REQUEST FOR APPLICATIONS

COLLABORATIVE PROGRAM PROJECT GRANT:
EPIGENETIC STUDIES IN MULTIPLE MYELOMA

March 2012
1. FUNDING OPPORTUNITY DESCRIPTION

Purpose:

The Multiple Myeloma Research Foundation (MMRF) is issuing this Collaborative Program Project Grant announcement in order to request proposals focused in areas of research that will lead to a better understanding of the role of epigenetics in myeloma biology and treatment. This initiative is inspired by findings from both the MMRF-funded Multiple Myeloma Genomics Initiative and published findings from other cancer research that the initiation and progression of disease is controlled by a combined regulation of gene expression and cellular processes at both the genetic and epigenetic levels. Specifically, this grant is designed to bring together researchers from different institutions that are willing to work together in a collaborative manner and enhance interdisciplinary research among the participants to study epigenetics and myeloma.

The overall goals of the research are to:

1) Identify and understand the impact of various epigenetic modifications of DNA and histones in the initiation, progression, and treatment of myeloma utilizing state of the art technologies

2) Ascertain the functional importance of proposed epigenetic targets in myeloma biology at the preclinical level

Background:

Epigenetics involve mechanisms that lead to heritable changes in DNA and chromatin without affecting the DNA sequence itself. Epigenetic regulation occurs through a series of enzyme-mediated covalent modifications that target genomic DNA, histones and other molecules. The functional consequence of epigenetic changes is the ability to regulate gene expression via changes in DNA promoter methylation, histone modifications including acetylation/deacetylation and methylation and expression of noncoding RNAs.

There is increasing evidence that epigenetic control mechanisms become dysregulated in cancer and may be involved in the initiation and progression of the disease. This dysregulation can affect the expression of a number of genes known to play an important role in cancer development including tumor suppressor genes, oncogenes and cancer-associated viral genes. Key enzymes involved in this dysregulation include: 1) DNA methyltransferases that transfer methyl groups to specific cytosine residues in the promoter regions of genes leading to gene silencing; 2) Histone deacetylases (HDACs) that deacetylate lysine moieties in the N-terminal histone tails leading to chromatin condensation resulting in transcriptional repression; 3) Histone acetyltransferases (HATs) having the ability to acetylate histone tails leading to a decondensation of chromatin and transcriptional upregulation and 4) Histone methyltransferases (HMTs) that methylate H3 and H4 histone proteins leading to alterations in gene expression. It is not surprising that DNA methyltransferases and HDACs have served as targets for therapeutic intervention in the treatment of cancer and HMTs are now being studied as well.
In myeloma there are several lines of evidence to support the involvement of epigenetic controls in disease initiation and progression. First of all, 15-20% of myeloma tumors are associated with the t(4:14) chromosomal translocation that leads to overexpression of both MMSET (WHSC1, NSD2) and FGFR3 genes via insertion of these genes next to the immunoglobulin promoter/enhancer element. Recently it has been shown that MMSET has histone methyltransferase activity and its overexpression in t(4:14) positive myeloma tumors may lead to changes in gene expression due to epigenetic regulation by MMSET. In addition recent genomic findings from initial sequencing of 38 myeloma tumors in the Multiple Myeloma Genomics Initiative funded by the MMRF identified mutations in various histone methyltransferase genes. The functional consequence of these mutations remains to be determined. Other genomic findings have identified inactivating mutations of a histone demethylase (UTX). Therefore, the combined results described above indicate that the regulation of histone methylation is a potential therapeutic target.

The second line of evidence supporting the involvement of epigenetic control mechanisms in myeloma is in the context of histone acetylation and deacetylation. HDAC inhibitors are active preclinically in myeloma specific cell assays and models. In addition, the positive results of different HDAC inhibitors in early clinical trials have led to Phase III clinical studies with the HDAC inhibitors, vorinostat and panobinostat.

Finally, and with respect to DNA methylation, initial studies have been conducted to look at the role of this epigenetic modification in the disease. Consistent with other cancer findings, there appears to be genomic hypomethylation as a mechanism of disease progression in myeloma and rare hypermethylation events that warrant further characterization.

Specific Research Objectives:
The specific research areas of interest for this collaborative program project grant include, but are not limited to, the following areas:

- Characterization of the global multiple myeloma epigenomic landscape in both MM cell lines and primary human myeloma samples including DNA methylation, histone markers and miRNA expression utilizing cutting edge technologies. Characterization in the context of different genetic alterations (i.e., chromosomal and gene mutation) that have been established in myeloma is encouraged

- Cross laboratory validation of top tier and emerging epigenetic targets in multiple myeloma. Characterization of the regulation of target activity and identification of the genes that are regulated by these targets would add value

- Functional validation of the mutations that have been identified in epigenetic targets in myeloma as driver or passenger mutations in the disease

- Generation of preclinical tools that will be useful across multiple epigenetic targets for potential drug discovery and biomarker analysis

- Epigenetic events that are associated with treatment of the disease (i.e., predictive/prognostic biomarkers)

All objectives can be applied to study the initiation and progression of the disease as well as epigenetic control events that are involved in the transition from MGUS to Smoldering Myeloma to
Symptomatic Myeloma. In addition the specific objectives are not limited to myeloma tumor cells but can also be applied to the cells in the tumor microenvironment.

2. KEY DATES

- Release of RFA: March 6\textsuperscript{th}
- Application Due Date: June 30\textsuperscript{th}
- Peer Review: July-September
- Award Announcement: October 1\textsuperscript{st}

3. ELIGIBILITY

Requirements:
This purpose of this program project grant (referred to as “Collaborative Program”) is to be a collaborative, multi-institutional program (at least 2 separate research institutions) consisting of a maximum of 3 major research aims (referred to as “research projects”) that collectively will lead to a better understanding of the role of epigenetics in myeloma disease biology and treatment. The specific research projects proposed in the Collaborative Program should be cohesive, sharply focused and enhanced by interdisciplinary research among the participants. The Collaborative Program grant can be used to support scientific core laboratories required by the component research projects, so as to provide access to key technology or facilities that might not otherwise be available to individual research projects.

The Collaborative Program will be judged as a unit and funding will not be available for otherwise meritorious parts of the application. The quality of all the projects and cores and the enhancement to be achieved by linking them together will determine the likelihood of funding. The Collaborative Program grant applicants will be judged principally, although not solely, on three main features of the application: 1) the significance of the research to the overriding goal of a better understanding of epigenetics in myeloma 2) prior accomplishments of the investigators in the field of myeloma and/or epigenetic research and 3) the synergy and collaboration that would result from knitting the projects together into an interactive program.

Leadership and staffing:

The Collaborative Program shall have a Principal Investigator (Program Director) who is responsible for the preparation and submission of the application and budget, the conduct of the research programs and for adherence with all stipulations in the MMRF’s guidelines. In the situation that a Collaborative Program has justification to name co-Principal Investigators, one of the co-Principal Investigators will serve as the Program Director. No more than 2 co-Principal Investigators can be named for a given Collaborative Program.

Each individual research project should have a Project Leader responsible for the management of that project under the overall direction of the Program’s Director. The Program Director and/or the additional co-Principal Investigator must also be the Project Leader of a research project. A detailed management plan must be provided with the application that clearly defines the roles and responsibilities of the Principal Investigator and/or co-Principal Investigators including the selection of the Program Director and the responsibilities of the Project Leaders.
The Program Director and the Project Leaders must hold an M.D., Ph.D., or equivalent degree, and be from not-for-profit 501(c) 3 organizations, or their international counterparts/equivalents, including universities, colleges, hospitals, research organizations and/or clinical laboratories.

If the Program Director leaves the institution to which the award is made, is incapacitated, or is otherwise unable to conduct the leadership expected, the MMRF must be notified immediately and the MMRF may in that circumstance terminate funding of the Collaborative Program grant within 30 days of the incapacity or departure of the Program Director unless a new Program Director with equivalent qualifications can be named. If a Project Leader leaves the institution or is incapacitated, the MMRF must be notified immediately. The Institution and Program Director must inform the MMRF of actions to be taken to replace the Project Leader and the project or core. The MMRF shall have the prerogative to suspend funding for the Collaborative Program within 30 days after notification should a resolution satisfactory to the MMRF not be proposed. If a Project Leader of a project or a core intends to move to a new institution during the course of the Program grant’s term of award and the Program Director feels that continued participation, integration and function as a Collaborative Program is desirable and possible, the Program Director must submit a detailed explanation and justification for continued participation at the new site. This request must have the approval of the institution at which the Collaborative Program resides and the new institution to which the Project Leader of the project or core is moving. The MMRF will retain the right to discontinue funding for the Collaborative Program within 30 days after departure of a Project Leader of a research project or scientific core if arrangements, acceptable to the MMRF, are not concluded.

4. Review Process
Each application will undergo a thorough review that consists of two parts: an internal review by the MMRF for compliance with guidelines, eligibility, and appropriateness; and a second more extensive external peer review by recognized experts in both the myeloma and epigenetics field.

The review criteria include:

1. Importance of the research to contributing to a better understanding of the role of epigenetics in myeloma
2. Demonstration of the synergy and interdisciplinary nature of the proposed collaborative projects and/or cores compared to the team members working independently
3. Clarity of thought and written presentation of the overall program goals and research projects
4. Likelihood of technical success as balanced by scope of work and novelty of the proposed collaborative program
5. Experience, background, and qualifications of investigators (Principal Investigator(s) and Project Leaders)
6. Appropriateness of the budget
7. Quality of the resources and environment (facilities, special equipment, patient population, etc)
8. Adequacy of provisions for protection of human subjects, laboratory animals and investigators and staff using biohazardous materials or procedures

Written critiques of the application are not provided to applicants.
5. Funds Available
The MMRF intends to fund 1 collaborative, multi-institutional program project grant for the study of epigenetics and myeloma. The Collaborative Program’s annual funding including both direct and indirect costs cannot exceed more than $500,000. The aggregate funding (direct and indirect) over the course of 3 years cannot exceed $1,500,000.

Permissible direct costs include:
- Personnel Expenses of the Program Director and Project Leaders, post-doctoral researchers, and non-administrative staff including salary, wage, or stipend with fringe benefits. No more than 40% of the direct costs may be requested for the salary and fringe benefit expenses of professional staff with a post-graduate degree (Ph.D., M.D., D.V.M.). The 40% limit does not include the salary and fringe of technical research staff.
- Supplies and materials as itemized in the budget
- Annual travel expenses of no more than $2000/meeting for 1 researcher/research project for attendance to a nationally-recognized scientific/medical conference

Permissible indirect (also referred to as institutional) costs:
- May not exceed 10% of direct costs.

Impermissible Costs:
- Membership dues, books, journals, publication costs and tuition

The funds awarded shall be used solely for the purposes specified in the application submitted to the MMRF as executed by the Principal Investigator (co-Principal Investigators), collaborating staff and institution in compliance with the budget annexed to the application, or any subsequent budget approved by the MMRF.

6. Progress Report and Annual Continuation

Annual progress reports are strictly required for continuation of annual funding of the program. The Program Director must submit a report (limit of 10 pages) of the progress of all research projects in the Collaborative Program 60 days prior to the grant anniversary date in each year that the grant is in effect. The report should briefly review both research progress since the last report and research plans over the course of the year for each project in the Collaborative Program. Furthermore there should be a list of any publications and a disclosure of intellectual property (see Section on Patents/Inventions) that were derived from the Collaborative Program. The report should include a report from the Financial Officer of the Sponsoring Institution detailing how the grant funds were expended over the course of the year. Finally, the Principal-Investigator (co-Principal-Investigators, and Project Leaders) will be expected to make an oral presentation to the MMRF summarizing the progress to date on an annual basis and within 30 days of submission of the written progress report.

These reports shall be reviewed by the MMRF in order to evaluate the research progress of each Program. The MMRF will use that report as the basis for continuation of the Collaborative Program.
for an additional year of funding. This process will be used to annually fund the program for up to three years.

Although awards are for a three-year period, the MMRF reserves the right to terminate any grant if it determines that there has been inadequate research progress or if progress reports are delinquent for more than 30 days.

7. Final Reports

Within 90 days of the expiration of the grant period, the grantee shall submit a summation of the research, together with copies of all publications and/or disclosure of intellectual property derived from the research. A one paragraph summary of the research project must be included for the lay public. The final payment shall be made only after the receipt by the MMRF of a satisfactory final research report and a satisfactory final accounting report.

8. Application Information

Applications should be submitted through the proposalCENTRAL Application System.

For scientific inquiries contact:
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383 Main Ave., 5th Floor
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For administrative and budget inquiries contact:
Mariadora Saladino
Grants Coordinator
Multiple Myeloma Research Foundation
383 Main Avenue, 5th Floor
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Phone: 203.652.0229
Email: saladinom@themmrf.org

9. Contract and Terms of Award:

Upon receipt of the Notice of Grant Award, the applicant organization will provide the MMRF with the name and contact information for a legal representative who is authorized to negotiate on behalf of the institution. The MMRF reserves the right to withdraw the grant award if the parties fail to agree to grant terms within 90 days of the Notice of Grant Award.

The failure of the grantee and/or the sponsoring institution to adhere to any of the terms and conditions in the contract shall constitute sufficient grounds for the MMRF, in its discretion, to withhold any or all funds due until the deficiency is corrected. Either the MMRF or the sponsoring
institution may terminate the contract upon giving 90 days written notice, if the deficiency cannot be corrected. In such case, any unexpended balance of funds must be returned to the MMRF.

10. Assurances

Human Investigation

The grantee (Program Director and/or Project Leaders) must obtain approval from the sponsoring institution’s Institutional Review Board on use of human subjects in research if the project requires the use of human materials or subjects. Written approval of the Institutional Review Board on use of human subjects must be submitted to the MMRF. Failure to notify the MMRF of use of human materials or subjects in a grantee’s research may result in termination of the grant.

Laboratory Animals

The MMRF adheres to the most current guidelines applicable to the care and the treatment of animals in laboratory work as outlined by the National Institutes of Health. For projects which involve laboratory animals, approval from the Sponsor’s Institutional Animal Care and Use Committee (IACUC) must be obtained. The approval date and Animal Welfare Assurance number must be provided to the MMRF. Non US applicants should submit approval documentation from the Animal Ethics Committee. The grantee must include in the application a statement that the sponsoring institution meets and adheres to these policies whether or not the use of laboratory animals is planned in the proposal. Failure to notify the MMRF of compliance with these guidelines on the use of laboratory animals may result in termination of the grant.

Biohazards

The grantee must include in the application a statement about any potential biohazards and a description of the safeguards planned where such hazards to the investigator, other personnel or any other individuals may be encountered. The MMRF assumes no responsibility or liability for any such biohazards and shall be held harmless from the results of the use of any such biohazards.

Patents/Inventions

Notification of all patent applications resulting from research funded by the MMRF that may be filed by the grantee or by the grantee’s sponsoring institution must be made in writing to the MMRF as part of each annual and final report. The MMRF must also be notified of any patents filed, based on MMRF funded work, after submission of the final report. If a Collaborative Program Grant is awarded, the MMRF’s research contract requires that the funded institution negotiate an appropriate sharing of any future royalty income (as defined in Research Contract).

11. About the Multiple Myeloma Research Foundation (MMRF)

The Multiple Myeloma Research Foundation (MMRF) was established in 1998 as a 501(c)(3) non-profit organization by twin sisters Karen Andrews and Kathy Giusti, soon after Kathy’s diagnosis with multiple myeloma. The mission of the MMRF is to relentlessly pursue innovative means that
accelerate the development of next-generation multiple myeloma treatments to extend the lives of patients and lead to a cure. As the world's number-one private funder of multiple myeloma research, the MMRF has raised over $190 million since its inception and directs 90% of total budget to research and related programming. As a result, the MMRF has been awarded Charity Navigator’s coveted four star rating for nine consecutive years, the highest designation for outstanding fiscal responsibility and exceptional efficiency. For more information about the MMRF, please visit www.themmmrf.org.