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Epigenetic Therapy of Hematopoietic Malignancies: Novel Approaches for Tissue-Specific and Global Inhibition of EZH2 Enzymatic Activities

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14. ABSTRACT Direct sequencing of hematopoietic cancers identified gain-of-function mutations of EZH2, the gene encoding the enzymatic subunit of <i>Polycomb Repressive Complex-2 (PRC2)</i> , among ~10% germ-center B-cell lymphomas. EZH2 silences gene expression through catalysis of methylation of histone H3 lysine 27. However, the currently available EZH2-specific inhibitors are ineffective for treating EZH2-wildtype lymphomas. Novel therapeutics needs to be developed. We found overexpression of PHF19, a PRC2-associated cofactor, is common among B-cell derived malignancies. During this funding period, we have made significant progress in testing our central hypothesis is that, overexpression of PHF19 confers oncogenicity to lymphoma by either enhancing enzymatic activities or chromatin association of PRC2 complexes; in addition, we have evaluated the pan PRC2 inhibitor as a novel means for blockade of unwanted PRC2 hyperactivities among blood cancers including B-cell malignancies.					
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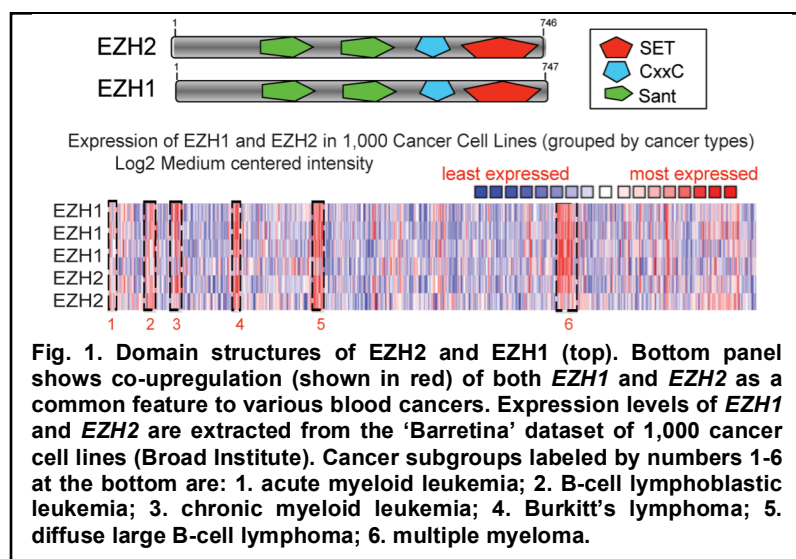
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1. INTRODUCTION:

EZH2 (enhancer of zeste homolog 2, also known as KMT6A (lysine methyltransferase 6A)) or EZH1 (enhancer of zeste homolog 1, also known as KMT6B) is the catalytic subunit of the polycomb repressive complex 2 (PRC2) that catalyzes methylation of histone H3 lysine 27 (H3K27)³⁴⁻³⁷. EZH2 and EZH1 are highly homologous (**Fig. 1**; sharing 96% sequence identity in their catalytic domains¹⁹). The trimethylation of H3K27 (H3K27me3) catalyzed by PRC2 is a transcriptionally repressive epigenetic mark that regulates gene expression, differentiation and development⁴.

EZH2 overexpression and/or gain-of-function mutations occur frequently in human B cell malignancies including germ-center B-cell lymphomas and multiple myeloma, a plasma B cell tumor. However, the currently strategy for suppressing oncogenic functions of PRC2 are ineffective especially for those PRC2-wildtype B cell tumors. We aim to develop new therapeutic approaches for targeting PRC2. Recently, we have found that overexpression of EZH1, an EZH2-related enzyme (**Fig. 1**, bottom), and/or PHF19, an EZH2/EZH1-associated cofactor, are common among the human B-cell derived malignancies. This finding led us to hypothesize that, **overexpression of EZH1 and/or PHF19 confers oncogenicity to lymphoma by either enhancing enzymatic activities or chromatin association of PRC2 complexes**, and that **targeting EZH1 or PHF19 provides a novel means for of blockade of unwanted PRC2 hyperactivities**.



The proposed experiments are organized along the following Specific Aims:

- Aim 1: to develop and evaluate the pan EZH2 and EZH1 inhibitor for treating B-cell lymphomas.
- Aim 2: to investigate PHF19 overexpression in conferring EZH2 and EZH1 hyperactivity to lymphoma to promote oncogenesis.
- Aim 3: to map the differential binding of EZH2 in B- versus T- cell lineages, and to identify the responsible tissue-specific recruiters.

2. KEYWORDS:

Hematopoietic cancer, Lymphoma, PRC2, inhibitor, histone methylation, EZH2, PHF19, EZH1

3. ACCOMPLISHMENTS:

In the Year 2 funding period, we have made significant progress toward all 3 aims in the proposed grant. As there are key and major tasks (see below) that require additional time and efforts to complete, here we request a 12-month, non-cost extension for completion of the proposed research. However, there is no need for making any significant change in the project or its overall direction.

▪ **What were the major goals of the project?**

Below list the major goals of the project as stated in the approved SOW, as well as the actual completion dates or the percentage of completion.

Completed major tasks by year 2

Major Task 1: To Treat various lymphoma cell lines with our pan EZH2 and EZH1 inhibitor in vitro

Subtask 1- To assess the effect of our pan EZH2 and EZH1 inhibitor on tumor cell proliferation in ~30 human cell lines

- completed

Subtask 2- To dissect the effect of our pan EZH2 and EZH1 inhibitor on cell cycle progression, tumor cell differentiation, and/or apoptosis

- completed

Subtask 3 – To identify a common “core signature” associated with cellular treatment of our EZH2 and EZH1 inhibitor

- completed

Summary of Major Task 1-

- completed

Major Task 2: To treat DLBCL xenograft animal models in vivo with the pan EZH2/EZH1 inhibitor

Subtask 4- perform the pharmacokinetic assay and toxicity evaluation of the pan EZH2/EZH1 inhibitor in animals using different compound administration methods

- completed

Subtask 5- establish tumor xenograft models using human cell lines of lymphoma and myeloma.

- completed

Summary of Major Task 2

- completed

Major Task 3 – to dissect the role of PHF19 overexpression using human B-cell derived malignant tumor lines

Subtask 6- perform gene knockdown of PHF19 followed by assays for tumor cell proliferation using >10 different B-cell derived malignant cell lines

- completed

Subtask 7 – assess the effect of knockdown of PHF19 on cell cycle, tumor cell differentiation, and apoptosis

- completed

Summary of Major Task 3

- completed

Major Task 4 – to dissect the role of PHF19 overexpression using xenograft models of lymphoma and myeloma

Subtask 8- to establish tumor xenograft models using human B-cell derived malignant cell lines

- completed

Major Task 5 - to investigate the role of PHF19's Tudor motif in regulation of PRC2 and H3K27me3 hyperactivity

Subtask 9- perform gene knockdown of PHF19 followed by quantitative mass spec of histone modifications and western blots

- completed

Subtask 10 – perform gene knockdown of PHF19 followed by rescue with shRNA-resistant PHF19 (wildtype or Tudor mutant forms) and RNA-Seq to identify PHF19-regulated downstream targets

- completed

Major Task 6- to use genomic approaches to map EZH2's binding sites among B-cell lymphoma versus T-cell leukemia lines

Subtask 11- identify EZH2's binding sites by ChIP-seq among B-cell versus T-cell derived malignant cells

- completed

Major Task 7 - to use biochemical approaches to identify EZH2-associated cofactors

Subtask 12- to generate stable expression cell lines using tagged EZH2

- completed

Major tasks that are NOT completed

Major Task 5 - to investigate the role of PHF19's Tudor motif in regulation of PRC2 and H3K27me3 hyperactivity

Subtask 13 – perform knockdown of PHF19 followed by ChIP-Seq of EZH2 and H3K27me3, in order to dissect the role of PHF19 in regulating EZH2's chromatin association and/or enzymatic activities

- targeted completion date (6 months; by the end of funding year 2)
- actual completion dates (% completion): to be completed in 1/1/2017 (100%)

Major Task 6- to use genomic approaches to map EZH2's binding sites among B-cell lymphoma versus T-cell leukemia lines

Subtask 14 – perform initial data analysis, repeating, and confirmation of EZH2's binding sites

- targeted completion date (6 months; by the end of funding year 2)
- actual completion dates (% completion): to be completed in 2/1/2017 (100%)

Subtask 15 – to identify EZH2's binding cofactors from B-cell and T-cell derived malignant tumor lines by biochemical pull-down and mass spectrometry analysis; Verification by western blots

- targeted completion date (6 months; by the end of funding year 2)
- actual completion dates (% completion): to be completed in 6/1/2017 (100%)

Subtask 16 – test the role of various EZH2 binding partners in regulation of expression of EZH2's target genes by RT-PCR; verification by western blot

- targeted completion date (6 months; by the end of funding year 2)
- actual completion dates (% completion): to be completed in 8/1/2017 (100%)

▪ **What was accomplished under these goals?**

- *For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

(1) Major activities

This current progress report covers the following aims as originally proposed:

Aim 1: to develop and evaluate the pan EZH2 and EZH1 inhibitor for treating B-cell lymphomas.

Aim 1.1- to treat tumor with our pan EZH2 and EZH1 inhibitor in vitro.

- Partly completed in year 1 (see report of year 1)
- See below for further works that were done in year 2.

Aim 1.2- to treat tumor xenograft animal models in vivo with the pan EZH2/EZH1 inhibitor.

- Partly completed in year 1 (see report of year 1)
- See below for further works that were done in year 2.

Major activity 1- To assess the effect of our pan EZH2 and EZH1 inhibitor on tumor cell proliferation in various human tumor cell lines

Major activity 2- To dissect the effect of our pan EZH2 and EZH1 inhibitor on cell cycle progression, tumor cell differentiation, and/or apoptosis

Major activity 3 – To identify a common “core signature” associated with cellular treatment of our EZH2 and EZH1 inhibitor

Major activity 4- establish tumor xenograft models using human cell lines of lymphoma and myeloma. And to treat xenograft animal models in vivo with the pan EZH2/EZH1 inhibitor

Aim 2: to investigate PHF19 overexpression in conferring EZH2/1 hyperactivity to lymphoma to promote oncogenesis.

The major activities include:

Major activity 5- establish tumor xenograft models using human cell lines of lymphoma and myeloma.

Major activity 6- perform gene knockdown of PHF19 followed by assays for tumor cell proliferation using B-cell derived malignant cell lines

Major activity 7 assess the effect of knockdown of PHF19 on cell cycle, tumor cell differentiation, and apoptosis

Major activity 8- establish tumor xenograft models using human B-cell derived malignant cell lines, and study the requirement of PHF19 in tumor development

(2) Specific objectives

2.1- to demonstrate that the pan EZH2 and EZH1 inhibitor represents a new means for achieving complete inhibition of EZH family enzymes in treating blood cancers.

2.2- to establish PHF19 as a new drug target of B-cell tumors.

In the funding year 2, we have expanded our studies into multiple myeloma, a plasma B-cell tumor. Multiple myeloma (MM) is a malignancy of plasma cells, the terminally differentiated B lymphocytes that generate and secrete antibodies. MM represents the 2nd most common hematological cancer, with about 30,330 new cases and 12,650 expected death in U.S. in 2016. It is believed that MM experiences a step-wise progression from a clinically insidious stage, such as monoclonal gammopathy of uncertain significance (MGUS), and acquires both genetic and epigenetic alterations that promote MM development. Unlike most of malignancies, the malignant MM cells are characterized by an extraordinary low mitotic rate, which possibly contributes to the almost universal resistance to chemotherapeutics. Despite recent FDA-approved proteasome inhibitors for MM treatment, new targeted therapeutics need to be developed to further improve clinical outcomes for this fatal disease, especially for those refractory cases. In Figure 1 (bottom), we have shown that EZH2 and/or EZH1 are both up-regulated in MM, which indicates targeting EZH2/1 as an attractive way for the treatment of MM. In the funding year 2, we have summarized our new progress and results in sections below.

(3) Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative);

(3.1) Related to Major activity 1- To assess the effect of our pan EZH2 and EZH1 inhibitor on tumor cell proliferation in various human tumor cell lines

We have identified a set of small-molecule inhibitors for specific targeting of both EZH2 and EZH1, including UNC1999, an EZH2 and EZH1 dual inhibitor, and UNC2400, an inactive analog compound useful for assessment of off-target effect (Figure 2 and also see report from year 1). The discovery of compounds was made with a structure based chemical compound design in a close collaboration with UNC Center for Drug Discovery and Chemical Biology.

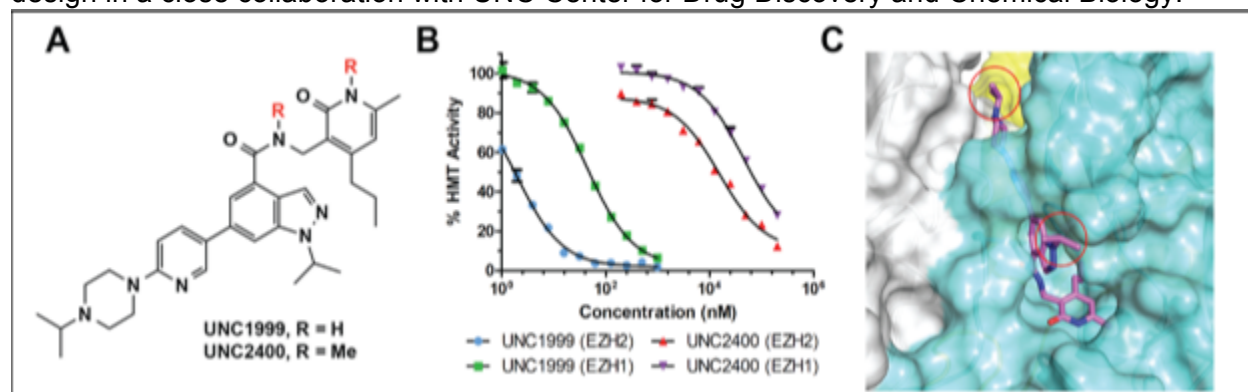


Fig. 2. (A) Structures of UNC1999 and UNC2400. (B) UNC1999 has high potency for EZH2 and EZH1. UNC2400 is > 1,000-fold less potent than UNC1999. (C) Docked pose of UNC1999 in human PRC2 complex. Red rings mark the solvent-exposed moieties.

We characterized molecular and cellular effects by these translational tools and aim to establish novel therapeutics for cancer cells. We have applied UNC1999 to a larger panel of myeloma cell lines. Many showed sensitivity to UNC1999 (Figure 3).

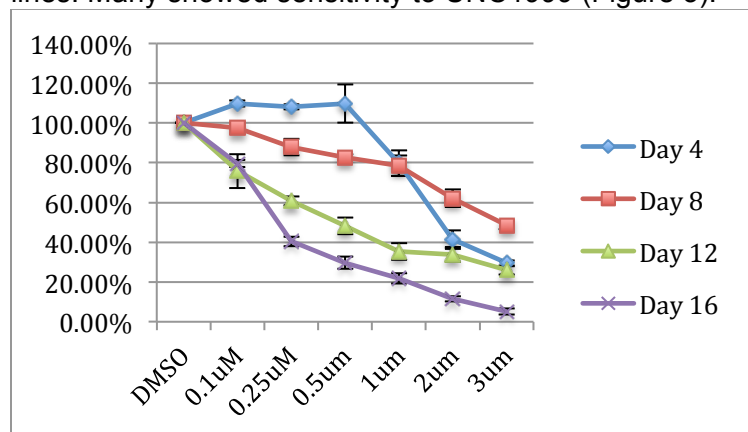


Fig 3. Relative proliferation of a panel of myeloma cell lines treated with various concentrations of UNC1999 for the indicated days (left panel). Y-axis, presented as the mean of triplicates \pm 6 SD, represents the relative percentage of accumulative cell numbers after normalization to DMSO treatment.

Major findings & conclusion

- UNC1999 induces potent and selective suppression of H3K27me3/2, whereas UNC2400 does not, highlighting them as a pair of compounds useful to manipulate both PRC2-EZH2 and PRC2-EZH1.
- UNC1999, an EZH2 and EZH1 dual inhibitor, efficiently suppresses proliferation of myeloma cells that co-express EZH2 and EZH1.

(3.2) Related to Major activity 2-To dissect the effect of our pan EZH2 and EZH1 inhibitor on cell cycle progression, tumor cell differentiation, and/or apoptosis

- We have also studied the effect of our pan EZH2 and EZH1 inhibitor on cancer cell apoptosis (Figure 4). We found a time- and concentration dependent induction of apoptosis and cell viability after treatment with UNC1999.

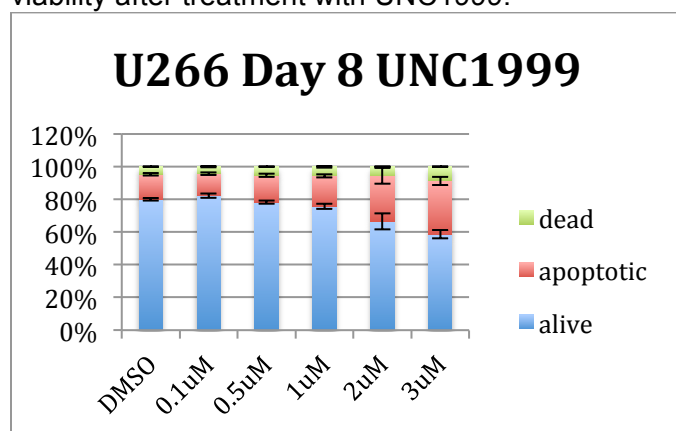


Fig 4. A summary of effect of UNC1999 on apoptosis and cell viability of U266, a myeloma cell line.

Major findings & conclusion-

- UNC1999 suppresses growth of malignant multiple myeloma tumor cells by inhibiting cell cycle progression and promoting apoptosis.

(3.3) Related to Major activity 3 – To identify a common “core signature” associated with cellular treatment of our EZH2 and EZH1 inhibitor

- To dissect the underlying mechanisms for the UNC1999-induced anti-cancer effect, we have carried out gene transcriptome profilings by RNA-seq and aimed to identifying a common “core signature” associated with cellular treatment of our EZH2 and EZH1 inhibitor. These analyses were carried out in UNC genomic core using an Affymetrix gene-array platform.

Major findings & conclusion-

- Deep analysis of the large datasets is on-going and to be completed in 12/1/2016.

(3.4) Related to Major activity 4 – We have performed the pharmacokinetic assay and toxicity evaluation of the pan EZH2/EZH1 inhibitor in animals using different compound administration methods (Fig 5);

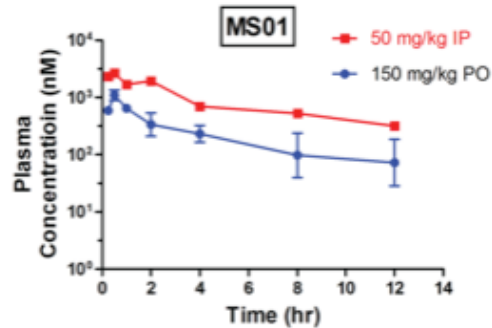


Figure 5. Plasma concentrations of MS01, a new EZH2/1 inhibitor, following a single IP injection (50 mg/kg) or PO dose (150 mg/kg) in mice (average values of 4 mice (2 male and 2 female) per time point).

(3.4) Related to Major activity 5

to establish tumor xenograft models using human cell lines of lymphoma and myeloma. To treat tumor xenograft models with inhibitor

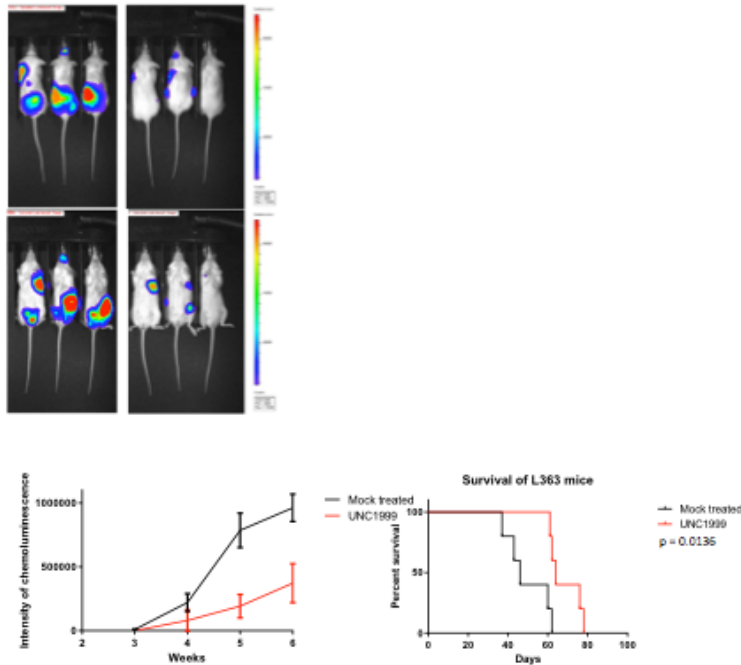


Fig 6. Images of the xenografted tumors in the vehicle- (upper, left) and UNC1999-treated (upper, right) mice. The bottom panels shows summary of growth of xenografted tumors and Kaplan-Meier curve showing cancer development kinetics.

- To examine the effect of UNC1999 on *in vivo* leukemogenesis, we developed a treatment regimen by administering either vehicle or 50 mg/kg UNC1999 by oral gavage to mice twice per day. We show that UNC1999 delayed cancer development and progression (Fig 6A, red versus blue lines).

Major findings & conclusion-

Collectively, these above data show that

- Our established protocol for oral administration of UNC1999 does not cause obvious toxicity in tested animals;
- Oral delivery of UNC1999 delays cancer development and progression *in vivo* and our EZH2 and EZH1 dual inhibitor provides a new therapeutics for multiple myeloma.

(3.5) Related to Major activity 6 to 8 -

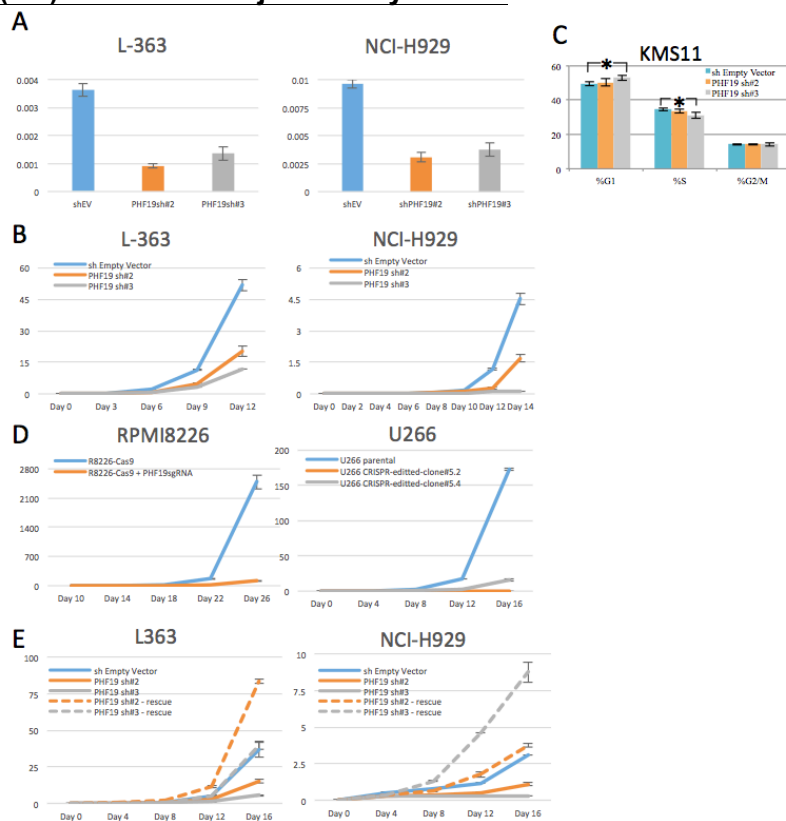


Fig 7. Effect of PHF19 expression in multiple myeloma growth in vitro.

We have successfully carried out Knockdown (KD) of *PHF19* in multiple B-cell derived malignant tumor lines (Fig 7A-B). We found that *PHF19* is required for *in vitro* tumor growth (Fig. 7B-E).

- we have used the SCID-NOD-gamma (SNG) mice which were xenografted intravenously with human multiple myeloma cell lines (Fig 8); we found that knockdown (KD) of *PHF19* delays the xenografted tumor formation *in vivo* (Fig. 8). The *in vivo* phenotypes of *PHF19* KD can be rescued by re-introduction of *PHF19* (Fig 8; bottom panels, red).

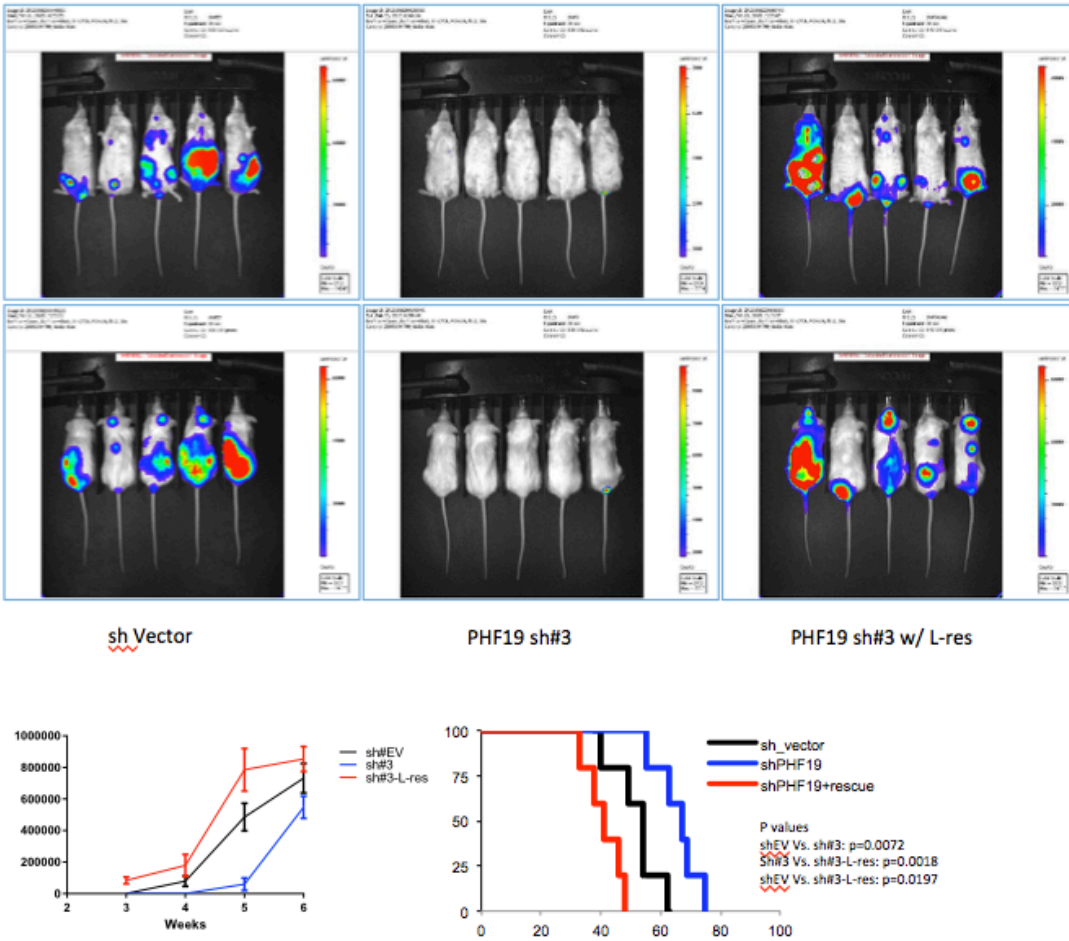


Fig 8. Effect of PHF19 expression in multiple myeloma growth in vivo.

Major findings & conclusion-

- We found that PHF19 is among the top overexpressed genes in multiple myeloma (MM). In addition, there is a steady increased expression level of PHF19 mRNA among multiple myeloma (MM) and plasma cell leukemia (PCL), in comparison to normal plasma cells.
- PHF19 is crucial for tumor cell proliferation in tested B-cell derived malignant cell lines
- we have established the tumor xenograft models (Fig 8) using human B-cell derived malignant cell lines
- we have shown a requirement of PHF19 for tumor xenograft growth in vivo (Fig 8)

(4) other achievements-
n/a

- **What opportunities for training and professional development has the project provided?**
Training and professional development provided to Dr. Zhihong Ren MD/PHD, who worked on the project as a postdoc researcher-
"Training" activities:
-ChIP, qRT-PCR, western blot

- xenograft studies with human cell lines and SCID nude mice models
- live imaging
- in-house postdoc seminar (weekly)

▪ **How were the results disseminated to communities of interest?**

We have published three papers related to our proposed works during the year 1 of the project. These papers are publicly available and can be downloaded and viewed by numerous researchers and clinicians via portal or databases such as PubMed Central. Our research is well received. As evidence, these 3 papers together have been cited over 60 times in less than 18 months.

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

Partly due to annual renewal of an expired animal protocol (see below section 5), some major tasks in Aim 2-3 are currently only partially completed and require deeper analysis or additional experimental repeats. Here we request a 12-month non-cost extension. I hope to publish two papers based on observations and data obtained.

Given our success in the previous year, we are confident that the research goals will be achieved. Since significant progress was made for all specific aims, no modification in our works as proposed in the original plan is needed at this point.

4. IMPACT:

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

The findings and research results are likely to make an impact on blood cancer research and therapies in the following ways:

- Define a set of new 'Achilles' heels' of blood cell derived malignancies.
- Targeting these new drug targets with inhibitors we develop shall provide novel therapeutic interventions.

▪ **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:

▪ **Changes in approach and reasons for change**

Nothing to Report.

▪ **Actual or anticipated problems or delays and actions or plans to resolve them**

Delays encountered during the reporting period and actions or plans to resolve them:

Due to an expired animal protocol and its renewal, we had to stop any animal related research or work relating to this funding. The delay was from 2/23/2015- 5/21/2015 and 2/20/2016- 4/1/2016.

We will be able to complete the proposed aims once a 12-month non-cost extension is granted.

▪ **Changes that had a significant impact on expenditures**

Nothing to Report.

▪ **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report.

6. PRODUCTS:

▪ Publications, conference papers, and presentations

Journal publications.

1. Lu R, Wang P, Parton T, Zhou Y, Chrysovergis K, Rockowitz S, Chen WY, Abdel-Wahab O, Wade PA, Zheng D, **Wang GG**. Epigenetic perturbations by Arg882-mutated DNMT3A potentiate aberrant stem cell gene expression program and acute leukemia development. *Cancer Cell* 2016 July 11;30(1):92-107. *
* Cover image story with News & Views at:
Cancer Cell July 11;30(1):9-10; *Cancer Discovery* July 08, 2016 DOI: 10.1158/2159-8290.CD-RW2016-126
2. Zhou Y, Wang L, Vaseghi HR, Liu Z, Lu R, Alimohamadi S, Yin C, Fu JD, **Wang GG**, Liu J, Qian L. Bmi1 Is a Key Epigenetic Barrier to Direct Cardiac Reprogramming. *Cell Stem Cell*. 2016 Mar 3;18(3):382-95.
3. Zhang ZM, Rothbart SB, Allison DF, Cai Q, Harrison JS, Li L, Wang Y, Strahl BD, **Wang GG**, Song J. An Allosteric Interaction Links USP7 to Deubiquitination and Chromatin Targeting of UHRF1. *Cell Rep*. 2015 Sep 1;12(9):1400-6. PMID: 26299963
4. Li Z, Chen P, Su R, Hu C, Li Y, Elkahloun AG, Zuo Z, Gurbuxani S, Arnovitz S, Weng H, Wang Y, Li S, Huang H, Neilly MB, **Wang GG**, Jiang X, Liu PP, Jin J, Chen J. PBX3 and MEIS1 Cooperate in Hematopoietic Cells to Drive Acute Myeloid Leukemias Characterized by a Core Transcriptome of the MLL-Rearranged Disease. *Cancer Res*. 2016 Feb 1;76(3):619-29. PMID: 26747896

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers, and presentations.

Nothing to Report.

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	<i>Gang (Greg) Wang, PHD & Assistant Professor</i>
Project Role:	<i>PI</i>
Researcher Identifier (e.g. ORCID ID):	<i>orcid.org/0000-0002-7210-9940</i>
Nearest person month worked:	<i>5</i>
Contribution to Project:	<i>Dr. Wang has served as team leader performing experimental design, guidance and data review/interpretation.</i>
Funding Support:	<i>NIH, Kimmel Foundation</i>

▪

Name:	<i>Zhihong Ren, PHD/MD (postdoc trainee)</i>
Project Role:	<i>postdoc</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>12</i>
Contribution to Project:	<i>Dr. Ren has served as postdoc research performing in vitro and in vivo experiments as proposed; he also carried out data review/interpretation.</i>
Funding Support:	<i>n/a</i>

▪

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

N/A

9. APPENDICES –n/a.