Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

https://cdmrp.army.mil

Bone Marrow Failure Research Program

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

PROGRAM HISTORY

Disorders affecting the stem cells or progenitor cells can lead to bone marrow failure (BMF), which are rare, potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. The Department of Defense Bone Marrow Failure Research Program (BMFRP) was initiated in fiscal year 2008 (FY08) to provide support for exceptional innovative research focused on BMF diseases. From FY08 through FY18, $35.55 million (M) has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. The appropriation for FY19 for the BMFRP is $3M. From FY08 through FY17, the BMFRP has invested in 65 awards, resulting in 100 publications in peer-reviewed scientific journals and 3 patent applications.

RESEARCH PORTFOLIO

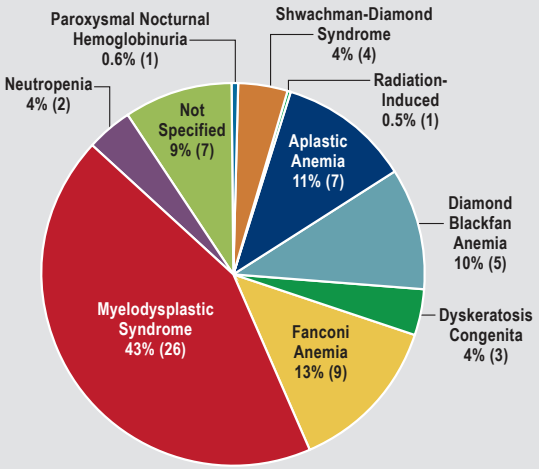
The BMFRP has funded projects addressing the many syndromes that can lead to BMF. These syndromes can be either inherited or acquired. Inherited BMF includes a group of diseases that are initiated by somatic genetic mutations that lead to BMF, which often presents itself in childhood. Acquired BMF includes 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. Examples of both inherited and acquired BMF syndromes are listed below, along with a pie chart illustrating the BMFRP investment in each.

EXAMPLES OF *INHERITED* BMF

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

EXAMPLES OF *ACQUIRED* BMF

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



FY08-FY17 BMFRP Disease Classification*

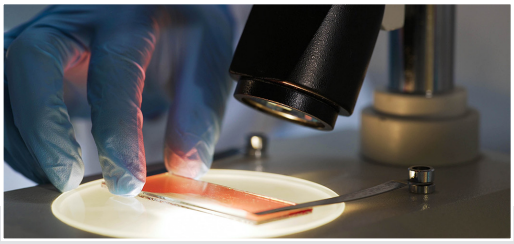
**Percentages of total spent, (number of awards).*

BMFRP ACCOMPLISHMENTS

The investments of the BMFRP 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.

HIGH-IMPACT RESULTS SUPPORTED BY THE BMFRP

- Generated multiple relevant mouse models for studying myelodysplastic syndromes (MDS).
- Identified a specialized immune-suppressive niche that protects hematopoietic stem cells from immune insult.
- Identified that inhibition of Ezh2 decreased graft-versus-host disease.
- Determined that the TIFAB protein exhibits important tumor suppressor-like functions in human hematopoietic cells.
- Constructed a database of gene expression profiles from MDS stem cells and healthy controls.
- Depletion of the Rip3 protein in the aplastic anemia (AA) mouse model completely prevented AA development.
- Treatment of spliceosome mutant cells, which are common in MDS, with a splicing modulator drug resulted in increased apoptosis in the mutant cells.
- Revealed that disruption of the LNK protein leads to the expansion of hematopoietic stem cells in both healthy and Fanconi anemia (FA) animal models.



BMFRP SUPPORTED PRODUCTS IN THE CLINICAL PIPELINE

- **E7107:** The effects of a splicing inhibitor for the splicing mutation, Srsf2, which is often observed in MDS, were investigated with support from a BMFRP award. 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. The possibility that targeting the S100A9-CD33 pathway could inactivate MDSCs was explored with support from the BMFRP. The humanized monoclonal antibody of CD33, BI 836858, was used to block CD33 signaling in MDS bone marrow primary specimens. There was a significant reduction in the MDSC population within these specimens. Furthermore, BI 836858 treatment in MDS bone-marrow-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*).

- **Metformin:** The diabetes drug, metformin, was determined to improve defective hematopoiesis and delay tumor formation in FA mouse models. The BMFRP supported research that led to a pilot study of metformin in patients with FA and cytopenias at Boston Children's Hospital (*https://clinicaltrials.gov/ct2/show/NCT03398824*).

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