



2017 MDS Research Fund Investigators

Dr. Gregory Abel – “A New Paradigm of Transfusion Support for Patients with MDS”

Dr. Coleman Lindsley – “The impact of somatic STAG2 mutations on MDS transformation in GATA2 deficiency syndrome”

Dr. Stephen Chung – “The Clinical Impact of MDS Stem Cells in Patients Undergoing Allogeneic Transplant”

2018 MDS Research Fund Investigators

Dr. Michael Becker – “Role for bone marrow mesenchymal populations in modulating Interleukin 1 signaling in MDS”

Dr. David Sallman – “Delineation of Immune Evasive Mechanisms Driving Poor Outcome in TP53 Mutant MDS”

Dr. Valeria Visconte – “Molecularly Targeted Agents in Myelodysplastic Syndrome”

2019 MDS Research Fund Investigators

Dr. Richard Padgett – “The Role of DDX41 in MDS”

Dr. Luisa Cimmino – “Targeted Maintenance of TET Activity in MDS Progression and Treatment”

Dr. Richard Lin – “Phase II Study of a Geriatric Vulnerability Based, Personalized Allogeneic Hematopoietic Transplantation Strategy for Older, Vulnerable Patients with MDS”

2020 MDS Research Fund Investigators

Dr. Stephanie Halene – “Exploiting DNA repair defects in IDH mutant MDS via combination therapies”

Dr. Stanley Lee – “Therapeutic targeting of aberrant mRNA splicing in MDS”

Dr. Kristen Schratz – “The role of short telomeres in age-related myelodysplastic syndromes”



2017 ESTABLISHED INVESTIGATOR

Principal Investigator: Dr. Gregory Abel

Institution: Dana-Farber Cancer Institute

Location: Boston, MA

Research Project Title: A New Paradigm of Transfusion Support for Patients with Myelodysplastic Syndromes

Lay-Language Summary of the Presentation

While many patients with myelodysplastic syndromes (MDS) receive red cell transfusions, it is not known if patients' quality of life (QOL) improves after transfusion, nor whether peri-transfusion QOL assessment (PTQA) can guide future transfusion decisions. We conducted a pilot study of adults with MDS at three centers. Participants, who had to have $Hb \geq 7.5$, completed an MDS-specific measure of QOL (the QUALMS) one day before and seven days after red cell transfusion. A report was sent to each patient and provider before the next transfusion opportunity indicating if there were clinically significant changes in QOL. We assessed the proportion of patients experiencing changes, and with a follow-up questionnaire, whether they perceived their PTQA data were used for future transfusion decisions. 62 patients enrolled, and 37 completed both pre-and post-transfusion QOL assessments. Of these, 35% experienced a significant increase in QUALMS score seven days after transfusion; 46% no change; and 19% a decrease. Among those completing the follow-up questionnaire, 23% reported PTQA result were discussed by their provider when considering repeat transfusion. These data (published in the journal *Transfusion* in 2021) suggest PTQA is feasible for patients with MDS but more work is needed to assure that results are discussed with patients.



2017 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Coleman Lindsley

Mentors: Dr. Benjamin Ebert

Institution: Dana-Farber Cancer Institute

Location: Boston, MA

Research Project Title: The Impact of Somatic STAG2 Mutations on MDS Transformation in GATA2 Deficiency Syndrome

Lay-Language Summary of the Presentation

Myelodysplastic syndrome (MDS) is most often diagnosed in older adults, arising as a complication of aging. In rare cases, MDS develops as a result of an inherited bone marrow disease, such as GATA2-deficiency syndrome, which causes a defect in blood cell function and an increased risk of developing MDS and leukemia. We set out to determine how acquired changes in genes (“mutations”) cause progression to MDS. First, we used sensitive gene sequencing technology to scan DNA from bone marrow samples of 32 patients with GATA2-deficiency syndrome and a group of young patients with different inherited MDS predisposition syndromes. We found that acquired mutations in the gene *STAG2* were present in the majority of patients with GATA2 deficiency, but not in young patients with other diseases. Next, we developed laboratory models to test how GATA2 and *STAG2* mutations might cooperate to cause MDS. We found that *STAG2* mutations alter how efficiently bone marrow stem cells can generate mature blood cells, causing slower cell growth, reduced differentiation, and a higher likelihood of cell death.



2017 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Stephen S. Chung

Mentors: Dr. Robert Collins and Dr. Sean Morrison

Institution: University of Texas Southwestern

Location: Dallas, TX

Research Project Title: The Clinical Impact of MDS Stem Cells in Patients Undergoing Allogeneic Transplant

Lay-Language Summary of the Presentation

The myelodysplastic syndromes (MDS) develop when blood forming stem cells called hematopoietic stem cells (HSCs) accumulate mistakes, or mutations, in their DNA. These abnormal HSCs, termed MDS HSCs, give rise to and sustain all other abnormal MDS cells, and they are present at very high levels at the time of MDS diagnosis. When patients respond to standard non-transplant therapies for MDS, these MDS HSCs persist even when all other disease cells have been wiped out. Thus, when patients stop responding to standard non-transplant therapies for MDS, MDS HSCs serve as the source of resistant disease cells. The only curative therapy for MDS is bone marrow transplantation, which allow for replacement of MDS HSCs with HSCs from healthy donors, but this strategy fails to cure up to half of patients with high-risk MDS. In such patients who relapse after bone marrow transplant, we seek to detect MDS HSCs that remain after transplant and determine what is different about these MDS HSCs that allow them to persist. To detect such MDS HSCs, we have identified cell surface proteins that distinguish MDS HSCs from normal HSCs, allowing us to use a technique called flow cytometry to selectively collect MDS HSCs, for further studies. We have additionally found that some of these cell surface markers have important functions that support MDS HSCs, and that treatment strategies targeting them might help get rid of MDS HSCs. Together, this work promises to lead to tools that can predict what patients may be a high risk for relapse of MDS after bone marrow transplantation, as well as methods to more effectively eradicate MDS HSCs to cure patients with MDS.



2018 ESTABLISHED INVESTIGATOR

Principal Investigator: Dr. Michael W. Becker

Institution: University of Rochester

Location: Rochester, NY

Research Project Title: Role for Bone Marrow Mesenchymal Populations in Modulating Interleukin-1 Signaling in Myelodysplastic Syndrome

Lay-Language Summary of the Presentation

Our research and that of others highlights the importance of the bone marrow microenvironment, BMME, on how normal blood cell formation occurs as well as on how blood cancers develop. Mesenchymal stem and progenitor cells, MSPCs, and their progeny are a major component of the BMME and play a role in the development and the marrow failure associated with myelodysplastic syndrome, MDS. Through our study of MSCs from mouse models of aging and MDS, as well as MSCs from the bone marrow samples from aged donors and patients with MDS, we have strong initial evidence that IL-1 is a key mediator of BMME injury in MDS and that the MSCs are an important target for therapy. The central hypothesis of this proposal is that aging and other injuries lead increased IL-1 signaling in the BMME altering MSC function and promoting the development and progression of MDS. To address this hypothesis, we have employed a novel age-appropriate mouse model of MDS. We found that genetic loss of the Il1 receptor in the BMME blocks the development of the macrocytic anemia associated with this model and restores BMME MSC function without effecting the size of the MDS clone. Using three different approaches to therapeutically targeting TLR/IL1 signaling in the same age-appropriate mouse model of MDS, we found that inhibition of Il1 signaling with anakinra or the IRAK1/4 inhibitor, PF06650833, reverses the macrocytic anemia, restores BMME MSC function and effectively targets the MDS clone. Our findings demonstrate the impact of IL-1 in mediating MDS related BMME dysfunction as well as the possible impact of targeting IL1 signaling in patients with MDS. We are currently validating our findings using in vitro human pre-clinical studies to move this approach quickly to the clinic to improve the care of patients with MDS.



2018 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. David Sallman

Mentor: Dr. Eric Padron

Institution: H. Lee Moffitt Cancer Center and Research Institute

Location: Tampa, FL

Research Project Title: Delineation of Immune Evasive Mechanisms Driving Poor Outcome in TP53 Mutant Myelodysplastic Syndromes

Lay-Language Summary of the Presentation

Myelodysplastic syndrome (MDS) represents a spectrum of blood cancers in which bone marrow fails to produce sufficient numbers of healthy blood cells as well as a risk to progress to acute myeloid leukemia (AML). Mutations in TP53 are found in ~10% of MDS and AML patients and are associated with poor overall prognosis (median overall survival of 6 to 12 months) and lack of good treatment options. Together, these data support urgent need for new therapies for TP53 mutant patients. With support from the Vera and Joseph Dresner Foundation, we were able to make several novel discoveries. Critically, in the setting of two high impact publications, we identified that serial sequencing of TP53 patients during treatment is intimately tied to the clinical trajectory of patients. Specifically, patients that clear the mutation (i.e. have deep molecular remissions) have significant improved outcomes whereas patients that have expansion of the mutation at any time have inferior outcomes. These data support future clinical trials where clearance of the TP53 should be a key outcome of the study and may help us identify which therapies are the most efficacious in this patient population. To try and understand the mechanistic reasons why TP53 mutant patients have poor outcomes, we analyzed the immune microenvironment of these patients and clearly showed that there is a very immune adverse microenvironment in TP53 mutant patients and ideally therapies can be used to target these negative factors. Last, we completed a phase 2 trial with APR-246 (eprenetapopt), which is a novel agent that has been shown to reactivate mutant p53 protein by restoring wild-type (non-mutant) shape in order to function normally with the end result of selectively killing the TP53 mutant cancer cells. The study was published in the *Journal of Clinical Oncology* and have supported the ongoing phase 3 study of eprenetapopt with azacitidine with the goal of having the first TP53 mutant selective therapy. Importantly there is now a 2nd generation inhibitor as well as novel combination strategies planned to further improve outcomes in this patient population. My team and patients are indebted to the generosity of the Vera and Joseph Dresner Foundation, and we sincerely thank everyone for the support.



2018 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Valeria Visconte

Mentor: Dr. Jaroslaw P. Maciejewski

Institution: The Cleveland Clinic Foundation

Location: Cleveland, OH

Research Project Title: Molecular Targeted Agents in Myelodysplastic Syndrome

Lay-Language Summary of the Presentation

Genetic mutations in the splicing factor 3B, subunit 1 (*SF3B1*) gene are frequent in myelodysplastic syndromes. Changes in *SF3B1* gene associate with defects in the production of red blood cells and dysfunction in iron metabolism. It is believed that repairing the defective function caused by *SF3B1* mutations will be the strategy of the future to treat patients with myelodysplastic syndromes. *SF3B1* encodes for a protein that is involved in RNA-splicing, a process required for the transfer of genetic information from DNA to messenger RNA which are then translated into proteins. To date only very few drugs exist for myelodysplastic syndromes and there is an urgent need to develop new effective therapies. Because splicing is very ubiquitous, specific approaches are needed to avoid toxicities. We have identified a novel chemical that can selectively eliminate cells with *SF3B1* mutation to allow normal hematopoietic cells to restore blood cell production.



2019 ESTABLISHED INVESTIGATOR

Principal Investigator: Dr. Richard A. Padgett

Institution: Cleveland Clinic Foundation

Location: Cleveland, OH

Research Project Title: Role of DDX41 in MDS

Lay-Language Summary of the Presentation

A few years ago, our group and others found that a gene called DDX41 was often missing one copy or had mutations in one or both copies in MDS patients. We also noticed that some of these mutations were inherited which is unusual in adult leukemia. We studied the function of DDX41 and found that it plays a role in the process of RNA splicing like several other MDS associated genes. We collaborated with other groups to study DDX41 in mouse and zebrafish models. We identified defects in different cellular processes in these models that can also be seen in our analyses of human patient samples. Further studies will work to reveal the details of these defects and link them to the hallmarks of MDS disease to direct therapeutic efforts.



2019 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Luisa Cimmino

Mentor: Dr. Stephen L. Nimer

Institution: University of Miami

Location: Miami, FL

Research Project Title: Targeted Maintenance of TET Activity in MDS Progression and Treatment

Lay-Language Summary of the Presentation

Vitamin C is an essential nutrient that is used by our bodies to maintain healthy hair, skin, immune system and heart function. In addition to these health benefits, vitamin C enhances the activity of a group of enzymes called TET proteins that are required for normal blood cell development. Up to 30% of patients with MDS have a mutation in the gene for TET2, leading to a decrease in its activity and defective blood cell production. We hypothesized that restoring TET2 activity, by increasing vitamin C bioavailability, could reverse and block the progression of MDS. High doses of vitamin C are currently being tested in clinical trials for the treatment of blood cancers and MDS. The success of vitamin C treatment in blocking MDS progressions may vary patient-to-patient, and could depend on multiple factors including how much vitamin C is available for uptake and how much TET protein is present in MDS cells that can respond to the increase in vitamin C levels. Maintaining optimal dietary levels from vitamin C could also be beneficial to MD patients in combination with standard therapies, and higher doses delivered directly into the bloodstream could have a greater chance at targeting disease-initiating stem cells in the bone marrow. Using models of MDS disease and patient samples we hope these studies will show that vitamin C treatment can be used as a safe and effective strategy to improve outcome for patients living with MDS.



2019 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Richard J. Lin

Mentor: Dr. Sergio A. Giralt

Institution: Memorial Sloan-Kettering Cancer Center

Location: New York, NY

Research Project Title: Phase II Study of a Geriatric Vulnerability Based, Personalized Allogeneic Hematopoietic Transplantation Strategy for Older, Vulnerable Patients with Myelodysplastic Syndrome

Lay-Language Summary of the Presentation

Myelodysplastic syndrome (MDS) predominantly affects older people with a median age of onset in the 70s. Despite therapeutic advances in last decade, allogeneic hematopoietic cell transplantation remains the only curative treatment modality. However, transplantation has considerable risk of treatment-related complications, as well as at least short-term decline in quality of life and function especially in older adults. Geriatric assessment, a comprehensive, holistic approach to evaluate an older adult, is increasingly used in older cancer patients. Some of its domains, such as physical function and comorbidities, have shown to be prognostic of survival for older transplant patients. In this prospective study of older MDS patients undergoing transplant, we aim to study the effectiveness of geriatric assessment driven, risk adapted, transplant strategy to select appropriate conditioning intensity to reduce transplant-related mortality and to maintain function and quality of life post-transplant. This study has the potential to establish best practice for older MDS patients considering allogeneic hematopoietic transplantation.



2020 ESTABLISHED INVESTIGATOR

Principal Investigator: Dr. Stephanie Halene

Institution: Yale Cancer Center

Location: New Haven, CT

Research Project Title: Exploiting DNA Repair Defects in IDH mutant MDS via Combination Therapies

Lay-Language Summary of the Presentation

Mutations in key proteins, isocitrate dehydrogenase -1 and -2 (IDH1/2), in the cell's major energy generating pathway, the citric acid cycle, are found in up to 12% of both patients with myelodysplastic syndromes (MDS) and 20% of patients with newly diagnosed acute myeloid leukemia (AML). MDS and AML are cancers of the blood- generating cells in the bone marrow. Mutations in IDH1/2 result in the generation of an abnormal substance, 2-hydroxyglutarate (2HG) that inhibits many enzymes critical for numerous functions in the cell. Specific inhibitors of mutant IDH1/2 are now FDA-approved but they do not cure cancers. We have figured out that 2HG makes cells more sensitive to drugs already in the clinic that can damage the DNA in cells and kill mutant but not normal cells. To test whether these drugs are effective against patient derived cells we have transplanted IDH mutant MDS and AML into mice that have been engineered to grow these diseased cells. We show that a drug that inhibits the DNA repair enzyme Poly (ADP-ribose) polymerase (PARP) results in decreased engraftment of human MDS/AML in mice specifically engineered to allow human cells to grow.

Importantly, inhibition of PARP also works in AML that has become resistant to a specific drug directly targeting the mutant IDH2 enzyme. Single drugs can work but are often not effective enough and last for a short time. We will now test drug combinations in IDH mutant MDS/AML to further improve treatment of these diseases.



2020 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Stanley Lee

Mentor: Dr. Joachim Deeg

Institution: Fred Hutchinson Cancer Research Center

Location: Seattle, WA

Research Project Title: Therapeutic Targeting of Aberrant mRNA Splicing in Myelodysplastic Syndromes

Lay-Language Summary of the Presentation

Myelodysplastic Syndromes (MDS) are a group of heterogeneous blood disorders characterized by inefficient blood cell production. A large proportion of MDS patients carry genetic changes that affect the function of a macromolecular cellular machinery known as the spliceosome, which helps process the genetic information required for protein production. Mutations in the spliceosome genes occur early in the disease onset, which makes them very attractive targets for therapeutic interventions. Despite our increased understanding on how spliceosome contribute to MDS, we still lack effective therapies to fully treat or even cure these patients. In this presentation, I will provide updates on our recent effort to design and test novel therapeutic approaches for the treatment of MDS.



2020 EARLY CAREER INVESTIGATOR

Principal Investigator: Dr. Kristen E. Schratz

Mentor: Dr. Mary Armanios

Institution: Johns Hopkins University

Location: Baltimore, MD

Research Project Title: The Role of Short Telomeres in Age-Related MDS

Lay-Language Summary of the Presentation

Myelodysplastic Syndromes (MDS) are age-related diseases, but the factors underlying this risk with aging are not fully understood. Telomeres are protective caps on our chromosomes; they shorten with age. Inherited defects in the machinery that lengthens telomeres cause accelerated shortening. In patients born with these short telomere disorders, MDS is the most common cancer and affects one in ten patients with short telomeres. In contrast to other inherited causes of MDS that predominantly occur in children and young adults, telomere-related MDS most often affects adults over age 50, suggesting a potential link between telomere length and the risk of MDS with aging. We sought to determine mechanisms that allow normal bone marrow cells in patients with short telomeres to become malignant. Using ultra-deep genetic sequencing, we discovered several “self-correcting” mutations in genes associated with telomere maintenance. Nearly one-third of patients acquired these mutations and our study showed that they are in fact protective against developing MDS and acute myeloid leukemia. For patients with MDS-prone inherited disorders, these and other self-correcting mutations may serve as molecular predictors of MDS risk and allow a personalized approach to their care.