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TITLE: Understanding and Targeting Epigenetic Alterations in Acquired Bone Marrow Failure

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Fort Detrick, Maryland 21702-5012

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**Understanding and Targeting Epigenetic Alterations in Acquired Bone Marrow Failure**

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U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

**Distribution / Availability Statement**
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**Abstract**
Systematic genomic discovery efforts in patients with bone marrow failure due to myelodysplastic syndrome (MDS) has led to the rapid discovery of recurrent somatic genetic alterations underlying these disorders. Remarkably, a large number of these mutations occur in genes whose function is known, or suspected, to be involved in epigenetic regulation of gene transcription or in RNA splicing. This includes mutations in ASXL1, TET2, and EZH2 as well as mutations in the RNA splicing factors SF3B1, SRSF2, and U2AF1. Over the course of funding of this award we have made major progress in (1) understanding the impact of ASXL1 mutations and loss on chromatin (Abdel-Wahab, et al. Cancer Cell 2012), (2) identifying the in vivo biological effects of deletion of Asxl1 and Tet2 alone and in combination with one another (Abdel-Wahab, et al. J Exp Med 2013), (3) identified the genome-wide effects of Asxl1 on transcription (Abdel-Wahab, O, et al. Leukemia 2013 and Abdel-Wahab, O, et al. J Exp Med 2013 and Abdel-Wahab, O, et al. Leukemia 2013), (4) identified that mutations in the splicing machinery in MDS may also impact the function of epigenetic modifiers (Kim, E, et al. Cancer Cell 2015), (5) developed therapeutic approach to target spliceosomal mutant MDS (Lee, SCW, et al. Nat Med 2016), and (6) identified a function of ASXL2, a paralog of ASXL1, in normal and malignant hematopoiesis (Micol, J-B, et al. Nat Comm 2017).

**Subject Terms**
ASXL1; Bone marrow failure; Myelodysplastic Syndrome; RNA splicing; SF3B1; SRSP2; TET2

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Introduction

Increasing use of genomic discovery efforts in patients with bone marrow failure due to myelodysplastic syndrome (MDS) has led to the rapid discovery of a series of recurrent genetic abnormalities underlying these disorders. Remarkably, a large number of these alterations appear to be in genes whose function is known, or suspected, to be involved in (1) epigenetic regulation of gene transcription and (2) mRNA splicing. This includes mutations in the genes encoding the epigenetic modifiers TET2, ASXL1, DNMT3a, and EZH2 have all been found to be frequent mutations amongst patients with MDS. In addition, mutations in the spliceosomal genes SRSF2, U2AF1 and SF3B1 are now known to be commonly found in patients with MDS. These mutations occur at highly restricted amino acid residues, are always heterozygous, and never co-occur with one another. These data suggest that splicing mutations confer an alteration of splicing function and/or that cells may only tolerate a certain degree of splicing modulation.

Identification of frequent mutations in epigenetic modifiers and RNA splicing factors has highlighted the fact that a number of these genes encode enzymes and/or result in alterations in enzymatic function which may represent novel, tractable therapeutic targets for MDS patients. In this proposal, we originally aimed to identify (a) if mice with genetically engineered deletion of epigenetic modifiers mutated in MDS would serve as valuable murine models of MDS, (b) if mutations in epigenetic modifiers may specifically impact DNA methylation and/or histone post-translational modifications in a manner that is therapeutically targetable, and (c) if additional mutations must exist in patients with specific subsets of MDS with the worst clinical outcome. Since awarding of the proposal, we have made major insights into the epigenomic function of ASXL1 as well as the biological impact of conditional deletion of Asxl1 alone and in combination with other genetic alterations including Tet2 deletions and NRasG12D overexpression. In addition, we have recently identified that an additional class of very frequency mutations in MDS patients affecting the spliceosome impacts EZH2 function.

We previously showed that mice expressing the heterozygous Srsf2P95H mutation develop MDS-like features due to altered RNA binding and splicing preference of the mutant protein. These biological and mechanistic features of the mutant SRSF2 protein are distinct from those seen with loss of 1 or copies of SRSF2, indicating that SRSF2 mutations confer an alteration of function. Specifically, mutations in SRSF2 alter its binding to exonic splicing enhancers (ESEs) such that the mutant protein recognizes C-rich ESE sequences over G-rich ESEs whereas the wildtype protein recognizes C- and G-rich ESEs similarly. Recent work from others has revealed that mutations in the core spliceosomal protein U2AF1 also result in altered RNA binding and splicing preference based on the nucleotide sequence immediately surrounding the 3’ splice site. Finally we have identified that spliceosomal mutant MDS cells display greater sensitivity towards pharmacologic inhibition of splicing function than spliceosomal wildtype counterparts. This latter finding has resulted in a novel phase I clinical trial of spliceosome inhibitor compound in patients with refractory MDS and other myeloid leuemias (clinicaltrials.gov identifier NCT02841540). In addition, this work has resulted in several publications, multiple oral presentations at national meetings, and has been used as the basis for several additional foundation and NIH R01 awards.

Keywords:
5-azacytidine, ASXL1, Decitabine, Epigenetics, EZH2, Genomics, Mouse models, Myelodysplastic Syndromes, Splicing, SF3B1, SRSF2, TET2.
Accomplishments

Key Research Accomplishments

- Developed and published the first conditional knockout mouse for Asxl1 as well as the first murine model with combined Asxl1 and Tet2 deletion. We believe these models are valuable genetically accurate murine models of acquired bone marrow failure.
- Identified the biological effects of Asxl1 loss on hematopoiesis, alone and in combination with other co-occurring genetic alterations.
- Generated the first murine model of spliceosomal mutations as seen in patients with MDS.
- Identified an important intersection of spliceosomal gene alterations on the epigenome of MDS.
- Identified a novel therapeutic approach for cells bearing spliceosomal gene alterations.
- Identified the biological role for ASXL2, a paralog of ASXL1, in normal and malignant hematopoiesis.

In addition to the above summary, below is a more detailed summary of accomplishments organized by Tasks from the original grant submission:

Task 1. “Obtain DoD ACURO approval for the use of animals in the experiments outlined below in Tasks 2 to 4.”

This was completed.

Task 2. “Complete characterization of mice with conditional deletion of Asxl1 alone and Asxl1 combined with Tet2 (Months 1-24) at the work performance site of Memorial Sloan-Kettering Cancer Center.”

This work was published in 2013 in the Journal of Experimental Medicine (Abdel-Wahab, O, et al. J Exp Med 2013 Nov 18;210(12):2641-59) and have been used by the MDS research community internationally. We have deposited these mice at the Jackson Laboratory for public use.

In addition, we also recently created mice with compound loss of Asxl1 and Asxl2 in order to understand the role and potential redundancy of Asxl2 with Asxl1 in hematopoiesis. This work is now in press at Nature Communications in the following publication:


Task 3. Continue development of mice with Ezh2 deletion alone and characterize mice with compound deletion of Ezh2/Tet2 and Ezh2/Asxl1 (Months 1-24) at the work performance site of Memorial Sloan-Kettering Cancer Center.
We recently generated mice with Ezh2 deletion in the postnatal compartment (Mx1-cre Ezh2fl/fl) mice and mice with compound deletion of Ezh2 and Asxl1. From these murine models we have identified that:

(i) Hematopoietic stem cells (HSCs) from mice with compound Asxl1/Ezh2 loss have impaired self-renewal compared with HSCs from littermate control mice as well as mice with deletion of either gene alone.

(ii) A high proportion of wildtype mice reconstituted with bone marrow from mice with compound Asxl1/Ezh2 (Mx1-cre Asxl1fl/fl Ezh2fl/fl) deletion die of bone marrow failure within weeks of deletion of these genes. Surviving mice are characterized by anemia and leukopenia as well as morphologic dysplasia.

The above phenotypes of mice with compound deletion of both Asxl1 and Ezh2 are dramatic and we are now working to functionally understand the mechanism by which deletion of these 2 genes impairs HSC function.

In addition to the above, we have recently identified the unexpected observation that mutations in the spliceosomal protein SRSF2, commonly identified in MDS patients, results in mis-splicing of EZH2. Interestingly, SRSF2 mutations and loss-of-function EZH2 mutations in MDS are 100% mutually exclusive but the functional basis for this interaction was not known previously. Our work provided the basis for this observation and identified another mechanism by which EZH2 is dysregulated in MDS. These data were published in the following manuscript:


Task 4. Determine the epigenetic contribution of Asxl1 and Ezh2 loss to bone marrow failure through Chromatin immunoprecipitation (ChIP) of histone H3 lysine 27 trimethyl (H3K27me3) followed by next-generation sequencing in primary murine hematopoietic cells (Months 1-24) at the work performance site of Memorial Sloan-Kettering Cancer Center.

As noted in 2 prior annual reports, we have completed detailed characterization of the effects of ASXL1 mutations and loss using cell lines and primary cells from knockout mice. These results have been published now in 2 papers (Abdel-Wahab, O, et al. Cancer Cell 2012 and Abdel-Wahab, O, et al. J Exp Med 2013).

Task 5: Determine the effect of Tet2, Asxl1, and Ezh2 loss to a panel of currently clinically utilized compounds in patients with MDS. Drug panel will include decitabine, 5-azacytidine, lenalidomide, cytarabine, daunorubicin, HDACi (vorinostat, romidepsin, panobinostat, AR-42, trichostatin A), HSP-90 inhibitors (AUY-922, PUH-71), and parthenolide (Months 1-24) at the work performance site of Memorial Sloan-Kettering Cancer Center.
We are now performing these experiments ex vivo through use of methylcellulose colony assays. In brief, hematopoietic stem/progenitor cells (HSPCs; lineage-negative Sca1+ c-Kit+ cells) from Tet2 knockout, Asxl1 knockout, Ezh2 knockout, and Tet2/Asxl1 double knockout mice are being plated in methylcellulose with a variety of the above compounds for 7 days. We are evaluating the effects of these compounds on restoring colony formation (for Asxl1 and Ezh2 knockout HSPCs) or reducing colony formation (for Tet2 and Tet2/Asxl1 knockout HSPCs). This work is underway.

In addition to the above experiments, we have identified that spliceosomal mutant MDS and other cancer cells are critically dependent on wildtype splicing catalysis. This was identified in a paper we published in *Nature Medicine* last year and an ongoing phase I clinical trial (clinicaltrials.gov identifier NCT02841540):


**Task 5:** Perform candidate gene and exome sequencing on DNA samples from 20 MDS patients with ASXL1 mutations alone (Months 1-6) at the work performance site of Memorial Sloan-Kettering Cancer Center.

In order to complete this task and to inform task #5, we recently performed targeted DNA sequencing on pretreatment DNA samples from a cohort of MDS patients uniformly treated with decitabine. This work, performed in collaboration with MDS clinical expert Dr. Valeria Santini, revealed that ASXL1 mutations frequently co-occur with mutations in the spliceosome-associated protein SRSF2 in patients with MDS/MPN overlap syndromes. This interesting finding suggests an interaction by mutations in the epigenome with mutations in the spliceosome. Moreover, this work has resulted in one recent publication as noted above (in “Task 5”).

**Task 6:** Perform candidate gene and exome sequencing on DNA samples from 40 patients with MDS accompanied by moderate to severe bone marrow fibrosis (Months 1-6) at the work performance site of Memorial Sloan-Kettering Cancer Center.

We have now collected samples from 40 such patients with MDS with bone marrow fibrosis and hope to begin performing DNA sequencing soon. We recently helped to generate a DNA next-generation sequencing panel of 300 genes implicated in cancer pathogenesis at our institution. We will apply this sequencing platform to these MDS samples with the hopes of characterizing any novel mutations associated with this unique subtype of MDS.

**Task 7:** Present findings at national meetings and publish in peer-reviewed journals (Month 6-36).

I have given >20 presentations at national/international meetings on the work performed with funding from this award in the last year (see list of presentations in Products below).
I have also been invited to write several reviews related to the work described in this proposal in well-respected journals including *Nature Medicine*, *Genes & Development*, *Blood*, and *Nature Reviews Cancer* (cited in *Products* below).

Impact

Genomic discovery efforts in patients with MDS have revealed that the most frequent somatic mutations in these disorders are in genes involved in either epigenetic regulation or RNA splicing. We and others have recently shown that mutations in the Polycomb-associated gene ASXL1 and the spliceosomal gene SRSF2 have adverse prognostic importance in patients with all myeloid malignancies including MDS, acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), and primary myelofibrosis. We therefore have focused on understanding the role of these mutations in MDS pathogenesis. In brief, we have identified that the loss-of-function mutations in ASXL1 as well as the gain-of-function mutations in SRSF2 both converge on decreased function of the Polycomb Repressive Complex 2 (PRC2). This work has resulted in multiple genetically accurate models of MDS as well as reagents to screen for novel therapeutic targets for *TET2*, *ASXL1*- or *SRSF2*-mutant cells.

Changes/Problems

Nothing to report.

Reportable Outcomes

Original Manuscripts:


**Review Papers:**


Presentations:

2016  Human Biology Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA
2016  5th Annual Symposium of the Critical Reviews in Hematological Malignancies, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
2016  5th International Bone Marrow Failure Disease Scientific Symposium, Aplastic Anemia and MDS International Foundation, Rockville, MD
2016  36th Annual Congress of the French Society of Hematology, Paris, France
2016  Leukemia Grand Rounds, MD Anderson Cancer Center, Houston, TX
2016  AACR Educational Session, AACR Annual Meeting, New Orleans, LA
2016  AACR Recent Advances in Diagnosis and Therapy Session, AACR Annual Meeting, New Orleans, LA
2016  Starr Cancer Consortium Retreat, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY
2016  Hematology Grand Rounds, Fred Hutchinson Cancer Research Center, Seattle, WA
2016  1st Dotan International Symposium, Tel Aviv University, Tel Aviv, Israel
2016  Winthrop Rockefeller Seminar Series, University of Arkansas Medical School, Little Rock, Arkansas, USA
2016  Plenary Speaker, Japanese Society of Hematology, 78th Annual Meeting, Yokohama, Japan
2016  Plenary Speaker, 2nd Spliceosomal Gene Mutations in Cancer Workshop, Broad Institute of Harvard & MIT, Cambridge, MA
2016  Developmental Therapeutics Research Seminar, Amgen Inc., Thousand Oaks, CA
2016  Grand Rounds, Winshop Cancer Institute of Emory University
2016  Ingrim Cancer Center Seminar Series, Vanderbilt University School of Medicine, Nashville, TN
2016  Tisch Cancer Institute Seminar Series, Icahn School of Medicine at Mount Sinai, New York, NY
2016  11th CML & MPN Post-ASH Workshop, La Jolla, California
2016  8th Clinical Translation of Epigenetics and Cancer Therapy, Jekyll Island, GA
2017  Phase Separation and RNA Processing as Drivers of Cancer and Neurodegenerative Disease, UCSD, San Diego, CA
2017  Keystone Symposium RNA Processing in Human Disease, Taos, New Mexico
2017  EHA/ASH Translational Research Training In Hematology Course, Milan, Italy
2017  Curie Institute, Future of Oncology Symposium, Paris, France
2017  Massachusetts General Hospital Cancer Center Seminar Series, Boston, MA

Informatics:
We have generated and published multiple new mRNA sequencing (RNA-Seq) datasets as follows:

- Deep RNA-seq analysis of primary MDS patient samples with and without spliceosomal gene mutations for the purpose of identifying novel splice isoforms.
- Deep RNA-seq analysis of cells with and without spliceosomal gene mutations and with and without treatment with spliceosomal inhibitory compounds. The purpose of this dataset is to identify the effects of spliceosomal modulatory compounds on splicing and gene expression.
Funding applied for based on this work:
Applied for and successfully received numerous foundation awards and an NIH R01 award as follows:

National Institutes of Health 7/1/2015 - 6/30/2020
NIH, 1R01 HL128239 (PIs: Bradley / Abdel-Wahab)
“Genetic and molecular basis for SRSF2 mutations in myelodysplasia”

Dept. of Defense, Bone Marrow Failure Research Program 4/1/2016-3/31/2018
BM150092 (PI: Abdel-Wahab)
“Therapeutic targeting of spliceosomal mutant acquired bone marrow failure disorders”

Starr Cancer Consortium 1/1/2015 - 12/31/2016
I8-A8-075 (PI: Abdel-Wahab)
"Understanding and Targeting Spliceosomal-Mutation Hematopoietic Malignancies"

Pershing Square Sohn Cancer Research Alliance 7/1/2016 - 6/30/2019
GC228160 (PI: Abdel-Wahab)
“Identification of novel transcripts, pathways, and therapeutic strategies to target spliceosomal-mutant malignancies”

Edward P. Evans Foundation 9/1/2016 - 8/31/2017
"Elucidating Critical Targets, Transcripts, and Collaborating Events in Spliceosomal-Mutant MDS"

Conclusion
Bone marrow failure due to myelodysplastic syndrome (MDS) is driven by alterations in transcriptional regulation due to mutations in epigenetic modifiers and RNA splicing factors. Over the course of funding of this award we have made major progress in understanding the impact of mutations in both categories of alterations in MDS. This has led to the development of numerous novel genetically engineered mouse models of MDS all of which have been deposited for public use. In addition, we have developed a novel therapeutic approach to target spliceosomal mutant MDS which is currently the basis of a phase I clinical trial for patients with MDS and other refractory myeloid leukemias.

References
All papers have been cited above.

Appendices
Updated CV for Omar Abdel-Wahab
Curriculum Vitae

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Assistant Member, Human Oncology and Pathogenesis Program
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Education and Training
2007-2009 Memorial Sloan Kettering Cancer Center, New York, NY.
Fellow, Hematology/Oncology.

2004-2007 Massachusetts General Hospital, Boston, MA
Intern/Resident in Internal Medicine,

2000-2004 Duke University School of Medicine,
M.D., Alpha Omega Alpha

1996-2000 Duke University, Durham, N.C.
B.Sc. Biology, Summa Cum Laude

Research Fellowships:
2008-2011 Postdoctoral Research Fellow
Human Oncology & Pathogenesis Program,
Memorial Sloan-Kettering Cancer Center
Ross L. Levine, MD, Associate Member

2002-2003 Medical Student Research Fellowship
Dept. of Surgery, Duke University School of Medicine
Doug Tyler, MD, Professor and Vice Chair Dept. of Surgery

Positions and Employment:
2016 – Current Co-director, Hematology/Medical Oncology Fellowship Program, Dept. of Medicine, Memorial Sloan Kettering Cancer Center

2012 – Current Assistant Level I, tenure track, Dept. of Medicine, Leukemia Service
Assistant Member, Human Oncology and Pathogenesis Program
Memorial Sloan-Kettering Cancer Center

2011- 2012 Assistant Level I, non-tenure track, Dept. of Medicine, Leukemia Service
Memorial Sloan-Kettering Cancer Center

2010-2011 Instructor, Dept. of Medicine
Memorial Sloan-Kettering Cancer Center

Honors and Awards:
2017 The Donald Seldin-Holly Smith Award for Pioneering Research, American Society of Clinical Investigation

2016 Pershing Square Sohn Prize for Young Investigators in Cancer Research
2015 Joanne Levy, MD, Memorial Award for Outstanding Achievement, American Society of Hematology (ASH)
2015 Leukemia and Lymphoma Society Clinical Scholar Award
2015 House-staff Teaching Award, MSKCC
2015 Boyer Clinical Investigator Award, MSKCC
2015 American Society of Clinical Investigation (ASCI) Young Physician-Scientist Award
2014 V Foundation Scholar Award
2013 American Society of Hematology (ASH) Junior Faculty Scholar Award
2013 Damon Runyon Clinical Investigator Award
2012 Dept. of Defense Post-doctoral Award in Bone Marrow Failure Research
2012 Josie Robertson Young Investigator Award
2012 Paul Sherlock House-staff Teaching Award, MSKCC
2011 Gabrielle’s Angel Foundation Fellow Scholar Award
2010-2012 American Society of Hematology (ASH) Fellow Scholar Award
2009 American Society of Hematology (ASH) Research Training Award for Fellows
2008 Chief Fellow, Memorial Sloan Kettering Cancer Center, Medical Oncology/Hematology
2008-2010 Dana Foundation Research Fellowship
2008 John Mendelsohn House-staff Teaching Award
2004 Phillips Medical Systems Award
2004 Alpha Omega Alpha, Duke University School of Medicine
2003 Duke University School of Medicine Barham Merit Scholarship
2002 Duke University Medical Research Scholarship in General and Cardiothoracic Surgery.
1999 Phi Beta Kappa, Duke University

Licensure and Board Certification:
2007 Certification, Internal Medicine (American Board of Internal Medicine)
2007 Medical License, State of New York, #243567-1
2010 Certification, Medical Oncology (American Board of Internal Medicine)

Professional Societies:
2007 Member, American Society of Hematology
2013 Member, American Association of Cancer Research
2016 Medical Advisory Board, Bohring Opitz Syndrome Foundation

Editorial Board:
Editorial Board of Blood and Haematologica.
Associate Editor, Clinical Cancer Research, International Journal of Hematology, and Leukemia.

Ad Hoc Reviewer:


29. Walter, RB, Othus, M, Paietta, EM, Racevskis, J, Fernandez, HF, Lee, J-


lenalidomide combination for elderly patients with untreated acute myeloid leukemia. 


94. Abdel-Wahab, O, Kilipivaara, O, Patel, J, Busque, L, Levine, RL. The most commonly reported variant in ASXL1 (c.1934dupG;p.Gly646TrpfsX12) is not a somatic alteration. *Leukemia* 2010 Sep;24(9):1656-7. PMID:20596031.


Books, Book Chapters and Reviews


Oral Presentations:

2009 International Conference on Differentiation Therapy, Samuel Waxman Foundation, Chicago, IL
2010 Post-ASH Myeloproliferative Neoplasm Workshop, Orlando Fla.
2011 International Working Group for Myelofibrosis Research and Treatment Workshop, Florence, Italy
2011 Leukemia Grand Rounds, Leukemia Dept, MD Anderson Cancer Center, Houston, TX
2011 Lineberger Cancer Center Grand Rounds, UNC Chapel Hill, Chapel Hill, NC
2011 FASEB Hematologic Malignancies, Saxtons River, VT
2011 Northwestern University, Hematology Grand Rounds, Chicago, IL
2011 American Society of Hematology, Oral Presentation in “Oncogenes and Tumor Suppressors”
2011 Post-ASH Myeloproliferative Neoplasm Workshop, La Jolla, CA
2012 UTSW Simmons Cancer Center Molecular Therapeutics of Cancer Program, Dallas, TX
2012 University of Pennsylvania, Dept of Cancer Biology, Philadelphia, Pennsylvania
2012 Cincinnati Children’s Hospital, Experimental Hematology and Cancer Pathology Program, Cincinnati, Ohio
2012 Dept. of Hematology/Oncology, Mount Sinai College of Medicine, New York, NY
2012 Dept. of Genetics, Albert Einstein College of Medicine, Bronx, NY
2012 Chromatin Club of New York, Mount Sinai College of Medicine, New York, NY
2012 Division of Hematologic Neoplasia, Dept. of Medicine, Dana Farber Cancer Institute, Boston, MA
2012 Institut Gustave Roussy Research Seminar, INSERM, Villejuif cedex, France
2012 International Working Group for Myelofibrosis Research and Treatment Workshop, Florence, Italy
2012 Hematologic Malignancies Grand Rounds, Massachusetts General Hospital Cancer Center, Boston MA
2012 Mayo Clinic Arizona, Cancer Center Grand Rounds, Scottsdale AZ
2012 Dept. of Hematology Grand Rounds, First Affiliated Hospital of Nanjing Medical University, Nanjing, China
2012 Plenary Speaker, Chinese Society of Hematology 2012 Annual Meeting, Suzhou China
2012 XII Uruguayan Congress of Hematology, Punta Del Este Uruguay
2012 Innovation Approaches to JAK Inhibition and Continued Clinical Questions in th Management of Myelofibrosis. Atlanta, GA.
2012 American Society of Hematology, Biology of MDS Oral Session, Atlanta, GA.
2012 Post-ASH International CML and MPN Workshop, Atlanta, GA.
2013 Clinical Translation of Epigenetics in Cancer Therapy, Asheville NC
2013 St. Jude’s Children’s Research Hospital, Dept. Pharmaceutical Sciences Seminar Series
2013 Leukemia Lymphoma Society Panel at the Annual Cancer Progress Research Conference
2013 New York City Regional CLL Summit, Long Island Jewish Hospital
2013 International Working Group for Myelofibrosis Research and Treatment Workshop, Florence, Italy
2013 American Association of Cancer Research, Current Concepts Session “The Genetic and Epigenetic Landscape of Leukemia Revealed”
2013 Symposium of Molecular Oncology and Personalized Medicine, Albert Einstein Instituto Israelita De Ensino e Pesquisa, Sao Paulo Brazil
2013 VII Board Review Curso De Revisao Em Hematologia e Hemoterapia, Albert Einstein Instituto Israelita De Ensino e Pesquisa, Sao Paulo Brazil
2013 2013 ASCO — Clinical Problems in Oncology Session
2013 FASEB Hematologic Malignancies, Saxton’s River, Vermont
2013 Society of Hematologic Oncology (SOHO) Meeting, Houston, Texas. "Epigenetic Drivers of Myelodysplasia"
2013 New York Regional CLL Summit Meeting, New York, NY
2013 Foundation Medicine, Cambridge, MA
2013 National Cancer Research Center, Tokyo Japan
2013 10th International Nikko Symposium, Utsonomiya Japan
2013 Dept. of Cell and Molecular Biology, Chiba University, Chiba Japan
2013 Hematology/Oncology Grand Rounds, Marshall University, Huntington, W. Virginia
2013 ASH Educational Session on Myeloproliferative Neoplasms
2013 ASH Oral Abstract Presentation
2013 Cold Spring Harbor Laboratories Scientific Seminar
2014 H3 Biomedicine, Inc, Cambridge MA
2014 Damon Runyon Cancer Research Foundation Accelerating Cancer Cures Symposium
2014 Aplastic Anemia & MDS Foundation International Foundation Bone Marrow Failure Disease Scientific Symposium
2014 Center for Medical Genetics, Ghent University, Ghent, Belgium
2014 The Nikolas Symposium XXIII, Athens, Greece
2014 Hairy Cell Leukemia Foundation, Houston, TX
2014 Evans Foundation MDS Summit, Philadelphia, PA
2014 Plenary Session, AACR Hematologic Sessions, Philadelphia, PA
2014 73rd Annual Meeting of the Japanese Cancer Association, Yokohama, Japan
2014 Seminar, Institute of Medical Sciences, University of Tokyo, Tokyo, Japan
2014 John Pritchard Lectureship, 30th Annual Meeting of the Histiocyte Society, Toronto, Canada
2014 "Think Tank" on Integrating New Molecular Targets in AML. Dallas, Texas
2014 Eastern Cooperative Oncology Group (ECOG) Leukemia Lab Committee. Orlando, Florida
2014 Scientific Workshop on Myeloid Development, 56th Annual Meeting of the American Society of Hematology (ASH), San Francisco, California
2014 Oral Session of Basic and Translation Studies in MDS, 56th Annual Meeting of the American Society of Hematology (ASH), San Francisco, California
2014 9th International CML and MPN post-ASH Workshop, San Francisco, California
2015 7th Biennial Workshop on “Clinical Translation of Epigenetics in Cancer Therapy”, St. Augustine, Florida
2015 Plenary Speaker, Molecular Med Tri-Con, San Francisco, CA
2015 Dept. of Biochemistry Seminar, University of Virginia, Charlottesville, VA.
2015 Leukemia and Lymphoma Society Symposium on Hematological Malignancies, Northwestern University, Chicago, IL
2015 Panel on B-cell Malignancies, Cancer Progress Conference, New York, NY
2015 Research Seminar Series, Boston Children's Hospital, Boston, MA
2015 Indiana University, Wells Center for Pediatric Research Seminar Series
2015 Evans Foundation, MDS Research Summit, Washington D.C.
2015  Hairy Cell Leukemia Foundation Meeting, Chicago, IL
2015  Lineberger Cancer Center Seminar, UNC Chapel Hill, Chapel Hill, N.C.
2015  Annual Meeting of the French Histiocyte Society, Hopital Pitie Salpetriere, Paris, France
2015  Molecular Aspects of Hematology Workshop, Erasmus University, Rotterdam, Netherlands
2015  20th annual meeting of the European Hematology Association (EHA), Invited Speaker
2015  NY Genome Center, 5 Points Seminar Series, New York, N.Y.
2015  Agios Pharmaceuticals, Inc. Cambridge, M.A.
2015  FASEB Hematological Malignancies. Saxton’s River, V.T.
2015  National Center for Tumor Disease (NCT)/The German Cancer Research Center (DKFZ) Heidelberg, Germany
2015  European School of Hematology AML Meeting, Budapest, Hungary
2015  Dept. of Cell and Molecular Biology, SUNY Downstate, Brooklyn, N.Y.
2015  10th Annual CML and MPN Post-ASH Workshop, Orlando, F.L.
2016  Institute for Cancer Genetics Seminar Series, Columbia University
2016  Human Biology Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA
2016  5th Annual Symposium of the Critical Reviews in Hematological Malignancies, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
2016  5th International Bone Marrow Failure Disease Scientific Symposium, Aplastic Anemia and MDS International Foundation, Rockville, MD
2016  36th Annual Congress of the French Society of Hematology, Paris, France
2016  Research Seminar, Rigel Pharmaceuticals Inc., South San Francisco, CA
2016  Leukemia Grand Rounds, MD Anderson Cancer Center, Houston, TX
2016  24th Meeting of the Henry Kunkel Society, Rockefeller University, New York, NY
2016  AACR Educational Session, AACR Annual Meeting, New Orleans, LA
2016  AACR Recent Advances in Diagnosis and Therapy Session, AACR Annual Meeting, New Orleans, LA
2016  Research Seminar, Janssen Research & Development, Spring House, PA
2016  Starr Cancer Consortium Retreat, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY
2016  Hematology Grand Rounds, Fred Hutchinson Cancer Research Center, Seattle, WA
2016  Hairy Cell Leukemia Foundation Meeting, Heidelberg, Germany
2016  1st Dotan International Symposium, Tel Aviv University, Tel Aviv, Israel
2016  4th Annual Erdheim-Chester Disease Medical Symposium, Paris, France
2016  Winthrop Rockefeller Seminar Series, University of Arkansas Medical School, Little Rock, Arkansas, USA
2016  Plenary Speaker, Japanese Society of Hematology, 78th Annual Meeting, Yokohama, Japan
2016  Plenary Speaker, 2nd Spliceosomal Gene Mutations in Cancer Workshop, Broad Institute of Harvard & MIT, Cambridge, MA
2016  Developmental Therapeutics Research Seminar, Amgen Inc., Thousand Oaks, CA
2016  Grand Rounds, Winshop Cancer Institute of Emory University
2016  Ingrim Cancer Center Seminar Series, Vanderbilt University School of Medicine, Nashville, TN
2016  Tisch Cancer Institute Seminar Series, Icahn School of Medicine at Mount Sinai, New York, NY
2016  11th CML & MPN Post-ASH Workshop, La Jolla, California
2016  8th Clinical Translation of Epigenetics and Cancer Therapy, Jekyll Island, GA
2017  Phase Separation and RNA Processing as Drivers of Cancer and Neurodegenerative Disease, UCSD, San Diego, CA
2017  Keystone Symposium RNA Processing in Human Disease, Taos, New Mexico
2017  EHA/ASH Translational Research Training In Hematology Course, Milan, Italy
2017  Curie Institute, Future of Oncology Symposium, Paris, France
2017  Massachusetts General Hospital Cancer Center Seminar Series, Boston, MA
**ACTIVE RESEARCH SUPPORT:**

National Institutes of Health
NIH, 1R01 HL128239 (PIs: Bradley / Abdel-Wahab)
“Genetic and molecular basis for SRSF2 mutations in myelodysplasia”

National Institutes of Health
NIH, 1 R01 CA201247-01A1 (PIs: Abdel-Wahab / Park)
"Origins of BRAF-mutant hematologic malignancies and their therapeutic resistance"

Dept. of Defense, Bone Marrow Failure Research Program
BM150092 (PI: Abdel-Wahab)
“Therapeutic targeting of spliceosomal mutant acquired bone marrow failure disorders”

Starr Cancer Consortium
I8-A8-075 (PI: Abdel-Wahab)
“Understanding and Targeting Spliceosomal-Mutation Hematopoietic Malignancies”

Leukemia and Lymphoma Society Scholar Award (PI: Abdel-Wahab)
“Understanding and targeting Diverse Kinase Alterations in Systemic Histiocytic Neoplasms”

Josie Robertson Investigator (PI: Abdel-Wahab)
Josie Robertson Investigator Program
9/1/12 – 8/31/17 $

Tri-Institutional Stem Cell Initiative (PI: Park)
“Hematopoietic stem cell origins of mature B-cell neoplasms”

Starr Cancer Consortium $ 375,000
I9-A9-059 (PI: Mullally)
“Personalized immunotherapy for the treatment of hematological malignancies"

Hairy Cell Leukemia Foundation (PI: Abdel-Wahab)
“Functional Characterization of Mutations Collaborating with BRAFV600E in HCL”

Erdheim Chester Disease Global Alliance (PI: Abdel Wahab)
“Identification of novel molecular targets for therapy in Erdheim Chester disease without BRAF mutation”

Histiocytosis Association (PI: Janku)
“MEK Inhibition in the Therapy of Histiocytic Neoplasms”

Pershing Square Sohn Cancer Research Alliance
“Identification of novel transcripts, pathways, and therapeutic strategies to target spliceosomal-mutant malignancies”

GC228160 (PI: Abdel-Wahab)
Edward P. Evans Foundation
"Elucidating Critical Targets, Transcripts, and Collaborating Events in Spliceosomal-Mutant MDS"

**PRIOR RESEARCH SUPPORT**

When Everyone Survives Award in Leukemia Research (Abdel-Wahab) 7/1/11 – 6/30/12
When Everyone Survives Foundation
“Understanding the biologic and therapeutic relevance of ASXL1 mutations in acute myeloid leukemia”
To determine how exactly mutations in ASXL1 contribute to leukemia development.
The goal of this project is to fully uncover (1) the effect of ASXL1 mutations of outcome in AML, (2) a comprehensive list of the genes whose expression is regulated by ASXL1 and a genome-wide view of the effects of ASXL1 loss on histone proteins at the sites of those genes and (3) the role of ASXL1 loss in the blood cells in a mouse model which we are currently creating.

The goal of this project is to investigate the biologic and clinical relevance of ASXL1 mutations and how ASXL1 regulates the epigenetic state of genes involved in normal and malignant hematopoiesis.

To identify strategies to aid in the therapy of AML patients with this genetic abnormality.

The relative rarity and protean clinical nature of the histiocytic disorders has made it difficult to clearly delineate the pathophysiology of these conditions. This grant is aimed at the study of histiocytic disorders using high-throughput unbiased techniques and serially through clinical trials of mutant BRAF inhibition.

To understand and target aberrant epigenetic modifiers in the pathogenesis of myelodysplastic syndromes.

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To understand and target aberrant epigenetic modifiers in the pathogenesis of myelodysplastic syndromes.
Systemic Histiocytic Neoplasms

Edward P. Evans Foundation  (PI: Abdel-Wahab)
“Molecular and Biological Consequences of SRSF2 Mutations in the Myelodysplastic Syndromes”