

Bone Marrow Failure Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,¹ the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Bone Marrow Failure Research Program (BMFRP). The BMFRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the BMFRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The BMFRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

BMFRP BACKGROUND AND OVERVIEW

The BMFRP was initiated in 2008 to support innovative and impactful research that addresses fundamental issues and gaps in bone marrow failure. The BMFRP provides support for research of exceptional scientific merit and promotes innovative research focused on bone marrow failure (BMF) diseases. Investigator-initiated research has been encouraged in the areas of congenital or acquired BMF. The program accepts studies focused on BMF syndromes and their progression to other malignancies, such as leukemia. However, research primarily focused on leukemia, myeloproliferative neoplasms or other malignancies is discouraged. The program requires stem cell biology studies and translational projects, including bone marrow transplantation studies, to be clearly related to BMF diseases.

Through the recommendations of the BMFRP Programmatic Panel, the BMFRP has developed the following Vision and Mission:

VISION: To understand and cure bone marrow failure diseases

MISSION: To encourage and support innovative research that is committed to advancing the understanding and treatment of inherited and acquired bone marrow failure diseases, thereby improving the health of affected Service Members, Veterans, and the general public, with the ultimate goals of prevention and cure

FUNDING HISTORY AND NUMBER OF AWARDS

The BMFRP has received \$32.55 million (M) in appropriations since the program's inception in 2008. As shown in **Figure 1**, the program has funded a total of 66 projects during this time.

RESEARCH PORTFOLIO AND ACCOMPLISHMENTS

The BMFRP has funded projects addressing the many syndromes that can lead to BMF. These syndromes can be either inherited or acquired. Inherited BMF includes a group of diseases that are initiated by somatic genetic mutations that lead to BMF, which often presents itself in childhood. Acquired BMF includes diseases that usually develop in older adults; they can occur as a consequence of environmental exposure or the long-term effects of chemotherapeutics. Both types of BMF can lead to life-long chronic illness, with the potential to develop into cancer. The following are examples of both inherited and acquired BMF syndromes:

Inherited BMF Syndromes

- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Inherited neutropenias

Acquired BMF Syndromes

- Aplastic anemia
- Myelodysplasia
- Paroxysmal nocturnal hemoglobinuria
- Pure red cell aplasia

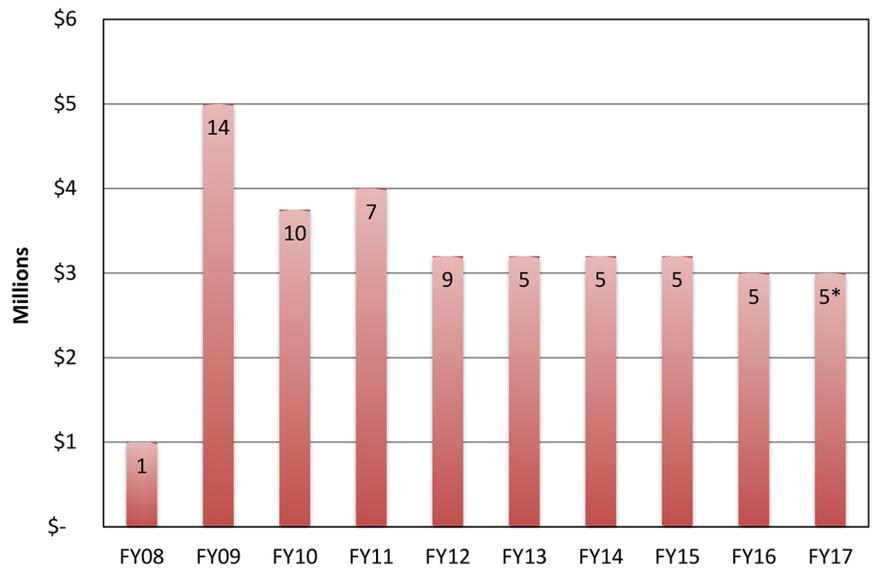


Figure 1. BMFRP Fiscal Year 2008-2017 Funding History: Total Appropriation Dollars (Number of Awards Obligated Are Indicated at the Top of Each Bar)
*Anticipated number of awards for fiscal year 2017.

Figure 2 below depicts the amounts of investment in each BMF syndrome from fiscal year 2008 (FY08) to FY16.

Figure 3 specifies the type of research being supported by the BMFRP, including all BMFRP research investment classified using the scientific classification system.

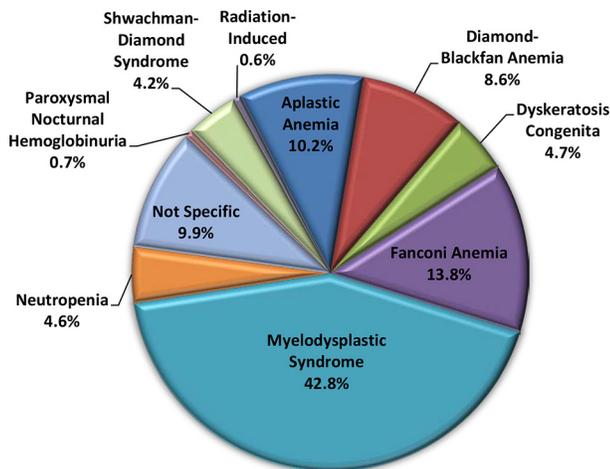


Figure 2. FY08-FY16 BMFRP Disease Classification of Investment: Percent Dollars Spent

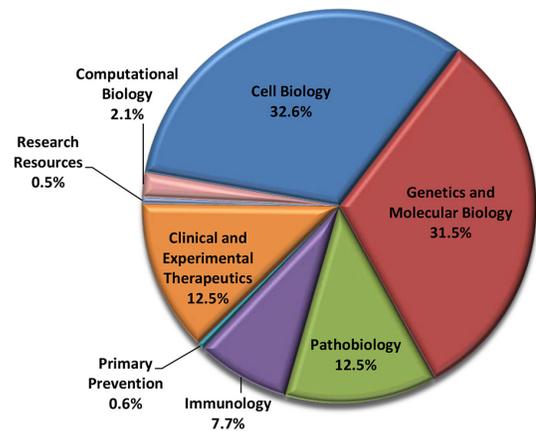


Figure 3. FY08-FY16 BMFRP Investment in Scientific Research Areas



BMFRP SUPPORTED PRODUCTS IN THE CLINICAL PIPELINE

- E7107: Through a BMFRP Postdoctoral Fellowship Award and a subsequent Idea Development Award, the effects of a splicing inhibitor were investigated for the splicing mutation, Srsf2, which is often observed in Myelodysplastic Syndromes (MDS). The inhibitor, E7107, was found to increase survival and decrease leukemic burden in Srsf2 mutant leukemia samples. These findings contributed to a Phase I clinical trial of a novel RNA splicing inhibitor for MDS, H3B-8800. (<https://clinicaltrials.gov/ct2/show/NCT02841540>).
- BI 836858: Myeloid-derived suppressor cells (MDSCs) function as regulators of the immune response. These cells can induce cell death in bone marrow stem cells, which may contribute to MDS. Secreted inflammation-associated signaling molecules, such as S100A9, through interaction with the MDSC receptor, CD33, have been identified as mediators of MDSC activation. A BMFRP Idea Development Award explored whether targeting the S100A9-CD33 pathway could inactivate MDSCs. The humanized monoclonal antibody of CD33, BI 836858, was used to block CD33 signaling in MDS bone marrow (BM) primary specimens. There was a significant reduction in the MDSC population within these specimens. Furthermore, BI 836858 treatment in MDS BM-derived stem cells from patient specimens also demonstrated the potential to restore the hematopoietic capability ex vivo. These results demonstrate the potential for targeting MDSCs to improve hematopoiesis in MDS patients. A Phase I clinical trial for BI 836858 treatment in MDS is currently ongoing (<https://clinicaltrials.gov/show/NCT02240706>).

RESEARCH AND FUNDING ENVIRONMENT

BMF syndromes encompass a diverse group of disorders characterized by insufficient blood cell production by the bone marrow. To date, there is no other funding agency or foundation solely dedicated to BMF other than the BMFRP. Rather, foundations such as the Aplastic Anemia and MDS International Foundation, the Fanconi Anemia Research Fund, the MDS Foundation, and the Diamond Blackfan Anemia Foundation support research focused on a particular syndrome.

The NIH, mainly through the National Heart, Lung, and Blood Institute and National Cancer Institute, support research targeted at the various syndromes that lead to BMF. Over the past 5 years the NIH has supported between \$20M and \$40M/year on studies investigating these syndromes.

STRATEGIC DIRECTION

The pathology of BMF is complex. It is complicated by the diverse syndromes that contribute to it, which vary in etiology, age of onset, symptoms, and severity. There are many unanswered BMF research questions; thus, the strategy of the BMFRP is to retain a broad set of research priorities. There are two driving reasons for this:

- The unanswered research questions surrounding BMF vary by disease.
- The unanswered research questions span the spectrum from basic science to clinical practice; thus, permitting innovation across the spectrum is essential for the BMFRP.

This strategic direction and the investments of the BMFRP will positively impact not only the general public, but Service members as well. Service members, especially Veterans, are faced with the challenges of acquired BMF diseases that occur late in life. These diseases could be a result of hazardous exposures during military Service. Congenital BMF diseases often develop in children, potentially affecting Service members' families.

NEAR-TERM STRATEGIC GOALS

The BMFRP is interested in basic research that has a clear potential to lead to translational findings. Toward that end, the program has consistently challenged the scientific community to design innovative research approaches based on sound scientific evidence. The BMFRP seeks to support research that will find answers regarding the following near-term gaps, while enabling investigators to propose their best ideas in all areas of BMF research:

- Understanding the causes and progression of BMF diseases
- Finding effective BMF treatments and cures

While the BMFRP recognizes that diverse unanswered questions surround BMF diseases, the program has identified some of the most compelling research questions within the two overarching research gaps:

Understanding the causes and progression of BMF diseases

- What are the contributing factors (e.g., microenvironment, stressors, genes) to BMF diseases and how are these factors integrated?



Finding effective BMF treatments and cures

- What will translate into a novel clinical therapy in the next 5 years?
- Which drugs can be helpful in curing or treating BMF diseases?
- How do we optimize gene therapy in BMF diseases?

LONG-TERM STRATEGIC GOALS

Over the long-term horizon (5 to 10 years), the BMFRP is interested in studies that will further investigate effective therapies. Long-term priorities may be added to or replace some of the near-term priorities noted above, should advances in research, techniques, and technologies make them more achievable. The BMFRP's long-term strategic goals include the following:

- Identify the reasons why the effects of currently available treatments are only transient
- Investigate the potential use of combinatorial therapies
- Maximize the use of currently available drugs for treatment effectiveness
- Determine why some patients respond to therapy and others do not
- Find ways to make bone marrow transplants safer for BMF patients
- Determine how to manage BMF disorders to improve patient care and quality of life

INVESTMENT STRATEGY

NEAR TERM

If Congressional funding is directed to the BMFRP during the next 5 years, the program will continue to solicit novel research ideas that are investigator-driven. Additionally, the BMFRP will continue to invest in early-career investigators who are researching this rare disorder. The BMFRP will support innovative ideas and high-impact approaches based on scientifically sound evidence to move toward the BMFRP vision of understanding and curing BMF diseases, as noted above. By utilizing the Idea Development Award mechanism, the program will continue supporting new ideas that have a high probability of revealing novel avenues of investigation in BMF research to aid in understanding these complex diseases.

This investment strategy will be re-evaluated and updated as necessary during the program's annual Vision Setting meeting.

LONG TERM

As the understanding of BMF grows over the long term, the BMFRP investment strategy will reflect these changes. It is envisioned that a move toward more translational award mechanisms may be necessary to answer more of the clinically focused questions. Offering this type of award mechanism will be balanced against the state of the science, as well as the availability and amount of Congressional appropriations for the program.

MEASURING PROGRESS

Measuring strategic outcomes provides a means by which progress toward the strategic goals can be gauged. The BMFRP will measure its success in the near term based on successful investments in areas important to the strategy. Longer-term success will be evaluated based on contributions to the scientific community and by following research linked to BMFRP-funded projects. The BMFRP will use the following measurements to gauge its progress in meeting its near- and long-term strategic goals.

NEAR-TERM OUTCOMES

- Investment in innovative ideas and high-impact approaches that are investigator-driven
- Investment in research investigating the causes and progression of BMF diseases
- Investment in studies examining effective BMF treatments and cures
- Contributions to the scientific community (e.g., publications, patents, presentations)
- Subsequent investment from funding agencies/foundations based upon research findings leveraged from BMFRP-funded studies



LONG-TERM OUTCOMES

- Early-career investigators continuing to research BMF
- Contributions to the scientific community (e.g., publications, patents, presentations)
- Completion of early-phase clinical trials

REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process, a Report of the National Academies of Sciences, Engineering, and Medicine*. 2016. The National Academies Press, Washington, DC. (<http://nationalacademies.org/hmd/reports/2016/cdmrp.aspx>).