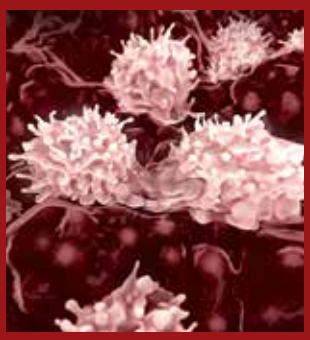
CDMRP

Department of Defense

Bone Marrow Failure Research Program





U.S. Army Medical Research and Development Command

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

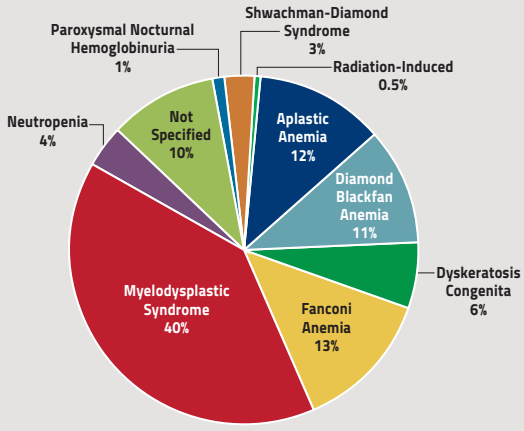
The cavities of bones are made up of a spongy tissue that contains stem cells capable of maturing to blood cells in a process known as hematopoiesis. The hematopoietic cascade is responsible for the development of all cellular blood components, including red blood cells, white blood cells, and platelets. 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 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. Thus far, the BMFRP has funded 71 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases.

Examples of *inherited* BMF

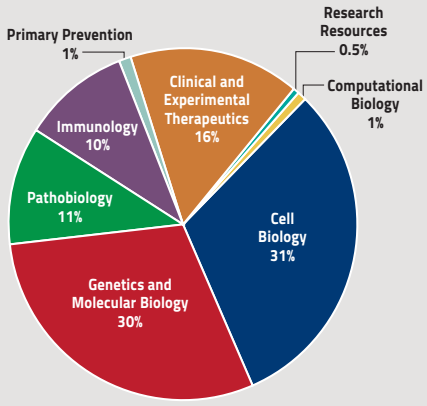
- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Inherited neutropenia

Examples of *acquired* BMF

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



FY08-FY18 Disease Classification*



FY08-FY18 Research Portfolio*

*Percent Dollars Invested

Highlights

A Method for Rescuing Hematopoietic Stem Cell Functions in Fanconi Anemia

Wei Tong, Ph.D., Children's Hospital of Philadelphia

Fanconi anemia (FA) is a rare and fatal inherited blood disorder caused by a mutation in one of 22 FA genes. These genes promote stable hematopoietic stem cell (HSC) development, which becomes diminished when FA occurs, leading to severe BMF, leukemia, and loss of life. Stem cell transplant remains a standard course of treatment, but comes with associated risks. Dr. Wei Tong discovered a gene, LNK (also called SH2B3), which, when disrupted, leads to the expansion of HSCs in both healthy and FA animal models. Through an FY16 BMFRP Idea Development Award, her team sought to determine the role of LNK mechanism in the maintenance of HSCs. They determined that the mechanism for restored HSC activity was through the JAK pathway, which is known for promoting blood formation and immune response. The work was done in mouse models of FA, and the intended next research steps are to study the LNK mechanism for HSC restoration in human FA patients. Dr. Tong's work represents the first published incident of an investigator successfully reversing FA-associated HSC defects and restoring function and genomic stability to HSC progenitor cells in FA-associated animal models to healthy levels. This line of research offers new targets and treatment strategies for FA and other BMF diseases. It has uncovered a possible means of restoring function in HSCs without stem cell transplants, thus avoiding the high risks of morbidity and mortality associated with that treatment.

Replicating the Patient-Specific Bone Marrow Failure Disease in Order to Identify Therapeutic Response

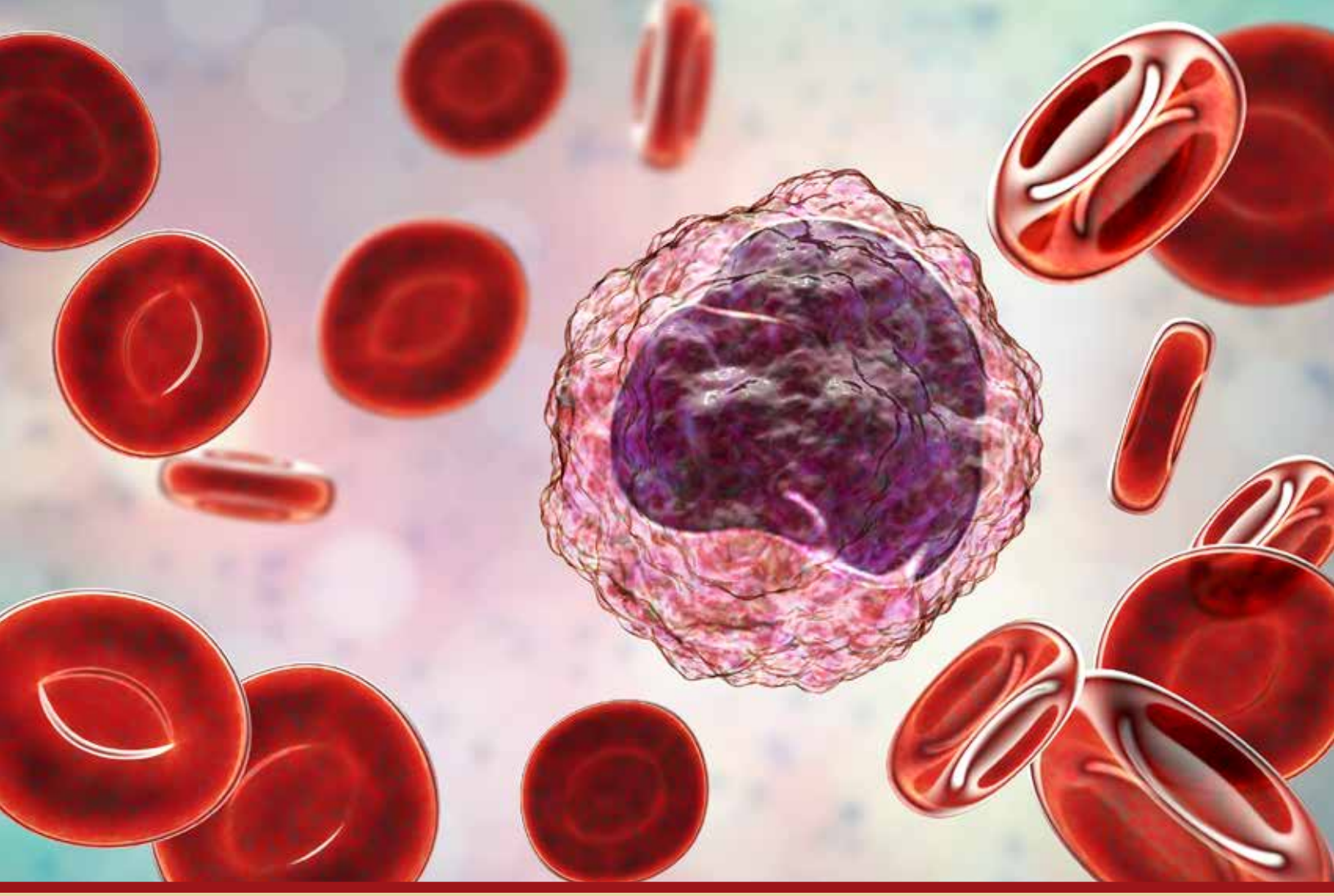
Benjamin Ebert, Ph.D., Brigham and Women's Hospital

Myelodysplastic syndromes (MDSs) are the most common cause of acquired BMF in the United States. A current form of therapy involves hypomethylating agents, but patients have varying responses to the agents. Dr. Ebert hypothesized that patient-specific mutations alter the response to the therapy, and with support from an FY13 BMFRP award, he set out to identify mutations that will predict response to hypomethylating therapy. MDS-treated patient samples were screened, and mutations were identified that predicted.response to hypomethylating agents. To confirm that these mutations reflect patient sensitivity, Dr. Ebert's team developed models of human bone marrow diseases that reflect the complexity of genetic mutations. This was accomplished by simultaneously modifying the disease driver genes, along with multiple other genes in human HSCs, and then permitting their expansion in a mouse model. The team determined that mutations in TET2 and in the cohesion protein subunits increased the sensitivity of human HSCs to hypomethylating agents, while ASXL1 mutations decreased the sensitivity. Dr. Ebert's results indicate which MDS patients would most benefit from treatment with hypomethylating agents, as well as highlight a model system for precision medicine that could have immediate clinical impact. With Dr. Ebert's model system, researchers are able to mimic the genetic complexity of BMF, which could then facilitate pharmacologic testing in a patient-specific fashion.

"In 2003, my family's life changed forever. Our 21-year-old son, Jake, was diagnosed with FA. To say we were stunned is an understatement. He needed a bone marrow transplant immediately. We were ecstatic when we found that our youngest son, Spencer, was a perfect match. As he was being tested to be Jake's donor, it was discovered that Spencer had the same disease. Now not only did Jake not have a sibling matched donor, Spencer would be battling the same devastating thing. Jake tragically passed away from complications of his transplant 8 months after being diagnosed. Thankfully, Spencer is stable at this time.

Since Jake passed away, I have gotten over a thousand people on the bone marrow registry and raised over a million dollars for FA research. Research is our hope, and it has become my passion in life. This was my third year participating as a consumer peer reviewer for the Bone Marrow Failure Research Program. I am very interested in bone marrow failure research and am happy to do something that could benefit not only those with FA, but those with other bone marrow failure diseases as well."

Peggy Padden (FY15, FY18 Peer Review Panel Member)



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