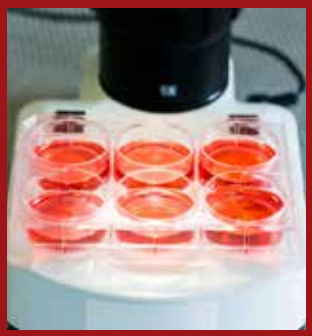
CDMRP

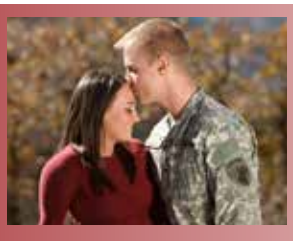
Department of Defense

# Bone Marrow Failure Research Program


*U.S. Army Medical Research and Materiel Command*




# Bone Marrow Failure Research Program

## Vision

*To understand and cure bone marrow failure disease*

## Mission

*To encourage and support innovative research that is committed to advancing the understanding of inherited and acquired bone marrow failure diseases, thereby improving the health of affected individuals, with the ultimate goals of prevention and cure*

### Some examples of inherited bone marrow failure diseases:

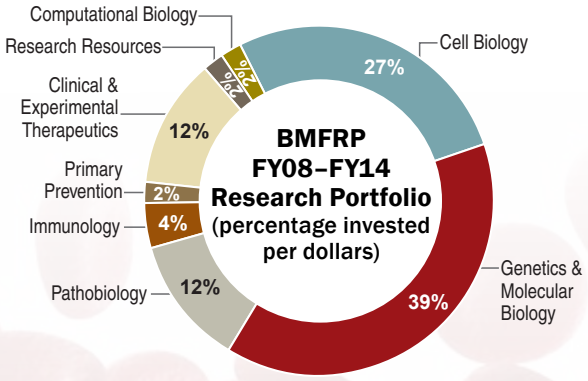
- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Neutropenia

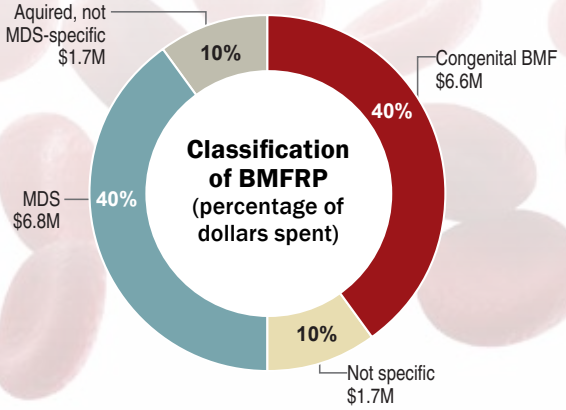
### Some examples of acquired bone marrow failure diseases

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

## Program History

Inside bones, the marrow is the spongy-like tissue that contains blood-forming stem cells. These stem cells initiate the hematopoietic cascade for the development of the different cells within the blood including red blood cells, white blood cells, and platelets. Disorders affecting the stem cells or progenitor cells can lead to bone marrow failure – rare, potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. These diseases are classified into two major categories: acquired bone marrow failure and inherited bone marrow failure. In fiscal year 2008 (FY08), Congress appropriated $1 million (M) for bone marrow failure research. With continued appropriations, the Bone Marrow Failure Research Program (BMFRP) was established. From FY08 through FY14, $23.4M has been appropriated by Congress to research the prevention, causes, and treatment of bone marrow failures diseases. The appropriation for FY15 is $3.2M. Thus far, the BMFRP has invested in 51 awards with the mission to support innovative research committed to advancing the understanding of inherited and acquired bone marrow failures diseases.



# Timeline of Excellence in Bone Marrow Failure Research

ACHIEVEMENTS IN BONE MARROW FAILURE RESEARCH

## 2008

**FY08 – $1M Appropriation targeted toward Bone Marrow Failure Research**

## 2009

**FY09 – Dr. Charles Lin** showed the critical role of regulatory T cells in immune privilege mechanisms.

## 2010

**FY10 – Dr. Jose Cancelas** examined the mechanism mediating hematopoietic stem cell recovery after exogenous stress (ionizing radiation, chemotherapy).

**FY10 – Dr. Yi Zhang** investigated graft versus host disease, and the role of Notch and Ezh2 in the progression to bone marrow failure.

**FY10 – Dr. Daniel Starczynowski** explored novel research areas related to Myelodysplastic Syndrome (MDS) to identify and characterize a gene, TRAF-interacting protein with forkhead associated domain B (TIFAB). The gene is deleted in 10% of MDS patients, resulting in unrestricted immune pathway activation in MDS hematopoietic stem/progenitor cells. Dr. Starczynowski and his team of researchers at the Cincinnati Children's Hospital used a combination of mouse genetic and molecular biology approaches to understand the role of TIFAB in normal and MDS hematopoietic cells. With genetically engineered mice that carry a deletion of TIFAB, the researchers showed that hematopoietic defects the mice exhibit are consistent with human MDS and bone marrow failure. Further research will focus on finding alternative approaches to revert the phenotype associated with TIFAB deletion in MDS and other BMF diseases.

## 2011

**FY11 – Dr. Omar Abdel-Wahab** created a genetically relevant model showing the hallmark features of Myelodysplastic disorders by deletion of Asxl1.

**FY11 – Dr. Kathleen Sakamoto** studied the rare inherited bone marrow failure syndrome known as Diamond Blackfan Anemia (DBA) that is associated with severe anemia, birth defects, and increased cancer risk. Approximately 25% of DBA patients have a mutation in the RPS19 gene, and Dr. Sakamoto's team at Stanford University investigated the molecular pathways contributing to the anemia phenotype due to RPS19 deficiency. Working in collaboration with Dr. Stan Nelson at UCLA, Dr. Sakamoto performed RNA-sequencing to identify genes and microRNAs that abnormally regulate RPS19-deficient hematopoietic stem cells. They found that the erythroid-specific transcription factor GATA-1 is abnormally regulated by the inflammatory cytokine TNF alpha p38 MAP kinase pathway, thus suggesting that anti-inflammatory agents could be useful in the treatment of patients with DBA.

## 2012

**FY12 – Dr. Marshall Horwitz's** research team examined neutropenia, a deficiency in the production of neutrophils, the major type of white blood cells, that offer a first line of defense against infection. Inherited forms of neutropenia often progress to MDS. Heritable mutations in several genes can cause congenital forms of neutropenia, although most often the gene ELANE, encoding neutrophil elastase, is responsible. Dr. Horwitz's team focused on a particular type of mutation disrupting the start site for protein synthesis, found in just a few patients. The researchers discovered that in these individuals, neutrophil elastase is still produced, but the protein initiates from internal start sites and bypasses appropriate signals responsible for directing its subcellular localization, preventing premature activity. These observations suggest that drugs inhibiting neutrophil elastase enzymatic activity could ultimately prove therapeutic.

## 2013

**FY13 – Appropriation of $3.2M and 5 research projects awarded**

## 2014

**FY14 – Appropriation of $3.2M and 5 research projects awarded**

For more information, visit
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