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14. ABSTRACT

Osteoarthritis (OA) is a painful disease that causes the progressive destruction of joint structures, and is the most common cause of disability among military service members who are removed from active duty for medical reasons. In preliminary work with a small number of animals, we have found that the natural product derivative halofuginone (HF) shows promise with respect to reducing cartilage damage in the destabilized medial meniscus (DMM) mouse model of PTOA. HF inhibits glutamyl- prolyl-tRNA synthetase (EPRS), the enzyme responsible for charging tRNAs with the amino acid proline. The goal of this grant is to test the hypothesis that EPRS inhibitors will provide the basis for a new therapeutic strategy for PTOA. We report here: 1) Preliminary analysis of a study of efficacy of the EPRS inhibitors HF and its less toxic derivative HFol, on PTOA in mice, using the DMM model; 2) Data examining the transcriptomics of HF effects on responses to cytokines in synoviocytes. 3) preliminary characterization of an in vitro chondrocyte system in which chondrocytes retain strong responsiveness to cytokines.

15. SUBJECT TERMS
Post Traumatic Osteoarthritis (PTOA), Halofuginone (HF), Articular Cartilage, Chondrocyte, Destabilized Medial Meniscus (DMM), GCN2, TGF-β1, HTRA1, DDR2 and MMP-13

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INTRODUCTION:

Preserving of the mature articular cartilage of joints is a critical focus in the prevention and treatment of post-traumatic osteoarthritis (PTOA). Of note, there is significant evidence to indicate that mature articular cartilage has little capacity to regenerate after injuries. There are, currently, no approved disease modifying OA drugs (DMOADs) that can protect articular cartilage from being damaged during the pathogenesis of PTOA. In our preliminary work with a small number of animals, we have found that the natural product derivative halofuginone (HF) shows promise with respect to reducing cartilage damage in a mouse injurious model of OA, the destabilized medial meniscus (DMM). HF inhibits glutamyl- prolyl-tRNA synthetase (EPRS), the enzyme responsible for charging tRNAs with the amino acid proline. Low-level inhibition of EPRS triggers a metabolic sensor, a stress signal that initiates a sustained adaptive response across affected tissues. The goal of this grant is to test the hypothesis that EPRS inhibitors, acting to suppress a multi-cellular cytokine-driven tissue destructive program, will provide the basis for a new therapeutic strategy for PTOA. The Aims of this project are to: 1) to characterize the therapeutic timing and functional effects of HF, or novel related EPRS inhibitors, on PTOA in mice, using the DMM model; 2) to examine the early time course of cellular and molecular responses to EPRS inhibitor treatment in the DMM mouse model, as well as in ex vivo in chondrocytes and synoviocytes. We believe that these studies both will establish the molecular and cellular basis for the benefit of a new drug class for PTOA treatment, and provide tools to evaluate different therapeutic strategies (e.g. novel compounds, delivery methods) prior to the appearance of joint pain or dysfunction.; 3) To develop and apply tools for testing the efficacy of EPRS inhibitors following drug delivery to the joint in DMM mice.

KEYWORDS: Post Traumatic Osteoarthritis (PTOA), Halofuginone (HF), Articular Cartilage, Chondrocyte, Destabilized Medial Meniscus (DMM), GCN2, TGF-β1, HTRA1, DDR2 and MMP-13

ACCOMPLISHMENTS:

In this project, there are three major goals: i) Characterization of the timing and functional effects of HF on the progression of PTOA in mice, ii) Identification of early markers of HF efficacy in PTOA, and iii) Developing and applying tools for testing the efficacy of new EPRS inhibitors. We have performed in vivo experiments to investigate the chondro-protective effects of HF on the articular cartilage of knee joints in an injurious mouse model of OA. We have also carried out in vitro experiments to study possible mechanism by which the progressive process of articular cartilage degeneration was significantly delayed in the mouse model of PTOA by the treatment of HF.

1) Major activities:

i. Completion of the characterization of the morphology of knee joints in DMM model treated by HF/Hfol.

ii. Examination of expressions of a number of genes, which may be affected by HF/Hfol, in articular cartilage of knee joints of DMM model.

iii. Analysis of mechanism, in vitro experiments, by which HF/Hfol protect articular cartilage from being degraded in a mouse model of PTOA.

2) Specific objectives:

i. To determine whether or not HF/Hfol can delay the progressive process of articular cartilage degeneration, induced by DMM surgery, in mouse knee joints. We examined the morphology of articular cartilage by histology analysis. The condition of the cartilage was also evaluated by a modified Mankin scoring system.

ii. To analyze whether or not the expressions of genes were affected in articular cartilage of knee joints by the treatment of HF/Hfol. Those genes are involved in articular cartilage degeneration, including transforming growth factor beta 1 (TGF-β1), high temperature requirement A1 (HTRA1), discoidin domain receptor 2 (DDR2), matrix metalloproteinase 13 (MMP-13) and Zip8.
iii. To elucidate a possible mechanism by which the expression of Mmp-13 was inhibited in chondrocytes by HF/Hfol in vitro.

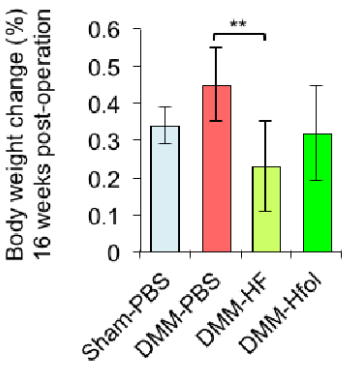
3) Significant results
Objective 1: To determine whether HF and HFOL can prevent/delay the progression of the articular cartilage degeneration, induced by DMM

Rationales: In our previous studies, we found that it took about 16 weeks for mice to develop a typical OA knee joint after DMM surgery. Therefore, we planed to use 16 weeks after DMM surgery as the end point to characterize mouse knee joints for evidences of articular cartilage degeneration in this study.

***Methods and results*:**
Experiment 1. Treatment of mice with HF or HFOL

There are four groups of mice: sham surgery treated with PBS, DMM surgery treated with PBS, DMM surgery treated with HF and DMM surgery treated with HFOL. There are 8 mice in each group. Mice (C57BL/6j) at the age of 10 weeks old were subject to the surgery. Two weeks after the surgery, mice were treated either with PBS or HF (0.2 mg/kg body weight) or HFOL (1 mg/kg body weight) every other day. At 8 weeks after the surgery, one set of four groups of mice was euthanized for the collection of knee joints. Another set of four groups of mice was kept alive to the age of 16 weeks after the surgery and then the mice were euthanized for the collection of knee joints.

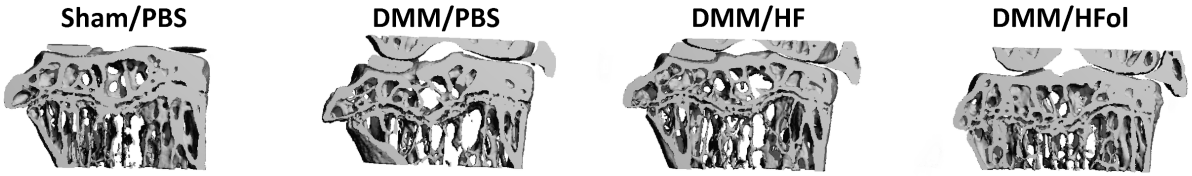
Experiment 2. Measurement of mouse body weights

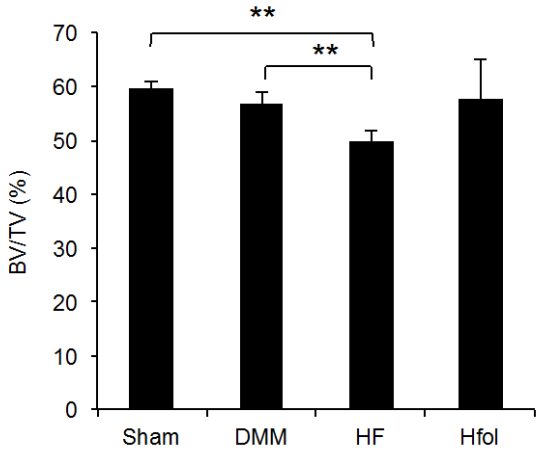


We measured the body weight of the mice during the drug treatment. Body weight changes (%) were calculated. There was no difference in body weight gain among the groups at 8 weeks following the surgery. However, the DMM/HF group showed a significantly less body weight gain compared with that of the DMM/PBS group, $p<0.01$, at 16 weeks after the surgery. There was no difference between DMM/HFol and DMM/PBS, $p>0.05$.

Experiment 3. Measurement of bone volume in epiphysis of tibia in mice by micro-computed tomography (μCT)

A high-resolution desktop micro-tomographic imaging system (μCT40, Scanco Medical AG, Brüttisellen, Switzerland) was used to assess trabecular bone microarchitecture, total and bone volumes, and mineral densities of the tibial epiphysis. Scans were acquired using a 10 μm^3 isotropic voxel size, 70 kVP, 114 mAs, 200 ms integration time, and were subjected to Gaussian filtration and segmentation. Images and results were shown below.





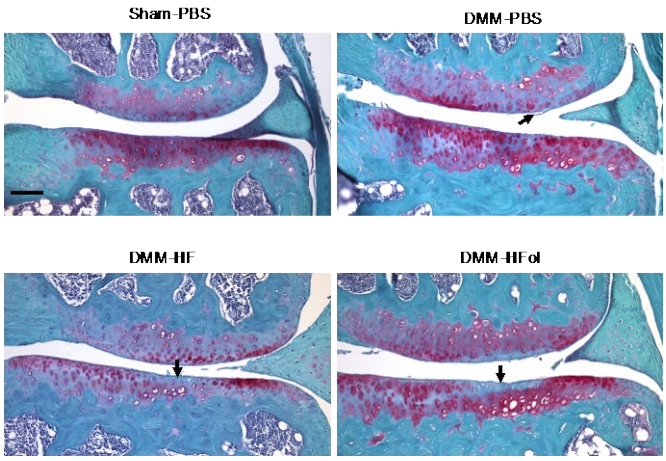
		p-value	
	BV/TV (%)	vs Sham	vs DMM
Sham	59.67	-	-
DMM	56.67	0.0840	-
HF	49.96	0.0040	0.0056
Hfol	57.52	0.6167	0.8443

As indicated in the image and the figure, the bone volume is reduced in DMM/HF group, compared with that in the sham (p=0.0040) and DMM (p=0.0056).

Experiment 4. Morphological analysis of knee joints

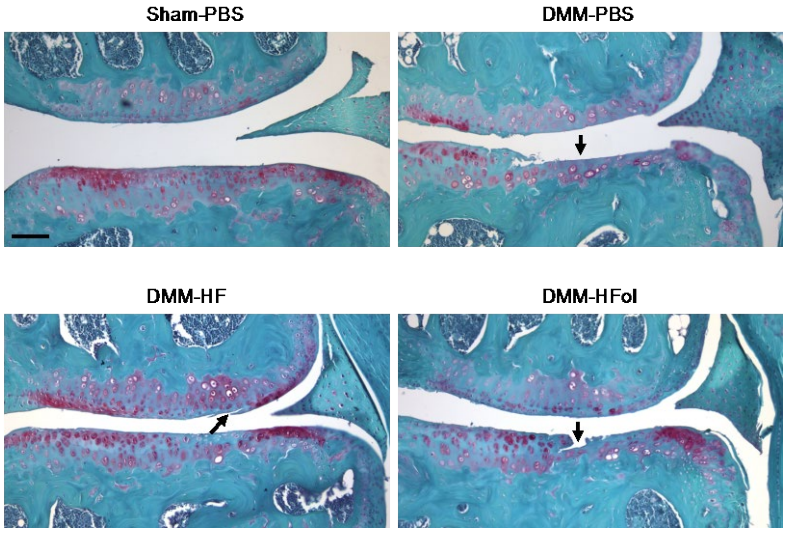
We have completed the histological analyses of mouse knee joints. In the experiment, there were four groups of mice: sham surgery treated with PBS, DMM surgery treated with PBS, DMM surgery treated with HF and DMM surgery treated with HFOL. There are 7-8 mice in each group. Mice (C57BL/6j) at the age of 10 weeks old were subject to the surgery. Two weeks after the surgery, mice were treated either with PBS or HF (0.2 mg/kg body weight) or HFOL (1 mg/kg body weight) every other day. At 8 weeks after the surgery, one set of four groups of mice was euthanized for the collection of knee joints. Another set of four groups of mice was kept alive to the age of 16 weeks after the surgery and then the mice were euthanized for the collection of knee joints. All of the samples were embedded in paraffin and 10 of them were sectioned and stained by Safranine O/Fast green. For histology analysis, Knee joints were decalcified in Morse's solution. For each knee joint, 6 μm thick serial sagittal sections were cut. Every tenth section was collected for Safranin O/Fast green staining.

Figure 1. Articular cartilages of mouse knee joints at 8 weeks after DMM



No over morphological changes were observed in mice with sham surgery (A) Small fibrillations were seen in mice with DMM (see arrow in B). However, there were only slight proteoglycan degradations observed in DMM/HF (see arrow in C) and DMM/HFol (see arrow in D) treatment groups. This indicates that HF and HFol treatments delay the progressive process of articular cartilage degeneration induced by DMM. Bar = 100 mm

Figure 2. Articular cartilages of mouse knee joints at 16 weeks after DMM



Slightly localized proteoglycan degradations were seen in mice with sham surgery (A). Loss of articular cartilages were observed in mice after DMM (see arrow in B). However, only fibrillations were seen in DMM/HF (see arrow in C) and DMM/HFol (see arrow in D) treatment groups. This indicates that HF and HFol treatments delay the progressive process of articular cartilage degeneration induced by DMM. Bar = 100 mm

The condition of articular cartilages was also evaluated by a modified Mankin Score system for mouse articular cartilage, recommended by Osteoarthritis Research Society International (Glasson et. al., The OARSI histopathology initiative e recommendations for

histological assessments of osteoarthritis in the mouse. Osteoarthritis and Cartilage, 2010, 18:S17-S23).

Table 1. Scores of articular cartilages of mouse knee joints after DMM

Time (weeks after the surgery)	Sham-PBS		DMM-PBS		DMM-HF		DMM-HFol	
	n	Means ± SD	n	Means ± SD	n	Means ± SD	n	Means ± SD
8	7	0.14 ± 0.23	7	2.00 ± 0.53	7	0.57 ± 0.17	7	0.71 ± 0.52
16	8	0.94 ± 0.30	7	4.14 ± 0.83	8	2.13 ± 0.78	7	2.14 ± 0.99

Figure 3. Evaluation of articular cartilage of mouse knee joints at 8 weeks after surgery

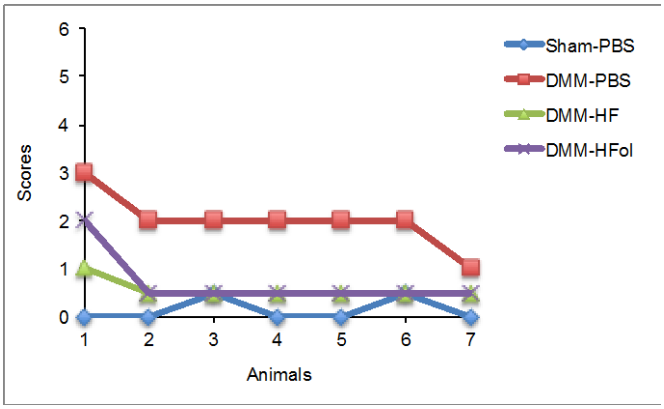


Figure 4. Evaluation of articular cartilage of mouse knee joints at 16 weeks after surgery

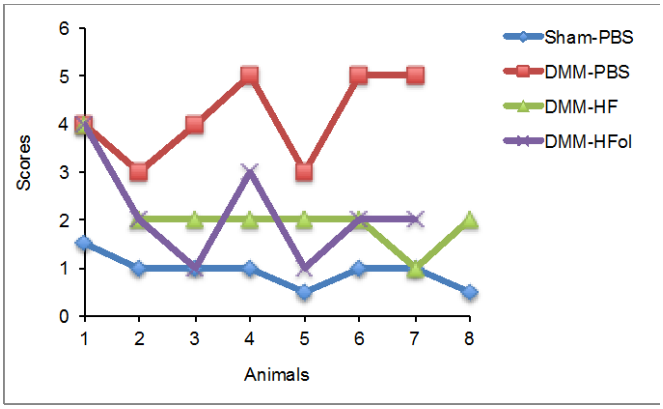
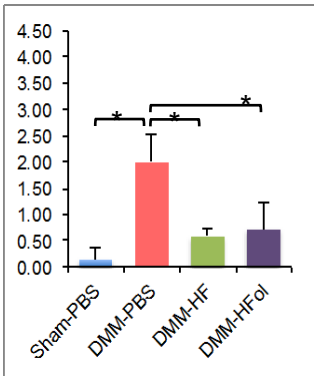


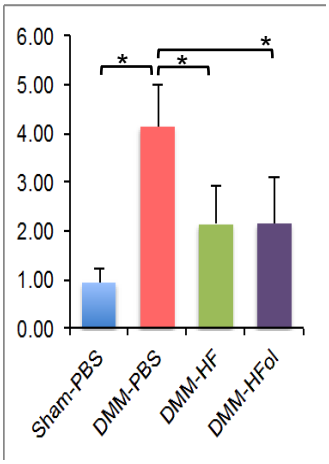
Figure 5. Comparison of scores between the experimental groups at 8 weeks after surgery



**: p<0.001

***: p<0.0001

Figure 6. Comparison of scores between the experimental groups at 16 weeks after surgery



**: p<0.001

***: p<0.0001

Conclusion: HF and HFol can significantly delay the progressive process of articular cartilage degeneration induced by DMM.

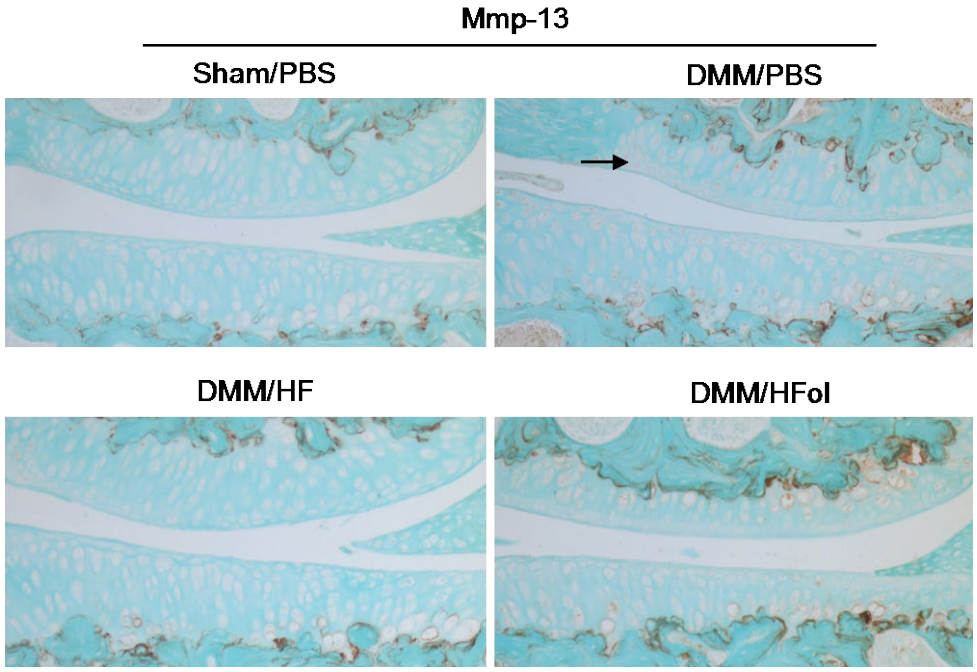
Objective 2: To analyze whether or not the expressions of genes were affected in articular cartilage of knee joints by the treatment of HF/Hfol

Rationales: A number of genes have been shown to involve in articular cartilage degeneration, which eventually leads to OA, genes such as MMP-13, Zip8, TGF-β1, HTRA1 and DDR2. We analyzed whether or not the expressions of those genes were affected by the treatment of HF/Hfol in articular cartilage of mouse knee joints.

Methods and results:

We performed immunohistostaining to examine the expressions of genes, including MMP-13), ZIP8, TGF-β1, HTRA1 and DDR2 in the articular cartilage of mouse knee joints. Four knee joints were randomly selected from each group of mice at 8 weeks after DMM. Eight to ten paraffin sections, distributed throughout each knee joint, of articular cartilage were selected for immunohistostaining. Paraffin sections were incubated with a polyclonal antibody against the genes. An appropriate concentration of each primary antibody for the experiment was determined by the examination of a serial dilution of the antibody on the sections. After overnight incubation with a primary antibody at 4°C, the sections were washed and incubated with a biotinylated secondary antibody. Color development was performed using a peroxidase substrate (VECTOR Laboratories, Burlingame, CA). Staining without primary antibody was performed as a negative control.

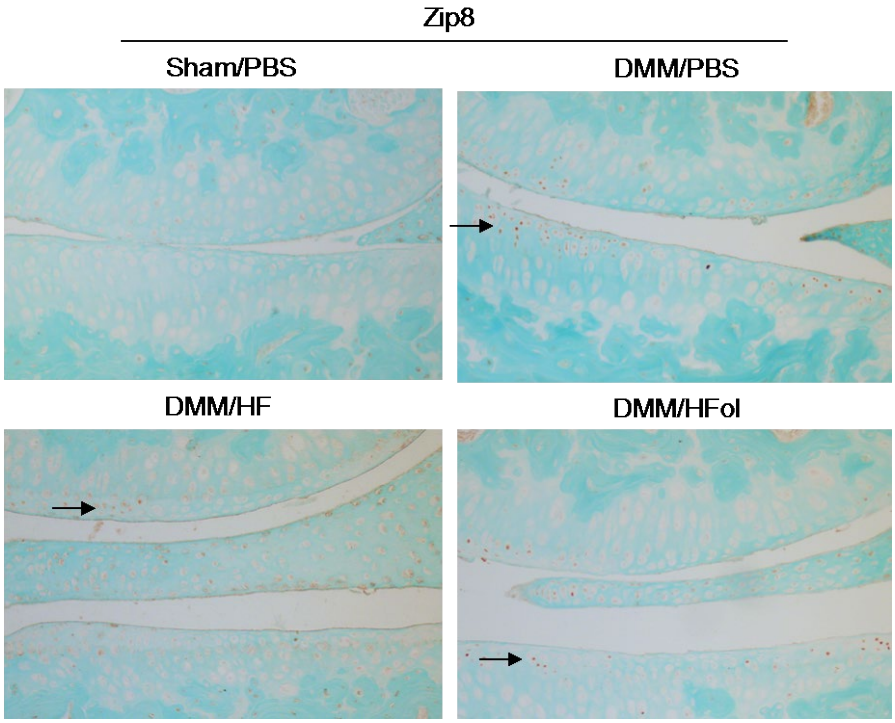
Figure 7. The expression of Mmp-13 in mouse knee articular cartilages



A rabbit polyclonal antibody (1μg/μl at the final concentration of 1:400 dilution) against Mmp-13 (Abcam, Cambridge, MA) was used in this experiment. The expression of Mmp-13 was increased in the DMM/PBS group (see the arrow in figure 7). There were no positive staining cells detected in other groups. This suggests that HF or HFol inhibits the induction of Mmp-13 in the articular cartilage of mouse knee joints induced by DMM.

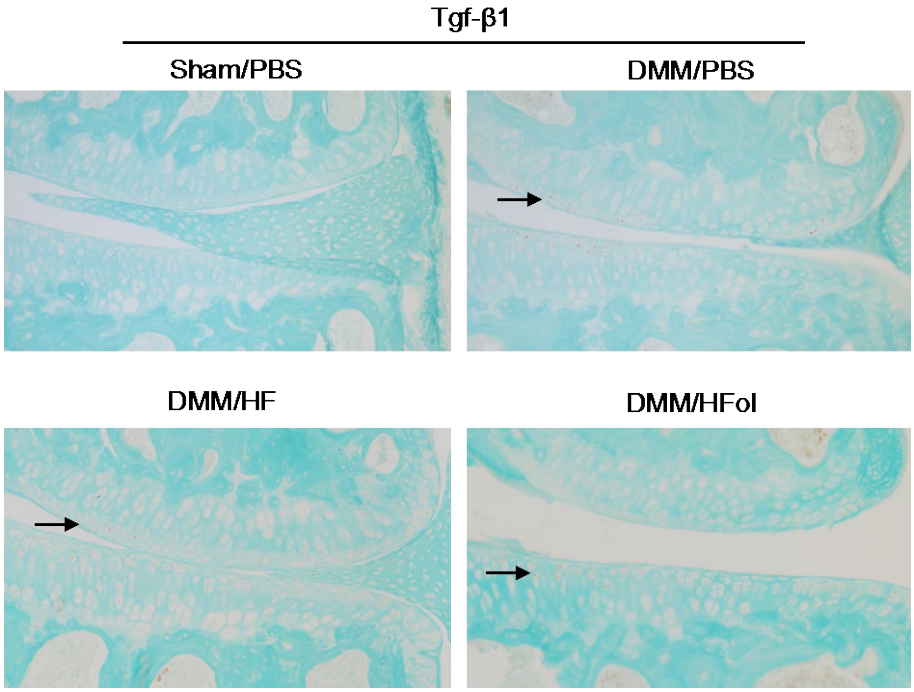
To understand possible mechanisms responsible for the down-regulation expression of Mmp-13 by HF or HFol, we investigated whether or not two regulatory molecular pathways were involved in the induction of Mmp-13 in the articular chondrocytes of mouse knee joints. The result from a study indicates that the zinc-ZIP8-MTF1 (metalregulatory transcription factor-1) axis induces expression of MMP-13 in chondrocytes. Data from several independent research groups demonstrate that the TGF-β1-HTRA1-DDR2 forms a molecular pathway to induce the expression of MMP-13 in chondrocytes.

Figure 8. The expression of Zip 8 in mouse knee articular cartilages



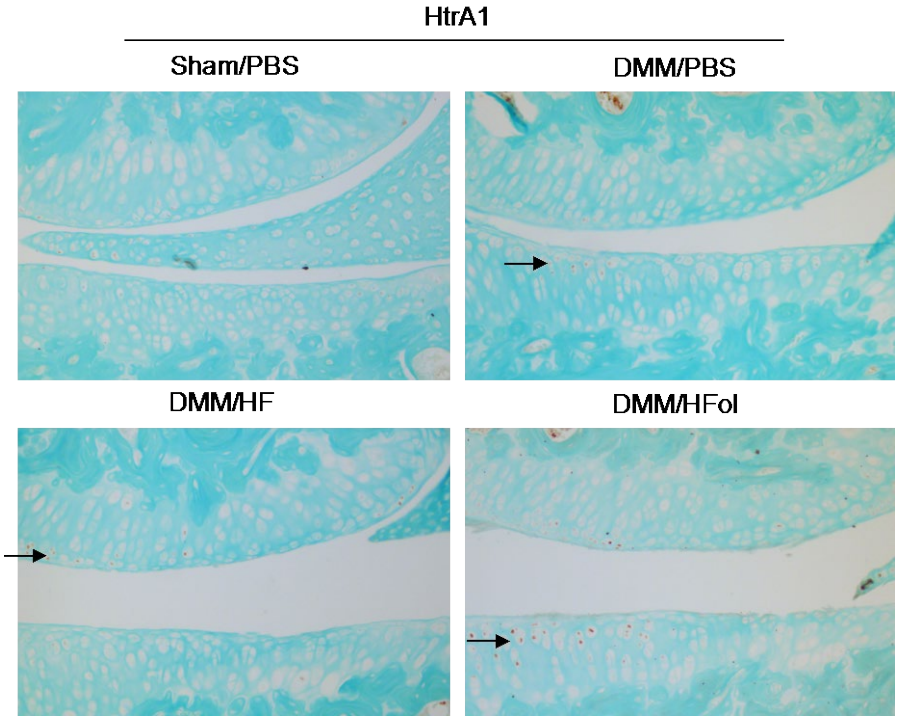
A rabbit polyclonal antibody (the final concentration of 1:150 dilution) against Zip 8 was used. The expression of Zip8 was increased in DMM/PBS group (see brown-color staining cells in figure 8). The expression of Zip8 was also detected in DMM/HF and DMM/HFol groups.

Figure 9. The expression of TGF-β1 in mouse knee articular cartilages



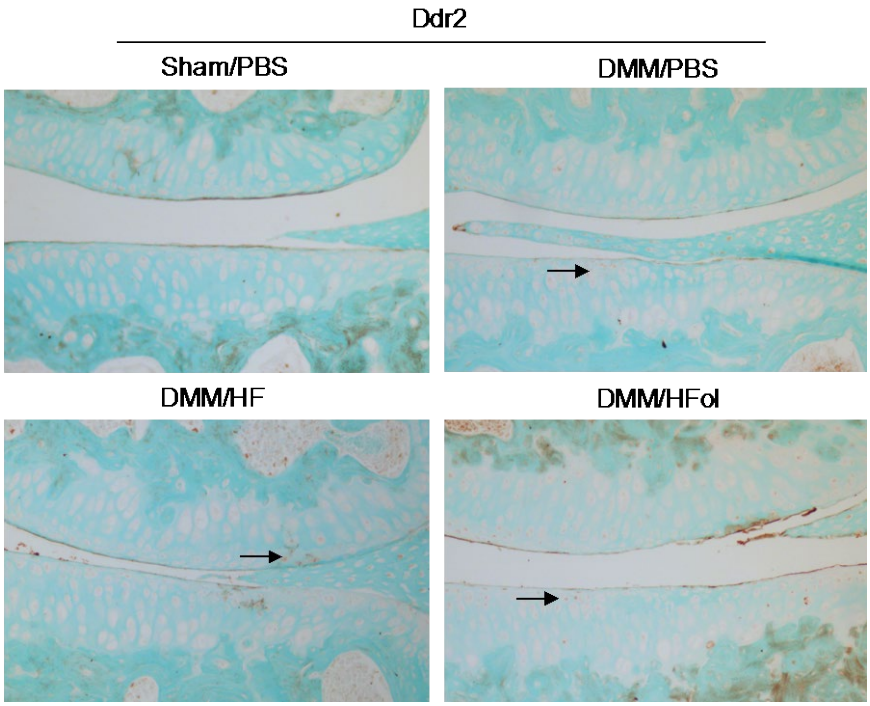
A rabbit polyclonal antibody (the final concentration of 1:200 dilution) against Tgf-β1 was used. The expression of Tgf-β1 was increased in DMM/PBS group (see brown-color staining cells in figure 9). The expression of Tgf-β1 was also detected in DMM/HF and DMM/HFol groups.

Figure 10. The expression of HtrA1 in mouse knee articular cartilages



A rabbit polyclonal antibody (the final concentration of 1:200 dilution) against HtrA1 was used. We found the similar expression of patterns of HtrA1 to what was observed in the expression pattern of Tgf-β1 group, see figure 10).

Figure 11. The expression of Ddr2 in mouse knee articular cartilages



A rabbit polyclonal antibody against Ddr2 (a final concentration of 1:200 dilution) was used in this experiment. We found the similar expression of patterns of Ddr2 to what were observed in the expression patterns of Tgf-β1 and HtrA1 groups, see figures 10 and 11).

Conclusion: HF or HFol inhibits the up-regulation expression of Mmp-13 in the articular cartilage of mouse knee joints at 8 weeks after DMM. However, no evidence indicates that zinc-ZIP8-MTF1 axis and the TGF-β1-HTRA1-DDR2 pathway are involved in the inhibition expression of Mmp-13 by HF or HFol with the exception of one remaining question, whether or not HF or HFol inhibits induction of MMP-13 by DDR2.

Objective 3: To elucidate a possible mechanism by which the expression of Mmp-13 was inhibited in chondrocytes by HF/Hfol in vitro

Rationales: By immunohistostaining, no evidence indicates that HF or HFol could inhibit the increased expression of Ddr2 in the joints. We are aware that the immunohistostaining technique that we used may not be sensitive enough to detect a subtle change of Ddr2 expression by HF or HFol treatment. Thus, we decided to carry out in vitro experiments to know whether or not HF or HFol could inhibit the expression of Ddr2, which leads to the down-regulated expression of Mm-13.

***Methods and results*:**
Preparation of type II collagen coated plates: make a type II collagen solution at the concentration of 10μg/ml. Add 1.5 ml of the above solution to each well of a 6-well plate and dry up in hood overnight.
Preparation of HFol: make the stock solution at the concentration of 0.1μM in media. Add 4 or 8 μl of the stock solution to each well containing 2, 000 μl media to make a final concentration of HFol is 200 nM or 400 nM in each well.
Articular chondrocyte culture: Mouse articular chondrocytes of knee joints from 6 days old mice were used in the experiment. Briefly, articular chondrocytes were isolated by digestion with

Collagenase D at a concentration of 3mg/ml overnight. The chondrocytes were then collected and cultured on a cell-culture dish. The cells were harvested at about 90-100% confluence and seeded at a density of 2.5 x 10^5/well on 6-well collagen type II-coated plate with 2 ml of culture media. 20 µg of collagen type II was added to the culture media in each well. The cells were treated with or without HFol inhibitor for 18 hr.

Real time-PCR analysis: Total RNAs were isolated for cDNA synthesis. The cDNA was synthesized with oligo(dT). Real-time PCR conditions were optimized for maximal PCR efficiency by the adjustment of concentrations of PCR primers for Ddr2, forward 5'-CTGTCGGATGAGCAGGTTAT-3' and reverse 5'- CTCGGCTCCTTGCTGAAGAA-3' and for Mmp-13, forward 5'-GTGTGGAGTTATGATGATGT-3' and reverse 5-TGCGATTACTCCAGATACTG-3' and for Gapdh 5'-ACTGAGGACCAGGTTGTC-3' and reverse 5'-TGCTGTAGCCGTATTCATTG-3'. Real-time PCR was performed using the StepOnePlus, Applied Biosystems. PCR reaction was carried out at 95°C for 3 minutes followed by 50 cycles of 95°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds, with a final extension at 72°C for 4 min. At the end of the PCR cycles, a melting curve, using a temperature range between 550C to 950C with +0.5°C intervals, was generated to test the specificity of the PCR product. A cDNA sample in the experiment was tested in triplicate.

This experiment was performed twice independently.

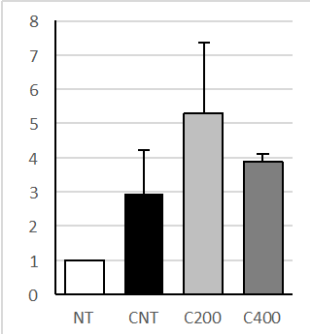


Figure 12. The level of *Ddr2* mRNAs in mouse chondrocytes. As shown in figure 12, the level of *Ddr2* mRNA was increased in HFol treatment, which indicates that HFol cannot inhibit up-regulation expression of Ddr2 in chondrocytes cultured on type II collagen-coated plates by HFol treatment, at both 200 nM and 400 nM. NT: non type II collagen-coated well and no HFol treatment, CNT: type II collagen-coated well and no HFol treatment, C200: type II collagen-coated well with HFol at 200 nM and C400: type II collagen-coated well with HFol at 400 nM.

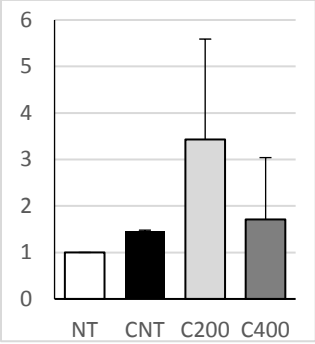


Figure 13. The level of *Mmp-13* mRNAs in mouse chondrocytes. As shown in figure 13, the level of *Mmp-13* mRNA was also increased in HFol treatment, which indicates that HFol

cannot inhibit up-regulation expression of Mmp-13 in chondrocytes on type II collagen-coated plates by HFol treatment, at both 200 nM and 400 nM.

Conclusion: Results from this experiment are consistent with our previous observation that the level of DDR2 mRNA is increased in chondrocytes cultured on type II collagen-coated plates. This, in turn, induces MMP-13 in chondrocytes. However, HFol does not inhibit the increase in the levels of Ddr2 and Mmp-13 mRNAs in chondrocytes cultured on type II collagen-coated plates. This suggests that DDR2 may not be responsible for the down-regulation expression of MMP-13 in the articular cartilage of mouse knee joints at 8 weeks following DMM surgery by HFol treatment, which we observed in our previous histologic examination.

We also worked with Dr. Whitman, the partner in this project, to establish molecular assays for early outcome testing of HF efficacy in PTOA

We performed DMM on the medial condyle of the right knee join of mice at the age of 10 weeks old. We started to administer HFol (10 μg/10g body weight) subcutaneously four days after the surgery. We treated the mice with either vehicle (PBS) or HFol every other day. The mice were then sacrificed at 2 or 4 weeks after DMM surgery. There are ten mice in each experimental group, four groups at each time point. There were eighty mice in total.

	Sham		DMM	
post surgery	NT	HFol	NT	HFol
2 weeks	10	10	10	10
4 weeks	10	10	10	10

Two days after the last injection, knee joints of the mice were harvested and processed in RNALater solution. Articular cartilages were sliced off from the medial condyles of tibia and femur. The cartilage was stored in RNALater at -80^{o}C. In order to get enough RNA from the articular cartilage, we pooled the cartilage from two mice, so there were five sets of tissues in each group. For RNA isolation, the cartilage was homogenized in Trizol with a motor-driven plastic pestle. Total RNAs were then isolated by using RNeasy Micro Kit (Qiagen). Gene-expression profile will be analyzed by real time-PCR.

Training and professional development:

Fan Jie was a visiting PhD student from West China University of Chengdu, China. She worked on this project since the beginning. She carried out the experiments and joined the discussion and interpretation of the results. During the training, she learned how to design and perform experiments to test a hypothesis. She also learned how to interpret results from experiments. She finished her training in May, 2017.

In February, 2017, A post-doctoral fellow, Dr. Chenlu Liu, joined our group. She continued working on this project. Dr. Liu learned how to design and perform experiments and how to interpret results from experiments. She finished her training in May, 2018.

In October, 2018, a visiting scholar, Dr. Beiyu Wang, joined our group. Dr. Wang is a spine surgeon from Hospital of West China University Medical School. He performed the experiments, participation of discussion and interpretation of the results.

Dissemination of results to communities of interest?

Results to date were presented at the CDMRP IPR meeting at Ft. Detrick in May 2017 to scientific and military participants associated with the CDMRP program.

IMPACT:

We found that HF/Hfol have chondro-protective effects on articular cartilage of knee joints in an injurious mouse model of OA. Our finding that HFol has a >4-fold improvement in therapeutic index over HF establishes Hfol as a new lead compound for the study of EPRS inhibitors as therapeutics in PTOA. Our data regarding the mechanism of action of HF/HFol on cytokine responses in synoviocytes establishes a new class of potential drug targets for future mechanism based therapeutics for PTOA. The manuscript reporting these findings is in final stages of preparation for submission.

CHANGES/PROBLEMS.

The large number of surgeries and associated animal care for the second phase of in vivo studies have taken significantly longer than originally planned and have delayed achievement of milestones as originally planned. Difficulties in obtaining suitable HFol for these studies has also introduced a major delay (a Chinese CRO spent 6 months failing to produce usable material). Suitable HFol has subsequently been obtained, and all surgeries and treatments have now been completed, and will be analyzed as part of the requested no-cost extension for this project. We have also encountered technical problems with the study of chondrocytes ex vivo. These cells appear to be quite vulnerable to stresses that change their behavior in culture, making them poorly reproducible tools for studying mechanism of HF/Hfol action. While we had hoped that freshly isolated chondrons would solve this problem, variability inherent to fresh surgical isolates has also made these problematic. For these reasons we have continued to focus on synoviocytes as the primary joint tissue for study ex vivo. Since a growing body of data point to synoviocytes as a key source of tissue damaging factors in arthritis, we feel that the study of these cells effectively advances our study of PTOA therapeutics. An additional problem that has not delayed experimental progress but does create a new hurdle for manuscript submission has been the publication of several papers describing the efficacy of HF in OA, proposing a mechanism of HF action based on its effects on TGFß signaling. While these publications confirm our findings that HF is efficacious in models of arthritis, we believe their proposed
model for HF action to be incorrect. The need for us to address this published model in our own publication significantly raises the bar for the data we will need to present regarding HF mechanism in our own publication. We believe that we can generate such data in the remaining no-cost extension period of Dr. Whitman group (The partner in our project), but this has delayed our plans for publication of some of these data. We do have a manuscript that begins to address the issue of HF mechanism of action on cytokine responses in synoviocytes in the final stages of preparation for publication.

PRODUCTS

Data described above reflect work product that are in preparation for publications. From Malcolm

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
The following individuals have participated in the project.

Name: Project Role:	Malcolm Whitman, Ph.D Principal Investigator	**NO CHANGE**
Name: Project Role:	Tracy Keller Co-Investigator	**NO CHANGE**
Name: Project Role:	Yefu Li MD/PhD. Principal Investigator	**NO CHANGE**
Name: Project Role:	Lin Xu, MD/PhD. Co-Investigator	**NO CHANGE**
Name: Project Role	Fan Jie, PhD Research Assistant	**NO CHANGE**
Name: Project Role	Kristen Powers Research Scientist	**NO CHANGE**
Name: Project Role	Yeon Jin Kim, PhD. Postdoctoral scientist	**NO CHANGE**

Name: Edenius Maja, PhD.
Project Role: Postdoctoral scientist
Researcher Identifier: (leave blank):
Nearest person month worked: 10.0
Contribution to Project: Design and execution of experiments on HF effects in vitro, development of Q-PCR assays and execution of transcriptomics.
Funding Support:

Name: Chenlu Liu, DDS/PhD
Project Role: research scientist
Research Identifier: (leave Blank)
Nearest Person-Month Worked: 5
Contribution to Project Assist on surgery, care for mice and HF injections, tissues harvesting and subsequent analysis of tissues.
Finding Support:

Name: Beiyu Wang, MD/PhD
Project Role: research scientist
Research Identifier: (leave Blank)
Nearest Person-Month Worked: 5
Contribution to Project Assist on care for mouse tissues harvesting and subsequent analysis of tissues.
Funding Support:

Changes in Active Support

Whitman (PI) 11/13/2018 – 10/31/2020 0.6 Cal. Mos.
NIH-1R21AI142343-01 $150,000
Title: Novel Nutrient-sensing Pathway Suppresses Pathologic Tissue Remodeling
The major goal of this project is to identify mechanisms by which tRNA synthetase inhibition changes inflammatory responses to cytokines in fibroblasts.
Program Official: David R. Johnson
Email:drjohnson@niaid.nih.gov
Phone: 301-627-3499
Fax: 301-480-1899

LI (PI) 04-15-2018 – 10-31-2019 2.4 Calendar Mos.
DoD W81XWH1810097 $200,000
Title: Evaluation of a Small-Molecule Inhibitor of DDR2 as a Drug in Treatment of Osteoarthritis
The goal is to determine whether or not a small-molecule inhibitor of DDR2 can protect articular cartilage of knee joints from being damaged in an injurious mouse model of OA.
Program Official Abigail Strock
Email: abigail.l.strock.civ@mail.mil
Phone: 301-619-2342
Fax: N/A

Other Organizations
None

Special Reporting Requirements
None

Appendices:
None