



REQUEST FOR APPLICATIONS

**Identification and Validation of Novel High Risk
Multiple Myeloma Targets Leveraging CoMMpass
and Existing Genomic Data Sets**

July 2017

FUNDING OPPORTUNITY DESCRIPTION

Purpose/Overall Goal

The Multiple Myeloma Research Foundation (MMRF) is issuing this Request for Application (RFA) in order to attract innovative projects aimed at identifying the next generation of therapeutic targets and/or pathways or biomarkers for high risk multiple myeloma (MM). Applications for the MMRF *“Identification and Validation of Novel High Risk Multiple Myeloma Targets Leveraging CoMMpass and Existing Genomic Data Sets”* are due Monday, October 2, 2017 at 5pm EDT. Recent genomic studies including the MMRF CoMMpass study have provided many potential targets to be further studied and validated in high risk multiple myeloma. The goals of this RFA is to support efforts to identify and validate novel target(s) that could be exploited for therapeutic intervention. Proposals may request up to \$500,000/year for two (2) years and will be reviewed by a committee of myeloma and translational research experts appointed by the MMRF.

Rationale for the RFA

Multiple myeloma (MM), a plasma cell malignancy, is the second most common blood cancer and still remains largely a fatal disease. In 2017 there will be an estimated 30,000 new cases of MM diagnosed and 12,500 deaths from the disease in the United States alone. With over 118,000 patients, there still exists critical unmet medical needs in MM. The last three years have seen an exceptional number of new myeloma therapeutics approved and benefitting patients. Even with these new treatments, approximately 20% of myeloma patients lose their battle with the disease within 3 years of diagnosis. The identification of the molecular drivers that contribute to this early disease progression are urgently needed. Using current genomic data sets, like CoMMpass, it may be possible to identify and gain a better scientific understanding of these drivers and allow for the discovery of new therapeutics or the ability to better utilize current therapies.

Over the last decade, several large scale genomic studies have focused on MM. Two such efforts led by the MMRF are the Multiple Myeloma Genomics Initiative (MMGI) and the Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile (CoMMpass) study. CoMMpass is a prospective, longitudinal, observational study and has collected and analyzed tissue samples, clinical data and genomic information from 1,154 newly diagnosed multiple myeloma patients for the last six years. The goal is to map the genomic profile of each patient to clinical outcomes in order to develop a more complete understanding of patient responses to treatments. As the data continues to mature, many genomic alterations that were first observed by MMGI have been confirmed by analysis of CoMMpass data. This comprehensive genomic approach in MM has uncovered a number of novel genetic alterations (translocations; overexpression/deletion of genes, point mutations) implicating specific genes as potential targets to further explore for their involvement in high risk multiple myeloma. The overall purpose of this RFA is to leverage CoMMpass data in conjunction with other existing genomic data to select novel molecular targets and pathways that may be relevant to high risk myeloma and validate the selected novel targets. The target validation studies proposed in the grant application should assemble a package of data utilizing a variety of assays, technologies, and reagents to demonstrate the relevance of the target(s) in high risk myeloma establishing its importance for further translational work and potential therapeutic intervention.

Specific RFA Objectives

The MMRF is requiring investigators to use genomic data generated via CoMMpass as well as information from other data sources to select potential targets. Using the information from genomic studies, applicants will identify a target (gene and/or pathway) that will require further

validation for relevance to high risk myeloma. The proposed target(s) should be novel for high risk multiple myeloma. They may include cancer targets that have been well characterized but have not yet been validated in the MM high risk setting. In addition, the RFA is not intended to support new, large scale target screening efforts, but rather leverage CoMMpass and existing genomic data and related observations towards selecting and validating the next generation of high risk MM targets ultimately for potential therapeutic intervention.

The focus of the grant proposal is to validate the selected target(s) in myeloma by generating a robust data package of scientific information in order to help guide the decision on proceeding with further translational activities. Validation methodologies may include but are not be limited to:

- RNA interference and CRISPR technologies aimed at validating individual genes or sets of genes in selected pathways
- Cell-based assays designed to generate information, not only about phenotypic alteration, such as growth arrest or cell death, but also about the effect on particular molecular targets of pathways known or suspected to have biological relevance
- Engineered mammalian cell lines or animal models of various types (transgene-expressing, knock-out, knock-in etc.)
- Pharmacological validation with small, bioactive molecules, or biologics (antibodies, peptides) where the cellular effects of such agents can be placed rapidly in the context of expected action against the target

Ideally one would demonstrate that manipulation of the target function would cause phenotypic changes in the myeloma cell itself or in the way it interacts with its microenvironment *in vitro* or *in vivo*. Such phenotypic or functional effects may include for example myeloma cell death, the elimination or reversal of dysregulated growth, changes in the activity of given cellular pathways and altered production of validated surrogate markers such as the M-protein or free light chain.

In keeping with the MMRF mission to find a cure for multiple myeloma by relentlessly pursuing innovation that accelerates the development of next-generation treatments to extend the lives of patients, thoughtful consideration should be given to translation of the findings on a given target(s) from the bench to the clinic. To that end, all funded PIs are required to attend and present results and plans at an annual meeting hosted by the MMRF to share progress and plans (one additional senior investigator from each program may also attend). This meeting will be held under confidentiality agreements signed by the attendees. Travel fees to attend this meeting are paid through the grant and therefore must be included in the budget and no additional funding will be provided. In theory, once a target is fully validated, efforts can be initiated toward the discovery of drug molecules through screening and/or drug design programs. The annual meeting will provide a forum to gather input from the group potentially leading to more efficient translation of results to the clinic. Alternatively, there may already be agents targeting a given protein/pathway in clinical development in other indications that could be repurposed for myeloma. It should be noted that other MMRF RFAs to support such screening activities could become available in the future.

KEY DATES:

- July 31, 2017 – Request for Applications issued
- August 14, 2017; 5PM EST- LOI Due Date
- October 2, 2017; 5PM EST – Application due date
- Early December – Applicant notification
- First quarter 2018 - Anticipated funding start date

FUNDS AVAILABLE:

The MMRF intends to fund awards up to \$500,000/year total costs, including up to 10% indirect costs, for a two (2) year period.

SUBMISSION OF LOI:

- A 1-2 page letter of intent should be submitted by 5 PM EDT on August 14, 2017 and include the following information:
 - Name of Principal Investigator and Institution
 - Name of other Co-Investigators and their respective institutions
 - Brief summary of expertise/value add from each investigator and institution
- Submission by email to:

Christopher Williams
Vice President, Business Development
Multiple Myeloma Research Foundation
383 Main Ave., 5th Floor
Norwalk, CT 06851
Tel. (203) 652-0206
Email: williamsc@themmrf.org

Full application will be due on October 2nd by 5 PM EDT

ELIGIBILITY:

Applications for the *“Identification and Validation of Novel High Risk Multiple Myeloma Targets Leveraging CoMMpass and Existing Genomic Data Sets”* are solicited from investigators at academic, not-for-profit institutions, and for profit organizations in the United States and abroad. Since this RFA may involve utilization of bioinformatics capabilities as well as various types of assays for validation purposes, the MMRF highly encourages collaborative, multi-institutional applications to collectively assemble the appropriate assays, tools and models in order to study critical research questions that will drive new targets or treatments into the clinic for myeloma patients. Collaborations between not-for-profit institutions and for profit organizations are also

encouraged. Applications should provide letters of collaboration from partners including other departments, institutions or industry.

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 immune oncology fields.

Selection Criteria

- Appropriate proposed analysis of genomic data to select novel genes and pathways that can be further validated
- Selection of assays and integration and application of state of the art technologies to form a comprehensive validation package
- Demonstration of the synergy and interdisciplinary nature of the proposed collaborative projects that encompass a broad range of expertise
- Clarity of thought and written presentation of the overall program goals and research projects
- Likelihood of technical success as balanced by scope of work and novelty of the proposed collaborative program
- Experience, background, and qualifications of investigators (Principal Investigator(s) and co-Principal Investigator)
- Appropriateness of the budget
- Quality of the resources and environment (facilities, special equipment, patient population, etc.)
- Adequacy of provisions for protection of human subjects, laboratory animals and investigators and staff using biohazardous materials or procedures

Written review critiques of the application will not be provided back to applicants.

PROGRESS REPORT AND SECOND YEAR CONTINUATION OF FUNDING:

A first year milestone-driven progress report is strictly required for second year funding of the program. The Principal Investigator must submit a report (limit of 10 pages) of their progress 60 days prior to the first year grant anniversary date. The report should briefly review all research progress during the first year and should also include any potential pharma or biotech partners that could drive the target toward therapeutic development. Furthermore there should be a list of any publications and a disclosure of intellectual property that were derived from the funded work. 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(s) will be expected to have semi-annual meetings with the MMRF and a Steering Committee.

The written reports shall be reviewed by the MMRF in order to evaluate the research progress of the program. The MMRF will use that report as the basis for continuation for the second year of funding. Although awards are for a two-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.

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.

APPLICATION SUBMISSION AND INQUIRIES:

Applications should be submitted through the [proposalCENTRAL Application System](#).

For scientific inquiries contact:

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Norwalk, CT 06851
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Email: williamsc@themmrf.org

For administrative and budget inquiries contact:

Jeannie Calcano Peare
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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 60 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.

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.

About The MMRF

The mission of the Multiple Myeloma Research Foundation (MMRF) is to find a cure for multiple myeloma by relentlessly pursuing innovation that accelerates the development of next-generation treatments to extend the lives of patients. Founded in 1998 by Kathy Giusti, a multiple myeloma patient, and her twin sister Karen Andrews as a 501 (c) (3) nonprofit organization, the MMRF is a world-recognized leader in cancer research. Together with its partners, the MMRF has created the only end-to-end solution in precision medicine and the single largest genomic dataset in all cancers. The MMRF continues to disrupt the industry today, as a pioneer and leader at the helm of new research efforts. Since its inception, the organization has raised over \$350 million and directs nearly 90% of the total funds to research and related programs. As a result, the MMRF has been awarded by Charity Navigator's coveted four-star rating for 12 years, the highest designation for outstanding fiscal responsibility and exceptional efficiency.