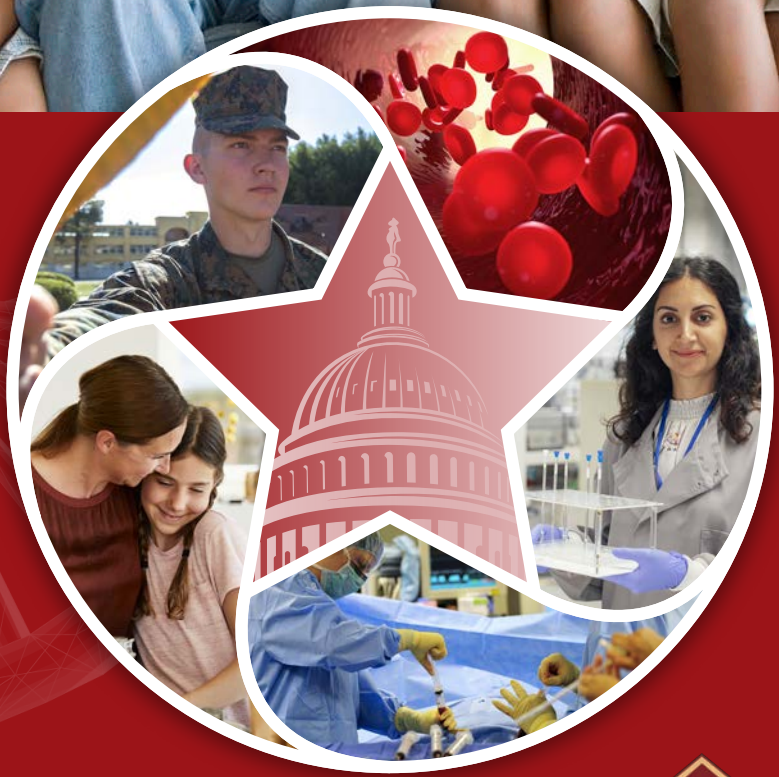
Bone Marrow Failure Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense



U.S. Army Medical Research and Development Command

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 managed over $15.9 billion in research funds from its inception through fiscal year 2020 (FY20). 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

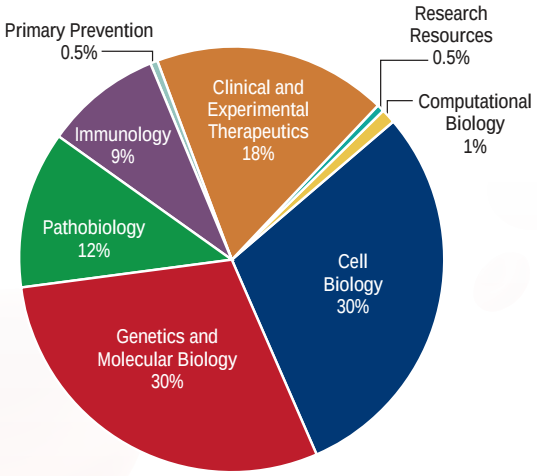
The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

Bone Marrow Failure Research Program

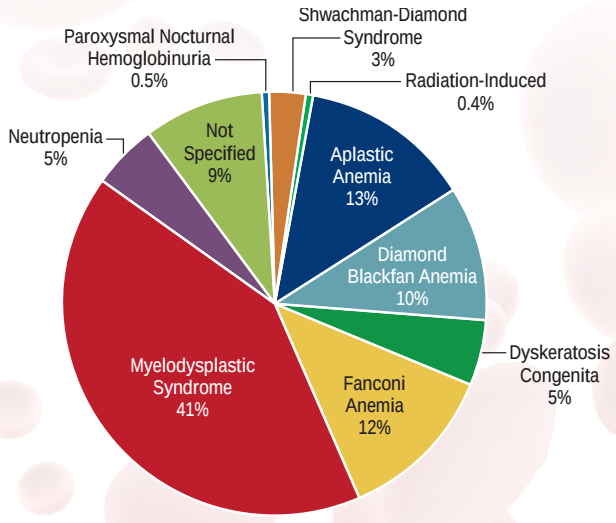
Program History

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 lifelong chronic illnesses with the potential to develop cancer. The BMFRP was initiated in FY08 to provide support for exceptional innovative research focused on BMF diseases. From FY08–FY20, $41.55 million (M) has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. The appropriation for FY21 for the BMFRP is $7.5M. Thus far, the BMFRP has funded 77 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases.

FY08–FY19 BMFRP Research Portfolio: Percent Dollars Invested



FY08–FY19 Disease Classification: Percent Dollars Invested



Our Vision

To understand and cure bone marrow failure diseases

Our 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

Examples of Inherited BMF

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

Examples of Acquired BMF

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

BMF Research in the Clinical Pipeline

Targeted Therapies for Spliceosomal-Mutant Acquired Bone Marrow Failure Disorders

Omar Abdel-Wahab, M.D., Sloan Kettering Institute for Cancer Research

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

Myelodysplastic syndromes (MDS) are a group of cancers with limited treatment options due to limited mechanistic understanding of ribonucleic acid (RNA) splicing. Through a BMFRP FY15 Award, Dr. Abdel-Wahab and Dr. Bradley sought to identify therapeutic strategies that interfere with the altered function of MDS mutant splicing proteins.

Findings from this project have yielded significant clinical impact. Drs. Abdel-Wahab's and Bradley's research provided support for the therapeutic implications for a splicing inhibitor for MDS and acute myeloid leukemia patients with specific splicing mutations. Collaborating with H3 Biomedicine, Inc., Dr. Abdel-Wahab was part of a group of researchers that developed a splicing modulating drug known as H3B-8800 and evaluated it in a phase 1 clinical trial. Preliminary results demonstrate dose-dependent target engagement, a predictable pharmacokinetic profile of H3B-8800, and safety even with prolonged dosing.

They also found that splicing factor mutant cells are preferentially sensitive to RNA-binding protein 39 (RBM39) degraders such as the sulfonamide E7820, offering a novel strategy for treatment. Through a separate organizational initiative, Dr. Abdel-Wahab is currently leading an effort with a pharmaceutical company to conduct a phase 2 clinical trial of E7820 in patients with MDS and related myeloid leukemias who have relapsed or have not successfully responded to conventional therapies.

Finally, more recently, they have identified that inhibiting protein arginine methyltransferase (PRMT) enzymes also alter RNA splicing due to the impact of these enzymes on assembly of the splicing machinery. Consequently, PRMT inhibitors appear to have therapeutic impact on splicing factor mutant MDS, and Dr. Abdel-Wahab is collaborating with several companies on phase 1 trials of PRMT5 inhibitors for MDS patients based on mutational genotype.

Metformin Shows Promise in Treatment of Inherited Bone Marrow Failure Disorder, Fanconi Anemia

Markus Grompe, M.D., Oregon Health and Science University

Using a preclinical mouse model of Fanconi Anemia (FA), Dr. Markus Grompe discovered that metformin improved peripheral blood counts faster than the current standard of care steroid. Metformin also amplified hematopoiesis, the creation of new blood cells from hematopoietic stem cells (HSCs) found in bone marrow. In a special strain of tumor-prone FA mice, metformin delayed tumor formation and extended the tumor-free survival time. Importantly, metformin had no effect on control mice, and these beneficial effects were specific to FA mice.

Another promising finding was related to the mechanistic effect of metformin. Dr. Grompe found that metformin may be able to limit spontaneous chromosome breakage and radicals in human cells and in doing so, protect the DNA from injury.

In light of Dr. Grompe's preclinical results, a clinical trial was initiated in 2018 at Boston University to determine whether metformin has an effect on the hematologic response in patients with FA. The pilot trial enrolled 15 patients and is expected to have promising results available by October 2021.

Research Outcomes

FY	Proposal Number	Principal Investigator	Project	Disease	Presentations	Publications	Funding Obtained
2008	PR080047	Jiwang Zhang	The Role of TAK1 in the Pathogenesis of Bone Marrow Failure Syndromes	Bone Marrow Failure	2		
2009	BM090066	Shi Pan	Redox Regulation in Bone Marrow Failure	Bone Marrow Failure	1		
	BM090086	Alison Bertuch	Molecular Mechanism of Bone Marrow Failure Associated with TINF2 Mutations	Dyskeratosis Congenita	1	2	
	BM090088	Daniel Lindner	Complementation of Myelodysplastic Syndrome Clones with Lentivirus Expression Libraries	Myelodysplastic Syndrome	2		
	BM090089	Amit Verma	Epigenomic Analysis of Hematopoietic Progenitor and Stem Cells in Myelodysplasis	Myelodysplastic Syndrome		1	
	BM090093	Charles Lin	In Vivo Imaging of Bone Marrow Regulatory T Cells and Their Role in the Prevention of Bone Marrow Failure	Aplastic Anemia	2	1	
	BM090168	Michelle Weiss	The Study of Bone Marrow Failure in Patient-Derived Induced Pluripotent Stem Cells (iPSCs)	Diamond Blackfan Anemia	6	2	
	BM090168P1	Monica Bessler	The Study of Bone Marrow Failure in Patient-Derived Induced Pluripotent Stem Cells (iPSCs)	Diamond Blackfan Anemia	4	1	
	BM090207	Bruce Blazar	Correction of Human Fanconi Anemia-Induced Pluripotent Cells by Homologous Recombination	Fanconi Anemia	4		
	BM090207P1	Jae Joung	Correction of Fanconi Anemia-Induced Pluripotent Cells by Homologous Recombination	Fanconi Anemia	5		
	BM090216	Margaret Goodell	Interferon-gamma-Induced Proliferation and Premature Senescence Lead to Hematopoietic Stem Cell Dysfunction in Acquired Aplastic Anemia	Aplastic Anemia		2	
2010	BM100012	Jose Cancelas	Gap Junction Intercellular Communication in Bone Marrow Failure	Bone Marrow Failure	1	4	
	BM100015	Daniel Starczynowski	Regulation and Function of TIFAB in Myelodysplastic Syndrome	Myelodysplastic Syndrome	2	9	1
	BM100035	Christopher Park	Functional Role of microRNAs in Hematopoietic Stem Cells in the Myelodysplastic Syndromes	Myelodysplastic Syndrome	6	2	2
	BM100055	Yi Zhang	Modulation of Memory T Cells to Control Acquired Bone Marrow Failure	Aplastic Anemia	9	8	
	BM100059	Niall Howlett	De Novo Chromosome Copy Number Variation in Fanconi Anemia-Associated Hematopoietic Defects	Fanconi Anemia		1	
	BM100093	Paul de Figueiredo	Shwachman Diamond Syndrome: Linking Bone Marrow Failure to Global Acetylome Dysregulation	Shwachman Diamond Syndrome		1	1
2011	BM110060	Kathleen Sakamoto	Signaling Pathways in Pathogenesis of Diamond Blackfan Anemia	Diamond Blackfan Anemia	3	4	6
	BM110081	Haiming Xu	Molecular Mechanism of Severe Cytopenia in a Mouse Model of Myelodysplastic Syndromes (MDS)	Myelodysplastic Syndrome	1	1	
	BM110104	Amit Verma	Meta-Analytical Online Repository of Gene Expression Profiles of MDS Stem Cells	Myelodysplastic Syndrome		3	
	BM110106	Michael Becker	Therapeutic Targeting of the Bone Marrow Microenvironment in Patients with Myelodysplastic Syndrome	Myelodysplastic Syndrome	4	1	
	BM110172	Omar Abdel-Wahab	Understanding and Targeting Epigenetic Alterations in Acquired Bone Marrow Failure	Myelodysplastic Syndrome	41	23	7
	BM110181	Alan D'Andrea	Bone Marrow Failure Secondary to Cytokinesis Failure	Fanconi Anemia	2		

For additional information about an award, including summary abstracts and publication citations, please visit the CDMRP award search page (https://cdmrp.army.mil/search.aspx).

FY	Proposal Number	Principal Investigator	Project	Disease	Presentations	Publications	Funding Obtained
2012	BM120004	Anderson Wang	A Biochemical Approach to Understanding the Fanconi Anemia Pathway-Regulated Nucleases in Genome Maintenance for Preventing Bone Marrow Failure and Cancer	Fanconi Anemia			1
	BM120018	Matthew Walter	The Role of U2AF1 Mutations in the Pathogenesis of Myelodysplastic Syndromes	Myelodysplastic Syndrome	9	3	
	BM120048	Shuyun Rao	Study of Rpl22 in MDS and AML	Myelodysplastic Syndrome	2	1	1
	BM120072	Jiwang Zhang	The Role of Necroptosis in the Pathophysiology of Bone Marrow Failure	Bone Marrow Failure		1	
	BM120096	Stephen Chung	An Analysis of microRNA Expression in the Myelodysplastic Syndromes Using Hematopoietic Stem Cells	Myelodysplastic Syndrome		4	1
	BM120114	Julien Duxin	Role of Fanconi Anemia Pathway in Repairing Formaldehyde-Induced DNA Lesions	Fanconi Anemia	4	1	
	BM120136	Mridul Mukherji	Rescue of TET2 Haploinsufficiency in Myelodysplastic Syndrome Patients Using Turbo Cosubstrate	Myelodysplastic Syndrome	2	3	
	BM120152	Marshall Horwitz	Translational Control in Bone Marrow Failure	Neutropenia		2	1
2013	BM130070	Carl Novina	Dysregulated microRNA Activity in Shwachman-Diamond Syndrome	Shwachman Diamond Syndrome	5	1	
	BM130081	Benjamin Ebert	Role of Hypomethylating Agents in the Treatment of Bone Marrow Failure	Myelodysplastic Syndrome		2	
	BM130116	Irving Weissman	Clonal Evolution and Novel Therapeutic Approaches for the Treatment of Myelodysplastic Syndrome	Myelodysplastic Syndrome			6
	BM130174	Raymond Monnat	Small Molecule Protection of Bone Marrow Hematopoietic Stem Cells	Fanconi Anemia	2	3	
	BM130173	Daniel Link	Accelerate Genomic Aging in Congenital Neutropenia	Neutropenia	2	1	
2014	BM140082	Shai Izreali	GATA2-GATA1 Axis in Diamond Blackfan Anemia	Diamond Blackfan Anemia	3		
	BM140087	Sheng Wei	Novel therapeutic approaches targeting MDSC in Myelodysplastic Syndrome	Myelodysplastic Syndrome		2	
	BM140102	Seth Corey	Alternative RNA Splicing of CSF3R in Promoting Myelodysplastic Syndromes	Myelodysplastic Syndrome	1	4	
2015	BM150040	Markus Grompe	Metformin Therapy for Fanconis Anemia	Fanconi Anemia		1	
	BM150092	Omar Abdel-Wahab	Therapeutic Targeting of Spliceosomal-Mutant Acquired Bone Marrow Failure Disorders	Myelodysplastic Syndrome	1	7	2
	BM150095	Sandra Zinkel	Regulation of Programmed Necrosis and Bone Marrow Failure	Myelodysplastic Syndrome	5	1	
	BM150110	Yi Zhang	The Role of Histone Demethylase Jmjd3 in Immune-Mediated Aplastic Anemia	Aplastic Anemia		9	
2016	BM160035	Wei Tong	Rescue Hematopoietic Stem and Progenitor Cell Functions in Bone Marrow Failure Syndromes	Fanconi Anemia	2	1	
	BM160071	Katherine MacNamara	Macrophage-Mediated HSC Dysfunction in Bone Marrow Failure	Aplastic Anemia	2	1	
2017	BM170062	Laura Calvi	Role of the Aged Bone Marrow Microenvironment in Modulation of Hematopoietic Failure and Transformation in Myelodysplastic Syndrome	Myelodysplastic Syndrome		1	
	BM170068	Yan Liu	Understanding and Targeting Mutant p53 in Myelodysplastic Syndromes	Myelodysplastic Syndrome	2	5	

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High-Impact Advances in BMF Research

Macrophage-Mediated Hematopoietic Stem Cell Dysfunction in Severe Aplastic Anemia

Katherine MacNamara, Ph.D., Albany Medical College

Severe Aplastic Anemia (SAA) is a rare type of bone marrow disease that occurs when there is an extreme loss of HSCs, which can be lethal. Interferon gamma (IFNγ) has long been associated with SAA; however, its mechanism of action in relation to the disease is not fully understood. Through an FY16 BMFRP Idea Development Award, Dr. Katherine MacNamara utilized murine models of SAA to investigate the mechanistic role of IFNγ on HSC loss. Research conducted in this study showed that reduced macrophages or blocking IFNγ signaling in macrophages rescued disease, but did not impair production of IFNγ in the mouse models, which suggested that macrophages act as key sensors of IFNγ in the disease process. Results show that an IFNγ-dependent increase in bone marrow macrophages during SAA drives HSC loss and thrombocytopenia, creating a case for targeting macrophages and understanding how macrophages contribute to disease pathogenesis. Studies examined the efficacy of targeting two factors associated with IFNγ signaling in macrophages, the chemokine CCL5 and the protein podoplanin (PDPN), to improve SAA disease outcomes. The team showed that macrophages errantly express PDPN during SAA and that ligating PDPN to mimic receptor interaction improved HSC numbers and platelet output. Dr. MacNamara and her team believe that a deeper understanding of this macrophage-mediated process is crucial to the development of targeted therapy options for disease management.

Understanding and Targeting Mutant p53 in Clonal Hematopoiesis and MDS

Yan Liu, Ph.D., Indiana University, Indianapolis

Clonal hematopoiesis of indeterminate potential (CHIP) is a condition in which somatic mutations occur in hematopoietic stem and progenitor cells (HSPCs), giving rise to a genetically distinct blood lineage. Mutations in the tumor suppressor gene TP53 can drive the expansion of HSPCs as one ages and increase the risk of blood-related cancers, including MDS and acute myeloid leukemia, resulting in less than average clinical outcomes. TP53 mutations are associated with short survival and drug resistance, thus constituting a critical area of research work. With an FY17 BMFRP Idea Development Award, Dr. Yan Liu sought to characterize the role of mutant p53 in the pathogenesis of MDS and identify novel therapeutic targets for MDS treatment. Using humanized knock-in mice, the team analyzed the peripheral blood and performed bone marrow transplantation assays. They observed an increased frequency of donor-derived HSPCs in the bone marrow of recipient mice; findings that suggest the expression of mutant p53 in normal HSCs does not cause leukemic transformation, but rather generates a premalignant state. This illustrates disease pathogenesis. Dr. Liu's team also discovered that HSCs with mutant p53 had a competitive advantage for cellular repopulation following transplantation and that mutant p53 promoted HSC expansion after genotoxic stress. They showed that the genetic and pharmacological inhibition of EZH2 (a functional part of a protein complex needed for HSC self-renewal and differentiation) reduces the repopulating potential of p53 mutant HSCs, indicating EZH2 as a novel therapeutic target in the prevention of CHIP progression and the treatment of hematological malignancies that are associated with TP53 mutations.

Consumer Review – Ed Russo (Peer Review Panel Member – FY16, FY18, FY19)

"I was diagnosed with polycythemia vera in 1997 as a 21-year-old, and the disease was cured via stem cell transplant in 2013. Due in part to the advancements discovered/implemented by applicants and reviewers within the BMFRP over the years, I had a much better outcome from my transplant than I likely would have had if I needed a transplant in 1997. My disease is cured, and I only have very slight issues that resulted from the transplant. I am married and have an amazing 4-year-old daughter. It was a pleasure to serve as part of the panel in the hopes that these scientists and doctors can provide better outcomes for as many patients as possible in the future so others can be as fortunate as I have been."

Identifying Therapeutic Targets for Dyskeratosis Congenita

Luis Batista Ph.D., Washington University in St. Louis

Dyskeratosis congenita (DC) is an inherited BMF syndrome in which the bone marrow is unable to produce sufficient blood cells. Patients with DC have mutations that result in defects in telomerase, a protein involved in telomere maintenance. In the absence of telomerase, telomeres progressively shorten, and once telomeres have reached a critically short length, the cells stop dividing, which leads to the inability of the bone marrow stem cells (HSCs) to maintain blood production. With support from an FY16 BMFRP Idea Development Award – Early Career Investigator, Dr. Luis Batista has identified therapeutic targets able to improve telomerase function and blood cell production in HSCs harboring DC mutations.

The telomerase impairment in DC patients is often a result of mutations causing reduced levels of the Telomerase RNA component (TERC). Dr. Batista and his team set out to understand whether the modulation of TERC degradation in HSCs can improve telomere function and, ultimately, the production of blood cells or hematopoiesis. Recent data have indicated that TERC degradation can be controlled by inhibition of poly(A) polymerase PAPD5. Dr. Batista and his team used human embryonic stem cells harboring a common DC mutation, which recapitulates key aspects of the hematopoietic defects of DC (reduced TERC levels, defective telomere maintenance, and reduced ability to differentiate into blood cells) to assess the effect of silencing PAPD5. In DC mutant stem cells, silencing of PAPD5 increased telomerase activity, elongated telomeres, lowered levels of DNA damage, and restored the cell's ability to differentiate into blood cells. While targeted therapies for DC do not currently exist, these results suggest the potential of therapeutics targeting the regulation of TERC by PAPD5 in DC patients.

Understanding the Impact of RNA Splicing on MDS Progression

Seth Corey, M.D., Cleveland Clinic

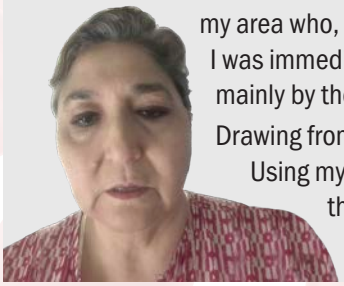
MDS comprise a diverse group of blood cancers in which blood stem cells fail to differentiate into red blood cells, platelets, and white blood cells within the bone marrow. Dr. Seth Corey of the Cleveland Clinic has focused his research on determining how specific genomic mutations impacting RNA splicing can drive MDS progression. Splicing factors are proteins that modify messenger RNA by removing introns, allowing the coding exon sections to bind together. Dr. Corey's work examines how signal transduction by the receptor for Granulocyte Colony Stimulating Factor (GCSF) can determine myelodysplasia and cell fate depending on aberrant splicing of the transcripts for the GCSF receptor. GCSF is the most important cytokine to stimulate the production of granulocytes. Excessive or deficient stimulation leads to myeloid leukemia or neutropenia, respectively.

Through his FY15 BMFRP Idea Development Award, Dr. Corey has developed a minigene model of CSF3R that encodes the receptor for GCSF. Several types of variants have been identified in CSF3R, each of which is associated with a particular type of myeloid disorders. By introducing the CSF3R minigene into human cells, Dr. Corey has been able to analyze how the gene is spliced and what factors are needed for the splicing to occur. Through this research, he has identified several splicing factors, including U2AF1 and SRSF2, plus certain post-translational modifications as regulators of GCSF receptor transcript processing that promote MDS-like phenotypes.

Continuing his research, Dr. Corey's future work under this award will involve finalizing the mouse models of his findings and further studying these pathways in living systems. He plans on validating the results found in his cellular studies and then moving on to targeted treatments that will not only provide more information on MDS disease progression, but may provide data to inform the development of potential therapies for use in humans.

Consumer Review – Carmen Romo de Vivar, Consumer Peer Reviewer – FY19

I am Carmen Romo de Vivar, a Severe Aplastic Anemia survivor enjoying my 11th anniversary on remission. The story of my illness is very long and full of twists and turns that could take days to be told; therefore, I will only point out the crucial moments of my journey.



It took the oncologist who first saw me a month and a battery of invasive exams to tell me the worst information anyone can receive: "I do not know what your disease is. Sorry, I cannot help you." Fortunately, he referred me to a team of researchers in my area who, within two days of my being hospitalized, were able to diagnose me with Very Severe Aplastic Anemia. I was immediately treated with a combination of drugs that had been discovered with the aid of grants funded mainly by the DOD BMFRP.

Drawing from that experience, I was able and honored to serve as a patient consumer for the BMFRP last fall. Using my experiences as a patient and advocate, I wish to aid other patients who are presently experiencing these diseases or could in the future. Being able to aid in the examination and selection of the best research grants to be awarded has been one of the most rewarding experiences of my life.

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