AWARD NUMBER: W81XWH-15-1-0567

TITLE: A Biologic Joint Replacement Strategy to Treat Patients with Severe Knee Trauma and Posttraumatic Knee Osteoarthritis

PRINCIPAL INVESTIGATOR: James P. Stannard, MD

CONTRACTING ORGANIZATION: The Curators of the University of Missouri
Columbia, MO 65211-0001

REPORT DATE: December 2019

TYPE OF REPORT: Final

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
December 2019	FINAL	28Sep2015-27Sep2019

4. TITLE AND SUBTITLE
A Biologic Joint Replacement Strategy to Treat Patients with Severe Knee Trauma and Post-Traumatic Knee Osteoarthritis

5a. CONTRACT NUMBER
OR140148

5b. GRANT NUMBER
W81XWH-15-1-0567

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
James P. Stannard, MD (Principal Investigator)
James L. Cook, DVM, PhD (Co-Investigator and Research Director)

E-Mail: stannardj@health.missouri.edu; cookjl@health.missouri.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Curators of the University of Missouri
DOB University of Missouri
Department of Orthopaedic Surgery
OSPA
115 Business Loop 70W
Mizzou North, Room 501
Columbia, MO 65211-0001

8. PERFORMING ORGANIZATION REPORT

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

Significant knee damage from athletic activities, military training, blunt trauma, or penetrating trauma inevitably leads to dysfunction, pain, and post-traumatic osteoarthritis (PTOA), and is the most common unfitting condition in medically retired military personnel. **The subject and purpose of the research was optimization of articular tissue transplantation strategies to functionally rebuild damaged knees**. Biologic joint restoration, in the form of osteochondral and meniscal allograft transplantation, mitigates the limitations of artificial joint replacements while allowing return to full activity when successful. We have developed novel methods and techniques that allow for biologic restoration of damaged cartilage, meniscus and bone with viable tissues that can integrate and function at high levels. Our approach allows us to preserve organ donor tissues at the highest level of quality for more than twice as long as standard tissue bank methods, replace entire joint surfaces with healthy bone and cartilage, and replace the entire meniscus with a viable, functional meniscus. **The scope of the research for this project was to complete basic science, preclinical translational, and clinical aims that determine and validate the most optimal implementation of methods and techniques in order to improve outcomes in civilian and military patients.**

15. SUBJECT TERMS

Knee arthroplasty; unicompartmental biologic technique; osteochondral allografts; chondrocyte viability; translational research model

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	27	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Significant knee damage from athletic activities, military training, blunt trauma, or penetrating trauma inevitably leads to dysfunction, pain, and post-traumatic osteoarthritis (PTOA), and is the most common unfitting condition in medically retired military personnel. **The subject and purpose of the research was optimization of articular tissue transplantation strategies to functionally rebuild damaged knees**. Biologic joint restoration, in the form of osteochondral and meniscal allograft transplantation, mitigates the limitations of artificial joint replacements while allowing return to full activity when successful. We have developed novel methods and techniques that allow for biologic restoration of damaged cartilage, meniscus and bone with viable tissues that can integrate and function at high levels. Our approach allows us to preserve organ donor tissues at the highest level of quality for more than twice as long as standard tissue bank methods, replace entire joint surfaces with healthy bone and cartilage, and replace the entire meniscus with a viable, functional meniscus. **The scope of the research for this project was to complete basic science, preclinical translational, and clinical aims that determine and validate the most optimal implementation of methods and techniques in order to improve outcomes in civilian and military patients.**

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Knee arthroplasty; unicompartmental biologic technique; osteochondral allografts; chondrocyte viability; translational research model.

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Optimize and validate the technique for unicompartmental biologic arthroplasty of the knee in an *ex vivo* model.	**Timeline**	**Status**
Major Tasks	Months	
All ACUC approvals are approved and in place Awaiting approval of submitted ACURO	0-1	Completed
Acquire cadaveric human knee joints (n=20) and materials for *in vitro* study	1-2	Completed
Perform biologic joint surgeries in lab: femoral condylar and meniscal-tibial allografts will be implanted via a medial approach to the knee using custom cutting guides and press-fit as well as plate and screw fixation Submit prepared IRB for approval Submit HRPO for review and approval	2-6	Completed Completed Completed
Biomechanics (cyclic) and cell viability evaluations on cadaveric knees: • Repeatability of graft and site preparation, as well as graft positioning, will be evaluated using 3D surface analysis. Native and allograft contact areas will be measured at implantation and following cyclic loading. • Graft congruency (contact surface area) and extraction properties will be measured immediately after implantation and after 4 weeks in culture. • Meniscus failure strength as well as cyclic loading properties will be measured. • Meniscal fibrochondrocyte and articular chondrocyte viability will be determined using live/dead staining.	6-9	Completed Completed Completed Completed

Specific Aim 2: Evaluate safety and efficacy of unicompartmental biologic arthroplasty of the knee in a translational animal model. Acquire canine subjects (n=12), instrumentation, and implants and perform pre-op measures: clinical assessments (lameness scoring, forcemat kinetics, range of motion, and VAS pain scores), radiographic assessment of joint health, and arthroscopic assessment of joint health prior to surgery. Perform canine surgeries: Medial compartment osteoarthritis will be induced in one knee of each dog using our validated arthroscopic meniscal release (MR) model. Three months after MR, the presence of OA in the operated knees will be documented radiographically and arthroscopically, and pre-treatment assessments (same as above) will be performed. The dogs will be divided into two treatment groups: • Control group (n = 6): This group will receive no surgical intervention but will be managed with daily NSAIDs (Carprofen 4.4 mg/kg po q24h) for the duration of the study. • OCA group (n = 6): Large surface area non-circular anatomically-matched osteochondral and meniscal-osteochondral allografts obtained from canine cadavers euthanatized for reasons unrelated to this study and preserved for 30 days using the Missouri Osteochondral Preservation System (MOPS^{SM}) will be implanted into the medial femoral condyles and medial tibial condyle of the same knee in each dog using technique and instrumentation described above for the cadaveric study (sized for dogs).		
Longitudinal outcome measures on dogs: clinical assessments (lameness scoring, forcemat kinetics, range of motion, and VAS pain scores), radiographic assessment of integration and joint health, and arthroscopic assessment of graft appearance and joint health at 1, 3 and 6 months after surgery.	9-12	Completed

Prepare manuscript for SA1		In progress
Milestone(s) Achieved: SA1 completed, SA2 initiated (all dogs on-study), HRPO/ACURO Approval	12	
Complete canine study: Dogs will be humanely euthanatized 6 months after surgery and the knees evaluated by OARSI whole joint histologic assessments and cell viability using live-dead staining to determine viable chondrocyte density, glycosaminoglycan and collagen content using DMMB and HP assay, and biomechanical properties of grafts, including instantaneous tissue modulus and dynamic modulus under 10% strain using an Instron materials testing machine and Certus optical tracking system.	12-16	Completed
Specific Aim 3: Evaluate safety and efficacy of unicompartmental biologic arthroplasty of the knee in a limited clinical trial. Optimize technique for human patients based on results of SA1 and SA2 Prepare manuscript for SA2	16-18	Completed
Enrollment for SA3: With IRB/HRPO approval and informed consent, patients (n = 10) will be enrolled. Primary criteria for inclusion are: • 18 to 50 years old with post-traumatic knee OA and requiring a tibial plateau and meniscus arthroplasty plus a femoral condyle arthroplasty • Grade IV changes in the articular cartilage of the femoral condyle and tibial plateau and meniscal pathology in the medial or lateral femorotibial joint as determined by physical examination, diagnostic imaging and knee arthroscopy Exclusion criteria include: • Grade III or IV changes in any other compartment of the knee • Acute injury to any other part of the affected lower extremity • Inability to comply with the protocol After enrollment, patients will undergo standardized knee radiography, and complete	18-22	Completed

assessments (described below). Size-matched proximal tibia with meniscus and distal femur allografts from the same donor will be obtained from a tissue. The medial or lateral femoral condyle will be replaced using our novel instrumentation and technique described above. Tibial plateau-meniscus grafts will be used to replace the entire medial or lateral tibial condyle and stabilized with plate and screws.		
Longitudinal outcome measures for SA3: Range of motion, VAS pain score/PROMIS Pain Interference CAT, SF-12/PROMIS Global 10, Tegner score, International Knee Documentation Committee (IKDC) subjective and objective scores, and PROMIS Physical Function and Mobility CATs as well as complete radiographs of the affected knee will be obtained prior to surgery and at 6 weeks, 3 months, 6 months, and 12 months after surgery to evaluate healing, function and evidence for arthrosis. We will document all complications, including joint or incision infection, graft failure, hardware failure, and arthrofibrosis. Patients with a VAS pain score >5 beyond 3 months postoperatively or clinical or radiographic evidence for nonunion or graft collapse will undergo MRI of the knee to determine the appropriate clinical course of action.	22-24	Completed
Milestone(s) Achieved: SA2 completed, SA3 initiated (all subjects enrolled)	24	Completed
Complete SA3: Range of motion, VAS pain score/PROMIS Pain Interference CAT, SF-12/PROMIS Global 10, Tegner score, International Knee Documentation Committee (IKDC) subjective and objective scores, and PROMIS Physical Function and Mobility CATs as well as complete radiographs of the affected knee will be obtained prior to surgery and at 6 weeks, 3 months, 6 months, and 12 months after surgery to evaluate healing, function and evidence for arthrosis. We will document all complications, including joint or incision infection, graft failure, hardware failure, and arthrofibrosis. Patients with a VAS pain score >5 beyond 3 months postoperatively or clinical or radiographic evidence for nonunion or graft collapse will undergo MRI of the knee to determine the appropriate clinical course of action.	24-34	Completed

Complete all final paper work, prepare manuscript for SA3	34-36	Completed
Milestone(s) Achieved: All aims complete, final report submitted	36	Completed

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

- ACUC and ACURO completed and approved
- IRB and HRPO completed and approved
- Cadaveric knee joints acquired and tested
- Canine subjects acquired and pre-op assessments completed
- Custom cutting guides developed and tested
- SA1 completed
- SA2 completed
- SA3 completed

Specific objectives SA1 – Optimize and validate the technique for unicompartmental biologic arthroplasty of the knee in an *ex vivo* model.

Significant results

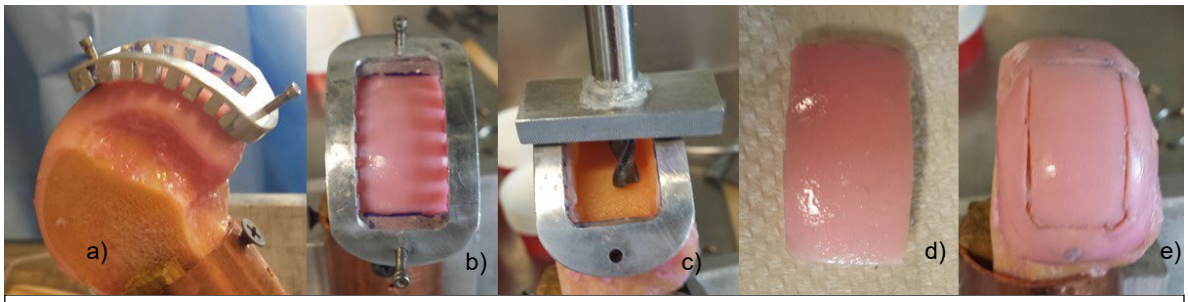


Figure 1. Example harvest procedure for anatomical osteochondral allograft including a),b) guide placement, c) site preparation, d) anatomical graft, and e) implanted graft.

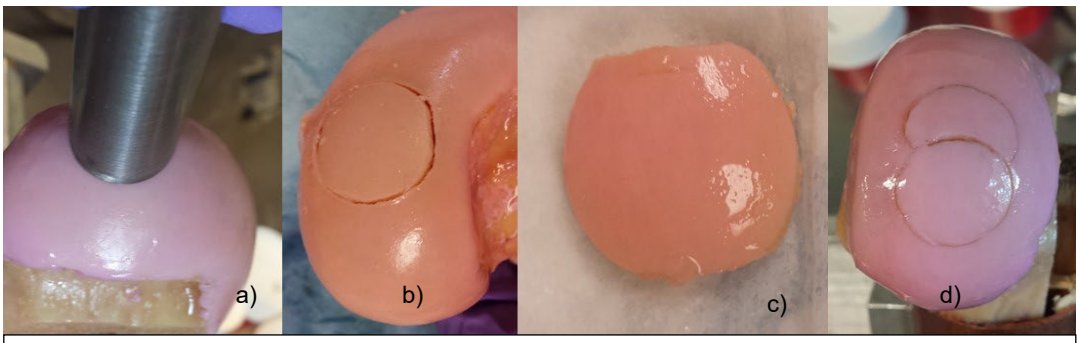


Figure 2. Example harvest procedure for "snowman" osteochondral allograft including a) trephine harvest, b),c) single harvested graft, and d) implanted grafts.

A total of 28 cadaveric knees (human and canine) were acquired and tested as described in the grant proposal. Femoral condyle and tibial plateau grafts were preserved using the Missouri Osteochondral Preservation System (MOPS^{SM}) as described in the proposal. Prior to graft transplantation and following graft harvest, site preparation, and graft implantation using anatomic (Fig. 1) or "snowman" (Fig. 2) techniques for the femoral condyle grafts, the recipient site was scanned using a 3D laser scanning system (David Laser, Germany) to compare the pre-implant geometry with the post implanted geometry. Surface images were evaluated using Matlab (Mathworks, Natik, MA) to quantify congruency. Following implantation, condyles were mounted in a materials test machine (Textural Analyzer, Stable Micro Systems, London) and placed against an opposing tibial plateau grafts (Fig. 3). Contact pressure was measured using a pressure mapping system (Tekscan, Boston, MA) by placing a condyle sensor between the implanted condyle and the opposing tibial plateau. Contact pressure was measured immediately following implantation and following 500 cycles at 1Hz. Finally, the extraction strength was measured by applying an

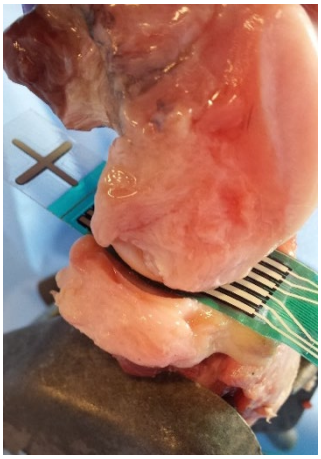


Figure 3. Experimental setup for contact pressure testing in canine BioJoint samples.

extraction force to the underside of the OCA using a rigid rod placed through a pre-drilled hole under the OCA.

Completion of SA1 showed that graft extraction force was significantly higher for the single anatomical graft versus the multiple "snowman" grafts (Fig. 4).

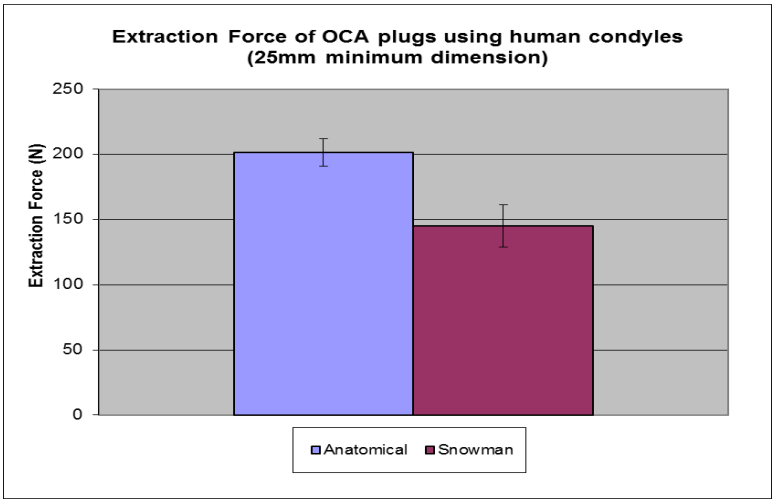


Figure 4. Graft extraction force for a single (25mm minimum dimension) human anatomical OCA vs 2 (25mm diameter) "snowman" grafts.

A marked difference was observed between contact pressures in the joints with a single anatomical graft (Fig. 5) versus joints with multiple "snowman" grafts (Fig. 6). The single anatomical grafts had a more evenly distributed pressure and demonstrated fewer "hot spots" as compared to the multiple grafts of the "snowman" procedure.

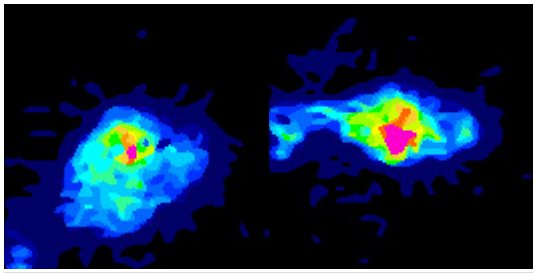


Figure 5. Representative pressure map results for a single anatomical graft.

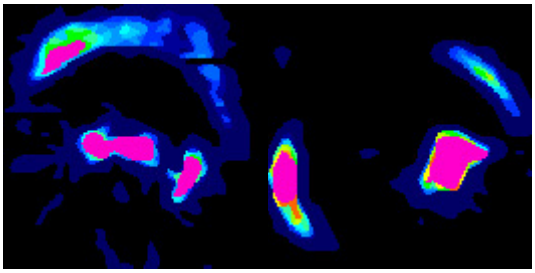


Figure 6. Representative pressure map results for multiple "snowman" grafts.

Pre- and post-transplantation surface scanned images were compared using a custom Matlab program to quantify deviations in surface congruency. Representative surface comparison plots for the transplanted anatomical grafts are shown in Figures 7 and 8 and for snowman grafts in Figures 9 and 10. In these figures, lighter colors indicated a larger deviation from the surface (all measurements are in mm).

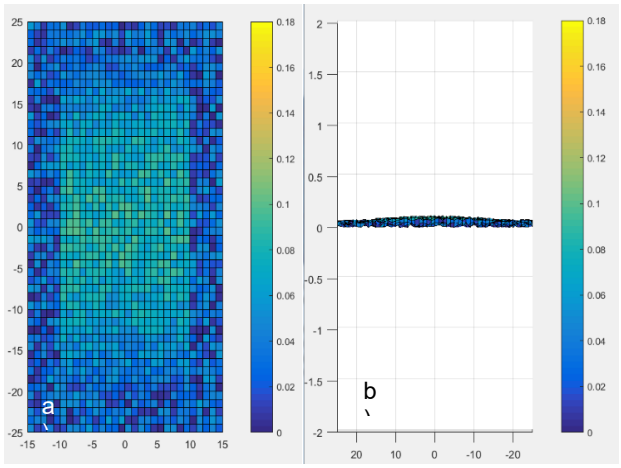


Figure 7. Representative a) normal and b) side view surface comparison plot for a "best case" anatomical graft. Measurements are in mm.

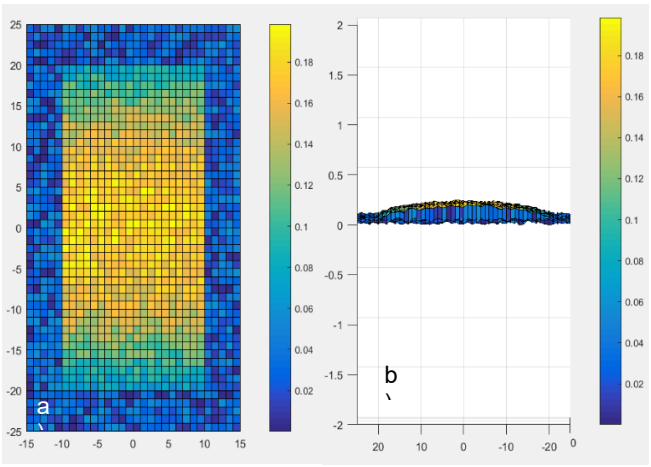


Figure 8. Representative a) normal and b) side view surface comparison plot for a "worst case" anatomical graft. Measurements are in mm.

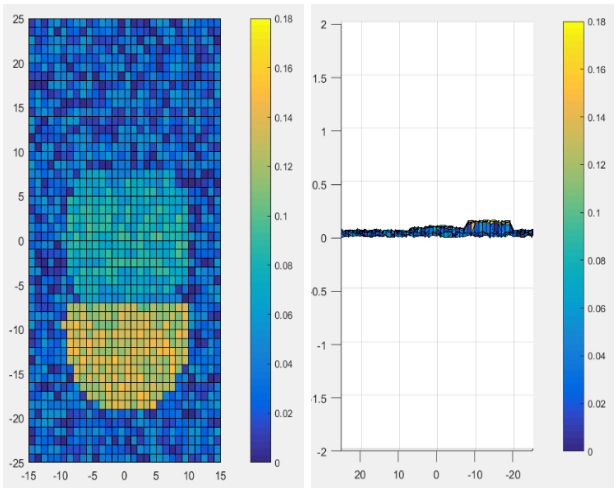


Figure 9. Representative a) normal and b) side view surface comparison plot for a "best case" "snowman" graft. Measurements are in mm.

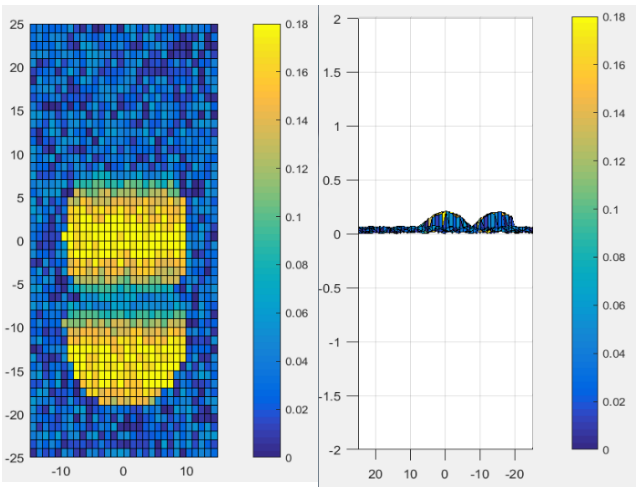


Figure 10. Representative a) normal and b) side view surface comparison plot for a "worst case" "snowman" graft. Measurements are in mm.

For cell viability testing of the tissue after graft creation and insertion, femoral condyles and tibial plateaus were tested using the live-dead cell viability assay as described in the proposal. For SA1, tibial plateau-meniscal grafts maintained high viability in all cases (Fig. 11). Femoral condylar grafts created and implanted using the snowman or anatomical techniques both maintained relatively high viability of the cartilage after graft creation, transplantation and testing. However, snowman grafts showed more loss of viability in the superficial zone compared to matched anatomical grafts (Fig. 12).

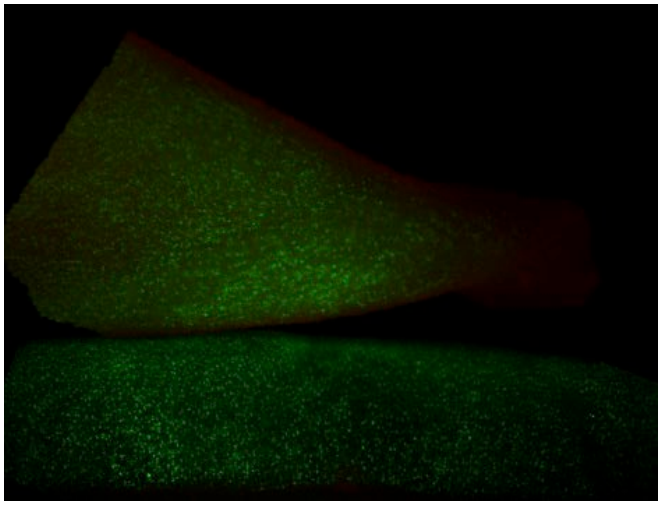


Figure 11. Representative image of cell viability in tibial plateau-meniscal allografts in this study.

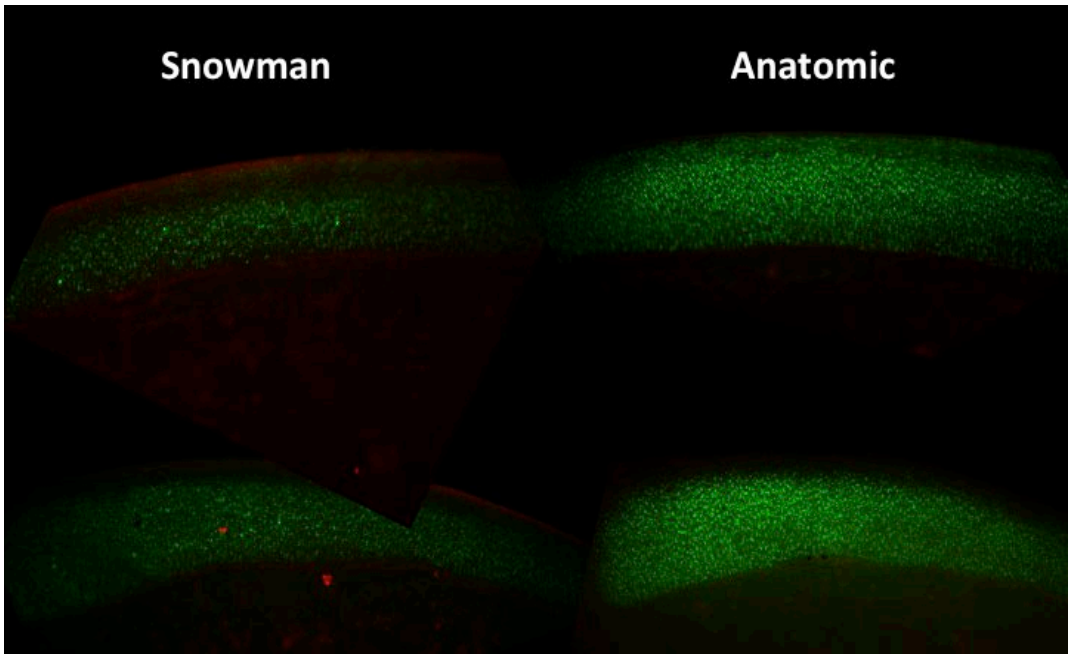
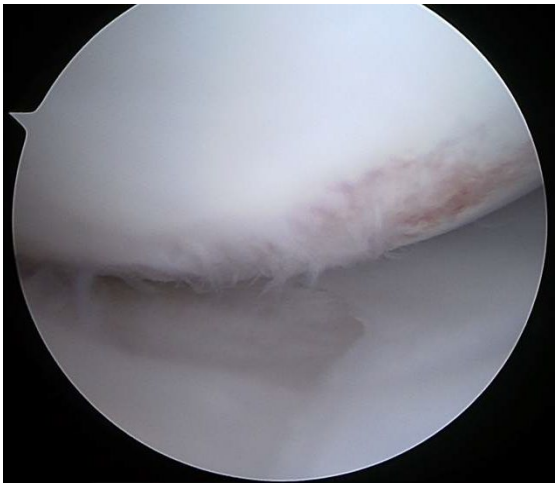


Figure 12. Representative images of cell viability in femoral condylar allografts transplanted using either the snowman or anatomical technique in this study.

Completion of SA1 has allowed us to optimize and validate the technique for unicompartmental biologic knee arthroplasty in an *ex vivo* model. We now can effectively evaluate the safety and efficacy of unicompartmental biologic knee arthroplasty using a translational animal model in SA2.

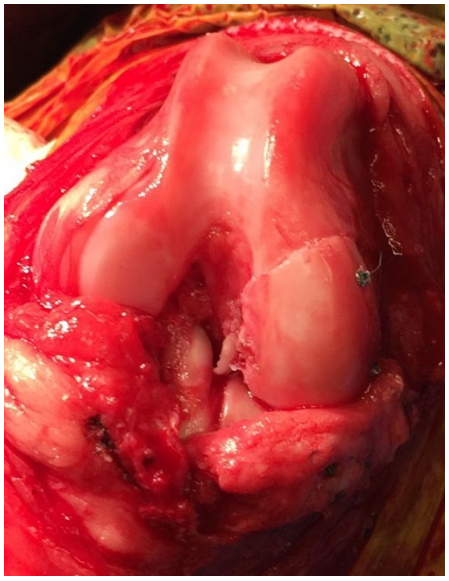
SA2 – Evaluate safety and efficacy of unicompartmental biologic arthroplasty of the knee in a translational animal model.

Canine surgeries: With ACUC and ACURO approval, medial compartment osteoarthritis was induced in one knee of each dog using our validated arthroscopic meniscal release (MR) model. Three months after MR, the presence of OA in the operated knees was documented radiographically and arthroscopically, and pre-treatment assessments were performed. All biologic unicomparmental arthroplasties and control surgeries were performed without complications and all dogs are on study.



Medial compartment OA induced by meniscal release 3 mos previously

Three months after induction of OA, half of the dogs (Control group) received no surgical intervention, but began treatment with daily NSAIDs. In the other half of the dogs (OCA group, BioJoint), large surface area non-circular anatomically-matched osteochondral allografts preserved for 30 days using our optimized system were implanted into the medial femoral condyles using our novel instrumentation and technique. Anatomically-matched meniscal-osteochondral allografts preserved for 30 days using our optimized system were implanted into the medial tibial condyle of the same knee in each surgically-treated dog using our novel instrumentation and technique. The allografts effectively replaced the entire medial femorotibial joint of each dog in the OCA group.



Medial compartment OCA and meniscus transplantation (BioJoint)

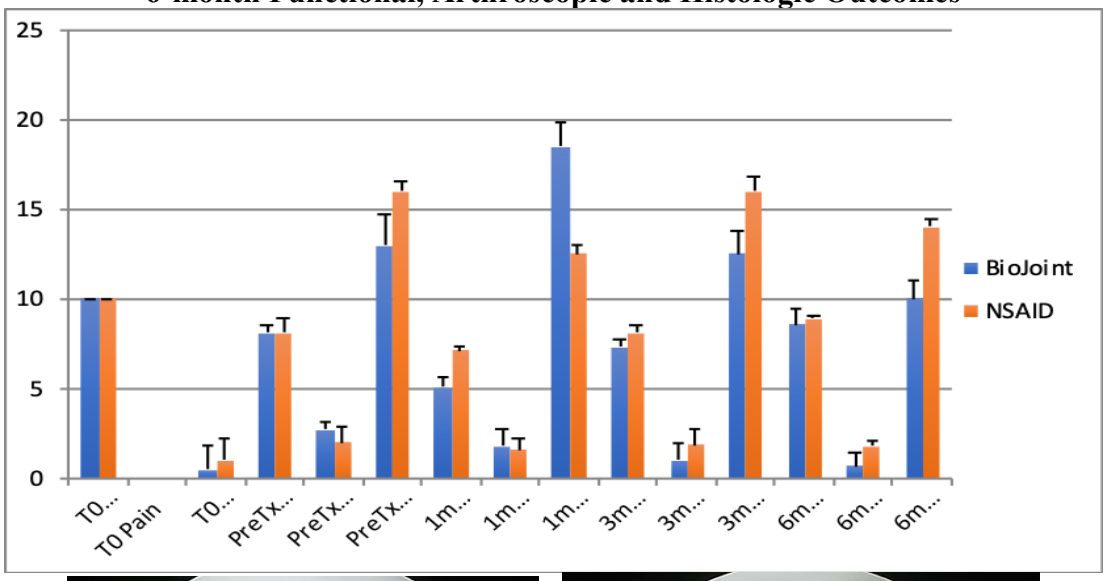
Dogs were maintained for 6 months after implantation with clinical assessments (lameness scoring, forcemat kinetics, range of motion, and VAS pain scores), radiographic assessment of integration and joint health, and arthroscopic assessment of graft appearance and joint health at 1, 3, and 6 months after surgery.

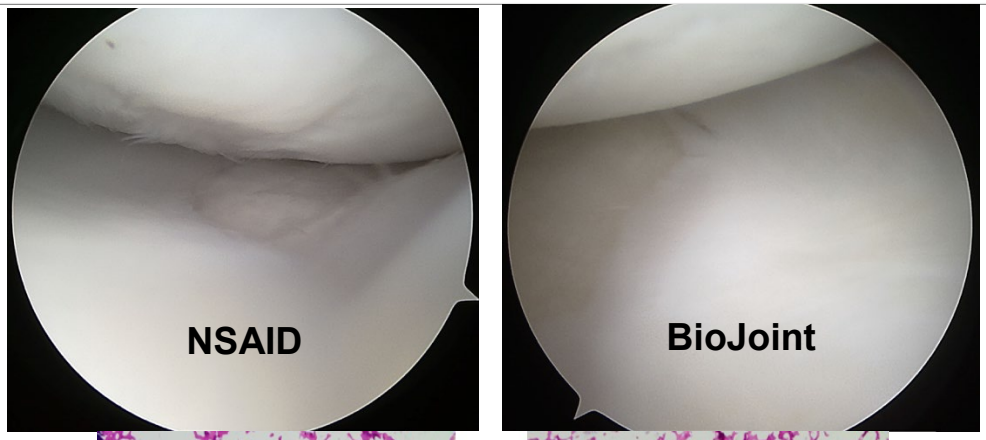
Dogs were humanely euthanatized 6 months after surgery and the knees evaluated by OARSI whole joint histologic assessments and cell viability, biochemical content and biomechanical properties of grafts.

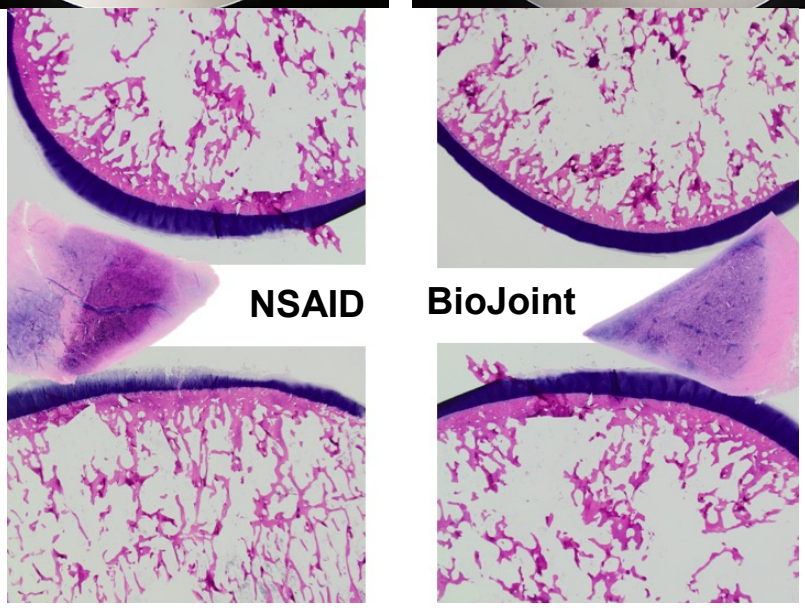
Results

All dogs survived for intended study duration without complications. At the 6-month study endpoint, functional measures, radiographic assessment of integration and joint health, and arthroscopic evaluation of graft appearance and joint health showed non-inferior or superior ($p<0.05$) outcomes (range of motion, pain, radiographic OA, arthroscopic OA) for BioJoints compared to NSAID Controls. Based on mechanistic outcome measures (cell viability, biochemical and biomechanical assessments), osteochondral and meniscal transplants maintained donor cell viability, integrated into host tissues, and allowed for maintenance of joint function without progression of OA as noted in NSAID-treated controls.

6-month Functional, Arthroscopic and Histologic Outcomes







Discussion

The findings support the safety and efficacy of unicompartmental bipolar osteochondral and meniscal allograft transplantation in a rigorous preclinical large animal model. The improved results for extensive bipolar OCA transplantation noted in this study compared to historical controls are thought to be related to high chondrocyte viability in OCAs at time of transplantation, anatomically-shaped grafts, use of fresh meniscal allografts with intact meniscotibial ligaments, BMC to enhance allograft bone integration, and careful attention to postoperative management.

Significance

These pre-clinical animal model data suggest that unicompartmental bipolar osteochondral and meniscal allograft transplantation for treatment of medial compartment gonarthrosis can result in highly functional outcomes that prevent early progression of knee osteoarthritis such that further clinical use and evaluation are warranted.

SA3: – Evaluate safety and efficacy of unicompartmental biologic arthroplasty of the knee in a limited clinical trial

With IRB and HRPO approval and informed consent, patients (n=10) (18-50 years old) with post-traumatic knee OA and requiring a tibial plateau and meniscus arthroplasty plus a femoral condyle arthroplasty were enrolled. Primary criteria for inclusion were Grade IV changes in the articular cartilage of the femoral condyle and tibial plateau and meniscal pathology in the medial or lateral femorotibial joint as determined by physical examination, diagnostic imaging and knee arthroscopy by the PI. Exclusion criteria included Grade III or IV changes in any other compartment of the knee, acute injury to any other part of the affected lower extremity, or inability to comply with the protocol.

After enrollment, patients underwent standardized knee radiography, and complete assessments (described below). Size-matched (standard clinical methodology) proximal tibia with meniscus and distal femur allografts from the same donor will be obtained from a tissue bank (Musculoskeletal Transplant Foundation, Edison, NJ) who has licensed the MOPS technology. The medial or lateral femoral condyle was replaced using our novel techniques. Tibial plateau-meniscus grafts were trimmed and used to replace the entire medial or lateral tibial hemiplateau while sparing the attachments of ACL, PCL and respective collateral ligament. The tibial plateau graft was stabilized with screws and/or bioabsorbable pins. The periphery of the meniscus was sutured to the capsule.

Patients were allowed knee range of motion from 0-90 degrees with toe-touch weightbearing for the six weeks after surgery. Patients then advanced to normal weightbearing progressively with full range of motion, as tolerated, under the guidance of the PI in conjunction with in-house physical therapists. Range of motion, VAS pain score, SF-12, Tegner score, International Knee Documentation Committee (IKDC) subjective and objective scores, and Marx score as well as complete radiographs of the affected knee were obtained prior to surgery and at 6 weeks, 3 months, 6 months, and 12 months after surgery to evaluate healing, function and evidence for arthrosis. All complications, including joint or incision infection, graft failure, hardware failure, and arthrofibrosis were documented.

Data were compiled and analyzed using descriptive statistics as well as appropriate tests (*t*-Test, ANOVA, rank sum, repeated measures) for significant ($p<0.05$) differences using SigmaStat.

All surgeries have been completed and longitudinal outcomes data collection has been completed for nine of ten patients. One patient was lost to follow-up at 3 months postoperatively. The following table provides the summary of outcomes for SA3:

Time Point	Pain	IKDC	PROMIS PF	PROMIS Mob
PreOp	**4.8** ± 2	**39.8** ± 16	**42.7** ± 7	**39.3** ± 6
3 mo PostOp	**2.3** ± 2	**47.8** ± 10	**39** ± 6	**39.7** ± 6
6 mo PostOp	**1.6** ± 2*	**52** ± 14	**44.6** ± 6	**43.3** ± 4
1 yr PostOp	**1.2** ± 1*	**58.3** ± 5*	**48.1** ± 3*	**44.5** ± 3*

*=significantly improved from PreOp

Significant and clinically meaningful improvements were seen in all outcome measures. Failure (conversion to total knee arthroplasty) occurred in one patient (10%) during the study period. These clinical data suggest that unicompartmental bipolar osteochondral and meniscal allograft transplantation for treatment of medial compartment gonarthrosis can be done safely and result in highly functional outcomes for patients.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Related Publications from Complementary Research

1. Rucinski K, Cook JL, Crecelius CR, Stucky R, and Stannard JP. Effects of compliance with procedure-specific postoperative rehabilitation protocols on initial outcomes after osteochondral and meniscal allograft transplantation in the Knee. Orthop J Sports Med 2019; DOI: 10.1177/2325967119884291
2. Stoker AM, Caldwell KM, Stannard JP, Cook JL. Metabolic responses of osteochondral allografts to re-warming. J Orthop Res 2019;37:1530-1536.
3. Cook JL. Bone marrow aspirate biologics for osteochondral allografts – because we can or because we should? Arthroscopy 2019;35:2445-2447.
4. Thomas DM, Stannard JP, Pfeiffer FM, and Cook JL. Biomechanical properties of bioabsorbable fixation for osteochondral shell allografts. J Knee Surg 2019; doi: 10.1055/s-0039-1677837
5. Stoker AM, Stannard JP, Kuroki K, Bozynski CC, Pfeiffer FM and Cook JL. Validation of the Missouri Osteochondral Allograft Preservation System for the maintenance of osteochondral allograft quality during prolonged storage. Am J Sports Med 2018;46:58-65.
6. Stoker AM, Stannard JP, and Cook JL. Chondrocyte viability at time of transplantation for osteochondral allografts preserved by the Missouri Osteochondral Preservation System versus standard tissue bank protocol. J Knee Surg 2018;31:722-780.
7. Baumann CA, Baumann JR, Bozynski CC, Stoker AM, Stannard JP and Cook JL. Comparison of techniques for pre-implantation treatment of osteochondral allograft bone. J Knee Surg 2019;32:97-104.
8. Oladeji LO, Stannard JP, Cook CR, Kfuri M, Crist BD, Smith MJ and Cook JL. Effects of autogenous bone marrow aspirate concentrate on radiographic integration of femoral condyle osteochondral allografts. Am J Sports Med 2017;45:2797-2803.
9. Stoker AM, Baumann CA, Stannard JP and Cook JL. Bone marrow aspirate concentrate versus platelet rich plasma to enhance osseous integration potential for osteochondral allografts. J Knee Surg 2018;31:314-320.

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

Manuscripts will be submitted for peer-reviewed publication for SA2 and SA3.

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Our findings regarding enhanced cell viability and improved graft mechanics provided a paradigm shift in joint restoration surgery. The preclinical data provided evidence for changing practice with respect to graft preservation methodology and surgical technique for cartilage and meniscal transplants. The clinical data advance our progress for addressing the critical unmet need for more optimal treatment options for the millions of young to middle-aged, active patients with damaged knees, including active duty and veteran populations who have demonstrated a risk of injury at a level 10 times that of the civilian population. Taken together, the results of this body of research validate a safe and effective surgical option for functional restoration of injured joints in military and civilian patients, mitigating post-traumatic osteoarthritis and its consequences while still maintaining future surgical options if necessary.

Completion of the present grant also provided critical data for successful funding of continued efforts in this critical area of healthcare:

- Stannard JP (PI), Cook JL (Co-I), Crist BD (Co-I), Leary E (Co-I), Cook CR (Co-I), Stoker AM (Co-I), Kuroki K (Co-I), Bozynski CC (Co-I). A biologic joint replacement strategy to treat patients' post-traumatic osteoarthritis. Department of Defense US Army Medical Research (CDMRP GRANT W81XWH-18-1-0430). 9/1/18-8/31/21.
- Cook JL (PI), Stannard JP (Co-PI), Leary E (Co-I), Duren DL (Co-I), Keeney J (Co-I), Kfuri M (Co-I), Stoker AM (Co-I). Prospective comparison of BioJoints versus total and unicompartmental knee arthroplasty. NIH NIAMS 1R34AR074209-01A1. 7/1/2019-12/31/2020.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

These data provide further preclinical and clinical validation for the MOPS^{SM} technology and the surgical techniques we have refined for osteochondral and meniscal allograft transplantation.

The novel surgical instrumentation/guides worked well in the preclinical canine studies, but were not employed for the human clinical studies based on need for further optimization.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

These results are providing evidence for increased approvals by health insurance companies for osteochondral and meniscal transplants, and improved outcomes for patients.

The proposed research will allow us to move these solutions further forward in successfully treating traumatic joint injury in soldiers and civilians, while also benefitting their four-legged companions.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing Further to Report. All aims have been completed within the allowed NCTE.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report. Two manuscripts are in preparation at this time that we hope will be published in 2020. We will acknowledge DOD funding in all publications.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Cook JL, Stoker AM, Bozynski CC, Kuroki K, Cook CR, Pfeiffer FM and Stannard JP. Unicompartmental bipolar osteochondral and meniscal allograft transplantation is effective for treatment of medial compartment gonarthrosis in a canine model. Orthopaedic Research Society Annual Meeting, Austin, TX, February 2-5, 2019.

Cook JL, Stannard JP, Stoker AM, Crecelius C, Kfuri M, Crist BD, Smith MJ, Ma R. A comprehensive approach to optimizing outcomes for biologic joint resurfacing. American Academy of Orthopaedic Surgeons Annual Meeting, New Orleans, LA, March 6-10, 2018.

Cook JL, Stannard JP, Kfuri M, Crist BD, Smith MJ. OCA transplantation outcomes for replacing large bipolar defects in the knee using novel techniques. American Orthopaedic Society for Sports Medicine Annual Meeting, Toronto, ON, Canada, July 20-23, 2017.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

This website provides information regarding all of the institution's research activities: https://medicine.missouri.edu/centers-institutes-labs/thompson-laboratory-for-regenerative-orthopaedics

Technologies or techniques
Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*

- *new business creation; and*
- *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

We have no change in personnel costs from the last quarterly report.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

Please see our updated quad chart along with this final report.

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*