# DoD Bone Marrow Failure Research Program (BMFRP)

*Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.*

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<th>Year</th>
<th>BMFRP Research Contributions</th>
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• BMFRP Research Highlight |
| 2010 | Dr. Jose Cancelas investigated the mechanism of hematopoietic stem cell (HSC) recovery after stress (ionizing radiation, chemotherapy, etc.). Deficiency in the protein connexin-43 (Cx43) highly influenced hematopoietic recovery. Results indicated that Cx43 mediates the transfer of reactive oxygen species within the bone marrow environment. | • Taniguchi Ishikawa E, Gonzalez-Nieto D, et al. 2012. Connexin-43 prevents hematopoietic stem cell senescence through transfer of reactive oxygen species to bone marrow stromal cells. *Proc Natl Acad Sci USA* 109(23):9071-6.  
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| 2010 | Dr. Daniel Starczynowski and his team identified and characterized 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. 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. | • Fang J, Barker B, et al. 2014. Myeloid malignancies with chromosome 5q deletions acquire a dependency on an intrachromosomal NF-kB gene network. *Cell Rep* 8(5):1328-38.  
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<td>2010</td>
<td>Dr. Paul de Figueiredo studied Shwachman Diamond Syndrome (SDS), an inherited bone marrow failure syndrome whose hallmark is a combination of eutropenia and exocrine pancreatic dysfunction and progression to malignant myeloid transformation and leukemia. The gene, SBDS, is mutated in nearly all cases of SDS. 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), an inhibitor currently used as an anti-inflammatory agent, showed the most promising results. Dr. de Figueiredo found that TSA and suberoylanilide hydroxamic acid promoted the growth of both yeast and human cells, thus demonstrating that these inhibitors may correct the resulting SDS phenotype.</td>
<td>Ooi AG, Sahoo D, et al. 2010. MicroRNA-125b expands hematopoietic stem cells and enriches for the lymphoid-balanced and lymphoid-biased subsets. <em>Proc Natl Acad Sci U S A</em> 107(50):21505-10.</td>
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<td>2010</td>
<td>Dr. Christopher Park’s team compared myelodysplastic syndrome (MDS) patient-derived bone marrow hematopoietic stem cells (HSCs) with age-matched controls and found 31 differentially expressed miRNAs. Their studies on miR-125 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 observed in aged HSCs including the promotion of increased numbers of committed hematopoietic progenitors and mature lymphoid cell production. Further analyses on treatment options are underway.</td>
<td>Pang WW, Pluvinage JV, et al. 2013. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. <em>Proc Natl Acad Sci U S A</em> 110(8):3011-16.</td>
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| 2011 | Dr. Kathleen Sakamoto studies Diamond Blackfan Anemia, an inherited failure of the bone marrow. Approximately 25% of DBA patients have a mutation in the RPS19 gene. 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 transcription factor GATA1 and GATA2 are abnormally regulated by the inflammatory cytokine TNF alpha p38 MAP kinase pathway, suggesting that anti-inflammatory agents could be useful in the treatment of patients with DBA. | • Rankin EB, Narla A, et al. 2015. Biology of the bone marrow microenvironment and myelodysplastic syndromes. *Mol Genet Metab* 116(1-2):24-8.  
| 2012 | Dr. Marshall Horwitz researches neutropenia, a deficiency in the production of neutrophils, the major type of wide blood cells. Mutations in the genes, such as ELANE-encoding neutrophil elastase, can cause congenital forms of neutropenia. Dr. Horwitz’s team focused on a particular mutation disrupting the start site for protein synthesis. In a subset of patients, the researchers discovered that 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. This suggests that drugs inhibiting neutrophil elastase enzymatic activity could prove therapeutic. | • Tidwell T, Wechsler J, et al. 2014. Neutropenia-associated ELANE mutations disrupting translation initiation produce novel neutrophil elastase isoforms. *Blood* 123(4):562-69.  