AWARD NUMBER: W81XWH-15-1-0440

TITLE: Novel Therapeutic Approaches Targeting MDSC in Myelodysplastic Syndrome

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REPORT DATE: September 2018

TYPE OF REPORT: Annual Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
September 2018	Annual Report	09/01/2017 - 08/31/2018

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)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Materiel 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.

15. SUBJECT TERMS

None listed

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)*

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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 3rd 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?

Upon our established central hypothesis and following laboratory evidence gained in last research period, the major research activities and accomplishments for the 3rd 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. Particularly, how S100A9 activated MDSC activation inducing HSPC undergoing cell death leading to ineffective hematopoiesis is unclear. In past 12 months, we have made novel discovery that S100A9 induced bone marrow suppression is associated with the immune checkpoint protein programmed cell death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1). PD-1 is expressed on the surface of activated T cells, whereas PD L1 is predominantly expressed on antigen presenting cells, but also a variety of other immune cells. PD-L1 expression is induced during inflammation or within the tumor microenvironment to mediate immune suppression. Specifically, engagement of PD-L1 with PD-1 triggers a cascade of events that culminate in exhaustion/dysfunction of once activated T cells. Of note, abnormal expression of PD-1 and PD-L1 has been implicated in MDS, whereby patients treated with azanucleosides and hypomethylating agents demonstrated increased expression of checkpoint proteins post-treatment. The findings we made is that we identified a novel role for the PD-1/PD-L1 pathway in MDS pathobiology, beyond regulation of T cell biology, whereby aberrant activation of the pathway by HSPCs and MDSCs triggers hematopoietic cell death, contributing to BM failure and the hematopoietic suppression characteristic of MDS. Importantly, our new data provide direct evidence that PD-1/PD-L1 blockade therapy alone or in combination may have therapeutic potential to restore and promote effective hematopoiesis in MDS.

1. **PD-1 and PD-L1 surface receptor expression is increased in MDS.** Given the unexplored role of the PD-1/PD-L1 pathway in MDS, and the poorly understood function of PD-1 in non-lymphoid cells, we first examined PD 1 surface receptor expression on HSPCs and erythroid progenitors isolated from the BM of MDS patients (n=10) compared with normal donors (n=6). All patients examined had significantly increased surface expression of PD-1 on both CD71+ erythroid progenitors ($P<0.05$; Figure 1a) and CD34+ HSPCs ($P<0.01$; Figure 1b) versus corresponding healthy donor BM populations, suggesting that PD-1 upregulation may play a critical role in MDS. As PD-L1 ligation with PD-1 is known to mediate immune suppression in the tumor microenvironment, we next examined PD-L1 expression on CD33+CD14+ myeloid cells, which represent MDSCs. CD33+CD14+ MDSCs had significant upregulation of PD-L1 surface expression ($P<0.001$; Figure 1c). Notably, erythroid progenitors ($P<0.05$; Figure 1d) and HSPCs ($P<0.01$, Figure 1e) also demonstrated significantly increased surface expression of PD-L1, indicating an autonomous regulation of immune checkpoint signaling on these hematopoietic populations.

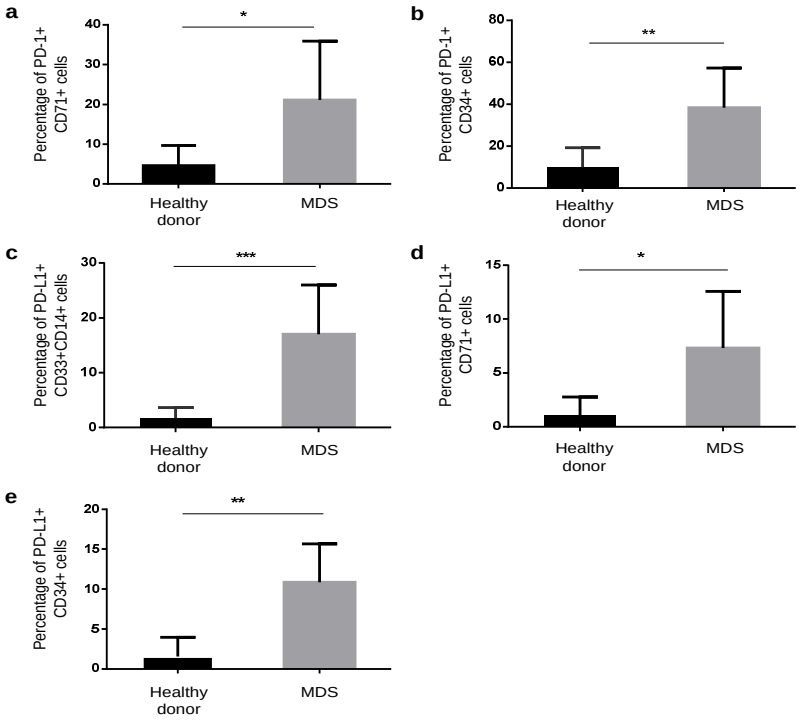

Figure 1. PD-1 and PD-L1 surface expression is increased in MDS. The percentage of PD-1+ and PD-L1+ hematopoietic cells was measured in BM-MNC isolated from MDS patients (n=10) compared with healthy donors (n=6): (a) PD-1+ CD71+ erythroid progenitors; (b) PD-1+ CD34+ HSPCs; (c) PD-L1+ CD33+CD14+ MDSCs; (d) PD-L1+ CD71+ erythroid progenitors; and (e) PD-L1+ CD34+ HSPCs. Positive population gating on viable cells was based on fluorescence minus one (FMO) controls (Supplementary Figure S2). *P<0.05, **P<0.01, ***P<0.001; data are presented as mean ± standard error of the mean. BM-MNC, bone marrow mononuclear cells; HSPC, hematopoietic stem and progenitor cell; MDSC, myeloid-derived suppressor cell.

2. PD-1 and PD-L1 are overexpressed in aged S100A9Tg mice

We previously reported that like human MDS, S100A9Tg mice evidence age-dependent, S100A9 induced MDSC activation, resultant in hematopoietic cell death and dysplastic, ineffective hematopoiesis. Using this model, we next assessed whether S100A9 functions to induce expression of PD-1 and PD-L1 in the BM of young and old S100A9Tg mice (3-4 and 14-16 months old, respectively) compared with age-matched wildtype (WT) littermates. Young WT and S100A9Tg mice evidenced minimal levels of PD-1 and PD-L1 expression on cKit+Lin-CD16/32- common myeloid progenitor (CMP) cells derived from BM (Figure 2a-c). Expression of PD-1 and PD-L1 was significantly greater in older versus younger mice, indicating an age-dependent effect. Importantly, significantly greater increases in PD-1 ($P<0.001$; Figure 2a) and PD-L1 ($P<0.05$; Figure 2b) expression were observed in the aged S100A9Tg mice versus aged WT littermates.

These data indicate S100A9-induced inflammation plays a critical role in the induction of PD-1 and PD-L1 surface expression beyond that observed with normal aging. Furthermore, increased PD-L1 surface receptor expression was also observed on Gr 1+CD11b- cells, which represent MDSCs (Figure 2c).

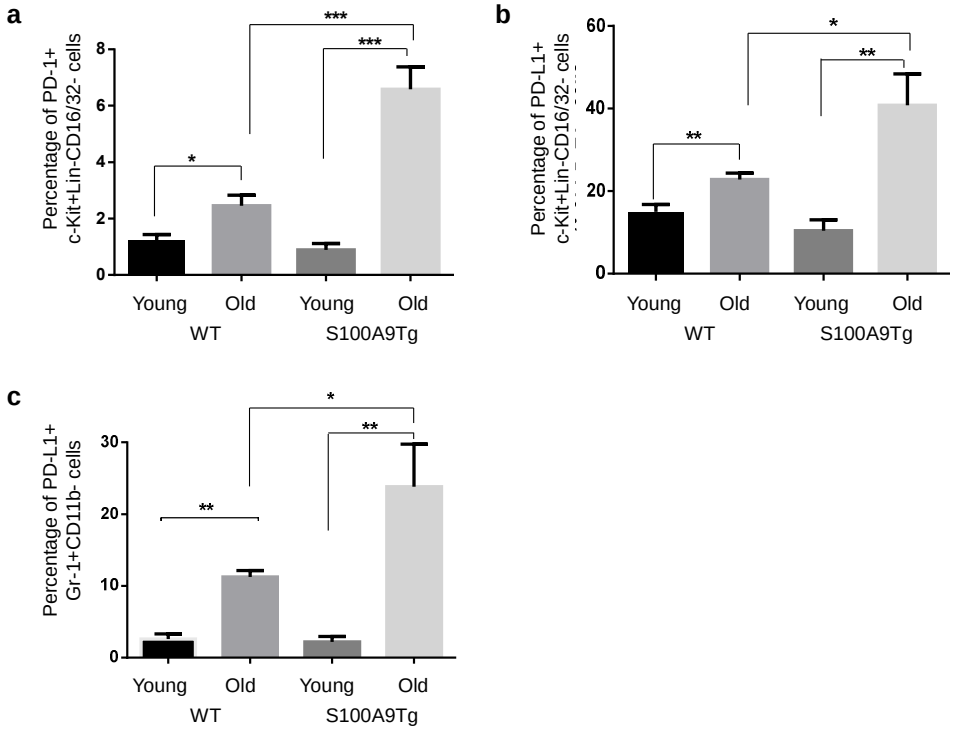

Figure 2. PD-1 and PD-L1 are overexpressed in aged S100A9Tg mice. The percentage of PD-1+ and PD-L1+ hematopoietic cells was measured in BM isolated from age matched (young, 3-4 months; old, 14-16 months) S100A9Tg and wildtype mice. Five mice were used per group and the experiment was repeated three times. (a) PD 1+ c-Kit+Lin-CD16/32- CMP cells; (b) PD-L1+ CMP cells; and (c) Gr-1+CD11b- MDSCs. Positive population gating on viable cells was based on fluorescence minus one (FMO) controls, P<0.05, **P<0.01, ***P<0.001; data are presented as mean ± standard error of the mean. BM, bone marrow; CMP, common myeloid progenitor; MDSC, myeloid-derived suppressor cell; Tg, transgenic; WT, wildtype.

These data indicate that the forced expression of S100A9 significantly increases surface receptor expression of PD 1 on ¬myeloid progenitors and PD-L1 on MDSCs.

3. S100A9 directly induces expression of PD-1 on progenitors and PD-L1 on MDSCs

To determine whether S100A9 induces surface receptor expression of PD-1 and PD L1 in primary hematopoietic cells, BM-MNC isolated from healthy donors (n=5) were treated with 10 μg/mL recombinant human S100A9 (rhS100A9) or IgG (control) for 48 hours. PD L1 expression was significantly increased on CD33+CD14+ MDSCs in all healthy donors analyzed (P<0.01), suggesting that PD L1 surface receptor expression is inducible by the inflammation-associated DAMP protein S100A9 (Figure 3a). Furthermore, rhS100A9 treatment also significantly induced PD-1 surface receptor expression on both CD34+ HSPCs (P<0.01; Figure 3b) and CD71+ erythroid progenitors (P<0.01; Figure 3c). As BM plasma concentration of S100A9 is significantly greater in MDS compared with healthy donors, healthy donor BM-MNC were incubated with MDS patient plasma to assess whether plasma derived S100A9 can induce surface receptor expression of PD-1 and PD-L1. In accordance with rhS100A9-induced findings (Figure 3a-c), incubation of healthy donor BM-MNC with MDS patient plasma resulted in a significant increase in the percentage of PD-1+ CD34+ HSPCs (P<0.05; Figure 3d) and CD71+ erythroid progenitors (P<0.001; Figure 3e). These data indicate that S100A9 directly induces expression of PD-1 and its corresponding ligand, PD-L1, which may have a pathobiological role in mediating a suppressive BM microenvironment.

4. S100A9/PD-1/PD-L1 axis induces hematopoietic cell death.

PD-1 and PD-L1 engagement can induce T cell exhaustion and apoptosis. We next investigated whether engagement of PD-1 on hematopoietic progenitors with PD-L1 induces cell death of progenitors, thereby contributing to the ineffective hematopoiesis characteristic of MDS. BM-MNC isolated from healthy donors (n=5) were treated with 10 μg/mL rhS100A9 or IgG (control) for 48 hours; cells were subsequently stained for flow cytometric assessment of surface receptors and anti-active caspase-3 expression, a marker of apoptosis. The percentage of active caspase-3+ CD34+ HSPCs (P<0.001; Figure 4a) and CD71+ erythroid progentiors (P<0.001; Figure 4b) was significantly increased following rhS100A9 treatment. As S100A9 induces cell surface receptor expression of PD-1 and PD-L1, and engagement of these checkpoint receptors can induce apoptosis, we hypothesized that the S100A9/PD-1/PD-L1 axis may induce hematopoietic progenitor cell death. BM-MNC isolated from MDS patients (n=3) and healthy donors (n=3) were cultured in plates coated with or without recombinant human PD-L1 for 24 hours; subsequently, active caspase-3 expression was assessed by flow cytometry. PD 1/PD L1 ligation resulted in marked increases in active caspase-3+ CD34+ HSPCs and CD71+ erythroid progenitors but not normal donors (Figure 4c, 4d). These data provide direct evidence that S100A9 may trigger hematopoietic progenitor cell death through PD-1 and PD-L1 interaction.

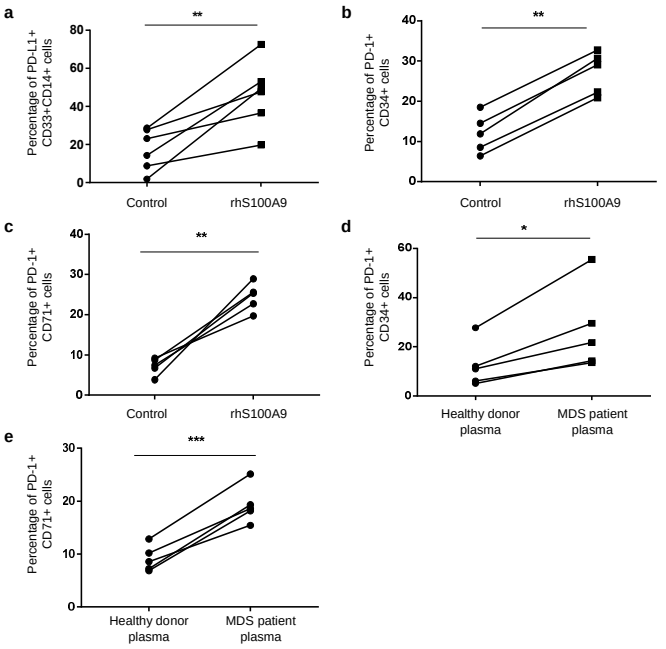

Figure 3 S100A9 directly induces expression of PD-1 on progenitors and PD-L1 on MDSCs. The percentage of PD-1+ and PD-L1+ hematopoietic cells was measured in BM-MNC isolated from healthy donors (n=5) treated with 10 μg/mL rhS100A9 or IgG (control) (a-c) or MDS patient or healthy donor BM plasma (d-e) for 48 hours. (a) PD L1+ CD33+CD14+ MDSCs; (b) PD-1+ CD34+ HSPCs; (c) PD-1+ CD71+ erythroid progenitors; (d) PD-1+ CD34+ HSPCs; and (e) PD 1+ CD71+ erythroid progenitors. Positive population gating on viable cells was based on fluorescence minus one (FMO) controls . *P<0.05, **P<0.01; data are presented as mean ± standard error of the mean. BM-MNC, bone marrow mononuclear cells; HSPC, hematopoietic stem and progenitor cell; MDSC, myeloid-derived suppressor cell; rh, recombinant human.

5. PD-1/PD-L1 pathway blockade promotes effective hematopoiesis in MDS

To test if blocking PD-1/PD-L1 interaction could improve hematopoiesis in MDS, colony forming capacity was assessed after treating MDS BM-MNC (n=5) with anti-PD-1 or anti PD-L1 blocking antibody for 48 hours. PD-1 and PD-L1 blockade significantly improved CFU-GM (P<0.01 and P<0.05, respectively) and BFU-E (P<0.05 for both) colony forming capacity versus IgG control (Figure 5a), suggesting that PD-1/PD-L1 pathway inhibition may be a beneficial treatment option to promote effective hematopoiesis in MDS. To validate these findings, old S100A9Tg (n=6) and age matched WT mice (n=6) were treated with 150 μg/mouse anti-PD-1 blocking antibody twice a week for 6 weeks. Complete blood counts were measured weekly. Treatment of S100A9Tg mice with anti-PD-1 significantly increased red blood cell (RBC) and white blood cell (WBC) counts versus IgG control (Figure 5b). Notably, no changes were observed in RBC and WBC counts in WT mice treated with anti-PD-1 blocking antibody; this

was expected given that WT mice have normal hematopoiesis and evidence low levels of PD-1 and PD-L1 surface receptor expression. To determine whether increased complete blood counts in S100A9Tg mice was resultant from improved hematopoiesis, BM cells from the aged S100A9Tg and WT mice were isolated to assess colony forming capacity. As expected, BFU-E and CFU-GM colony forming capacity was significantly reduced in S100A9Tg versus WT mice treated with IgG ($P<0.05$; Figure 5c). Importantly, anti-PD-1-treated S100A9Tg mice evidenced significant increases in BFU-E colony forming capacity versus WT treated mice ($P<0.01$; Figure 5c). In addition, we also observed a moderate restoration of CFU-GM in these mice after treatment. However, since BFU-E is the most important marker for improvement of anemia in MDS, these results suggest the critical role of therapeutic anti-PD1 treatment in this disease.

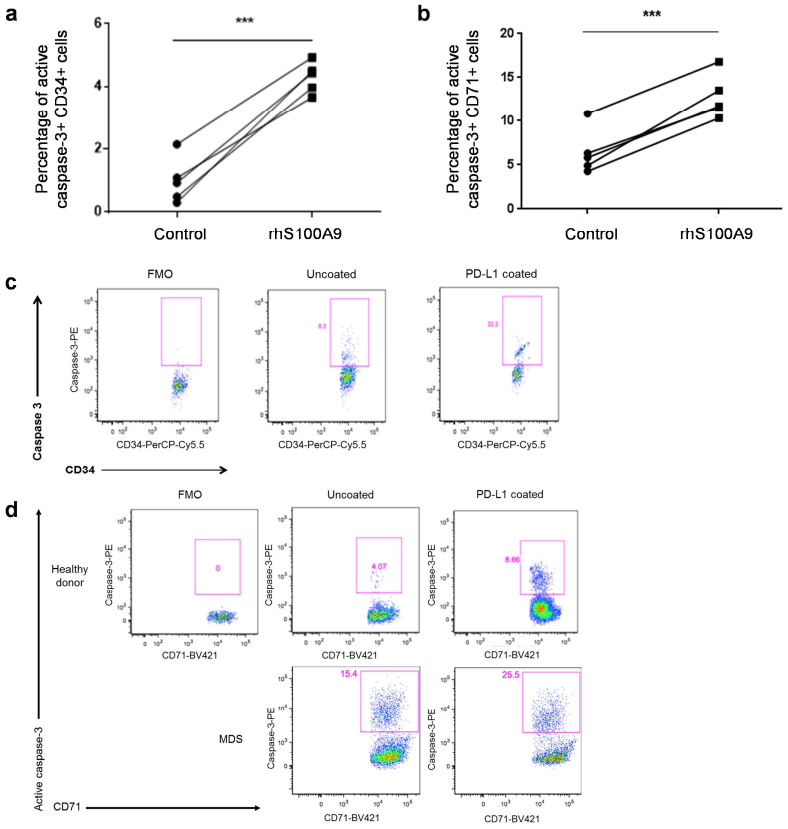

Figure 4. S100A9/PD-1/PD-L1 axis induces hematopoietic cell death. The percentage of active caspase-3+ hematopoietic cells was measured in BM-MNC isolated from healthy donors (n=5) treated with 10 µg/mL rhS100A9 or IgG (control) for 48 hours. Positive population gating on viable cells was based on fluorescence minus one (FMO) controls: percentage of active caspase-3 (a) CD34+ HSPCs and (b) CD71+ erythroid progenitors. ***$P<0.001$; data are presented as mean ± standard error of the mean. For PD-1/PD-L1 ligation experiments (c-d), 2 million BM-MNC were plated per well in 24-well plates coated with recombinant human PD-L1 (2 µg/mL) for 24 hours at 4 °C. The percentage of active caspase-3+ (c) CD34+ HSPCs and (d) CD71+ erythroid progenitors is shown in a representative sample from three healthy donors and MDS patients. BM-MNC, bone marrow mononuclear cells; HSPC, hematopoietic stem and progenitor cell; rh, recombinant human.

In summary, we have made significant research progress under the proposed goals and discovered that S100A9 activated MDSC activation is associated with increased immune-check point protein expression in HSPCs in MDs. These findings expand prior understanding of the role of PD 1/PD-L1 interaction beyond T cells, which has implications for general immunology and immunotherapy; and demonstrate, for the first time, that S100A9, which is instrumental in the pathogenesis of MDS, plays a critical role in the induction of PD 1/PD-L1 surface receptor expression on HSPCs and MDSCs, further contributing to ineffective hematopoiesis in MDS. These data suggest that anti-PD-1 or anti-PD-L1 blocking strategies, alone or in combination with other strategies such as those suggested above, offer therapeutic promise in MDS to improve the BM microenvironment and restore effective hematopoiesis. The current data has been resubmitted to Leukemia after 2nd revision.

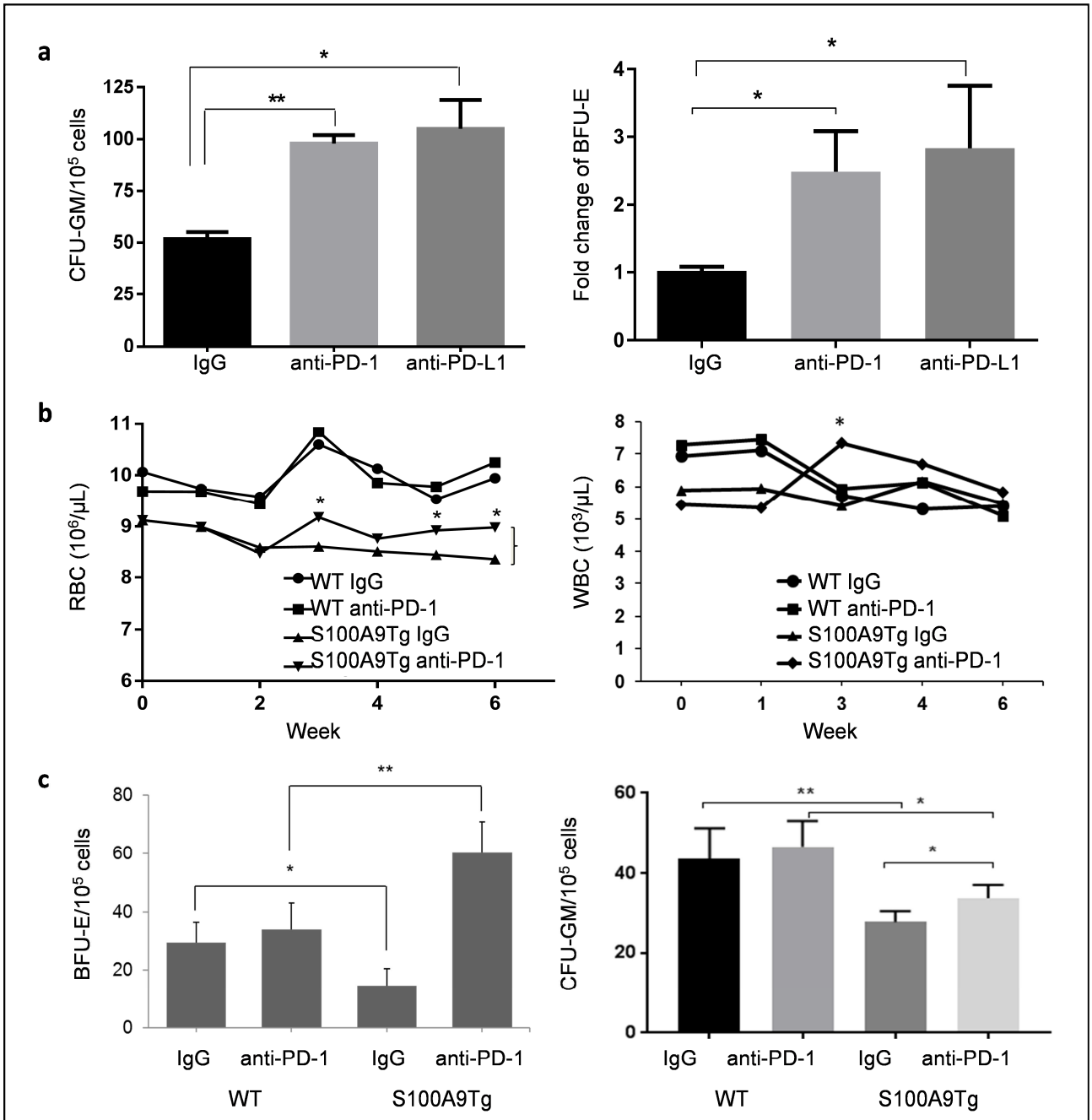

Figure 5. PD-1/PD-L1 pathway blockade augments colony forming capacity in MDS.
MDS BM-MNC (n=5) were treated with anti PD 1 or anti-PD-L1 blocking antibody for 48 hours; subsequently, cells were plated to assess colony forming capacity versus IgG control. (a) CFU GM and BFU-E colony counts are shown. Old S100A9Tg (n=6) and age matched WT mice (n=6) were treated with 150 μg/mouse anti-PD-1 blocking antibody twice a week for 6 weeks. Complete blood counts were measured weekly. (b) Mean RBC and WBC counts are shown through week 6. BM cells from the aged S100A9Tg and WT mice were isolated to assess colony forming capacity. (c) BFU-E colony counts are shown. *P<0.05, **P<0.01; data are presented as mean ± standard error of the mean. BFU-E, burst forming unit-erythroid; BM, bone marrow; BM MNC, BM mononuclear cells; CFU-GM, colony forming unit-granulocyte, monocyte; RBC, red blood cell; Tg, transgenic; WBC, white blood cell; WT, wildtype.

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?

We will follow our original proposal and SOW to further investigate our novel therapeutic approaches targeting S100A9 activated MDSC. 1) In addition to testing the ant-PD-1 and PD-L1 antibody, we will test the TandAb that can target CD33+ MDSC and compare its effect on T cell activation 2) We will test if the combination of TandAb with immune check point inhibitor have any effect on MDSC activation and improve bone marrow hematopoiesis. This will allow us to confirm and validate our novel approaches in an S100A9-associated disease model.

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 both PD-1 and PD-L1 are assoicatge with S100A9 associated MDSC activation leading HSPC undergo cell death. Target this pathway alone or in combination with other strategies have 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	9

worked:	
Contribution to Project:	She is responsible for carrying out all biological and biochemical assays and making all of 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:

One research article submitted for publication this year.

Title: S100A9-induced overexpression of PD-1/PD-L1 contributes to ineffective hematopoiesis in myelodysplastic syndromes

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