosis caused by a defective stem cell niche
 - ➤ Other models of fibrosis: e.g., pulmonary fibrosis, renal interstitial fibrosis, systemic sclerosis (scleroderma), progressive systemic sclerosis
 - > Cancer-initiating cells in myelofibrosis
 - ➤ Anti-fibrotic agents/anti-fibrotic therapy
- Innovation. Concept grants (as described by CIMIT, DOD and other agencies) are awards designed to allow initial exploration of new ideas with the potential to open new avenues of investigation. Concept grants are specifically NOT intended to support the logical progression of an already established research project. Preliminary data are not required to support your scientific rationale.
- Research Strategy and Feasibility. Does the scientific rationale logically support the project and its feasibility? Are the aims, experimental design, methods, and analyses well developed and integrated into the project? Does the PI acknowledge potential problems and pitfalls? It is a reasonable expectation that the studies will yield meaningful results in a one-year period of time?

Other Considerations:

- **Collaboration.** Proposals that engage interdisciplinary teams and approaches may receive favorable attention, as will proposals made by collaborative teams, either within or across research institutions.
- Commitment to Information Sharing: MPNRF and LLS believe that sharing data is critical for advancing the science as rapidly as possible. While understanding the confidential nature of the research process, it is our expectation that all data will be made public within a year of being generated. We encourage scientific papers, presentations at ASH or comparable venues, smaller meetings, and website publication.

KEY DATES

Call for proposals
Proposal due date
January 2013
April 1, 2013

Scientific Peer Review Committee May 31, 2013 (final review)

Notification of Awards July 1, 2013 Anticipated funding start date October 1, 2013

PROVISIONS RELATED TO INTELLECTUAL PROPERTY

The MPN Research Foundation and The Leukemia & Lymphoma Society are committed to moving the results of basic and translational research to MPN patients. To that end, we include in our contracts with the institutions of our awardees language meant to ensure that no critical results are left without productive follow-up. We ask that you review this language (which is attached to this email) with your grant/contract office and forward any questions to Allison Formal (Allison.formal@lls.org). This will greatly facilitate the contracting process following the award and help ensure grant payments begin as quickly as possible.

APPLICATION PROCESS

Applicants should prepare a grant application following the format described below and email this full proposal to the MPN Research Foundation no later than April 1, 2013. The proposal should be emailed to the attention of Barbara Van Husen at bvanhusen@mpnresearchfoundation.org.

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2013 MF CHALLENGE CONCEPT GRANT PROPOSAL Cover Sheet

Investigator Summary*
Investigator(s):
Investigator Title(s):
Investigator Position(s):
E-mail address(es):
Department(s)/Division(s)/Institution(s) or Company:
Address(es):
Phone Number(s):
Biographical Summary & relevant Published Work: (brief CV (max 5 pages) may be attached; do not attach longer CV, although a link may be provided)
*If there are co-principal investigators, please include identifying information for each

2013 MF CHALLENGE CONCEPT GRANT PROPOSAL Project Description

Project Summary

Institution/Company(s) where work will be done:	

Project Title:

Project Abstract (200 words or less):

Project Description

Project Description should be no more than three to five pages, single spaced, including any figures and tables.

- Specific Aims (please list)
- Scientific rationale/Previous Work (upon which this project will be based)
- Research Plan/Anticipated results
- Innovation statement
- Resources and Environment
- Plans for Investigator Interaction
- Human and/or Animal Investigation Statement (description of any IRB approval/status required for this project)

2013 MF CHALLENGE CONCEPT GRANT PROPOSAL Budget Information

Budget

Proposals may request up to the full amount of the grant including up to 8% indirect costs. Awards are anticipated to be up to \$100,000 for a one-year grant period.

Personnel:

Name	Role on Project	%	Salary	Fringe Amt.	Salary Total
PERSONNEL TOTAL					\$xxx,xxx

Budget Summary:

Category	Amount
Personnel Total (from table above)	
Consultant costs	
Equipment	
Supplies (itemize by category in budget justification)	
Procedures/labs	
Patient care	
General services	
Travel	
Other expenses	
TOTAL COST	\$xxx,xxx

Budget Justification: (if appropriate to further describe costs above; please limit justification to a maximum of one page)