AWARD NUMBER: W81XWH-15-1-0371

TITLE: “Elucidating the Role of Joint Disuse in the Development of Osteoarthritis following Return to High-Impact Loading

PRINCIPAL INVESTIGATOR: Douglas J. Adams, PhD

CONTRACTING ORGANIZATION: University of Connecticut
Farmington, CT 06032-5335

REPORT DATE: April 2017

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
4/29/2017 April 2017	Annual	30Sep2016-29Mar2017 ~~30 Oct 2016 - 29 Apr 2017~~

4. TITLE AND SUBTITLE

Elucidating the Role of Joint Disuse in the Development of Osteoarthritis Following Return to High-Impact Loading

5a. CONTRACT NUMBER	5b. GRANT NUMBER	5c. PROGRAM ELEMENT NUMBER
W81XWH-15-1-0371	PR141985	

6. AUTHOR(S)

Douglas J. Adams, PhD David W. Rowe, MD;
thomas M. Deberardino, MD, Colonel (Retired)

E-Mail: dadams@uchc.edu

5d. PROJECT NUMBER	5e. TASK NUMBER	5f. WORK UNIT NUMBER

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

University of Connecticut
263 Farmington Ave
Farmington, CT 06032-5335

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

The studies completed within the last six months added the experimental components of joint loadings imparted through direct external impact or joint instability via ACL transection (which also causes increased shear loading on articular surfaces). Recent experiments using animals at the proposed 20 week old age point revealed a lack of response to joint unloading of the articular cartilage tidemark (interface of uncalcified and calcified cartilage). Joint unloading via hindlimb suspension is known to "activate" the tidemark within articular cartilage as well as ligament entheses, a proposed hallmark of disuse in this study. With this lack of response evident in our joint disuse model for 2 weeks of joint unloading for slightly older, but young adult, animals, it will be important to distinguish this apparent age-related facet of cartilage response to joint unloading. Thereafter, the unloading-impact loading model will be exercised through the proposed variations in recovery time versus return to vigorous activities imparting joint impact loads. The results of our remaining studies may provide clinically relevant information toward establishing reasonable bounds on time to return to activities following periods of joint disuse. This may be particularly informative to individuals with occupations that require higher mechanical demands on joints.

15. SUBJECT TERMS
Osteoarthritis, cartilage, knee, joint, tidemark, impact, ACL

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
U	U	U	UU	16	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

1. INTRODUCTION (same as October 2016 report)

Joint immobilization and disuse, whether associated with treatment of joint injury or associated with bed rest, is known to be detrimental to joint health. Experimental studies using animal models of joint immobilization or reduced weight-bearing have shown that joint unloading for two weeks leads to degradation of the cartilage tissue. These relatively short periods of joint unloading may predispose some patients to developing long term arthritic problems if they return too quickly to activities that impart high forces to the joint in association with occupational demands, participation in high intensity athletic activities, or in the case of military personnel, the return to intense joint use associated with active duty. In fact, over 100,000 incidences of osteoarthritis (OA) were described in the Defense Medical Surveillance System from 1999-2008, and OA remains a leading cause of disability and medical discharge among service personnel (Cameron et al., 2011). While there are multiple causes of OA, **the goal of this study is to assess the contribution of return to high intensity activity after a period of joint disuse on the development of joint degeneration.** This study follows the responses of cells residing within knee joint articular cartilage, neighboring bone, and ligament tissues after a period of joint unloading followed by either normal ambulation or impact forces applied through the joint. Although unloading alone, or the impact force regimen alone, are not expected to initiate degradative cellular responses that would definitively be associated with long-term joint deterioration, **we hypothesize that following a period of disuse which is associated with a degree of recoverable degeneration of joint tissue, a premature return to high impact joint loading will elicit chronic degeneration. This project** capitalizes on mouse models of joint disuse and loading. Aim 1 examines the response to impact loading after disuse, as applied either in compression (Part A) or via a combination of compressive and shearing loads (Part B). Aim 2 examines the response to abnormal joint loading after disuse, as occurs following a destabilizing injury such as anterior cruciate ligament rupture.

2. KEYWORDS

Osteoarthritis, post-traumatic osteoarthritis, PTOA, cartilage, knee, joint degeneration

3. ACCOMPLISHMENTS

►What were the major goals of the project?

The major goals stated in the approved SOW are listed below with initially proposed target dates for completion and updated estimates for completion.

Major Goal	Timeline Proposed	Status/Estimated Completion
Animal use approvals	Months 1-3	Completed
Trouble shooting of histological staining and imaging	Not stated	Completed
Breeding and Growing mice necessary for Aims 1 and 2	Not stated	Completed, sufficient numbers of GFP reporter mice are available as needed
Specific Aim 1: Loading in Compression, Loading in Shear – Experiments studying temporal response to disuse followed by period of recovery and/or joint loading	Months 4-13	Preliminary study completed January-May, 2016, and refinements in experimental animal procedures completed May-September 2016. Aim 1 studies initiated September 2016. Twenty animals have completed all procedures and were euthanized since the last reporting period of October 2016, partially filling all seven experimental groups of Aim 1. Histological examination has been completed for 14 of these 20 animals.
Specific Aim 2: "ACL Transection	Months 10-16	Aim 2 studies began December 2016. Fifteen

Loading" – Experiments studying the temporal response to disuse and joint instability loading		animals have completed all procedures and were euthanized since the last reporting period of October 2016, partially filling the three experimental groups. Histological examination is in progress. Specimens have been cut and will be imaged in May 2017.
Publications & Project Wrap-Up	Months 12-18	March, 2018 onward. A publication may be warranted to report on an apparent age-related response of articular cartilage tidemark advancement to hindlimb suspension in young adult mice.

►What was accomplished under these goals?

Our October 2016 annual report noted achievements in breeding and growing dual fluorescent reporter mice, as well as completion of a pilot animal study conducted outside of the animal numbers approved for this study to refine cryohistological methods specific to this project and overcome longstanding problems investigators incur with hindlimb tail suspension experiments.

Since October 2016 we have applied these refined methods to in vivo experiments involving 20 animals, partially filling all ten experimental groups within Aim 1 (7 experimental groups) and Aim 2 (3 experimental groups). The experiments conducted in Aim 1 now indicate a likely age-related response in "activation" of the articular cartilage tidemark. Our pilot studies were conducted on mice at initial ages of 15-17 weeks, whereas this study was specified to initiate animal procedures at 20 weeks of age to better correspond to young human adults. To date, we are finding little to no indication of tidemark activation with hindlimb suspension unloading at this age point, and no indication that the chosen magnitude and duration of joint loading is causing joint degradation. The tidemark is the name given to the clearly apparent boundary between the uncalcified cartilage and deeper calcified cartilage, which serves to modulate growth and transition from relatively softer articulating cartilage and underlying subchondral bone.

We anticipated from prior work that joint loading would not cause degradation by itself, and hypothesized that in addition to the mild degradation caused by disuse the joint loading could "tip" the physiological response of some joints beyond a capability to repair. Our recent results suggest a diminished response of the mineralizing tidemark to "activate" in more mature mice when subjected to disuse. If true, this outcome represents a potentially favorable clinical message; however, it is generally contradictory to the published literature which demonstrated tidemark advancement in "adult" rats (O'Connnor, 1997, reference below). Our findings are also contradictory to the anticipated outcome of the proposed study, warranting tighter consideration of the age-related response of the articular cartilage tidemark to joint unloading. We anticipate that by utilizing younger mice, as was the case in the O'Connor study (14 week old rats), and/or increasing the time animal joints are subjected to disuse via tail suspension, we will reproduce the reported degree of activation and advancement of the articular cartilage tidemark. We have approached our animal experiments conservatively, given the unexplored nature of potentially variable temporal interplay between disuse and subsequent exacerbated use. We have thus far assigned just one male and female mouse to most experimental groups so that outcomes could be examined and adjustments can be made within the study. As a result, we maintained much of the remaining funds and are continuing the study for an additional year under a no-cost extension approved by the USAMRMC. Further details and plans are provided in section 5 Changes/Problems.

O'Connor KM: Unweighting Accelerates Tidemark Advancement in Articular Cartilage at the Knee Joint of Rats, J Bone Min Res, 12(4):580-589, 1997.

Figure 1 demonstrates this lack of tidemark response in Aim 1 using our cryohistological methods, whereby image layers containing multiple fluorescent markers or colorimetric stains are aligned to ascertain concomitant cellular responses to the mechanical perturbations imparted in these protocols.

Hindlimb Unloading (HLU) via Tail Suspension for 2 Weeks – both knee joints unloaded

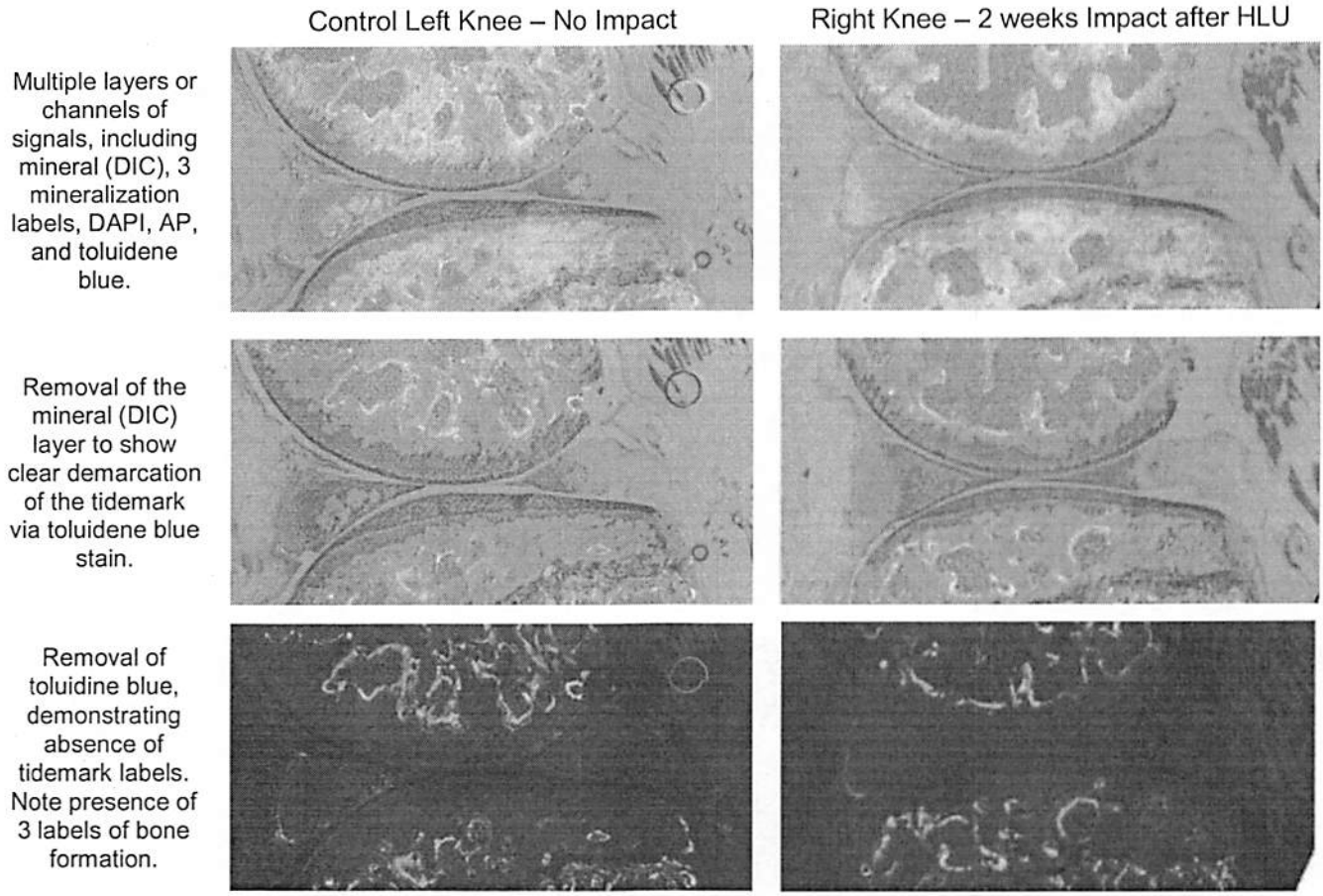

Figure 1: 6 µm thick cryohistological sagittal section through the medial condyles of the left and right knee joints of a mouse (Aim 1, Group 4) after two weeks of hindlimb unloading followed by two weeks of compression loading (10x body weight) applied to the right knee, and then two weeks of normal ambulation. This histological outcome was observed for all experimental groups 1-7, whereby the same two week hindlimb unloading protocol was employed prior to various temporal sequences of joint loading and ambulation. The three mineralization labels were administered at 0, 2, and 6 weeks following initiation of joint unloading [Alizarin complexone (red), Demeclocycline (yellow), and Calcein (green), respectively]. Although the mineralization labels clearly identify bone formation, the articular cartilage tidemark is not labeled. Cell nuclei were stained with fluorescent 4',6-diamidino-2-phenylindole (DAPI) and are shown in blue, bone is captured via differential interference contrast (DIC), bone forming cells and hypertrophic chondrocytes are stained with alkaline phosphatase (AP), and cartilage and marrow are stained with toluidine blue (uncalcified cartilage appears blue, calcified cartilage appears violet).

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

All personnel involved in this project have learned together how to manage the additional difficulties associated with cutting cryohistological sections of whole murine joints. Cutting is difficult to control and perfect in this study because the hardness of the various tissue components (soft cartilage, bone, partially mineralizing menisci, ligament, and embedding media) tends to cause artifact in tissue sections.

As reported previously, Dr. David Rowe continues to assist Dr. Adams to become more proficient in processing and interpreting the digital multiple-signal fluorescence images produced by the cryohistological techniques. The new experiments conducted since October 2016 added GFP reporters for articular chondrocytes to distinguish prehypertrophic and hypertrophic levels of chondrocyte differentiation.

As reported previously, Dr. Douglas Adams trained Liping Wang in the special animal-related procedures required for hindlimb/joint unloading rodents via tail suspension. Liping Wang has now learned to perform the ACL transection studies, and together with Dr. Adams has trained two core laboratory technicians.

Dr. Adams has shared his capabilities in setting up computer controlled loading protocols of murine lower limbs with other investigators at UConn Health who are now conducting pilot studies related to bone and joint loading protocols using this instrumentation.

►How were the results disseminated to communities of interest?

No manuscripts have yet been submitted for publication. Internal to UConn Health, many of the methods developed and refined for use in this study have been demonstrated to other investigators. The details of these refinements will be included in our publications.

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

We will complete both Aims and all experimental animal groups within each Aim. Prior to conducting the experiments involving joint loading and joint instability, we will seek to reproduce previously published observations demonstrating a clear and measurable tidemark activation and advancement following 2-4 weeks of hindlimb unloading by tail suspension (see O'Connor, 1997). Given the temporal nature of our hypothesis that a period of disuse may predispose joint cartilage to heightened risk of degradation when subsequently exposed to high joint loads, we have taken a conservative approach to pursuing the study aims rather than filling out all groups quickly. We want to understand this potential risk factor and its potential for temporal modulation.

We will continue to breed and grow dual-GFP reporter mice (Col2A1 × ColX) to complete the goals of this project. If an alternative reporter is indicated as potentially beneficial to the study, we will seek approval from the DoD prior to its use. For instance, our laboratories now study lubricin (*Prg4*) reporter mice. Since lubricin is abundant in the superficial tangential zone of articular cartilage, it could be a fruitful alternative to Col2A1 as an indicator of articular cartilage responses to mechanical perturbation.

4. IMPACT

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

As reported in October 2016, our previous findings that a relatively short period (2-3 weeks) of joint unloading alone (without reloading) can cause activation of the mineralizing tidemark and hypertrophic properties of chondrocytes within articular cartilage and entheses of the murine knee joint is, by itself, indicative that joint disuse initiates/activates a change in joint physiology that warrants a temporal study of its resolution to homeostatic baseline. Our recent findings that animals approximately one month older do not show this response is very important, as it suggests a definitive effect of joint maturation on the activation of the articular cartilage tidemark from a relatively quiescent status. It will be important to answer this question regarding age-related response of the tidemark. Thereafter, we can proceed to examine how long it takes to return to baseline, and what the effects of mild joint loading via ambulation versus more aggressive joint loading will be when imposed during the immediate post-disuse recovery period.

►What was the impact on other disciplines?

As stated in our October 2016 report, the cryohistological techniques which were improved and refined for this project, and the acute cellular response within articular cartilage and intra-articular ligament entheses, have provided a model system to our molecular biology colleagues for studying the role of individual molecules (genes) that are relevant to bone and joint tissue homeostasis. We are observing changes that are universally missed with traditional paraffin/decalcified histology. Some aspects of this approach are presented in our publication utilizing ACL transection to destabilize the murine knee, published just prior to award of this study:

Dyment NA, Hagiwara Y, Jiang X, Huang J, Adams DJ, Rowe DW: Response of knee fibrocartilage to joint destabilization. Osteoarthritis Cartilage, 23(6):996-1006, 2015. PMID 25680653

►What was the impact on technology transfer?

As stated in our October 2016 report, the combination of cryohistological methods, multiple-reporter mice, "all-in-one" histological slide examination, and joint unloading is an extension to joint tissues of the vast information and scientific rigor obtained using our cryohistology that we have demonstrated for bone histomorphometry. These methods are outlined in detail at our bone research website bonebase.org and within our recent video format publication (Dyment et al., J Vis Exp, (115), e54468, doi:10.3791/54468, 2016).

►What was the impact on society beyond science and technology?

Our most recent data suggests that post-natal growth and maturation of joint tissues may reach a relatively quiescent stage in terms of tidemark activity somewhat earlier in age and more abruptly than anticipated, meaning that potentially damaging events may interact with biological maturation of joint tissues. This notion is reminiscent of, or analogous to, other transient conditions that occur at younger ages, such as Legg-Calve-Perthes disease of the hip in children, which although rare and temporary is anecdotally observed to correspond to individuals who are athletically active.

As stated in our original grant application, we believe that the final scientific results of this study may provide reasonable clinical bounds on return to activities requiring various mechanical demands on the joints of patients following periods of joint disuse (such as required by sickness, injury, surgery, etc.). Analogous to current standard of care for traumatic brain injury (concussion), specific recommendations toward a more cautious return to work, sport, and active military duty than is currently prescribed may be supported.

5. CHANGES/PROBLEMS

►Changes in approach and reasons for change

Since our October, 2016 report we have identified a potential need to utilize animals at a younger age than proposed originally. We have not been observing the noted activation and advance of the articular cartilage tidemark that has been demonstrated previously in younger animals. Thus, since that activation is a proposed identifying feature of joint disuse, we will test the response of the mineralizing tidemark in articular cartilage (the boundary between uncalcified and calcified cartilage) in younger animals.

►Actual or anticipated problems or delays and actions or plans to resolve them

We prefer that the period of joint disuse achieved via tail suspension to unload the hindlimbs should result in an identifiable histological labeling of the mineralizing articular cartilage tidemark, thus allowing us to quantify its "advance" via standard histological measurement of mineral apposition rate (MAR) between timed labels. This feature, associated with hindlimb unloading disuse, is desired in addition to any other measured or assumed degradation to cartilage and other joint tissues, as it indicates a stark and reliable quantitative measure provided by our histological methods. Since we did not achieve this mineralization label indicating an activated tidemark in our recently studied animals (20 weeks old), which were older than those used in the seminal study of "adult" 14 week old rats (O'Connor, 1997), we will conduct a brief study using younger animals, toward replacement with a younger age point in this study. Likewise, we will examine the effect of increasing the period of disuse to 3-4 weeks duration, a potential pitfall that was discussed in the original grant application. Although the study published by O'Connor subjected animals to 4 weeks of hindlimb unloading, distinct tidemark labels were observed at 2 weeks (Figure 4A in O'Connor, 1997). Any resulting changes will be submitted for approval by the UConn Health IACUC as well as animal protocol review by the USAMRMC.

►Changes that had a significant impact on expenditures

As stated in our October 2016 report, due to the late grant award date and subsequent delay in funding (this proposal was in an "alternate" funding category for several months), we were not able to recruit our next postdoctoral surgical fellow from Dr. Shinro Takai's institution as intended, due to the resulting mismatch in annual calendar availability. Although this resulted in lower expenditures to date for funding salary, our solution toward completing the project is equivalent in both expertise and expenditures, employing the skills and experience of several individuals within Dr. Rowe's "Service Core for Skeletal Research" core facility to work with Dr. Adams on the project. All funding awarded will be required to complete the remaining work.

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

There is no use of human subjects. All vertebrate animal procedures were approved 8/27/2015 under UConn Health IACUC #101102-0518. A subsequent annual review was approved on 7/28/2016 (attached in appendices). Any changes in use of vertebrate animals will be approved by UConn Health IACUC as well as the USAMRMC.

►Significant changes in use or care of human subjects

Not applicable. No human subjects are used in this study.

►Significant changes in use or care of vertebrate animals

No significant changes in the use or care of vertebrate animals have been necessary or implemented. Any changes in use of vertebrate animals will be approved by UConn Health IACUC as well as the USAMRMC.

►Significant changes in use or care of biohazards and/or select agents

No significant changes in the use or care of biohazards and/or select agents have been implemented.

6. PRODUCTS

►Publications, conference papers, and presentations

The following publication was listed here in our October 2016 report. Although it is not primarily a result of this study or its funding, the publication includes techniques that were developed for use in this study.

Dyment NA, Jiang X, Chen L, Hong SH, Adams DJ, Ackert-Bicknell C, Shin DG, Rowe DW: High-Throughput Multi-Image Cryohistology of Mineralized Tissues, J Vis Exp, (115), e54468, doi:10.3791/54468, 2016.

►Website(s) or other Internet site(s)

www.bonebase.org includes detailed methods of the cryohistological techniques used in this and related studies. These methods are reviewed in the JoVE publication video viewable at http://www.jove.com/video/54468/high-throughput-multi-image-cryohistology-of-mineralized-tissues.

►Technologies or techniques

The previously reported refinements in experimental and cryohistological methods (October 2016) will be included in publication of the primary data at the completion of the study.

►**Inventions, patent applications, and/or licenses**

No inventions, patent applications, or licenses have resulted from this work.

►**Other Products**

Video tutorial - the aforementioned tutorial video which details the unique techniques of our cryohistological approach are viewable at http://www.jove.com/video/54468/high-throughput-multi-image-cryohistology-of-mineralized-tissues.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

►**What individuals have worked on the project?**

Name:	Douglas J. Adams
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	http://1.usa.gov/1JPqazR
Nearest person month worked:	3
Contribution to Project:	Dr. Adams performed experimental animal studies and histological outcome assessments toward completion of the project goals.
Funding Support:	This award

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

Current active support for Dr. Adams and Dr. Rowe is included in the appendices.

Two relatively minor changes in active support to Dr. Adams (PI) have occurred since the last reporting period of October, 2016. These changes in active support did not significantly impact the effort on the project that is the subject of this project report:

- Dr. Adams (PI) reduced his effort on NIH R01 AR070879 from 25% to 20%.
- Dr. Adams (PI, 5% effort) was awarded a short-term 4 month sub-award DAMD W81XWH-14-2-0136.

No changes in active support to Dr. Rowe (co-I) have occurred since the last reporting period of October, 2016 with the exception of reducing effort on this no-cost extension from 5% to 1%. This change in active support did not significantly impact the project that is the subject of this project report:

- Dr. Rowe has reduced his effort on this project from 5% to 1% during the one year no cost extension.

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

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

►**COLLABORATIVE AWARDS:** Not applicable to this project.

►**QUAD CHARTS:** Not applicable to this project.

9. APPENDICES

i. Annual renewal notice of our active animal protocol.
ii. Other support pages for Dr. Adams and Dr. Rowe.

Adams,Douglas

From:	NoReplyUCSHC@topazti.net
Sent:	Tuesday, August 02, 2016 9:30 AM
To:	Rowe,David; Adams,Douglas; Fraize,Sara; Pohl,Alison; Wallace,Ronald; Chen,Li; Rydzik,Renata; Chuba,Lisa; Hoyt,Kelly; Wang,Liping; Chidambaram,Ramaswamy; Butler,Jessica; Dyment,Nathaniel; Cohn,Susan; Wu,Zhihua; Evans,Marisa
Subject:	Annual Review for Animal Protocol 101102-0518 Approved on 7/28/2016

Hi, Dr. Adams ,

The annual review for your IACUC protocol 101102-0518, "Elucidating the Role of Joint Disuse in the Development of Osteoarthritis Following Return to High-Impact Loading", has been approved by the IACUC on 7/28/2016. This protocol will expire on 5/31/2018. The funding source(s) has/have been identified as Dept of Defense.

Species/amount approved for use include:

Mice #1

D- More than momentary pain or distress: 110

Potentially hazardous materials associated with this protocol include:
5-ethynyl-2'-deoxyuridine (edU) [C], Anesthetic Gas (Isoflurane, etc.) [Anesthetic gas], Demeclocycline (dcyc) [C], Transgenic animals [Tg/GT animals]

Please remember that any changes you may wish to make to your protocol, including the addition of qualified personnel, require that a modification be submitted to, and approved by, the IACUC prior to the implementation of those changes. It is the PI's responsibility to document all training given to each animal user on all procedures performed on animals. If you have animals with cage cards with an old protocol number, it is your responsibility to make sure those cage cards have been updated with the new protocol.

It is a condition of approval to use animals that the PI will report any adverse incidences (including unexpected morbidity and mortality) involving animals to the IACUC. This action is required by IACUC policy (http://acc.uchc.edu/policies/morbidity_mortality.html) in order to comply with federal regulations and laws.

Please review section 11 of your protocol to ensure that you are familiar with all the assurances you have agreed to. Please retain this email as it serves as your official approval letter.

The University of Connecticut Health Center has an Animal Welfare Assurance on file with the Office of Laboratory Animal Welfare (OLAW). The Assurance Number is A3471-01 and the effective dates are 4/1/14 - 4/30/18. It is your responsibility to notify the appropriate funding agency of this approval after review with the Office of Research and Sponsored Programs. Just-in-Time (JIT) notifications should be performed through the Office of Research and Sponsored Programs.

PLEASE NOTE: If your protocol involves the use of transgenic or gene targeted animals, an identification needs to be on the cage card. This must include at least one of the following: the full name of the line (e.g., such as the line name given by Jackson Labs), a "nickname" for the line (this must be identified in your protocol in the TgGT table), or the GMO number given to the animal.

ALSO NOTE: Please do not reply to this email, it will bounce back to you. Should you need help, please contact the

IACUC office at ooacc@uchc.edu.

If there is anything we can do for you in the future, please let us know. Thank you-

The IACUC Office

OTHER SUPPORT

ADAMS, Douglas J.
ACTIVE

1 R01 AR 070879-01 (Adams) 9/1/16 – 8/31/21 2.4 calendar
NIH/NIAMS $420,422
Identification of Genes Regulating Bone Matrix Composition and Quality

The goal of this study is to identify genes that contribute to the regulation of bone matrix quality and to investigate how genetic background interacts with aging-related changes in bone quality.

DAMD W81XWH-15-1-0371 (Adams) 9/30/15 – 3/29/18 2.76 calendar (NCE)
DOD/USAMRMC $140,756
Elucidating the Role of Joint Disuse in the Development of Osteoarthritis Following Return to High-Impact Loading

The goal of this project is to examine the temporal interaction of joint immobilization and return to activity on joint tissue degradation and recovery.

DAMD W81XWH-14-2-0136 (Wolf) 02/01/17-05/31/17 0.60 calendar
DOD/USMRMC (Adams sub-award) $35,128
Vitamin D Supplementation for Prevention of Post-Traumatic Osteoarthritis: Evaluation in Animal and Clinical Models

The goal of this study is to evaluate the effect of Vitamin D on joints subjected to trauma-induced osteoarthritis.

4 R01 AR 063702-04 (Rowe, Ackert-Bicknell, Shin) 8/1/13 – 5/31/18 1.92 calendar
NIH/NIAMS $499,094
Skeletal Phenotyping of KOMP Mice

The goal of this collaboration with The Jackson Laboratory is to provide high-throughput skeletal phenotyping of gene knock-out mice generated within the Knock-Out Mouse Phenotyping Program.

5 R01 AR 064867-02 (Delany, Lee) 6/1/15 – 4/30/20 0.48 calendar
NIH/NIAMS $220,000
Role of MIR29 in Osteoclastogenesis

The goal of this project is to examine the role of microRNA29 in osteoclastogenesis utilizing sponge mice which inhibit miR29 expression in osteoclasts using a TRAP promoter.

5 R01 AR 055607-07 (Kalajzic) 7/1/15 – 5/31/20 1.08 calendar
NIH/NIAMS $220,000
Notch Signaling and Bone Fracture Healing

The goal of this project is to evaluate the effects of Notch signaling modulation *in vivo* using stage specific Notch gain- and loss-of-function models during fracture healing.

University of Connecticut (Kelly) 01/1/14-06/30/17 0.48 calendar
SPARK Technology Commercialization Fund $50,000
Artificial Salivary Pump/Gland Concept

The goal of this study is to perform proof-of-concept experiments toward developing a saliva-supplying device.

1 R01 AR 070813-01 (Kalajzic)	4/1/17 – 3/31/22	1.2 calendar
NIH/NIAMS	$250,000	(Yrs 2-5, 4/1/18 start)
Growth Factor Based Enhancement of Bone Repair		

The goal of this study is to provide better understanding on the interactions of PDGF and BMP2 during osteogenesis and bone healing.

PENDING

R01 AR 072737-01 (Sanjay)	9/1/17 – 8/31/22	0.60 calendar
NIH/NIAMS	$284,877	
Role of PI3K in Fracture Healing		

The research proposed will identify novel mechanisms by which the periosteal cells integrate PI3K-AKT signaling to regulate fracture healing.

State of Connecticut, Connecticut Innovations (Maye)	1/1/18 – 12/31/21	0.60 calendar
Regenerative Medicine Research Fund	$150,000	
Bone Regenerative using Pluripotent Stem Cell Derived Skeletal Progenitors		

OVERLAP

None

OTHER SUPPORT

ROWE, DAVID
ACTIVE

1R01AR064381-01 (Rowe, PI) 4/1/13 – 3/31/18 .48 calendar months
NIH/NIAMS $212,500
Targeted corrections of dominant mutations of type I collagen causing severe OI

A method for correcting the OI gene mutation in stem cells derived from affected adult individuals will be developed. It utilizes the latest techniques from stem cell biology and target gene correction, and it will evaluate a new approach to make the method more faithful and less expensive than the methods that are in current use. The other aspect of the grant is to demonstrate that the bone formed by these corrected stem cells in repairing bone defects in mice is equivalent to bone formed from normal stem cells and dramatically better that the bone formed from OI stem cells.

R01 AR063702 (MPI Rowe, Shin, Ackert-Bicknell) 9/1/13 – 5/31/18 1.2 calendar months
NIH/NIAMS $499,094

Skeletal Phenotyping of KOMP Mice
The goal of this collaboration with The Jackson Laboratory will be to provide high-throughput skeletal phenotyping of gene knock-out mice generated within the Knock-Out Mouse Phenotyping Program (Komp^2).

PR141985 (Adams) 9/30/15-3/29/18* .12 calendar months
USAMRAA $200,000
Elucidating the role of joint disuse in the development of osteoarthritis following return to high impact loading
*NCE

The goal of this project is to examine the temporal interaction of joint immobilization and return to activity on joint tissue degradation and recovery.

R13 AR070574 (Rowe, PI) 9/1/16-8/31/17 .12 calendar months
NIH/NIAMS $15,000
Cryohistological assessment of the mineralized skeleton

This project will support a hands-on workshop to acquaint basic science research laboratories how to examine the activity of cells that participate in formation of the mineralized skeleton. Traditional methods are laborious and not amenable highly automated computer driven digital manipulation and image analysis. The new method enables multiple rounds of imaging from the same tissue section and computer processing of the entire workflow. It enables high throughput and consistent evaluation of experimental results across different laboratories and creation of image repositories accessible to the skeletal research community.

PENDING

1R21AR070991-01A1 (Rowe, PI) 7/1/2017-6/30/2019 .60 calendar months
NIH/NIAMS $125,000
Use of iPS-derived osteoblast and osteoclasts to discriminate between candidate genes obtained by WES as a contributor to human bone disease

A method for correcting the OI gene mutation in stem cells derived from affected adult individuals will be developed. It utilizes the latest techniques from stem cell biology and target gene correction, and it will evaluate a new approach to make the method more faithful and less expensive than the methods that are in current use. The other aspect of the grant is to demonstrate that the bone formed by these corrected stem cells in repairing bone defects in mice is equivalent to bone formed from normal stem cells and dramatically better that the bone formed from OI stem cells.

OVERLAP
None