CDMRP

Department of Defense

Bone Marrow Failure Research Program





U.S. Army Medical Research and Materiel Command

PROTECT · PROJECT · SUSTAIN

Bone Marrow Failure Research Program

VISION

To understand and cure bone marrow failure diseases

MISSION

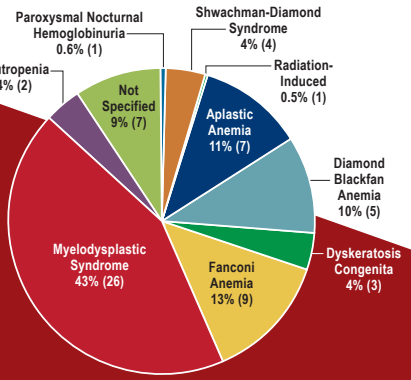
To encourage and support innovative research that is committed to advancing the understanding and treatment of inherited and acquired bone marrow failure diseases, thereby improving the health of affected Service Members, Veterans, and the general public, with the ultimate goals of prevention and cure

PROGRAM HISTORY

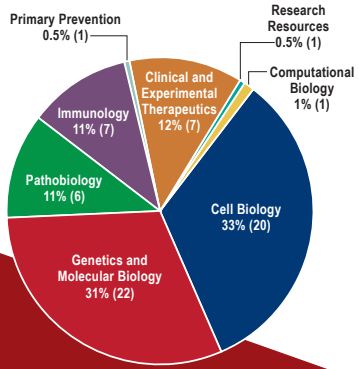
The cavities of bones are made up of a spongy tissue that contains stem cells capable of maturing to blood cells in a process known as hematopoiesis. The hematopoietic cascade is responsible for the development of all cellular blood components, including red blood cells, white blood cells, and platelets. Disorders affecting the stem cells or progenitor cells can lead to bone marrow failure (BMF)—rare, potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. These diseases can be either inherited or acquired. Inherited BMF includes a group of diseases where somatic genetic mutations lead to a deficiency in hematopoiesis that presents itself in childhood or early adulthood. Acquired BMF includes a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or the long-term effects of chemotherapeutics. Both types of BMF lead to life-long chronic illnesses with the potential to develop cancer. The 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 FY17, $32.55 million (M) has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. The appropriation for FY18 for the BMFRP is $3M. Thus far, the BMFRP has invested in 65 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases.

"I am honored to be a member of the BMFRP. The researchers and consumer reviewers who participate are profoundly dedicated to the research and to the patients. These are rare diseases; they suffer from a lack of pharmacological interest. That's what makes the BMFRP so important. It provides a consistent mechanism that BMF investigators can turn to for funding."

Deborah Cook
Programmatic Panel Member, FY14-FY18

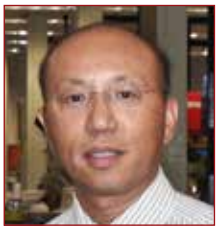


FY08-FY17 Disease Classification*



FY08-FY17 Research Portfolio*

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



NOVEL THERAPEUTIC APPROACHES TARGETING MDSC IN MYELODYSPLASTIC SYNDROME

Sheng Wei, M.D., Moffitt Cancer Center

Myeloid-derived suppressor cells (MDSCs) are immune regulator cells that originate in the bone marrow (BM). Aging-associated inflammation triggers MDSC expansion. These cells then induce cell death in BM stem cells, contributing to myelodysplastic syndromes (MDS) pathogenesis. Secreted inflammation-associated signaling molecules, such as S100A9, through interaction with the MDSC receptor CD33, have been identified as mediators of MDSC activation. Dr. Wei was awarded an FY14 BMFRP Idea Development Award to explore the possibility of targeting the S100A9-CD33 pathway to inactivate MDSCs. To accomplish this, an antibody of CD33, BI 836858, was used to block CD33 signaling. MDS BM primary specimens were treated with BI 836858, resulting in a significant reduction in the MDSC population and MDSC disease-promoting properties. BI 836858 treatment also demonstrated the potential to restore the hematopoietic capability of MDS BM-derived stem cells ex vivo. These results demonstrate the potential for targeting MDSCs to improve hematopoiesis in MDS patients. Currently, a Phase I clinical trial for BI 836858 treatment in MDS is ongoing.

A NOVEL THERAPY FOR TARGETING ACQUIRED BONE MARROW FAILURE DISEASES

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

Robert Bradley, Ph.D., Fred Hutchinson Cancer Research Center

Many patients with MDS progress to a rapidly growing cancer called acute myeloid leukemia. Treatment options are often limited due to patient age and poor health. With support from the BMFRP through an FY15 Idea Development Award, Drs. Abdel-Wahab and Bradley sought to develop therapeutic approaches to target the spliceosomal mutant MDS. They focused on the most commonly mutated spliceosomal gene in MDS, Srsf2. They hypothesized that treatment of MDS spliceosomal gene mutant cells with a spliceosome inhibitor drug, E7107, may cause an overwhelming amount of splicing dysregulation, rendering them defective. Results demonstrate that the combination of Srsf2 mutation and E7107 treatment had larger implications on splicing in the mutant cells—implications that resulted in their cell death and decreased leukemic burden in Srsf2-mutant patient leukemia models. Excitingly, these results have contributed to a Phase I clinical trial (NCT02841540). The use of a splicing inhibitor such as E7107 could provide alternative, less invasive, and less intensive treatment of malignancies with splicing mutations.

UNDERSTANDING THE IMMUNE-MEDIATED T CELL RESPONSE IN APLASTIC ANEMIA

Yi Zhang, M.D., Ph.D., Temple University of the Commonwealth System

Aplastic anemia (AA) is caused by the destruction of BM stem cells by immune-responsive T cells. BM transplantation has significantly improved the survival of AA patients. However, graft-versus-host disease (GVHD), a condition that occurs when the donor cells attack the patient's healthy tissues, poses a major barrier to transplantation success. Dr. Zhang obtained funding though a BMFRP FY10 New Investigator Award and FY15 Idea Development Award to elucidate the immune-mediated T cell response contributing to AA and GVHD. Dr. Zhang identified critical roles for histone modifier proteins in T cell pathways. Conditional loss of the histone methyltransferase, Ezh2, in donor T cells inhibited GVHD in a mouse model after BM transplantation. Most recently, Dr. Zhang has discovered a novel and clinically relevant pharmacological approach to target Ezh2 for preventing and treating GVHD. Currently, the regulation pathway initiated by the histone demethylase, Jmjd3, is being investigated for its role in controlling T cell immune responses. These results suggest multiple histone-modifying proteins that could present therapeutic strategies for controlling the inflammatory T cells that contribute to AA and GVHD.

For more information, visit
http://cdmrp.army.mil

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