AWARD NUMBER: W81XWH-18-1-0764

TITLE: A Novel Nutraceutical Drug for OA Treatment

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REPORT DATE: Oct 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command

Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
Oct 2019	Annual Report	9/30/2018-9/29/2019

4. TITLE AND SUBTITLE

A Novel Nutraceutical Drug for OA Treatment

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0764

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Development 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

Over 27 million Americans are currently diagnosed with osteoarthritis (OA), and OA is our nation's leading cause of pain and disability. Medically linked retirement caused by musculoskeletal disorders such as OA increased nearly 10-fold among active military service members between 2003 to 2009. The rate of OA in military populations is twice as high as that in non-military populations. Neither a disease-modifying OA drug nor a non-surgical cure presently exists. Therefore, it is extremely important to have a drug which mitigates OA disease progression and relieves OA pain, with minimal, if any, adverse effects. The aim of the current project is to determine the therapeutic efficacy of a novel botanical drug using a canine model of post-traumatic OA, a large animal model that replicates the pathology and symptoms of human OA. Successful completion of the proposed studies will provide critical evidence to the Food and Drug Administration for approval for human clinical trials.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	4	**19b. TELEPHONE NUMBER** *(include area code)*

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1. Introduction

Over 27 million Americans are currently diagnosed with osteoarthritis (OA), and OA is our nation's leading cause of pain and disability. Medically linked retirement caused by musculoskeletal disorders such as OA increased nearly 10-fold among active military service members between 2003 to 2009. The rate of OA in military populations is twice as high as that in non-military populations. Neither a disease-modifying OA drug nor a non-surgical cure presently exists. Therefore, it is extremely important to have a drug which mitigates OA disease progression and relieves OA pain, with minimal, if any, adverse effects. The aim of the current project is to determine the therapeutic efficacy of a novel botanical drug using a canine model of post-traumatic OA, a large animal model that replicates the pathology and symptoms of human OA. Successful completion of the proposed studies will provide critical evidence to the Food and Drug Administration for approval for human clinical trials.

2. Keywords

Post-traumatic osteoarthritis, botanical drug, canine osteoarthritis, gait analysis, disease-modifying drug, osteoarthritis pain

3. Accomplishments

Major goals of the project

The major goals of the project remain unchanged from the original proposal:
Specific Aim 1: Determine efficacy of C'-CEO in mitigating OA disease progression
Specific Aim 2: Determine efficacy of C'-CEO in mitigating OA-related pain

The next milestone as listed in the approved Statement of Work is at month 18 – "Surgical induction of OA, daily treatment with C'-CEO or placebo, and euthanasia." The approximate percentage of completion towards the entire project is approximately 50%.

What was accomplished under these goals?

During the first year, we accomplished all the milestones proposed for the 1st year, including:

1) Local IACUC approval
2) ACURO approval
3) Drug manufacturing

After the purchase of the botanical compounds which make up the botanical drug, we verified the purity of the each of the compounds through an independent third-party. The manufacturer then proceeded to manufacture the drug product and placebo for this study.

Skeletally mature canines (female hounds) without pre-existing musculoskeletal abnormalities of the pelvic limbs (determined by radiographic examination) were subjected to the meniscal release model of OA. At 4 weeks after induction of experimental OA canines were treated daily with oral administration of C'-CEO or placebo for 10 weeks (n=2/group). Prior to and every 4 weeks following surgery, OA pain-related outcome measurements were accessed by kinetic gait analysis. At 10 weeks after treatment, the animals were sacrificed, and the stifle joints were collected for histological analysis.

For gait analysis, peak vertical forces (PVF) and vertical impulses (VI) were recorded at baseline and approximately 4 weeks throughout the study. PVF and VI are expressed in percent of bodyweight (%BW for PVF; %BW for VI) (Figure 1). The data are currently blinded, and results are represented for each individual canine. Macroscopic scoring and gross analysis of the canine stifle joints was also carried out (Table 1). As the data are blinded, no conclusions can yet be made.

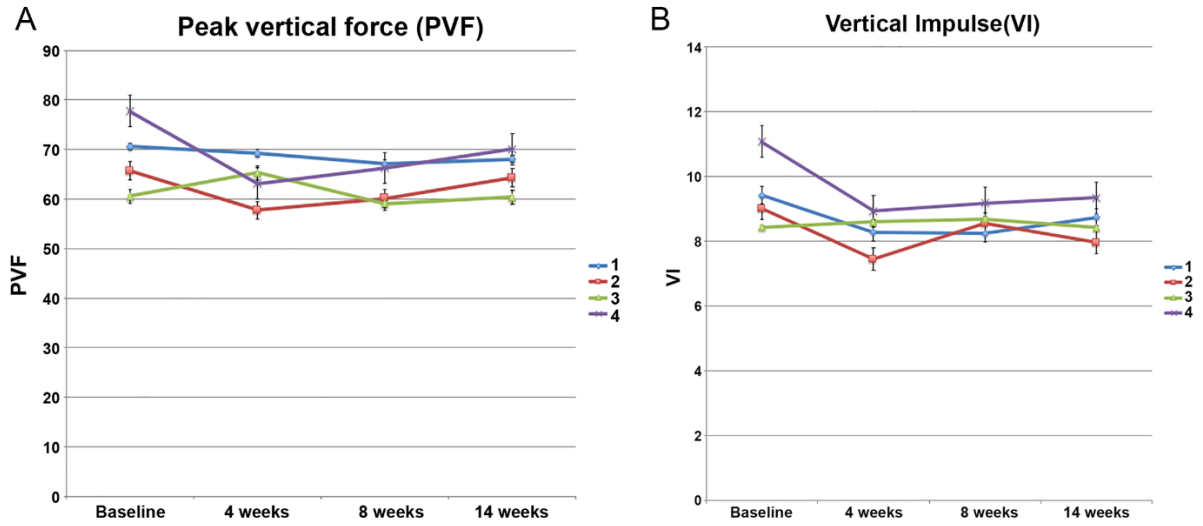

Figure 1. Force plate gait analysis of canines subjected to MR and treated with C'-CEO or placebo. (A) Change in Peak Vertical Force (%BW) or (B) change in Vertical Impulse (%BW) over the course of the study. N=4 total; n=2/group.

Table 1. Macroscopic scoring and gross analysis of the canine stifle joints.

Macroscopic scoring of joint surfaces				
	Dog #1	*Dog #2*	*Dog #3*	*Dog #4*
Medial femoral condyle	2	2	0	4
Lateral femoral condyle	3	0	2	0
Medial tibial plateau	3	3	1	3
Lateral tibial plateau	1	1	0	0
Macroscopic scoring of synovial alterations				
	Dog #1	*Dog #2*	*Dog #3*	*Dog #4*
Synovitis score	3	2	1	3
Presence of osteophytes				
	Dog #1	*Dog #2*	*Dog #3*	*Dog #4*
Femur	Yes	Yes	No	Yes

Tibia	No	No	No	No
Patella	No	No	No	Yes

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

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

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

During the next reporting period (10/1/2019-9/30/2020), we plan to complete all the proposed tasks/milestones remaining in the project. We are currently training the second batch of canines for gait analysis, and will likely start the OA induction surgery in December. The joints from the first batch of canines are being scanned by a micro-CT, and then will be subjected to histologic analysis.

4. Impact

Nothing to Report.

5. Changes/Problems

Nothing to Report.

6. Products

Nothing to Report.

7. Participants & Other Collaborating Organizations

Name	Hui B. Sun, PhD
Project Role	PI
Nearest person month worked	1
Contribution to Project	Dr. Sun coordinated the active ingredient testing of the drug product from an independent laboratory, picked up the drug product from the manufacturer, and shipped it to Dr. Budsberg. Dr. Sun worked with the research team at the University of Georgia for the sacrifice of the first group of canines

Name	Steven Budsberg, DVM, MS, DACVS
Project Role	Co-I
Nearest person month worked	1
Contribution to Project	Dr. Budsberg carried out the meniscal release surgeries, and oversaw the gait analysis and drug/placebo administration. Dr. Budsberg also coordinated the sacrifice and tissue harvest from the first group of canines and carried out the macroscopic evaluation of the stifle joints.

Name	Meghan Norton
Project Role	Research Technician
Nearest person month worked	9

Contribution to Project	Ms. Norton assisted with the canine surgeries, fed the dogs daily with drug/placebo, carried out the gait analysis, and assisted with the sacrifice and tissue harvest from the first group of canines.

8. Special Reporting Requirements

Updated Quad Chart attached.

9. Appendices

N/A