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TITLE: An Herbal Derivative as the Basis for a New Approach to Treating Post-Traumatic Osteoarthritis

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<b>14. ABSTRACT</b> 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) Data demonstrating that the EPRS inhibitors HF and its less toxic derivative HFol, are effective as therapeutics for PTOA in mice, using the DMM model; 2) Detailed immunohistochemical data examining the effect of HF/Hfol on effectors of OA 3) A new ex vivo assay using intact joint cartilage to test ex vivo efficacy of EPRS inhibitors as therapeutics for OA.					
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**INTRODUCTION** 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. The progressive period in PTOA provides a target for therapeutic intervention. 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. 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 grant are to: 1) *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), tRNA synthetase inhibitor, chondrocyte, MMP, GCN2, Destabilized Medial Meniscus (DMM) model.

**ACCOMPLISHMENTS** In the second year of the grant, we have completed planned in vivo experiments in the DMM model to test the efficacy of the EPRS inhibitors HF and Hfol, and shown similar efficacy of the two compounds in preventing tissue pathology in this model of PTOA. A second stage in vivo experiment is now in progress to examine the earliest markers of HFol efficacy following meniscal damage. In addition we have developed a new set of tools and assays to examine EPRS inhibitor efficacy in joint tissues ex vivo that will substantially expedite mechanistic characterization and new compound testing. We have therefore continued to make good progress the first two major goals of the project, and are using information gained in the first two years of the grant to initiate studies directed towards the third goal.

**A) Major activities:** i. In vivo analysis and comparison of the efficacy of systemic HF and Hfol in the DMM mouse model of PTOA. ii. Identification of markers of HF/Hfol action on arthritis effectors in synoviocytes and chondrocytes in culture, and characterization of associated molecular mechanisms iii. Initiation of a new DMM Study to examine early effects of HFol on mediators of arthritis. iv. Development of an experimental system for the study of HF effects in intact articular chondrons (chondrocytes in their native cartilaginous environment in the joint).

**B) Specific objectives:** i. to quantify molecular and pathological changes in joints from DMM animals following treatment with systemic EPRS inhibitors, and assess significance of changes. ii: to develop and test HF/HFol responsive markers and effectors of arthritic damage as tools for assessing treatment efficacy in vivo, and to test role of signaling molecules mediating HF/HFol action in articular cells. iii. to test HFol effects on DMM in vivo at early time points (2-4 weeks). iv. to develop and apply ex vivo tools for the study of arthritogenic responses to cytokines and the effects of HF/HFol on these responses.

**C) Significant results:** Objective i (Principal effort, Li Lab) : We have now completed analysis of data from a study of 32 mice (4 treatment groups, 8 mice each) over 16 weeks treatment with HF and the novel EPRS inhibitor HFol in the DMM mode of PTOA. We have generated fixed or frozen joint tissue for analysis of tissue histology and protein expression. Whole animal examination of body weight and bone volume (by micro-CT) indicate that HF causes some decrease in both (undesirable outcomes potentially reflecting toxicity), while HFol treatment showed no body weight or bone volume decreases, consistent with reduced toxicity of HFol relative to HF(detailed in previous progress report). Histological analysis of joints shows that treatment with HF or HFol results in a statistically significant reduction in arthritic damage (**Fig.1**). We have also performed immunohistochemical analysis of joint tissues to assess how HF/HFol treatment modulates different potential regulators or effectors of joint damage.

Detailed description of study:

**Objective:** To determine whether HF and HFOL can prevent/delay the progression of the articular cartilage degeneration induced by destabilization of the medial meniscus (DMM).

**Rationale:** In our previous studies, we found that it takes about 16 weeks for mice to develop a typical OA knee joint after DMM surgery. Therefore, we plan to use 16 weeks after DMM surgery as the end point to characterize mouse knee joints for evidences of articular cartilage degeneration. For analysis, we use OARSI blinded scoring of histological sections to assess overall efficacy, and immunohistochemistry of sections, staining against different potential regulators and effectors of arthritis, to assess critical targets of HF/Hfol action.

**Methods and results:**

Experiment 1. Histological analysis of joints from DMM mice treated 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, with 8 mice in each group. Specific methods for treatment and histological evaluation, and evaluation of body weight changes, were included in previous progress report and are not repeated here.  $\mu$ CT analysis was also reported previously and is not described here.

We have now completed full histological analysis of joints from animals, with blinded OARSI scoring. Data are summarized in **Fig.1**. HF and HFol each substantially reduce joint damage with every other day dosing. Hfol treatment was at 5X the dose of HF, and as we have found that HFol is ~20 fold less toxic than HF (MTD study performed at Charles River Laboratories), HFol represents at least a 4 fold improvement in therapeutic index relative to HF.

Experiment 2. Immunohistochemical analysis of joints from DMM mice treated with HF or HFOL. (Principal effort, Li Lab) Our prior work has identified a variety of candidate regulators of arthritic joint damage that are down regulated by HF/HFol. These include: MMP13, a major matrix degrading protease known to be essential for arthritic joint damage in mice; SLC39A8 (ZIP8), a zinc transporter shown to be up-regulated and associated with joint damage in the DMM model, possibly acting upstream of MMP13; TGF $\beta$ , a cytokine that controls tissue remodeling; HTRA1, a protease implicated in joint damage; DDR2, a collagen receptor responsible for activation of HTRA1. In earlier work for this project we have found that MMP13 and ZIP8 are strongly down regulated by HF/HFol, we have not seen regulation of TGF $\beta$ 1, DDR2, or HTRA1 in ex vivo models.

Detailed Description:

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. A prior study had proposed that ZIP8 might act as an upstream regulator of MMP13 in osteoarthritis. Data from several independent research groups has shown that the TGF- $\beta$ 1-HTRA1-DDR2 forms a molecular pathway that can induce the expression of MMP13 in chondrocytes. We therefore examined these various markers to assess their possible significance with respect to the action of HF/Hfol on arthritis. We performed immunohistostaining to examine the expressions of genes, including matrix metalloproteinase 13 (MMP13) (**Fig.2**), ZIP8 (**Fig.3**), transforming growth factor beta 1 (TGF- $\beta$ 1) (**Fig.4**, high temperature requirement A1 (HTRA1) (**Fig.5**) and discoidin domain receptor 2 (DDR2) (**Fig.6**) 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.

Conclusions: HF or HFol inhibits the up-regulation expression of Mmp-13 in the articular cartilage of mouse knee joints at 8 weeks after DMM, consistent with ex vivo results. These data strongly indicate that MMP13 is a major target for HF/HFol in PTOA. Surprisingly, however, ZIP8 appears to be

unaffected by HF/HFol in DMM articular cartilage, despite potent regulation in ex vivo assays. These data indicate that ZIP8 is not a target for HF/HFol upstream of MMP13 in vivo. We also find no evidence that the TGF- $\beta$ 1-HTRA1-DDR2 axis is involved in the inhibition of expression of joint damage or Mmp13 expression by HF or HFol.

Objective ii: Identification of key markers, effectors, and signaling mechanisms that mediate HF/Hfol action on arthritis (Principal effort, Whitman Lab). We have previously done transcriptomics to identify arthritis regulators downstream of HF in synovial fibroblasts. We have now validated key findings from these transcriptomic studies by Q-RT-PCR in both synoviocytes and chondrocytes. We have also performed a secondary transcriptomic study in synovial cells lacking cell signaling components thought to mediate the action of HF/Hfol. In addition to finding key arthritic regulators inhibited by HF (e.g. MMPs, SAA1/2, IL33, C5), we have found markers of HF action that should prove useful as in vivo biomarkers of tissue penetration by HF, Hfol, or other novel EPRS inhibitors. Identifying such markers is essential to allow us to assess new drugs or drug delivery systems in joints in vivo. We have found two markers, the lysosomal protein LAMP3 and inflammatory regulator IL1RL, which are up-regulated by >100 fold by HF in multiple cell types. We plan to use these markers to inform our studies of new drug/drug delivery efficacy.

Objective iii. (Li and Whitman labs). To examine HFol effects on early effectors of joint damage in the PTOA model. A study to examine HFol effects at 2 weeks and 4 weeks is now underway. Methods will be as described for DMM trial, with 10 animals in each experimental group (and 1mg/kg Hfol as only test treatment, due to its superiority to HF). Joints will be harvested at 2 and 4 weeks and analyzed for gene expression of a broad range of arthritic markers derived from data generated in the previous year. We have also done pilot experiments to analyze protein content in synovial fluid of treated or untreated DMM (or sham operated) joints, and will examine synovial fluid in parallel with articular cartilage gene expression.

Objective iv. (Principal effort, Whitman Lab) Improved ex vivo assays for HF/Hfol function. In the last grant period we established primary chondrocyte culture conditions to test HF effects on arthritogenic gene expression in chondrocytes. While successful, this system has substantial limitations in that chondrocytes in 2D culture rapidly lose many properties characteristic of chondrocytes in vivo. We have now shown that intact chondrons (chondrocytes in native cartilage environment) can be rapidly isolated from mouse femoral heads and show both potent cytokine induction of MMP13 mRNA and secreted, and potent inhibition of this induction by HF/HFol (**Fig.7, 8**). Consistent with our findings in the in vivo study, HFol did not, however, significantly inhibit induction of ZIP8 in intact joint tissue, despite the inhibition previously seen in cultured cells (**Fig.9**). We plan to exploit this system to develop a rapid assay for new drug function that it is more physiologically relevant to the in vivo situation than 2D cell culture.

#### **Training and professional development:**

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

In the last year, a PhD student, Fan Jie, from West China University of Chengdu worked on this project. She carried out the experiments and joined the discussion and interpretation of the results. She finished her PhD training in the last May. She currently is a faculty at Dental School of West China. A post-doctoral fellow, Dr. Chenlu Liu, continues working on this project. Dr. Liu will learn how to design and perform experiments and how to interpret results from experiments.

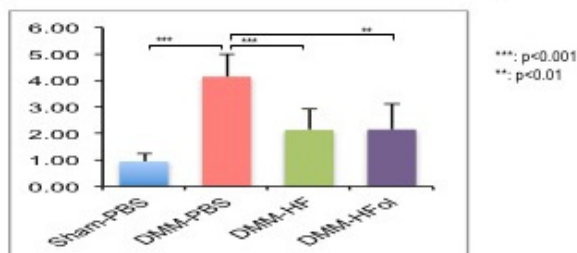
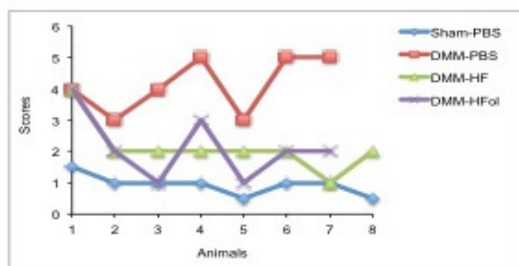
**Dissemination of results to communities of interest?** Results to date were presented at the CDMRP IPR meeting at Ft. Detrick in May 2017 to scientific and military participants associated with the CDMRP program.

Plans for the next reporting period to accomplish the goals: We will complete our early marker study and analyze the data to identify early steps modified by HFol. We will continue ex vivo analyses to identify key regulatory pathways and arthritogenic effectors modified by HFol. We will initiate studies of short term (4-12 hour) Hfol efficacy in activation of relevant signaling pathways in joint tissue to allow

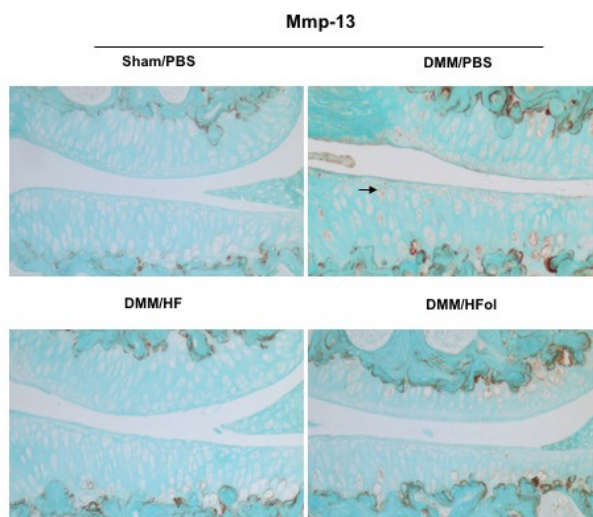
us to study alternate drug delivery methods (e.g. local delivery). We are preparing manuscript on HF/HFol efficacy in DMM during the next reporting period, as well as finalizing a manuscript on HF effects on tissue remodeling in synoviocytes and chondrocytes ex vivo.

**IMPACT:** 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 development of a chondron based ex vivo test system will substantially facilitate the assessment of future test compounds.

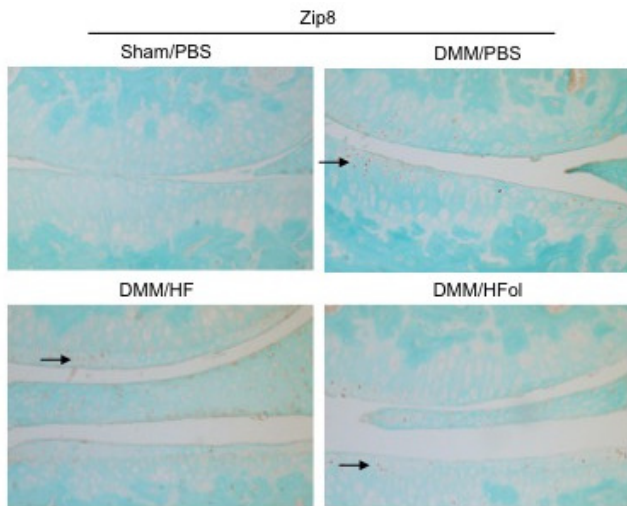
**CHANGES/PROBLEMS.** Because we found HFol to have an at least 4 fold improved therapeutic window relative to HF, it is the most promising lead compound for future work on PTOA treatment. We are therefore now using Hfol for current work. We plan to continue to explore new compounds as well. The difficulties in identifying cytokine responsive cultured chondrocyte populations originally delayed progress in the SOW timeline regarding the identification of novel transcriptional markers of EPRS inhibitor action in vitro. We believe that the isolation and use of chondrocytes from femoral cap cartilage will solve this problem. These issues do not entail any major revision to the long term goals of the project.



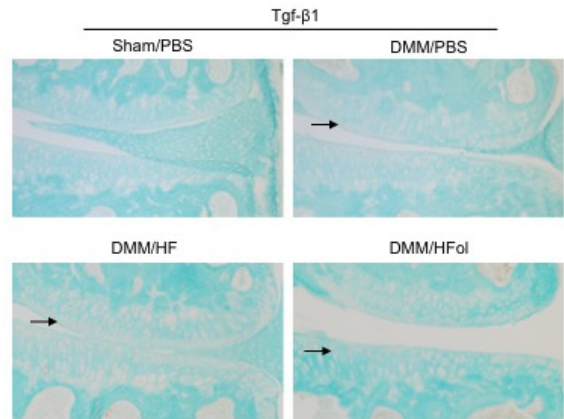
**Fig. 1. Hfol inhibits osteoarthritis in mice similarly to HF.** Osteoarthritis (OA) was induced by medial meniscus damage (DMM model). Two weeks after surgery, mice were treated with 0.2 mg/kg HF or 1 mg/Kg Hfol SC every other day. At 16 weeks post surgery, operated knees were scored for cartilage damage by an experienced investigator blinded to sample identity according to the OARSI scale (1-5).



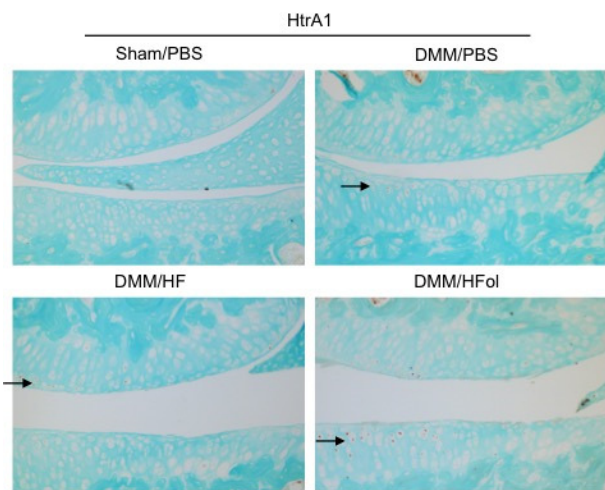
**Figure 2.** The expression of Mmp-13 in mouse knee articular cartilages. A rabbit polyclonal was used in this experiment. The expression of Mmp-13 was increased in the DMM/PBS group (see the arrow in figure 7). There were no positive staining cells detected in other groups. This suggests that HF or HFol inhibits the induction of Mmp-13 in the articular cartilage of mouse knee joints induced by DMM.



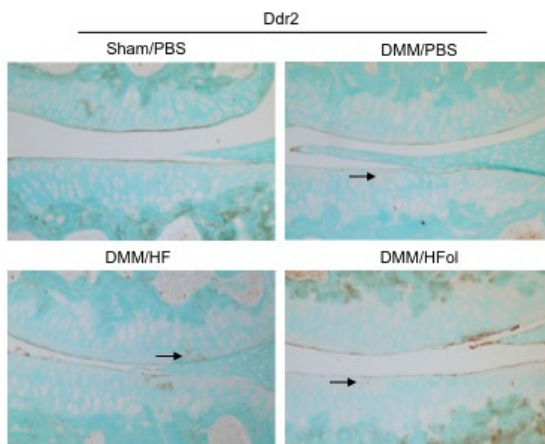
**Figure 3.** The expression of Zip 8 in mouse knee articular cartilages. A rabbit polyclonal antibody against Zip 8 was used. The expression of Zip8 was increased in DMM/PBS group (see brown-color staining cells in figure 8). The expression of Zip8 was also detected in DMM/HF and DMM/HFol groups.



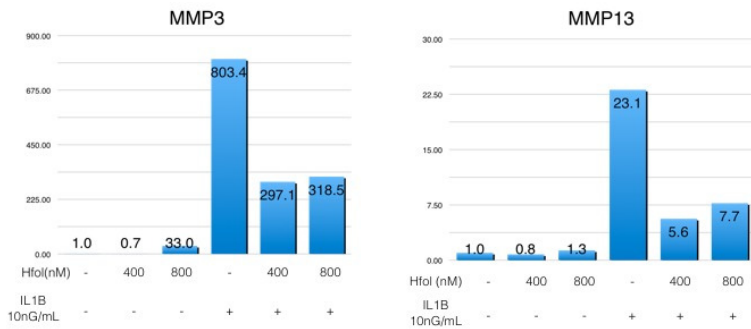
**Figure 4.** The expression of TGF-β1 in mouse knee articular cartilages. A rabbit polyclonal antibody against Tgf-β1 was used. The expression of Tgf-β1 was increased in DMM/PBS group (see brown-color staining cells in figure 9). The expression of Tgf-β1 was also detected in DMM/HF and DMM/HFol groups.



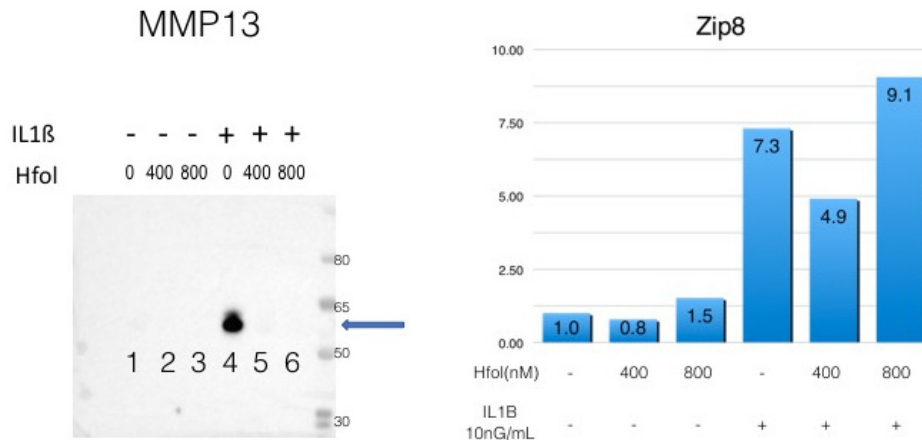
**Figure 5.** The expression of HtrA1 in mouse knee articular cartilages. A rabbit polyclonal antibody against HtrA1 was used. We found the similar expression of patterns of HtrA1 to what was observed in the expression pattern of Tgf-β1 group, see figure 4).



**Figure 6.** The expression of Ddr2 in mouse knee articular cartilages. A rabbit polyclonal antibody against Ddr2 was used. 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 4 and 5).



**Fig. 7. Hfol Inhibits Cytokine Induced MMP expression in Isolated femoral cap articular cartilage.** Fresh femoral cap joints (the femoral side of the hip joint) were surgically excised from 8 week old mice and culture for 24 hours, then treated overnight with Hfol, then for 48 hours and harvested for Q-RT-PCR analysis of gene expression



**Fig. 8. Hfol Inhibits Cytokine Induced MMP13 secretion from isolated femoral cap articular cartilage.** Femoral caps were isolated as in Fig.7 above, and conditioned medium isolated and analyzed for MMP13 by Western blot.

**Fig. 9. Hfol Does not inhibit Cytokine Induced MMP expression in Isolated femoral cap articular cartilage.** Femoral caps were analyzed as in Fig. 6.

**PRODUCTS.** Data described above reflect work product that are in preparation for publications

**PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

Name: Malcolm Whitman	
Project Role: Principal Investigator	
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked: 5	
Contribution to Project: develop overall project plan, obtain test compounds, establish experimental plan in consultation with other project members, review and analyze data in consultation with other project members.	
Funding Support: DoD, NIH, ABLIS, HSDM	

Name: Tracy Keller	
Project Role: Co-Investigator	
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked: 3	
Contribution to Project: plan and direct ex vivo experiments on chondrocytes and synoviocytes	
Funding Support: DoD, NIH, ABL	

Name: Yefu Li	
Project Role: Principal Investigator	
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked: 5	
Contribution to Project: DMM surgery and oversight of mice, participation in analysis of mice	
Funding Support: DoD, Servier, HSDM	

Name: Lin Xu	
Project Role: Co-Investigator	
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked: 7	
Contribution to Project: DMM surgery and oversight of mice, participation in analysis of mice	
Funding Support: DoD, Servier,	

Name: Fan Jie, PhD	
Project Role: Research Scientist	
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked: 12	
Contribution to Project: Assist on surgery, care for mice and HF injections, tissues harvesting and subsequent analysis of tissues.	
Funding Support: DoD	

Name: Kristen Powers	
Project Role: Research Assistant	
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked: 5.0	
Contribution to Project: execution of in vitro assays, harvest of primary cells	
Funding Support: DoD, NIH, ABL	

Name: Yeon Jin Kim, PhD.	
Project Role: Postdoctoral scientist	

Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 6.0
Contribution to Project: Design and execution of experiments on HF effects in vitro, development of Q-PCR assays and execution of transcriptomics.
Funding Support: DoD, NIH

### Changes in Active Support

Whitman (PI) 09/17/2015 – 08/31/2019 1.2 Cal. Mos.

NIH-NIAMS R01GM115417-01 \$228,650

Title: The first secreted Tyrosine kinase

The major goals of this project are to investigate the regulation of VLK, the first secreted Tyrosine kinase, within the secretory pathway, identify secreted targets for VLK phosphorylation in cells that express VLK endogenously, and begin to establish how VLK phosphorylation modifies the function of specific secreted or secretory pathway resident proteins.

Program Official: Bernadette Tyree

Email: [tyreeb@mail.nih.gov](mailto:tyreeb@mail.nih.gov)

Phone: 301-594-5032

Fax: 301-480-4543

Whitman (PI) 04-01-2015 – 03-31-2020 3.0 Calendar Mos.

NIH/NIAMS R01 AR066717 \$411,700

Title: Role of the first secreted tyrosine kinase in bone development, homeostasis, and repair

The major goal of this project is to investigate an identified new mechanism for the regulation of proteins that control bone and cartilage matrix homeostasis, with substantial implications for new therapeutic approaches to skeletal disease.

Program Official: Bernadette Tyree

Email: [tyreeb@mail.nih.gov](mailto:tyreeb@mail.nih.gov)

Phone: 301-594-5032

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### Other Organizations

None

### Special Reporting Requirements

This is a collaborative award to Dr. Whitman and Dr. Li, reports are filed for both Whitman and Li

### Appendices:

If applicable, PDF files for published manuscripts.

None