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TITLE: Integration and Recellularization of Microparticles for the Repair of Tissue Defects

PRINCIPAL INVESTIGATOR: Corey P. Neu

CONTRACTING ORGANIZATION: University of Colorado Boulder, Boulder, CO

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Corey Neu

E-Mail: cpneu@colorado.edu

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University of Colorado Boulder
Office of Contracts and Grants
3100 Marine St, Rm 481, 527 UCB
Boulder, CO. 80309

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14. ABSTRACT

Our proposal advances the use of reconstituted decellularized and particulated articular cartilage, termed 'cartilage clay', as a new tissue repair technology following trauma. Osteoarthritis is a debilitating disease that afflicts nearly 20% of people in the United States and is extremely common among military personnel. In an effort to understand and improve integrative cartilage repair for the treatment of osteoarthritis, we have pioneered tissue engineering technology that utilizes decellularized cartilage microparticles packed in a hydrogel. We are studying the extent that cartilage clay will 1) encourage a regenerative response in damaged tissue regions, 2) mimic the structural support of native tissue, 3) establish an environment that promotes attachment, migration, and differentiation of infiltrating cells, and 4) provide an inductive ECM and source of growth factors and other anti-catabolic growth factors and cytokines. We will optimize the cartilage clay design and establish preclinical efficacy of a new, easy-to-apply cartilage repair strategy that facilitates efficient host cell response *in vivo*.

15. SUBJECT TERMS
Arthritis

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INTRODUCTION

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KEYWORDS

Osteoarthritis, Arthritis, Osteoarthritis, Degeneration, Integrative Repair, Defect, Hydrogel, Microparticles, Morselize, Decellularization, Recellularization

ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of the project are detailed in our SOW table, below. The application listed specific milestones and target dates for important activities or phases of the project. We also identify the actual completion dates and/or percentage of completion.

Activity	Timeline (Months)	Percentage Complete	Completion Date
Specific Aim 1: Define how microparticle density promotes structural support and graft recellularization, and improves integrative defect repair			
Major Task 1: Create Composite Scaffolds and Define Microparticle Density Limits	1	100	11/01/2021
Subtask 1: Fabricate cartilage clay in cartilage defect models *in vitro*.	1-12	100	4/1/2021
Subtask 2: Investigate the role of percolation, cell type, and cell concentration.	3-6	100	11/01/2021
Subtask 3: Investigate integration quality: structural and ultrastructural properties, cell responses, chemotaxis and durotaxis	3-9	100	11/1/2020
Subtask 4: Multifactor statistical testing	6-12	100	11/1/2020
Milestone(s) Achieved: Define microparticle density that promotes graft support, evaluate tissue integration, identify cell migration mechanisms.	12	100	4/1/2021
Local IACUC approval for large animal studies	9-12	100	1/1/2021
Specific Aim 2: Evaluate integration and recellularization of cartilage clay against clinical benchmarks in a large animal model *in vivo*			
Major Task 2: Perform Goat Surgeries (12 animals)	12	100	*In progress*
Subtask 1: Radiographs at biweekly intervals	24 or earlier	100	4/1/2022
Subtask 2: Serum and synovial fluid collections	24 or earlier	100	4/1/2022

Milestone(s) Achieved: Animal timecourse complete	24	100	4/1/2022
Major Task 3: Analysis		5	
Subtask 1: Morphological MRI to assess tissue quality and structure	24-30	5	
Subtask 2: Quantify biomarkers from serum and synovial fluid	24-30		
Subtask 3: Structural analysis and mechanical testing	30-36		
Subtask 4: Multifactor statistical testing	30-36		
Milestone(s) Achieved: Determine the extent that cartilage clay protects the cartilage and joint from degeneration.	36		

What was accomplished under these goals?

We accomplished and completed activities related to Specific Aim 1 of our proposal, specifically to define how microparticle density promotes structural support and graft recellularization, and improves integrative defect repair. We recently found that cells in contact with microparticles express chondrogenic markers, suggesting that dense packing in cartilage clay increases chondrogenesis. We also showed that cells rapidly recellularize microparticles, and that close packing of particles improves structural support and mechanical properties. We will therefore study limits of particle packing to best provide an implantable scaffold suitable for *in vivo* transplantation, in addition to mechanisms of recellularization in dense cartilage tissue.

First, we found that cells embedded in the extracellular matrix of tissues play a critical role in maintaining homeostasis while promoting integration and regeneration following damage or disease. Emerging engineered biomaterials utilize decellularized extracellular matrix as a tissue-specific support structure; however, many dense, structured biomaterials unfortunately demonstrate limited formability, fail to promote cell migration, and result in limited tissue repair. Here, we developed a reinforced composite material of densely packed acellular extracellular matrix microparticles in a hydrogel, termed *tissue clay*, that can be molded and crosslinked to mimic native tissue architecture. We utilized hyaluronic acid-based hydrogels, amorphously packed with acellular articular cartilage tissue particulated to ~125-250 microns in diameter and defined a percolation threshold of 0.57 (v/v) beyond which the compressive modulus exceeded 300kPa. Remarkably, primary chondrocytes recellularized particles within 48 hours, a process driven by chemotaxis, exhibited distributed cellularity in large engineered composites, and expressed genes consistent with native cartilage repair. We additionally demonstrated broad utility of tissue clays through recellularization and persistence of muscle, skin, and cartilage composites in a subcutaneous *in vivo* mouse model. Our findings suggest optimal strategies and material architectures to balance concurrent demands for large-scale mechanical properties while also supporting recellularization and integration of dense musculoskeletal and connective tissues.

Second, we developed a new crosslinking chemistry for our biomaterial that informed our animal study. We noted that articular cartilage is a layered tissue with a complex, heterogeneous structure and lubricated surface which is challenging to reproduce using traditional tissue engineering methods. Three-dimensional printing techniques have enabled engineering of complex scaffolds for cartilage regeneration, but constructs fail to replicate the unique zonal layers, and limited cytocompatible crosslinkers exist. To address the need for mechanically robust, layered scaffolds, we developed an extracellular matrix particle-based biomaterial ink (pECM biomaterial ink) which can be extruded, polymerizes via disulfide bonding, and restores layered tissue structure and surface lubrication. Our cartilage pECM biomaterial ink utilizes functionalized hyaluronan (HA), a naturally occurring glycosaminoglycan, crosslinked directly to decellularized tissue particles (ø40-100μm). We experimentally determined that HA functionalized with thiol groups (t-HA) forms disulfide bonds with the ECM particles to form a 3D network. We showed that two inks can be co-printed to create a layered cartilage scaffold with bulk compressive and surface (friction coefficient, adhesion, and roughness) mechanics approaching values measured on native cartilage. We demonstrate that our printing process enables the addition of macropores throughout the construct, increasing the viability of introduced cells by 10%. The delivery of these 3D printed scaffolds to a defect is straightforward, customizable to any shape, and adheres to surrounding tissue. Also, the development of this new bioink represented a new formulation that ultimately was injected into animals and evaluated for translational potential.

Importantly, major findings related to Aim 1 were published in two manuscripts: one at *Advanced Functional Materials*, and a second at *BioFabrication*. Additionally, we supported an allograft study that enabled us to develop tools for our *in vivo* (Aim 2) analysis, which are ongoing. A manuscript is also reported as under submission, and we hope to provide the citation information in the next reporting period.

We also submitted a full (PCT) patent application based on the technology developed to treat cartilage defects, described in our *BioFabrication* manuscript, and this technology was licensed to TissueForm, Inc.

Additionally, through our clinical partner and subcontractor, Colorado State University, we initiated and currently have ongoing the major Aim 2 animal study. Initial studies found that cartilage clay exhibits exciting properties *in vitro*, suggesting successful translation *in vivo*. In large animal studies, we predict that cartilage clay restores the functional outcomes in an *in vivo* model of defect repair to levels observed in native tissues, and protects the joint from degeneration following trauma. In April, 2022, we completed the animal timecourse to study the influence of full thickness defects and cartilage clay repair on cartilage biomechanics in an established *in vivo* caprine (goat) model with treatment groups: microfracture as a standard of care, and graft repair using cartilage clay established in our laboratory. Through an IACUC- and ACURO-approved protocol, we implanted materials in 12 goats. All animals completed the study and were healthy and active. Additionally, all of the radiographic data shows that the joints of the goats are mostly healthy in animals, with some qualitative observations of joint space narrowing in microfracture joints, anticipated based on previous animal studies.

We retrieve animals from this study in April, 2022. We are currently scheduling a complete suite of analyses for these specimen, including a full MRI analysis of cadaveric joints obtained post-euthanasia, in addition to biomechanical and biochemical assays.

Additionally, we are excited to comprehensively analyze imaging and related assays, and to use this information to determine the efficacy of cartilage clay *in vivo*. Pending results from our preclinical study, and also based on presubmission meetings with the FDA in addition to acquisition of follow-on funding, we envision in future studies moving toward clinical analysis to test safety and efficacy in human patients. Of course, we will need to carefully examine preclinical data first; nevertheless, we would like to be positioned to conduct such human studies, should the opportunity present itself.

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

Our research has supported training and professional development of (e.g. graduate) students and a postdoctoral researcher. Training in specialized skills was attained in the fields of tissue engineering, tissue mechanics, data and image processing, and biomechanics of animal and human joints. We are now involving additional graduate students with expertise in magnetic resonance imaging, which will broaden the overall set of skills and methods used to analyze our unique data. To date, training was primarily achieved through one-on-one meetings and guidance from the mentor (PI), and additionally through selected auditing of courses (e.g. on biomaterials) and participation in experiences like large animal surgeries. Professional development has included presentations and networking at national and international meetings, and through attendance of seminars offered by our department and university. Additionally, extensive professional development was achieved through individual study of specialized topics like protocols and ethics involved with human subjects, and commercialization.

How were the results disseminated to communities of interest?

We have disseminated our work to communities of interest through submissions to journal articles and conferences of national and international meetings.

Journal Articles:

Barthold JE, St. Martin BM, Sridhar SL, Vernerey F, Schneider SE, Wacquez A., Ferguson V, Calve S, Neu CP (2021). Recellularization and Integration of Dense Extracellular Martix by Percolation of Tissue Microparticles. *Advanced Functional Materials*. 31(35): 2103355 https://doi.org/10.1002/adfm.202103355

Barthold JE, McCreery K, Martinez J, Bellerjeau C, Ding Y, Bryant SJ, Whiting GL, Neu CP (2022). Particulate ECM Biomaterial Ink is 3D Printed and Naturally Crosslinked to Form Layered and Lubricated Cartilage Tissue Mimics. *Biofabrication*. 14(2). doi: 10.1088/1758-5090/ac584c

Barthold J.E., Cai L., McCreery K.P., Fischenich K., Eckstein K., Ferguson V.L., Emery N., Breur G., Neu C.P. (2022). Acellular cartilage-bone allografts promote long-term mechanical function and integrative repair *in vivo*. (*in review*)

Patents:
Barthold J.E., Neu C.P. (2021). Particulate materials for tissue mimics. *Application US 63/125,280 and US 63/263,228; PCT/US2021/072895 (Exclusive license completed to TissueForm, Inc., in 5/2022)*

Invited Presentations:
Neu CP. ""Deformation mapping and cellular responses in mechanically-active tissues", Ecole des Mines de Saint-Étienne, Saint-Étienne, France (2022)

Neu CP. "Parallel approaches to study mechanoregulation at tissue and cellular length scales", Mechanobiology Laboratory, Escuela Técnica Superior de Ingeniería, Universidad de Sevilla, Sevilla, Spain (2022)

Neu CP. "Particulate allografts for the repair of tissues and interfaces", CSU-Allosource Summit Meeting, Ft. Collins, CO (2021)

Neu CP. "Extracellular matrix for musculoskeletal repair: dissociation and reconstitution of natural materials", Allosource, Centennial, CO (2021)

Neu CP. "Challenges for the noninvasive assessment of musculoskeletal disease and repair across scales", Rheumatology Research Conference, Division of Rheumatology, University of Colorado Anschutz, Aurora, CO (2021)

Conferences:
Barthold JE, St. Martin BM, Calve S, Neu CP (2020). Mechanically tunable scaffold that promotes cell migration and chondrogenic differentiation in a dense decellularized articular cartilage matrix both in vitro and in vivo. 2020 Annual Meeting of the Orthopaedic Research Society.

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

In the next reporting period, we anticipate making significant progress to accomplish our goals. We specifically anticipate continuing activities under Specific Aim 2, including the acquisition and analysis of MRI data for 24 joints (contralateral joints from 12 goats). These data will be used to form our initial impression of repair success in the joints. We will also begin to strategize and finalize our plans for biomechanical and biochemical analysis of the joints. We expect to present our findings in light of microparticle density that promotes graft support, evaluation of tissue integration, identification of cell migration mechanisms. Finally, we will begin preparations for follow-on first-in-human studies, including establishing industry, clinical, and academic partners who may help us advance our technology to the benefit of military personnel and the general public. We have already identified TissueForm, Inc., a CU Boulder startup, as a potential partner. We have also initiated very positive conversations with Viscous Biologics for manufacturing, in addition to Allosource and Essent Biologics, two Front Range companies that will likely be key partners that will help us bring this technology to the evaluation stage in humans.

IMPACT

What was the impact on the development of the principal disciplines of the project?

Our studies examine the use of new regenerative medicine techniques and therapies to prevent the progression of osteoarthritis. Our work also outlines basic and translational research to identify treatments that mitigate osteoarthritis especially in the knee. We will immediately identify several short-term gains: (1) define

fundamental knowledge on microparticle density that promotes graft support, evaluate tissue integration, identify cell migration mechanisms. (2) Complete animal (preclinical) studies that will position us for regulatory discussions with the FDA and funding discussions with potential investors. (3) Determine the extent that cartilage clay protects the cartilage and joint from degeneration, allowing us to transition toward clinical studies in humans.

What was the impact on other disciplines?

Tissue repair is a general problem in medicine, and advanced and effective therapies are generally lacking. We anticipate that the base technology we utilize will be applicable to multiple tissue types for the repair of common problems, including and not limited to musculoskeletal (e.g. ligament, meniscus), neurological (e.g. spinal cord), and immunological (e.g. skin). We envision applying what we learn through activities under this award to address multiple medical needs in future efforts.

What was the impact on technology transfer?

We believe there is significant translational potential for our proposed work, which we expect will move from large animal studies toward first-in-human testing as a natural extension of our results. Importantly, our work has already resulted in submission of a PCT patent application [see: Barthold J.E., **Neu C.P.** (2021). Particulate materials for tissue mimics. *Application US 63/125,280 and US 63/263,228; PCT/US2021/072895*]. As a key development in the transition toward commercialization and clinical trials, here we will focus on outcomes in a large animal study. Consequently, we will conduct all animal studies using IACUC approved protocols to ensure compliance with good laboratory practice regulations and animal welfare concerns. After completion of the proposed study, assuming successful outcomes, our plan is to target development toward class III device FDA approval. FDA approval for medical devices goes through the center for devices and radiological health. Past regeneration solutions that have been approved in this center include collagenous matrices, biphasic synthetic osteochondral implants, and hyaluronic acid injections. This is the anticipated regulatory pathway for our device due to the lack of cellularity and minimal processing in the proposed tissue graft. The pathway for approval requires a phased regulatory approach involving three phases. The first phase will be composed of a two-year trial to determine whether the implant is safe for humans and will be a smaller scale study (~20 individuals). If shown to be safe, researchers will pursue funding avenues for stage 2 and 3 clinical trials. The regulatory process is necessary to prove the safety and effectiveness of the technology, and to show that the regenerative benefits outweigh the surgical risks.

The hyaline cartilage repair and regeneration market was valued as a 787.1 million dollar market in 2020, and is projected to grow into a 1,603 million dollar market by 2025 (CAGR: 15.3%; Markets&Markets). The high growth rate over the next several years is attributed to rising incidence of osteoarthritis, the growing obese and geriatric populations, and also the increasing number of active injuries in both athletes and military personnel. The average cost of current cartilage repair procedures ranges from $4,000 to $6,000, making these repairs more expensive than a full knee replacement, and highly inaccessible for most of the population. Currently, the major players in the cartilage regeneration market are Zimmer Biomet, Smith and Nephew, Johnson and Johnson, Vericel Corporation, and CONMED. In order to fund the next level of development and commercialization following research proposed for this award, our research team plans to investigate many different funding avenues. We are already partnering with TissueForm, Inc., which is a university spin-out company formed in 2019. TissueForm is a development-stage company with a mission to improve the quality of life in individuals suffering from injury, scarring, aging, and disease, using a proprietary injectable material that serves as a device to provide volumetric support and mechanical stability of volumetric tissue loss. Based on the results of our proposed work, we anticipate that TissueForm will help us to establish a manufacturing pipeline for cartilage clay, in addition to advising and advancing the technology through preclinical and clinical studies that are required for FDA approval. TissueForm is also positioned to establish a distribution network and raise additional (e.g. SBIR, venture capital) funding as we scale manufacturing to reach an increasing base of customers. We have also initiated discussions with Viscous Biologics for manufacturing, in addition to Allosource and Essent Biologics, two Front Range companies that have extensive experience supplying allograft tissues and cells to physicians worldwide to treat musculoskeletal injuries. We are positioned to work with several companies that may help us reach the market to benefit patients suffering from joint defects and injury.

What was the impact on society beyond science and technology?

The physical, emotional, and healthcare demands on military service members and veterans are tremendous, especially for those personnel who have sustained combat-related orthopaedic injuries. Our proposal aims to develop new treatment options for soft tissue trauma, which we believe will greatly benefit military personnel by providing expanded options for return of function and improved quality of life. Soft tissue trauma to articular cartilage often results in arthritis and degradation of joints, detrimental loss of ability to perform tasks and mobility, and increased pain and associate healthcare costs. Our proposed development of decellularized and particulated tissues will promote joint preservation and restoration as a preferred option to joint loss or replacement, which will also benefit orthopaedic injuries sustained by the public.

CHANGES/PROBLEMS

Changes in approach and reasons for change?

No Changes / Nothing to Report.

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

With the conclusion of the animal timecourse in April, 2022, we are now positioned to begin the extensive analysis of joints using a multitude of analysis methods. A portion of the delay was due to COVID-19 related personnel issues (described below). However, we now have all personnel in place to complete the studies. Important: we expect to make use of a no-cost extension for one year to allow us the time to complete the proposed studies and effectively report our findings.

Changes that had a significant impact on expenditures?

Previously, we reported that due to the COVID-19 pandemic, we were delayed in hiring initial personnel to the project. Additionally, due to immigration policies by the federal government, we lost out on two highly skilled postdoctoral researcher applicants (one from United Kingdom, the other from Japan), who did not feel comfortable moving to and working in the United States. As a result, personnel hiring was delayed, and we had shifted our personnel temporarily to support two graduate students. However, we successfully hired an outstanding postdoc (as of January, 2021), and we continue to support a graduate student. Additionally, we recently also added a part-time research technician to our team to help us complete and accelerate study aims, and additionally evaluate related data (e.g. delivery methods, material formulations, and shelf life) that we expect will position us to move toward first-in-human testing, should the opportunity present itself (e.g., through acquisition of follow-on funding and successful outcomes of our present work). Consequently, we are excited to now be making excellent progress on all aspects of the project.

Additionally, because of the delay in hiring, we will require additional time to complete the analyses outlined in our proposal for our *in vivo*, large animal study. We will request a no-cost extension of our award, so that we will have additional time needed to complete the analysis of *in vivo* data. We plan to expend all remaining funds during the no-cost extension period.

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

No Changes / Nothing to Report.

Significant changes in use or care of human subject?

No Changes / Nothing to Report.

Significant changes in use or care of vertebrate animals?

No Changes / Nothing to Report.

Significant changes in use of biohazards and/or selected agents?

No Changes / Nothing to Report.

PRODUCTS

Journal Publications.

Barthold JE, St. Martin BM, Sridhar SL, Vernerey F, Schneider SE, Wacquez A., Ferguson V, Calve S, Neu CP (2021). Recellularization and Integration of Dense Extracellular Martix by Percolation of Tissue Microparticles. *Advanced Functional Materials*. 31(35): 2103355 https://doi.org/10.1002/adfm.202103355

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Books or other non-periodical, one-time publications.

No changes / nothing to report.

Other publications, conference papers, and presentations.

Barthold JE, St. Martin BM, Calve S, Neu CP (2020). Mechanically tunable scaffold that promotes cell migration and chondrogenic differentiation in a dense decellularized articular cartilage matrix both in vitro and in vivo. 2020 Annual Meeting of the Orthopaedic Research Society.

Websites or other internet sites.

No Changes / Nothing to Report.

Technologies or techniques.

No Changes / Nothing to Report.

Inventions, patent applications, and/or licenses.

Patent Application:
Barthold J.E., Neu C.P. (2021). Particulate materials for tissue mimics. *Application US 63/125,280 and US 63/263,228; PCT/US2021/072895 (Exclusive license completed to TissueForm, Inc., in 5/2022)*

Other products.

Invited Presentations:
Neu CP. ""Deformation mapping and cellular responses in mechanically-active tissues", Ecole des Mines de Saint-Étienne, Saint-Étienne, France (2022)

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Neu CP. “Challenges for the noninvasive assessment of musculoskeletal disease and repair across scales”, Rheumatology Research Conference, Division of Rheumatology, University of Colorado Anschutz, Aurora, CO (2021)

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Corey Neu
Project Role:	PI
Nearest Person Month Worked:	1.0 per year
Contribution to Project:	Overall project direction, assisting with tissue preparations and analysis.
Funding Support:	Institutional funds, NIH

Name:	Brian Johnstone
Project Role:	Consultant
Nearest Person Month Worked:	1.0 per year
Contribution to Project:	Assisting with experimental design, cell studies and analysis.
Funding Support:	Institutional funds

Name:	Jeremiah Easley
Project Role:	CoInvestigator
Nearest Person Month Worked:	1.0 per year
Contribution to Project:	Initial preparation of Animal Care approvals.
Funding Support:	Institutional funds

Name:	Nancy Emery
Project Role:	CoInvestigator
Nearest Person Month Worked:	1.0 per year
Contribution to Project:	Statistical design and analysis.
Funding Support:	Institutional funds

Name:	Jeanne Barthold
Project Role:	Postdoctoral Researcher
Nearest Person Month Worked:	11.0 per year
Contribution to Project:	Completion of Specific Aims 1 and 2.
Funding Support:	

Name:	Adrienne Scott
Project Role:	Graduate Research Assistant
Nearest Person Month Worked:	6.0 in 2021
Contribution to Project:	Completion of Specific Aim 1.
Funding Support:	

Name:	Juliet Heye
Project Role:	Graduate Research Assistant
Nearest Person Month Worked:	6.0 in 2022
Contribution to Project:	Completion of Specific Aims 1 and 2.
Funding Support:	

Name:	Claire Touslee
Project Role:	Research Technician

Nearest Person Month Worked:	6.0 in 2022
Contribution to Project:	Completion of Specific Aims 1 and 2.
Funding Support:	

Has there been a change in the active other support of the PI or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

We partner with Colorado State University for animal studies, with the following details:
Organization Name: Colorado State University
Location: Ft. Collins, Colorado.
Financial Support: Subcontract for animal studies initiated in February, 2021, and studies are ongoing.
In-kind Support: CoI Easley prepared IACUC forms, anticipating animal studies beginning in 2021.
Facilities: Nothing to Report.
Collaboration: CoI Easley performed goat implant studies in February 2021. Management of animals over a 12-month duration is currently ongoing.
Personnel Exchanges: Nothing to Report.
Other: Nothing to Report.

SPECIAL REPORTING REQUIREMENTS

Collaborative Awards

Not Applicable. This is a single PI application.

Quad Charts

All Quad Charts are up to date and complete.

APPENDICES

Nothing to Report.