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.

Year	BMFRP Research Contributions	Additional Information and Hyperlinks
2009	Dr. Charles Lin demonstrated the critical role of regulatory T cells in maintaining immune privilege mechanisms of the hematopoietic stem/progenitor cells (HSPC) niche. This work has established a novel concept of immune privilege in the HSPC niche and uncovered its molecular and cellular mechanisms.	• Fujisaki J, Wu J, et al. 2011. In vivo imaging of Treg cells providing immune privilege to hematopoietic stem-cell niche. Nature 474(7350):216- 20. • Spencer JA, Ferraro F, et al. 2014. Direct measurement of local oxygen concentration in the bone marrow of live animals. Nature 508(7495):269-73. • Wu JW, Runnels JM, and Lin CP. 2014. Intravital imaging of hematopoietic stem cells in the mouse skull. Methods Mol Biol 1185:247-65. • 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. • Gonzalez-Nieto D, Li L, et al. 2012. Connexin-43 in the osteogenic BM niche regulates its cellular composition and the bidirectional traffic of hematopoietic stem cells and progenitors. Blood 119(22):5144-54.
2010	Dr. Yi Zhang discovered that both Notch and Ezh2 are critical for modulating inflammatory T-cell responses that mediate graft versus host disease and bone marrow failure.	• He S, Xie F, et al. 2013. The histone methyltransferase Ezh2 is a crucial epigenetic regulator of allogeneic T-cell responses mediating graft-versus-host disease. Blood 122(25):4119-28. • Tong Q, He S, et al. 2014. Ezh2 regulates transcriptional and posttranslational expression of T-bet and promotes Th1 cell responses mediating aplastic anemia in mice. J Immunol 192(11):5012-22. • BMFRP Research Highlight
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. • Zhao JL and Starczynowski DT. 2014. Role of microRNA-146a in normal and malignant hematopoietic stem cell function. Front Genet 5:219. • Rhyasen GW, Wunderlich M, et al. 2014. An MDS xenograft model utilizing a patient-derived cell line. Leukemia 28(5):1142-45.

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2010	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.	• Ooi AG, Sahoo D, et al. 2010. MicroRNA-125b expands hematopoietic stem cells and enriches for the lymphoid-balanced and lymphoid-biased subsets. Proc Natl Acad Sci U S A 107(50):21505-10.
2010	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.	• Pang WW, Pluvinage JV, et al. 2013. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. Proc Natl Acad Sci U S A 110(8):3011-16.
2011	Dr. Omar Abdel-Wahab showed that deletion of Asxl1, a protein co-factor important in epigenetic regulation of gene transcription, resulted in hallmark features of myelodysplastic disorders (MDS), thus creating a disease-relevant, genetically accurate model of MDS.	• Abdel-Wahab O, Gao J, et al. 2013. Deletion of Asxl1 results in myelodysplasia and severe developmental defects in vivo. J Exp Med 210(12):2641-59. • Kim E, Ilagan JO, et al. 2015. SRSF2 mutations contribute to myelodysplasia by mutant-specific effects on exon recognition. Cancer Cell 27(5):617-30. • Meldi K, Qin T, et al. 2015. Specific molecular signatures predict decitabine response in chronic myelomonocytic leukemia. J Clin Invest 125(5):1857-72.

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2011	Dr. Kathleen Sakamoto studies Diamond Blackfan Anemi, 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. • Bibikova E, Youn MY, et al. 2014. TNF-mediated inflammation represses GATA2 and activates p38 MAP kinase in RPS19-deficient hematopoietic prognitors. Blood 124(25):3791-3798.
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. • Zhang MY, Churpek JE, et al. 2015. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. Nat Genet 47(2):180-5.