CDMRP
Department of Defense

Bone Marrow Failure Research Program





U.S. Army Medical Research and Materiel Command

"Without question, there are many avant-garde grant proposals offering true promise to further advance our understanding of disease pathology and treatment. Critical, revolutionary medical advancements depend on society's investment in them."

Carolyn Brokowski
Consumer Peer Reviewer
BMFRP 2011

"It is an honor to serve on the Bone Marrow Failure Research Program (BMFRP) Integration Panel. The panel is composed of bone marrow failure experts with varied experience and expertise who are passionately committed to advance the field of bone marrow failure. We are very excited by the breadth and depth of the submitted research applications offering novel approaches to tackle the myriad of challenges of marrow failure. We are passionately committed to fulfilling the mission of the BMFRP and are confident the funded research will provide much needed hope for affected individuals and their loved ones."

Margaret MacMillan, M.D.
FY13–14 Integration
Panel Chair-Elect

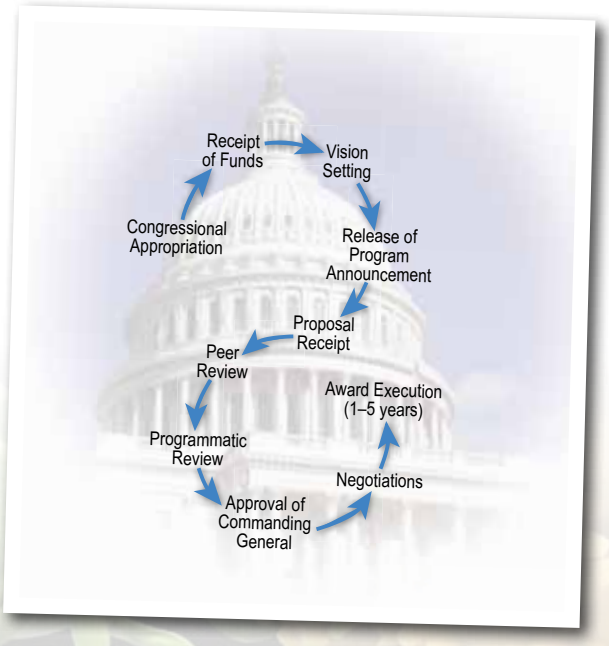
Congressionally Directed Medical Research Programs

HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received more than $7 billion in appropriations from its inception through fiscal year 2012 (FY12). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Bone Marrow Failure Research Program (BMFRP) is allocated via specific guidance from Congress.

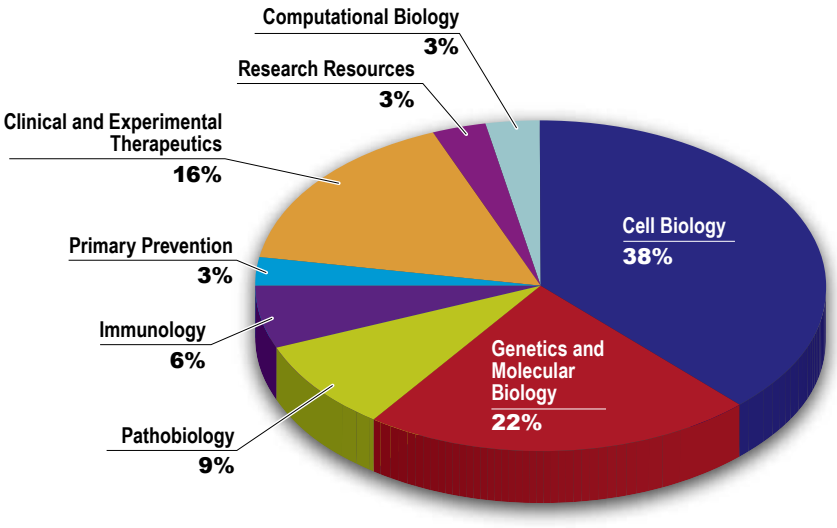
APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, with both tiers involving dynamic interaction among scientists and consumer advocates (disease survivors). The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Integration Panel (IP), which is composed of leading scientists, clinicians, and consumer advocates. The IP compares applications to each other and makes recommendations for funding based on scientific merit, portfolio composition, and relevance to program goals.

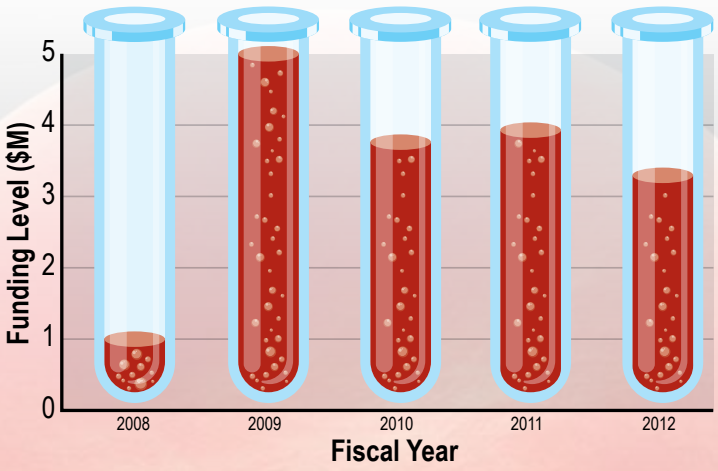


Bone Marrow Failure Research Program

In FY08 Congress appropriated $1 million (M) to the BMFRP to study innovative research to advance the understanding of and cure bone marrow failure. To date, a total of $16.95M has been appropriated and 33 applications funded through the BMFRP.



BMFRP FY08–FY11 Portfolio Analysis by Research Area



Funding Levels

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.

Bone marrow, the sponge-like tissue found inside bones, contains blood-forming stem cells that develop into red blood cells, white blood cells, and platelets. Disorders affecting cells of the bone marrow are potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. BMF syndromes can either be inherited through genetic disorders or acquired through exposure to certain chemicals, environmental toxins, and viruses, or caused by autoimmune responses. Current treatment options for BMF disorders include drug therapy and hematopoietic stem cell (HSC) transplant.

Bone marrow failure (BMF) is a general term that includes many diseases or syndromes.*

Acquired BMF Syndromes	
Aplastic Anemia (AA)	AA occurs when the blood-forming stem cells are damaged, resulting in the body's inability to produce all three types of blood cells. AA can be caused by exposure to toxins, radiation, chemotherapy, certain viruses, or autoimmune disorders, but most cases are idiopathic. Cases range from moderate to severe. AA occurs most often in children, adolescents, the elderly, and those of Asian descent. Individuals are at risk for developing myelodysplastic syndrome (MDS) and/or leukemia.
Myelodysplastic Syndrome (MDS)	MDS is characterized by the inability of the bone marrow to produce enough of one or more blood cell types and an increase in the number of abnormal blood cells. Although linked to exposure to some chemicals, radiation, or chemotherapy, most cases are idiopathic. MDS can range from mild to severe, and individuals are at an increased risk for developing leukemia.
Paroxysmal Nocturnal Hemoglobinuria (PNH)	Resulting from a mutation in a particular blood-forming stem cell and usually acquired in adulthood, PNH is characterized by breakdown of the red blood cells, which can cause red or dark urine and anemia. Affected individuals are at risk for developing AA; blood clots; pain in the legs, abdomen, or chest; jaundice; and leukemia.

Inherited BMF Syndromes	
Amegakaryocytic Thrombocytopenia (AMEGA)	Usually diagnosed before age 10, AMEGA is characterized by low platelet production and therefore excessive bruising. Individuals have an increased risk of developing AA and leukemia.
Diamond-Blackfan Anemia (DBA)	Usually diagnosed in the first year of life, DBA is characterized by anemia and in many cases, physical anomalies, including facial anomalies, short stature, and abnormal thumbs. Affected individuals are at an increased risk for leukemia and other cancers.
Dyskeratosis Congenita (DC)	Usually diagnosed between the ages of 10–30, DC is characterized by distinct anomalies of the skin, fingernails, and tongue. Affected individuals develop BMF and are at an increased risk for leukemia and other cancers.
Fanconi Anemia (FA)	FA is, in most cases, characterized by a number of physical features, including abnormal thumbs, short stature, small head and eyes, abnormal kidney, and brown birthmarks. Most individuals eventually develop AA and are at an increased risk for several types of cancer, including leukemia, head and neck cancers, and other solid tumors. Although diagnosed at any age, FA is usually diagnosed by adolescence.
Pearson Syndrome	Low white blood count, malabsorption, and short stature are the characteristics of this syndrome. Usually diagnosed in the first year of life, individuals also often develop anemia, low platelet count, liver and kidney disease, and are at an increased risk for leukemia.
Severe Congenital Neutropenia (SCN)	Unlike other BMF syndromes, SCN is present at birth. Characterized by low white blood count, serious recurring infections develop in infancy, no physical changes but an increased risk for leukemia.
Shwachman-Diamond Syndrome (SDS)	Often diagnosed in infancy, malabsorption, bone abnormalities, and short stature are characteristics of SDS. While malabsorption usually improves beyond infancy, BMF worsens. Low white blood count is the first to present, often followed by anemia and low platelet count. Individuals have an increased risk for developing leukemia.
Thrombocytopenia Absent Radii (TAR)	Characterized by low platelet count, absence of the radius bone, and other bone anomalies, TAR is diagnosed at birth. Individuals are at an increased risk for leukemia.

***Note:** *Washington University School of Medicine, Department of Medicine, Bone Marrow Failure Clinical and Research Program.* Bone Marrow Failure. Retrieved August 27, 2012 from http://bmf.im.wustl.edu/bmf_txt.html

National Cancer Institute. Inherited Bone Marrow Failure Syndromes. Retrieved August 27, 2012 from http://marrowfailure.cancer.gov/AMEGA.html

Marrowforums.org. Bone Marrow Failure Diseases. Copyright © 2006-2012. Retrieved August 27, 2012 from http://www.marrowforums.org/diseases.html

Consumer Highlights

Neil Horikoshi, J.D., Aplastic Anemia and MDS International Foundation, Integration Panel Member

On Wednesday, February 29, 2012, Neil Horikoshi observed the 12th anniversary of his diagnosis of a blood disorder ultimately identified as aplastic anemia.

Luck and fate have defined my journey as a person with Bone Marrow Failure disease, from the first appearance of symptoms, including shortness of breath and fatigue, to the diagnosis of AA, an acquired BMF disease, in February 2000. I was living in Japan at the time and had planned a trip to India. But for the luck of securing the last available appointment for a physical before leaving for India, I probably would not be here to write this story. The words "99% chance of leukemia" were life-changing: I received an infusion of red blood cells and platelets, took the last flight out of Tokyo, and flew overnight to Honolulu. I arrived early on the morning of February 29 (Leap Year 2000) and proceeded straight to a hematology appointment where I had a bone marrow biopsy. Within a few days, I was formally diagnosed with AA. Each passing leap year brings back powerful memories.

In 2000, the publicly available information and research on the Internet provided a very grim assessment of high mortality and a limited probability of long-term survival. I put my affairs in order. I was distressed to learn that AA was deemed an "orphan disease"—one that is mostly ignored by pharmaceutical companies because it does not promise much in the way of profit for the manufacturer. Because funding for research is limited, very few hematologists, researchers, or postdoctoral students pursue BMF research. Leading researchers who specialized in AA and who had demonstrated relatively successful treatment in clinical studies were my only hope. Bone marrow transplant was not an option.

But through crisis comes opportunity. Upon completing my overseas assignment and returning to the United States, I became a member and later Chair of the Board of Directors of the Aplastic Anemia and MDS International Foundation. The foundation works to encourage the next generation of researchers to pursue a career in BMF research. Then came an invitation to become involved with the BMFRP, and I came to understand how the BMFRP is supporting research and investment in this orphan disease. The BMFRP works in collaboration to find cures for both acquired and hereditary BMF, and it is a joy to witness the work of researchers across the BMF spectrum. It is also most gratifying to hear the stories of other BMF consumers and peer reviewers who reinforce the meaning of hope for all BMF patients. I am humbled by the talent and commitment of the IP members who are experts in their respective fields.

I thank all those doing research in BMF disease and all other orphan diseases. You are the angels providing hope to patients throughout the nation and around the world.

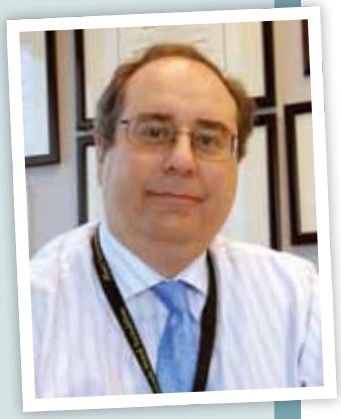
David Fiaschetti, D.D.S., Fanconi Anemia Research Fund, Integration Panel Member

As an oral and maxillofacial surgeon practicing dentistry since 1988, I knew clearly what AA entailed when my 6-month-old son was diagnosed with Fanconi Anemia in February 2000. I monitored Peter's declining blood counts over the next several years while closely studying the advancements in bone marrow transplant. The "luxury" of having almost 10 years between diagnosis and transplant did not lessen the severity of the situation for our family. This gift of time, however, allowed us to "accept the inevitable" and mentally prepare for all possible outcomes. Through the Fanconi Anemia Research Fund (FARF), we educated ourselves about the disease and gratefully accepted all of the family support that this organization offered. In December 2009, Peter received a lifesaving bone marrow transplant.

When FARF approached families in early 2009 regarding potential consumer involvement with the BMFRP, I immediately volunteered, not knowing Peter would be undergoing a bone marrow transplant later that year. In the fall of 2009, I flew directly from the BMFRP Programmatic Review meeting to my son's bone marrow transplant consult appointment. Participating in the BMFRP IP during that critical time, with panel members who truly understood the severity of my son's situation, provided a sense of purpose as well as support for me. Although Peter experienced complications, including acute graft-versus-host disease, the bone marrow transplant was ultimately successful. Indeed, it was a celebration of appreciation to all those patients, researchers, and health care providers whose lives and dedication contributed to the current protocols, yet it also provided immediate justification for further treatment improvements via research.

The continued opportunity to participate in the BMFRP IP enables me to directly interact with researchers, medical providers, and consumers, all with the same goal of enhancing treatment for BMF. I believe it is only through research that the day will come when a diagnosis of "bone marrow failure" no longer means potential early death.

Research Highlights

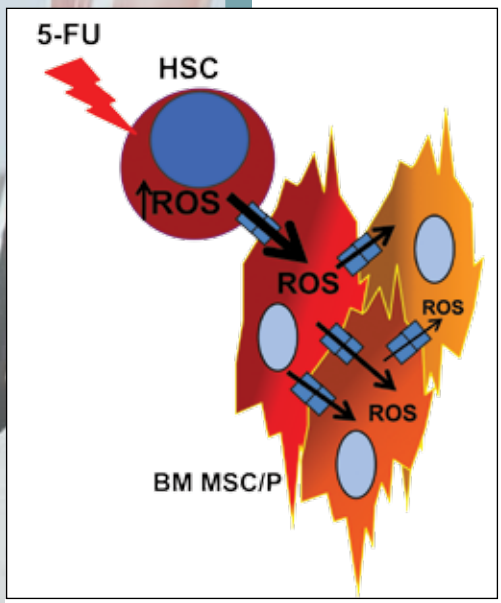


Understanding the Pathogenesis of Bone Marrow Failure

Jose Cancelas, M.D., Ph.D., Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

The mechanisms responsible for both acquired and inherited bone marrow failure are not yet understood. Although most inherited BMF syndromes can be linked to specific genetic defects, these defects do not fully explain the range of physical characteristics observed in affected individuals. In addition, animal models for observed BMF genetic defects have not been able to fully recreate the associated syndromes. With support from an FY10 BMFRP Exploration–Hypothesis Development Award, Dr. Jose Cancelas is investigating whether BMF syndromes are related to a defect in cell-to-cell communication between mesenchymal stem cells and progenitors (MSC/P) and hematopoietic stem cell (HSC). Blood cell formation in the bone marrow (hematopoiesis) is dependent on the close association of HSC and the surrounding microenvironment of which MSC/P are a major component.

Natural causes, such as aging, or external insults, such as radiation, toxin exposure, or chemotherapy, are known to cause DNA damage and affect HSC activity, which may in part be due to hematopoietic stress from increasing cellular levels of reactive oxygen species (ROS). Fanconi Anemia and Shwachman-Diamond Syndrome are two BMF syndromes with defects in DNA repair enzyme systems, making individuals with these syndromes highly sensitive to DNA-damaging events. However, researchers suspect that modifier genes or traits are responsible for the differences in the severity of these diseases and their relation to skeletal malformations in BMF syndromes. Using a model of DNA damage caused by chemotherapy-induced ROS production, Dr. Cancelas tested the ability of HSC to resume blood formation after hematopoietic stress. His results indicated that hematopoietic recovery is delayed when HSC are deficient in connexin-43 (Cx43), a gap junction protein involved in cell-to-cell communication and highly expressed in HSC and MSC/P. Furthermore, the results showed that Cx43 mediates the transfer of ROS to the MSC/P in the bone marrow microenvironment. This transfer of ROS to the MSC/P is a mechanism by which hematopoietic recovery is achieved after chemotherapy. The next stage of this study will investigate the relationship between the loss of cell-to-cell communication between HSC and MSC/P as a modifier trait and the genetic defects of Fanconi Anemia and Shwachman-Diamond Syndrome. This work was published recently in the *Proceedings of the National Academy of Sciences USA* (Taniguchi-Ishikawa et al., 2012).



Stress induced by chemotherapy (5-fluorouracil) results in increased levels of ROS in regenerating HSC. Cx43, a gap junction protein, protects HSC from ROS-induced damage by mediating the transfer of ROS to the BM stromal cells (MSC/P).

Myelodysplastic Syndromes

Amit Verma, M.B.B.S., Albert Einstein College of Medicine of Yeshiva University, Bronx, New York

Myelodysplastic syndromes are a group of incurable diseases that lead to bone marrow failure with one-third of cases ultimately advancing to leukemia. Research into the causes of MDS has been hampered by a lack of cell lines and relevant mouse models. Unfortunately, sufficient patient samples are difficult to obtain. The BMF research community needs a large resource of characterized patient samples to develop treatments for these devastating diseases.

In FY11, the BMFRP offered the Resource Development Award to support the development of research resources that could be shared by the BMF research community to promote basic BMF research. Microarray technology provides a wealth of gene expression (GE) data for the investigation of biological and medical processes and may offer a great foundation for building a genetic information network for BMF diseases. However, variability in experimental conditions and microarray platforms has limited the utility of these data. Dr. Amit Verma was awarded an FY11 Resource Development Award to use his newly developed meta-analytical approach to integrate data from the National Center for Biotechnology Information's Gene Expression Omnibus database. Using samples from individual investigators, Dr. Verma's team will create a large MDS GE expression database to include all subtypes. In previous studies, the Verma team members demonstrated the feasibility of this approach when they integrated data from several different laboratories, which had been generated using different platforms, to develop an MDS GE database capable of distinguishing biologically distinct cell types despite the experimental variability of the samples. Employing this database, they were able to elucidate the mechanism for TGF-β overactivation in MDS stem cells, a state that leads to BMF.

The database that Dr. Verma proposes to develop, with support from the BMFRP Resource Development Award, will represent one of the largest MDS GE databases. This database will include more than 200 MDS samples and 60 controls including patient demographics and disease characteristics. Available online, it will possess an easily searchable interface and will be continually updated, allowing investigators to search MDS samples to identify expression patterns in genes of interest and subtypes of MDS patients who may benefit from targeted therapies. The development of this resource and its subsequent sharing with the BMF research community will support the efforts of scientists and clinicians in understanding the causes of these diseases and developing lifesaving treatments for those affected with MDS and BMF.

For more information, visit
http://cdmrp.army.mil
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
(301) 619-7071

07-2012