CDMRP
Department of Defense

Bone Marrow Failure Research Program





U.S. Army Medical Research and Materiel Command

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Program History

The marrow of bones is made up of a spongy tissue containing the bio-manufacturing mechanism of blood cells, where stem cells initiate the hematopoietic cascade for the development of all 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: inherited bone marrow failure and acquired bone marrow failure. Inherited bone marrow failure is a group of diseases where somatic genetic mutations lead to a deficiency in hematopoiesis that presents in childhood or early adulthood. Acquired bone marrow failure is a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or long-term effects of chemotherapeutics to cure other diseases. Both types of bone marrow failure lead to life-long chronic illnesses with the potential to develop cancer. In fiscal year 2008 (FY08), the U.S. 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 FY15, $26.2M was appropriated by Congress to research the prevention, causes, and treatment of bone marrow failure diseases. The appropriation for FY16 for the BMFRP is $3M. Thus far, the BMFRP has invested in 56 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired bone marrow failure diseases.

Vision

To understand and cure bone marrow failure syndromes

Mission

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

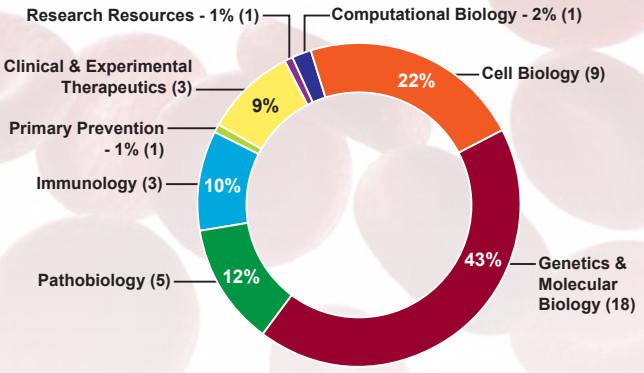
Examples of *inherited* bone marrow failure:

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

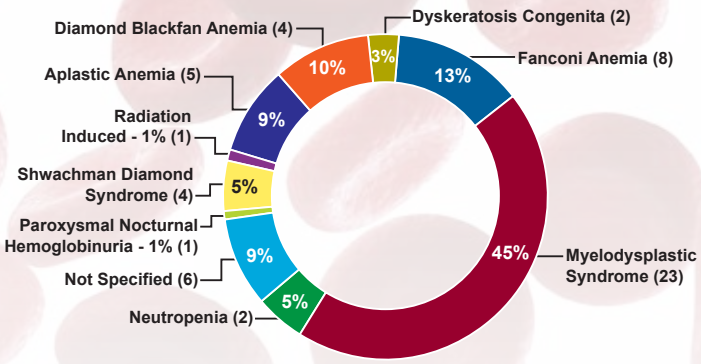
Examples of *acquired* bone marrow failure:

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

FY08–FY15 Research Portfolio Percent Dollars Invested*



FY08–FY15 Disease Classification*



*Percentages of total spent and (number of awards)

Understanding and Targeting Epigenetic Alterations in Acquired Bone Marrow Failure

Omar Abdel-Wahab, M.D., Memorial Sloan Kettering Cancer Center

The myelodysplastic syndromes (MDS) are disorders of the hematopoietic cascade within the bone marrow, leading to anemia and cytopenias, with potential progression to leukemia. With support from a BMFRP FY12 Postdoctoral Fellowship Award, Dr. Omar Abdel-Wahab has made significant discoveries in how various gene mutations contribute to the development of bone marrow failure in MDS patients. Dr. Abdel-Wahab's group discovered that a class of mutations frequently found in MDS patients that affect the ribonucleic acid (RNA) splicing machinery can impact the function of proteins involved in maintaining the epigenome. This finding implicates the critical role that the RNA splicing machinery plays in hematopoiesis and bone marrow failure. Furthermore, he has shown that mutations in genes responsible for chromatin remodeling and gene-silencing result in the decreased function of a protein complex involved in stem cell differentiation and early embryonic development. Dr. Abdel-Wahab's work has resulted in the development of the first conditional knockout mouse for Asxl1, as well as the first mouse model with combined Asxl1 and Tet2 deletion. These mice may serve as necessary resources for understanding the biology of MDS and developing new therapies.

Shwachman Diamond Syndrome Linking Bone Marrow Failure to Global Acetylome Dysregulation

Paul de Figueiredo, Ph.D., Texas A&M Research Foundation

Shwachman Diamond syndrome (SDS) is an inherited bone marrow failure syndrome whose hallmark is a combination of neutropenia and exocrine pancreatic dysfunction, with some patients progressing to malignant myeloid transformation and leukemia. SDS involves critical mechanisms underlying both hematopoiesis and leukemogenesis. The gene, SBDS, is mutated in nearly all cases of SDS. With support from an FY10 BMFRP award, Dr. Paul de Figueiredo's group performed a screen to find a compound that would reverse the SDS phenotype in yeast cells. Trichostatin A (TSA), a histone deacetylase (HDAC) inhibitor currently used an anti-inflammatory agent, is a small molecule that showed the most promising results. HDAC inhibitors induce expression changes of genes that may involve cell growth. Dr. de Figueiredo's research team found that TSA and suberoylanilide hydroxamic acid (an FDA-approved HDAC inhibitor) promoted the growth of both yeast and human cells, thus demonstrating that these inhibitors may correct the resulting SDS phenotype. These results suggest that the repurposing of FDA-approved HDAC inhibitors may be an appealing strategy for addressing the hematological dysfunctions associated with SDS.

Functional Role of microRNAs in Hematopoietic Stem Cells in the Myelodysplastic Syndromes

Christopher Park, M.D., Ph.D., Memorial Sloan Kettering Cancer Center

With support from an FY10 New Investigator Award, Dr. Christopher Park's team compared MDS patient-derived bone marrow hematopoietic stem cells (HSCs) with age-matched controls and found 31 differentially expressed miRNAs. They focused on two particular miRNAs – miR-125 and miR-99 – and showed that decreased levels of miR-125b induced morphologic dysplasia and decreased colony formation of mouse progenitor cells. Overexpression of miR-125b enhanced HSC self-renewal, promoted a lymphoid bias, and reversed most of the age-related changes, including the promotion of increased numbers of committed hematopoietic progenitors and mature lymphoid cell production. Additionally, decreased expression of miR-99 in mouse HSCs reduced their self-renewal capacity and induced differentiation to the myeloid lineage. Dr. Park's group showed that miR-125b expression in aged HSCs could be restored by anti-longevity regimens that also rejuvenate HSC function, such as calorie restriction and rapamycin treatment, suggesting avenues for possible treatment strategies for MDS.

For more information, visit
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