AWARD NUMBER: W81XWH-15-1-0440

TITLE: Novel Therapeutic Approaches Targeting MDSC in Myelodysplastic Syndrome

PRINCIPAL INVESTIGATOR: Sheng Wei

CONTRACTING ORGANIZATION: H. Lee Moffitt Cancer Center & Research Institute

REPORT DATE: November 2019

TYPE OF REPORT: Final

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
Nov 2019	Final Annual Report	09/01/2015 - 08/31/2019

4. TITLE AND SUBTITLE

Novel Therapeutic Approaches Targeting MDSC in Myelodysplastic Syndrome

5a. CONTRACT NUMBER

W81XWH-15-1-0440

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Sheng Wei

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

H. Lee Moffitt Cancer Center & Research Institute
12902 Magnolia Drive
Tampa, FL 33612-9497

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Development of targeted MDS therapies has been challenged by a limited insight of molecular mechanisms of disease pathogenesis and therefore, current therapeutic approaches remain highly empiric largely ignoring the role of the inflammatory bone marrow (BM) microenvironment. We identified S100A9 as a mediator of myeloid derived suppressor cell (MDSC) activation and as the native ligand to CD33, which is highly expressed in MDS. Therefore, our goals are to develop novel therapeutic strategies that inactivate MDSC to improve survival of HSPC and allow us to provide the basis for more effective, biologically rational MDS therapeutics. Based on our initial hypothesis of hematopoietic improvement through the targeting of the S100A9-CD33 pathway, this funding year we were able show that our proposed approaches can inactivate MDSC in vitro. This is achieved through the development of a specific S100A9 trap, the CD33-chimeric human IgG1 molecule (CD33-fusion). We demonstrated that CD33-fusion is able to neutralize soluble S100A9 and suppresses S100A9 induced pro-inflammatory cytokine production as well as improve hematopoiesis. This focused translational research represents the base to develop novel treatments for MDS providing a

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(Include area code)* 813-745-3934

Table of Contents

Page

1. INTRODUCTION

Understanding the selective pressures and mechanisms involved in the initiation of stem cell malignancies is critical for development of effective strategies for prevention and treatment. Myelodysplastic syndromes (MDS) are hematologically diverse bone marrow (BM) failure syndromes that share features of cytological dysplasia, ineffective hematopoiesis and a propensity for progression to acute myeloid leukemia (AML). MDS are senescence-dependent myeloid malignancies with a rising prevalence owing to the aging of the American population. Effective disease-altering therapies for patients with MDS are limited due largely to inadequate understanding of the precise pathobiological mechanisms involved in disease initiation and progression. Although innumerable somatic genetic events have been annotated in recent years, many of which are sufficient for disease initiation in murine models, microenvironmental factors conducive for emergence of these genetic events remain to be delineated. In the original proposal we hypothesized that inflammation and aging induce the accumulation of **myeloid-derived suppressor cells (MDSCs),** a heterogeneous group of immature myeloid cells, which play a critical role in MDS pathogenesis. A key finding of our recent studies was the identification of CD33 as a receptor that binds S100A9 to drive expansion and activation of BM MDSCs, and trigger cell death of myeloid progenitors. MDSC-mediated suppressive activity is stimulated by the danger-associated molecular pattern (DAMP) heterodimer S100A9, that heterodimerizes with its partner S100A8, and interacts with innate immune receptors involved in MDSC activation. Therefore **S100A9 is a key factor in MDSC activation.** Based on this preliminary evidence, we have hypothesized that CD33-S100A9 signaling is a critical driver of MDSC activation and MDS pathogenesis that can be therapeutically exploited in a selective fashion. We propose that inactivation of MDSCs through selective interference with S100A9/CD33 signaling offers a novel strategy for MDS therapeutic development. This approach would also further enhance our understanding of mechanisms underlying disease initiation. In the past year, we have made significant research progress and have discovered a novel signaling mechanisms that associated with S100A9 activated MDSC activation leading to PD-1 and PD-L1 interaction in HSPCs from MDS patients . These novel finding has selected for oral presentation in International MDS conference and manuscript under 2nd review in Leukemia.

2. KEYWORDS

Myeloid-derived suppressor cells (MDSC); Myelodysplastic syndromes (MDS); S100A9 proteins; inflammation, Genomic instability, bone marrow failure, hematopoiesis; Interleukin 10 (IL10); hematopoietic stem and progenitor cells (HSPC), programmed cell death protein 1 (PD-1); and programmed death-ligand 1 (PD-L1).

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of the project are:

Aim 1. To determine if strategies to block S100A9/CD33 signaling in MDSC improves the BM microenvironment and rescues hematopoiesis. We are investigating our recently developed CD33-IgG1 chimeric receptor as an S100A9 ligand trap to neutralize S100A9 and thereby suppress MDSC activation.

Aim 2. To validate a novel MDSC-inactivating compound that disrupts CD33-ITIM signaling. We will interrogate our recently described S100A9-CD33 pathway to characterize a novel compound, ICTA, to inactivate inflammatory suppression through the maturation of MDSCs as a novel preclinical approach.

Goals for the 4th 12 months: Following the major objectives of the proposal we have set up two subtasks for the 3rd 12 months: 1) Examine if TandAb promotes elimination of MDS-MDSCs by CD3+ T cells and 2) test the reduction in MDSCs suppressive activity after treatment with TandAb. The overall goal is to determine if there is an effective therapeutic approach to target MDSC and rescuer bone marrow suppression in MDS.

What was accomplished under these goals?

This project is on no-cost extension in the past 12 months and with limited support, we managed to accomplish the major tasks proposed on all the aims. The data obtained in the past two years allowing us published a research article in Leukemia early this year (*Leukemia. 2019 8:2034. PMID: 30737486*).

Upon our established central hypothesis and following laboratory evidence gained in last research period, the major research activities and accomplishments for the 4th 12 months were:

Based on the evidence that the accumulation of MDSC, defined as $CD33^{High}$ in patients with MDS where it plays an important role in MDSC-mediated hematopoietic suppressive function. These findings establish intrinsic and extrinsic roles for S100A9 as a driver of MDS, yet precisely how S100A9 signaling initiates and sustains MDS is unclear. We discovered that S100A9 induces expansion and activation of MDSCs, triggers cell death of HSPCs and myeloid and erythroid progenitors, and contributes to ineffective hematopoiesis. However, how S100A9 activated MDSC activation inducing HSPC undergoing cell death leading to ineffective hematopoiesis and immune suppression is unclear. In past 12 months, we have made novel discovery that S100A9 induced both bone marrow suppression and immune-suppression that is associated with the PD-1 and its ligand, PD-L1. The PD-1/PD-L1 impairs immune responses by inducing T cell exhaustion and apoptosis is well established, but we made novel finding that increased expression of PD-1 on HSPCs and PD-L1 on MDSCs in MDS versus healthy donors, and that this checkpoint is also activated in S100A9 transgenic (S100A9Tg) mice, and by treatment of BM mononuclear cells (BM-MNC) with S100A9. MDS BM-MNC treated with recombinant PD-L1 underwent cell death, suggesting the PD-1/PD-L1 interaction contributes to HSPC death in MDS. In accord with this notion, PD 1/PD L1 blockade restores effective hematopoiesis and improves colony-forming capacity in BM-MNC from MDS patients. Similar findings were observed in aged S100A9Tg mice. Most novel finding we made is that shown that this abnormal regulation of PD-1/PD-L1 are associated with metablitic changes in the HSPC stem cells after RNAseq analysis. We found that c-Myc is required for S100A9-induced upregulation of PD1/PD-L1, and that treatment of MDS HSPCs with anti-PD1 antibody suppresses the expression of Myc target genes and increases expression of hematopoietic pathway genes. We demonstrate that anti PD 1/anti PD-L1 blocking strategies in combination with strategies that targeting either S100A9 or $CD33^{high}$ MDSCs offer therapeutic promise in MDS in restoring effective hematopoiesis.

1. **S100A9-induced expression of PD-1 and PD-L1 is associated with abnormal c-Myc activation**

Recent studies have suggested that abnormal metabolic changes driven by the c-Myc (MYC) oncogenic transcription factor during tumorigenesis leads to PD-1/PD-L1 pathway activation and immunosuppression. Aged S100A9Tg mice display robust activation of S100A9 induced inflammatory pathways that lead to abnormal metabolic changes (Figure 1), as evidenced by increased body weight, insulin resistance, and hyperglycemia. To assess possible links of S100A9/PD-1/PD-L1 pathway activation and MYC in MDS, MYC protein levels were compared in BM-MNC from MDS patients versus healthy donors. Consistently (n=5 total), PD-1, PD-L1, and MYC protein expression were elevated in MDS BM MNC versus healthy donors (Figure 2a). Further, treatment of healthy donor BM-MNC with 10 µg/mL rhS100A9 for 48 hours was sufficient to induce expression of PD 1, PD-L1, and MYC versus untreated cells (Figure 2b). *

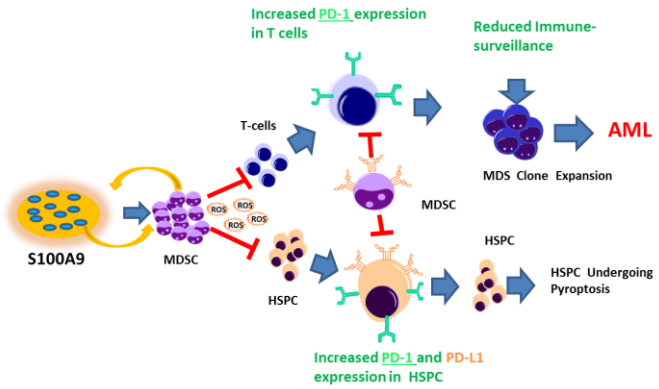


Figure 1. S100A9 directly induces expression of PD-1/PD-L1 interaction in both T cells and HSPC contributing to MDS pathogenesis. S100A9 in a feed-forward fashion activates MDSC via production of ROS to induce expression of PD-1 and PD-L1 contributing to both immune and bone marrow suppression.

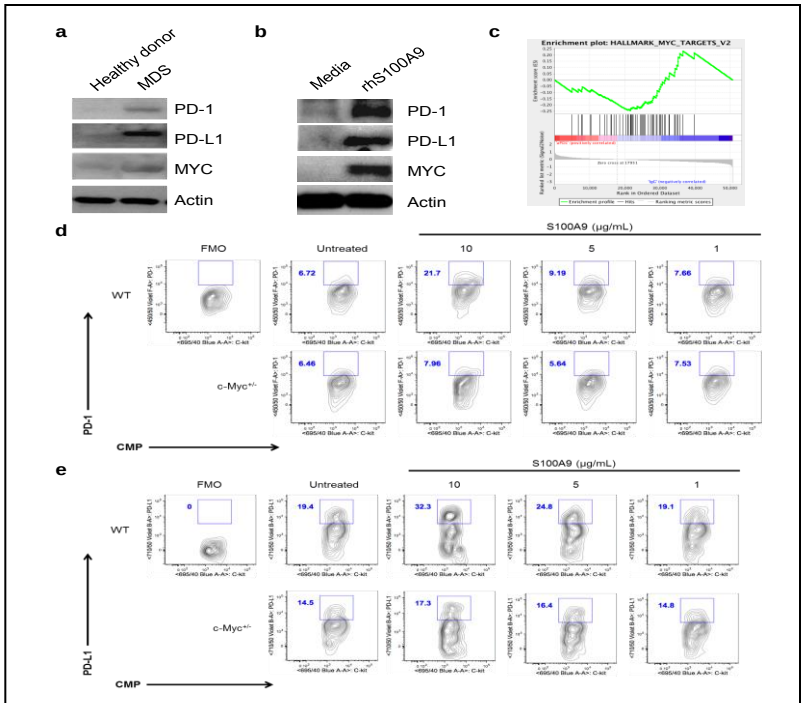


Figure 2. S100A9/PD-1/PD-L1 pathway activation augments MYC expression. Western blot were performed to assess levels of PD-1, PD-L1, and MYC protein in (a) MDS versus healthy donor BM-MNC and (b) healthy donor BM-MNC treated with 10 µg/mL rhS100A9 for 48 hr. Data are representative of 5 independent experiments. (c) RNA-seq based transcriptional network analysis indicating down-regulation of Hallmark Myc pathways in anti-PD1-treated CD34+ HSPC (n=5). The percentage of PD-1+ and PD-L1+ c Kit+Lin-CD16/32- CMP cells was measured in BM cells isolated from Myc+/- and WT littermates and treated with increasing concentrations of S100A9. Populations were gated on viable cells based on fluorescence minus one (FMO) controls. The percentage of (d) PD 1+ and (e) PD-L1+ CMP cells in BM of representative samples from five Myc+/- and WT mice is shown.

2. **Validation of Myc role in S100A9-induced PD-1/PD-L1 expression**

To test if Myc contributes to S100A9-directed increases in cell surface expression of PD 1 and PD L1 on BM-MNC, we assessed the effects of Myc heterozygosity using BM from heterozygous $Myc^{+/-}$ mice and WT littermates; $Myc^{+/-}$ BM cells expressed reduced levels of Myc protein versus WT littermate BM cells as judged by immunoblots (Figure 3a). These cells were then treated with increasing concentrations of

S100A9 for 48 hours and PD-1 and PD-L1 cell surface expression was assessed on c Kit+Lin-CD16/32- CMP cells by flow cytometry. Surface receptor expression of PD-1 (Figure 2d top panel) and PD L1 (Figure 2e top panel) increased in an S100A9 concentration dependent manner on WT-derived BM cells. Conversely, S100A9 treatment was insufficient to induce PD-1 and PD L1 cell surface receptor expression in heterozygous Myc$^{+/-}$ BM cells (Figure 2d and 2e bottom panels). A summary of

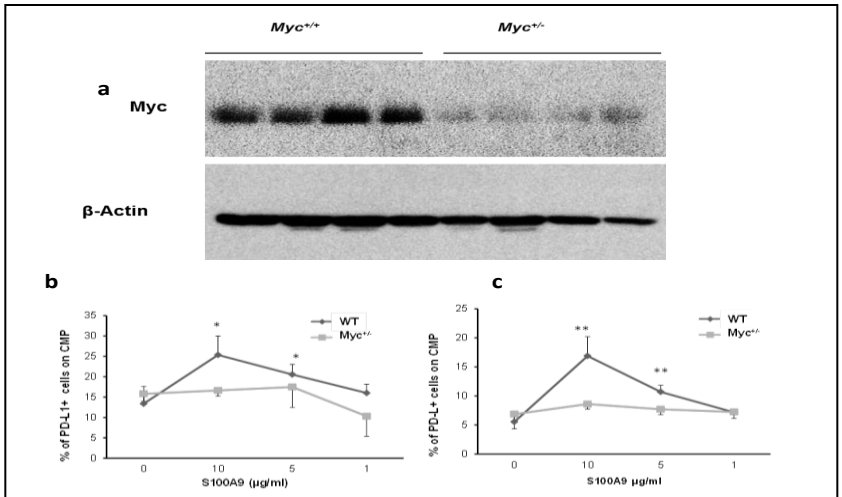
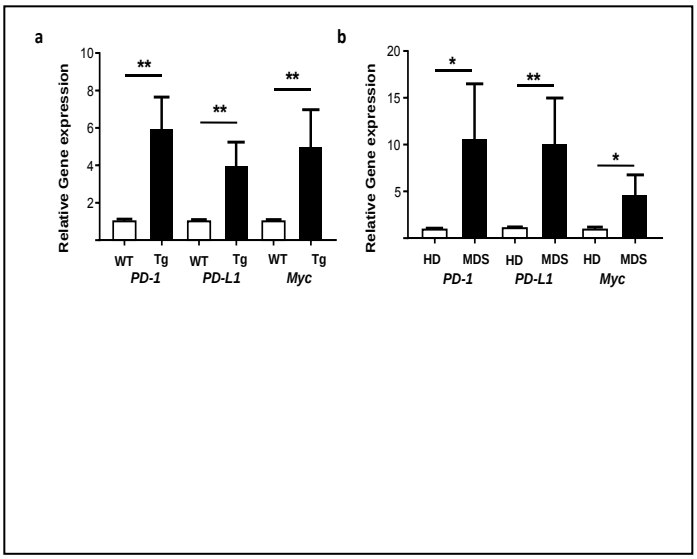


Figure 3. Western blotting analysis of Myc protein expression in Myc+/+ and Myc+/- mice. a) BM-MNC lysate of wild type or Myc+/- mice was subjected to western blotting analysis as indicated in the top panel. b and c) Summary of Flow cytometric analysis of PD-1 (b) or PD-L1 expression on CMP in response to various concentration of S100A9 stimulation in Myc+/+ and Myc+/- mice.



experiments showing statistical significance between Myc$^{+/-}$ and Myc$^{+/+}$ in responding to S100A9 stimulation in terms of PD-1 and PD-L1 upregulation is shown in Figure 3b and c. Thus, Myc contributes to control of the PD-1/PD-L1 axis by S100A9.

3. Myc is a regulator of PD-L1/PD-1 gene expression in MDS

To gain insights into the mechanism by which S100A9 controls expression of PD-1, PD-L1 and Myc, quantitative real time PCR analyses were performed. These studies revealed that PD-1, PD-L1 and Myc mRNA levels are elevated in S100A9Tg versus WT BM-MNC (Figure 4a) and in MDS patient versus normal BM-MNC (Figure 4b). Collectively these findings suggest that S100A9 induction of Myc triggers increases in PD-1 and PD-L1 expression that activate MDSC, provoke HSPC cell death and lead to immune evasion.

4. **RNAseq analysis of CD34+ stem cell of MDS patients suggested hematopoietic metabolism changes.** To

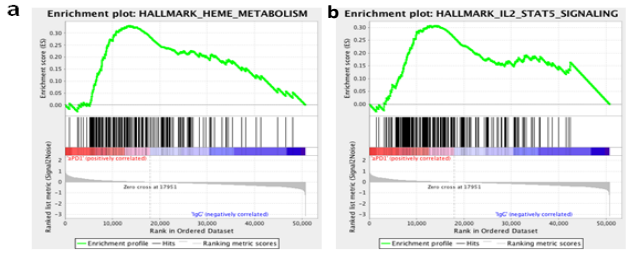


Figure 5. RNAseq analysis of CD34^{+} HSPC. BM-MNCs were treated with 10 μg/ml of IgG or anti-PD-1 BM-MNCs for 48h, CD34^{+} cells were isolated using EasySep™ Human CD34 Positive Selection Kit following the manufacturer's protocol. RNA-seq indicates changes in heme metabolism (a) or IL-2/STAT5 (b) signaling pathway gene expression in response to anti-PD-1 therapy.

gain the insight on the cMyc-PD-1 and PD-L1 axis mediated pathways critical role in the MDS pathogenies we isolated total RNA from CD34^{+} cells (isolated using StemCell positive selection kit) from both healthy and MDS BM specimens was obtained using the RNeasy Mini Kit (Qiagen). RNA was quantified in a NanoDrop 1000 and RNA quality was assessed by Agilent 2100 Bioanalyzer. These samples were then processed for RNA-Sequencing (RNA-seq) using the NuGen Ovation Human RNA-Seq Multiplex System (NuGEN Technologies). Gene Set Enrichment Analysis (GSEA) 3.0 software was used to assess significant enrichment of biological pathways or gene sets in PD-1 versus Ig treated patient and healthy donor datasets, respectively, against hallmark gene sets from the Molecular Signatures Database (MSigDB) v6.2. As shown in Figure 2c, RNA-seq analyses of MDS HSPC treated or not treated with anti-PD-1 for 48 hours revealed a decrease in MYC target genes following treatment with anti-PD-1 (Figure 2c), along with increases in the expression of genes involved in hematological metabolism pathway and IL2/STAT5 signaling, as would be expected with improvements in the hematopoiesis (Figure 5a & b). STAT 5 is the most critical signaling protein mediated by EPO receptor in the bone marrow HSPCs. These results clearly indicate that blockade of PD-1 signaling significantly improved hematopoiesis via upregulation of STAT5 in the HSPC isolated from MDS patients.

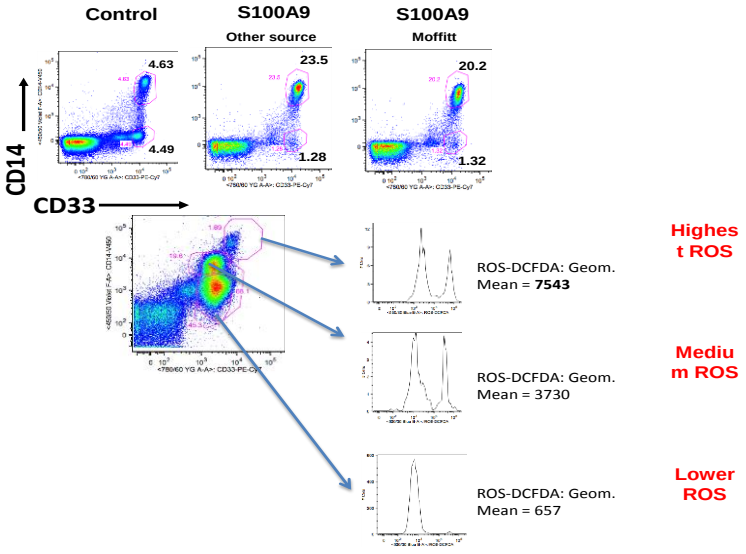


Figure 6. S100A9 induce a CD33^{high}CD14^{+} MDSC population with high ROS production. BMMNC isolated from healthy donor and treated with rhS100A9, as indicated before, were monitored for ROS production. Notably, after treatment there is an increased CD33^{high}CD14^{+} switch and it is correlated with the amount of ROS production.

5. S100A9 is a key regulator for increased CD33^{high} MDSC accumulation in MDS bone marrow.

Collectively, above data provide convincing evidence that S100A9 is able to upregulate PD-1 and PD-L1 expression in HSPCs contributing to bone marrow suppression. As we previously reported, the inflammation-associated myeloid-secreted protein S100A9 is a key modulator for MDSC accumulation

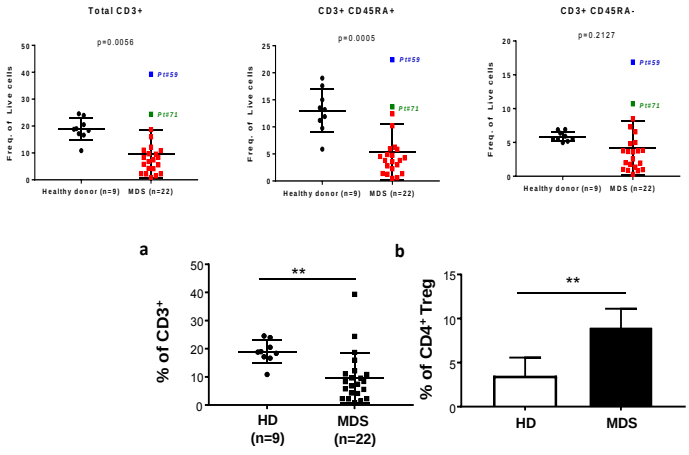


Figure 7. T cell populations are reduced in MDS bone marrow. BMMNC isolated from healthy donor or MDS patients as indicated. The specific T cell population was analyzed by flow cytometry.

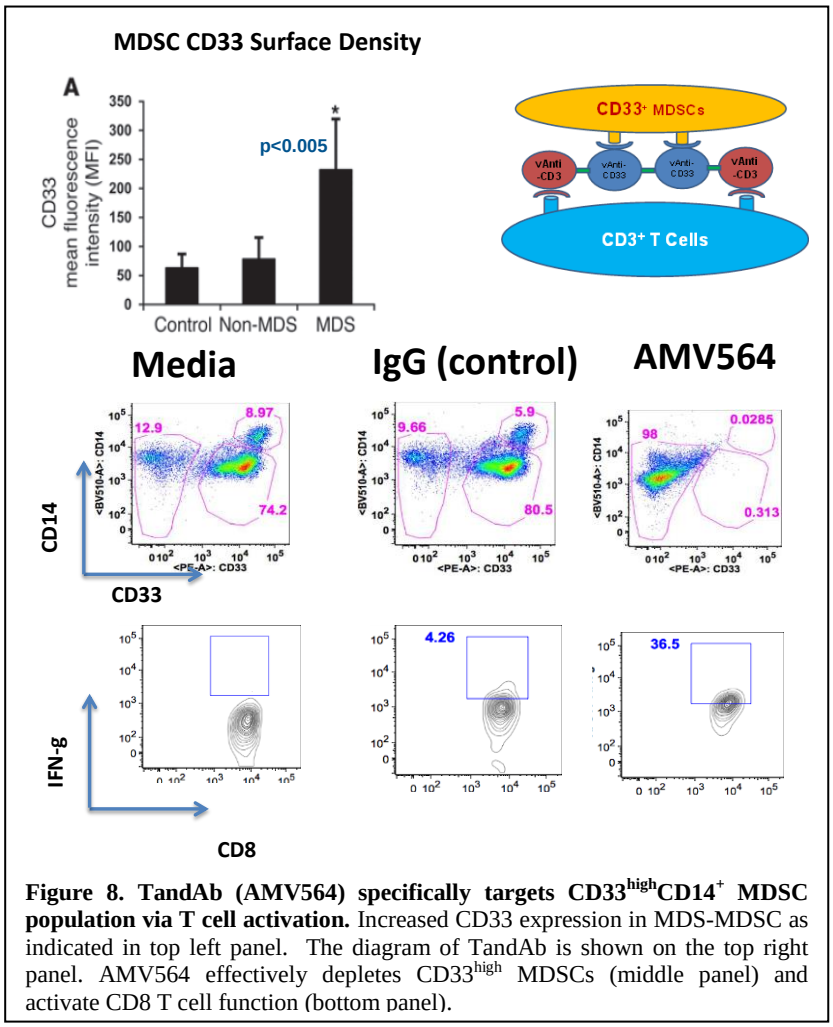


Figure 8. TandAb (AMV564) specifically targets CD33^{high}CD14^{+} MDSC population via T cell activation. Increased CD33 expression in MDS-MDSC as indicated in top left panel. The diagram of TandAb is shown on the top right panel. AMV564 effectively depletes CD33^{high} MDSCs (middle panel) and activate CD8 T cell function (bottom panel).

in MDS bone marrow. In the last funding period, we also wanted to establish the basis to validate if targeting CD33^{high} MDSC still supports our original hypothesis. We observed that treatment of bone marrow mononuclear cells isolated from healthy donor with recombinant human (rh) S100A9 for 24 hours, can upregulate a CD33^{high}CD14^{+} MDSC population and this group is responsible for over production of ROS (Figure 6). It is well established that ROS is the most important mediator of T cell and HSPC suppression. This data show evidence that S100A9 is a key factor driving CD33^{high} MDSC expansion and accumulation in MDS bone marrow. We conclude that targeting either S100A9 or CD33^{high} MDSC may have potential benefit for patients with MDS.

6. T cells isolated from MDS are greatly downregulated.

MDSCs are distinguished by their ability to specifically suppress T-cell responses and impair CD4^{+}/CD8^{+} function in solid tumor, suggesting that this may be a key mechanism fostering clonal escape from anti-tumor immune response in MDS as well. To provide evidence to validate this notion, BMMNCs were isolated from patients with MDS and the T cell populations were specifically analyzed by flow cytometry. As shown in Figure 7, the total of CD3, including naive and effector T cells, were significantly down regulated in MDS when compared with BMMNCs isolated from healthy donors. Interestingly, the suppressive Treg population was much expanded in MDS bone marrow when compared with BMMNC from healthy donors (Figure 7 lower panel).

7. Targeting CD33^{high}CD14^{+} MDSC using high affinity TandAbs to redirect CD3 T cells killing of CD33^{high} MDSCs

Based on the fact that S100A9 induced CD33^{high}CD14^{+} MDSC generating the highest ROS and likely the major suppressors of T cell and HSPC function. It is well established that MDSC population size limits the benefit of immune checkpoint antagonists in the treatment of solid

tumors and effective strategies to deplete MDSCs are lacking. Therefore, we take advantage of our ongoing collaboration with AMPHIVENA Therapeutics to test their tandem diabodies (TandAbs) that are tetravalent bi-specific molecules comprised of four immunoglobulin variable domains: two for CD3 and two for CD33 (Figure 8).
We hypothesized the high CD33 surface density in MDSCs can be exploited for selective immune-depletion by the TandAb (AMV564), a novel CD33/CD3 tetravalent bispecific antibody that recognizes both CD33 and CD3, currently in clinical development for AML. This allows the highly specific simultaneous engagement of effector $CD3^+$ T cells to lyse $CD33^+$ MDSCs with a single molecule, as done successfully with other epitopes. Furthermore, the absence of an Fc domain allows this antibody to avoid certain IgG-mediated side effects and its molecular weight (110 kDa) is far above the first-pass renal clearance limit, offering a pharmacokinetic advantage compared with smaller bi-specific antibody formats. As you can see in Figure 8, this antibody can significantly upregulate CD8 T activation identified by the increased IFNg production when compared with control IgG treated cells after 5 days stimulation (Figure bottom panel). Both $CD4^+$ and $CD8^+$ also displayed increased cell expansion and proliferation identified by Brdu incorporation and cell division assay after treatment with TandAb (data not shown) suggesting that engagement of effector T cells with CD33 target cells can enhance T cell activation and proliferation. Importantly, the majority of $CD33^{high}$ MDSCs were depleted after treatment with TandAb after 5 days incubation, indicating this strategy specifically inhibits MDSC in the local bone marrow suppressive microenvironment. At the current stage we are still in the process of characterizing the immune aspect of this novel approach. A phase II clinical trial for using TandAb (AMV564) now is planned to open after finalizing the dosage in MDS.

In summary, we have made significant research progress under the proposed goals and discovered that S100A9 activated MDSC activation is associated with increased ROS production by induction of $CD33^{high}CD14^+$ MDSCs and this group of MDSC plays a critical role in suppressing both T cell and HSPC function in MDS. Furthermore, the upregulation of immune-check point protein expression in HSPCs in MDS is associated with abnormal metabolism changes in MDS. Apparently, the upregulation by S100A9 is a key factor in this event. These findings expand prior understanding of the role of PD-1/PD-L1 interaction in both T cells and HSPCs. Importantly, using an novel therapeutic approach, TandAb that engage both T cell and MDSCs, has shown promising clinical implications that depletion of $CD33^{high}CD14^+$ MDSCs, could improve both immune and HSPC function in MDS. These data suggest that anti-PD-1 or anti-PD-L1 blocking strategies, in combination with TandAb, offer therapeutic promise in MDS to improve the BM microenvironment and restore effective hematopoiesis and immune surveillance. The current data is under preparation for publication.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

Publish latest results and apply for more extramural funding.

4. **IMPACT:**

MDS are the most common bone marrow failure (BMF) with variable survival ranging from a median of months in patients with high risk disease to years in low-risk patients. More than 50,000 cases are diagnosed annually in the US with the overall disease burden increasing as a result of the aging of the population in a disease characterized by high morbidity and mortality. Currently available treatment options have limited effect and can be associated with severe side-effects and high economical costs. This is mainly due to previous studies of the molecular pathogenesis of MDS focusing primarily on the already genetically altered malignant HSPC responsible for propagation of the malignant clone, rather than selection pressures conducive to the emergence of the clone. As a consequence, current treatments are largely empiric and non-specific. Instead, our hypothesis focuses on targeting S100A9/CD33 pathways to block the activation and accumulation of MDSCs in the local bone marrow microenvironment that suppresses healthy HSPC and induce DNA instability promoting MDS clone expansion. Our major findings obtained in the past year demonstrated that 1) S100A9 induce a $CD33^{high}$ MDSC population with increased ROS production. We believe this group of MDSC are major player causing T cell and HSPC suppression, 2) targeting $CD33^{high}$ MDSC with TandAb, to active T cell and deplete MDSC, shows promising potential for clinical application, and 3) PD-1 and PD-L1 are associated with S100A9-induced MDSC activation leading HSPC to undergo cell death. This dynamic change is linked with abnormal metabolic changes via activation of cMyc. Targeting this pathway alone, or in combination with other strategies, has a potential as a therapeutic approach to target MDSC activation and feasibly address a conceptually-novel hypothesis.

What was the impact on the development of the principal discipline(s) of the project?

We propose a paradigm shift that stems from a concept that understanding how the inflammatory microenvironment contributes to HSPC damage and malignant evaluation will have a profound and far-reaching effect on understanding MDS pathophysiology. If successful, this combined in vitro/in vivo approach can lead to immediate clinical application. Therefore, the conditions that these therapeutic approaches address represents an unmet medical need for a disease with few available treatments, thus providing a unique opportunity for success through the development of effective targeted therapeutics, like ours, in this patient population where it would have enormous clinical impact.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:,

Nothing to Report

6. **PRODUCTS:**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

None

What individuals have worked on the project?

Name:	Sheng Wei
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Dr. Wei is the PI of this project and for the overall direction of proposed project and He will oversee all molecular validation studies and data analysis and interpretation of experimental results.
Funding Support:	No change

Name:	Xianghong Chen
Project Role:	Research Scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to Project:	She is responsible for carring out all the biological and biochemical assays and make all the novel constructs
Funding Support:	No change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to Report

- **What other organizations were involved as partners?**

  Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

None

9. APPENDICES:

None