AWARD NUMBER: W81XWH-16-1-0794

TITLE: Design and Validation of Implantable Passive Mechanisms for Orthopedic Surgery

PRINCIPAL INVESTIGATOR: Ravi Balasubramanian

CONTRACTING ORGANIZATION:
Oregon State University
Attn: Clem Lacava
541-737-2373
308 Kerr Administration Bldg
Corvallis, OR 97331-8517

REPORT DATE: Oct 2020

TYPE OF REPORT: Annual report

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
Oct 2020

2. REPORT TYPE
Annual

3. DATES COVERED
09/30/2019 - 9/29/2020

4. TITLE AND SUBTITLE
Design and Validation of Implantable Passive Mechanisms for Orthopedic Surgery

5a. CONTRACT NUMBER
W81XWH-16-1-0794

5b. GRANT NUMBER
MR150091

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Ravi Balasubramanian

E-Mail: ravi.balasubramanian@oregonstate.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Oregon State University
Attn: Clem LaCava,
541-737-2373
308 Kerr Administration Bldg
Corvallis, OR 97331-8517

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 long-term goal of this research is to advance orthopedic surgery by designing implantable passive mechanisms (IPMs), such as artificial insertable rods and tendon networks, for enhancing and functionalizing the attachments of muscle to tendon(s) and bone and creating superior and customizable movement and force transmission. The specific objective of this work is to design, fabricate, and validate a biocompatible IPM that enables the surgical construction of a differential mechanism using existing biological tendons in order to improve the routing of forces and movements between muscle and tendons in the tendon transfer surgery for high median-ulnar nerve palsy. The key findings in this period relating to the project goals are as follows: (1) design and fabricate the implant using biocompatible materials; (2) develop a non-fouling coating for the implant; (3) validate the implant biomechanical function and coating using biomechanical simulations, human cadaver experiments, and cadaver and live animal experiments.

15. SUBJECT TERMS
Orthopedic surgery, biomechanics, biomaterials, implant design, non-fouling coating, robotics, cadaver, live-animal trials.

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
Unclassified	Unclassified	Unclassified	Unclassified	41	USAMRMC
					19b. TELEPHONE NUMBER *(include area code)*

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

TABLE OF CONTENTS

Page

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

The subject of this research is to advance orthopaedic surgery by designing implantable passive mechanisms (IPMs), such as artificial insertable rods and tendon networks, for enhancing and functionalizing the attachments between muscle to tendon(s) and bone. When used in place of the current surgical practice of direct suture repair to attach muscle to tendon(s) bone, the IPM will enable superior and customizable force and movement transmission using the patient's natural musculature without external power or control input. This work will design these implants so that the mechanism may be surgically constructed *in situ* by using the existing biological tendons maximally. The purpose of this research is to design, fabricate, and validate a biocompatible IPM that enables the surgical construction of a differential mechanism using existing biological tendons in order to improve the routing of forces and movements between muscle and tendons in the tendon transfer surgery for high median-ulnar nerve palsy. The scopes of the research are to (1) design and fabricate the implant using biocompatible materials, (2) develop a non-fouling coating for the implant, (3) validate the implant biomechanical function and coating using biomechanical simulations, human cadaver experiments, and live-animal experiments.

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

Orthopaedic surgery, biomechanics, biomaterials, implant design, non-fouling coatings, robotics, cadaver, live-animal trials

3. **ACCOMPLISHMENTS:**
What were the major goals of the project?

The primary goal of this project is to develop implantable passive mechanism for orthopaedic surgery. This goal can be divided into three objectives: 1) Design and fabricate the implantable mechanism; 2) Design and fabricate a non-fouling coating to reduce fibrosis; 3) Validate the implant in human cadaver and live-animal experiments.

What was accomplished under these goals?

Major activities
The team engaged in the following major activities

- Implant design
- Material selection
- Exploration of fabrication techniques
- Development of non-fouling coating
- Validation of the implant using human-cadaver and live-animal experiments

We now provide information on each of the major activities.

- Design of the implant

The work has culminated in a Minimum Viable Product design. The Minimum Viable Product is a single-piece device. The device will be securely attached to biological tendon using sutures. Future versions will include pores for promoting long-term implant-tendon attachment.

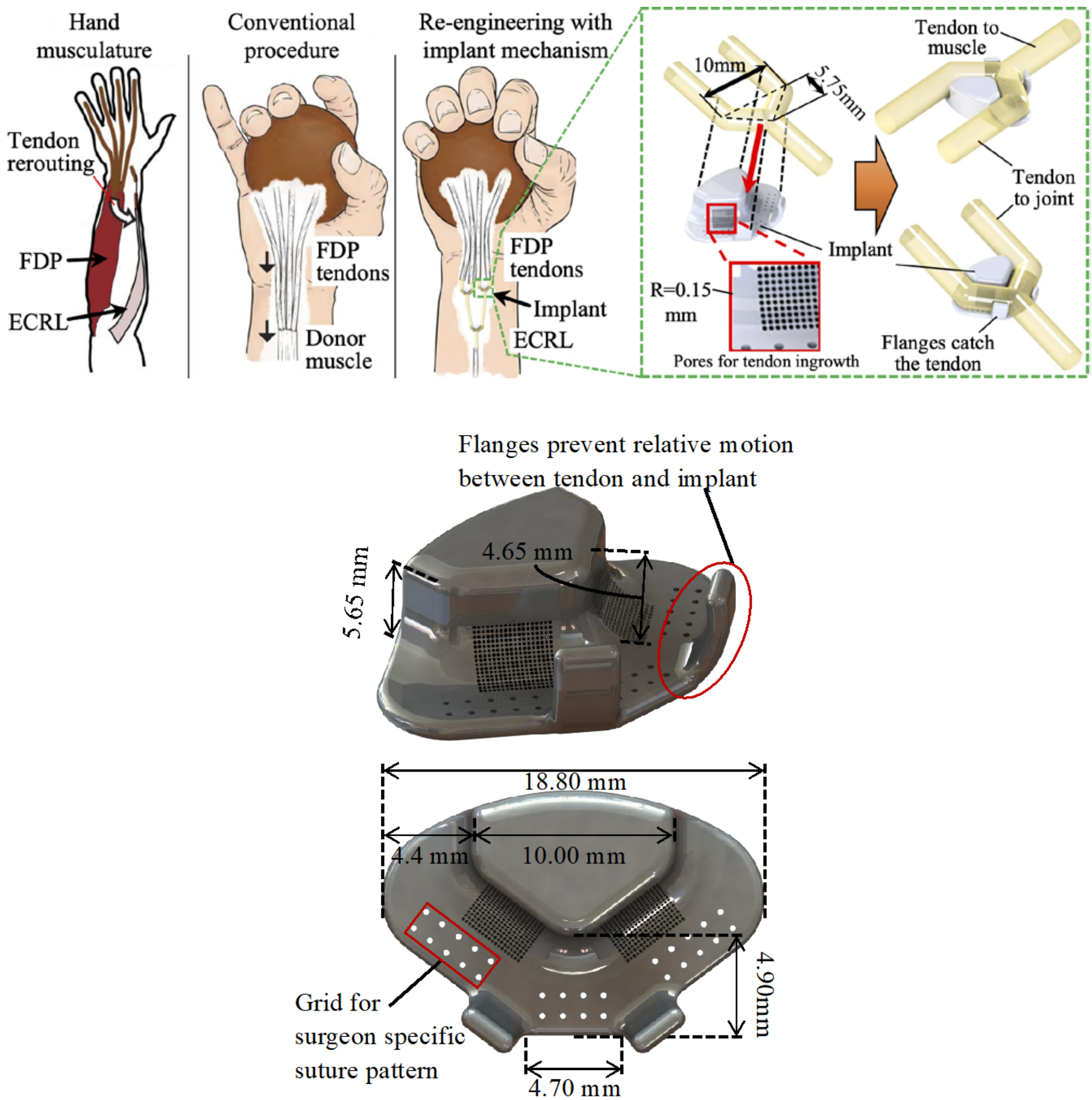


Figure 1: Implant schematic and CAD drawing of implant

- Material selection

Two materials were chosen for the implants:

- Grade 4 Pure Titanium or Grade 23 titanium alloy (Ti-6AL-4V): for its strength and precedence in the orthopedics domain
- Polyurethane: for its biocompatibility and strength

- Fabrication

The Minimum Viable Product will be manufactured using current techniques: 3D printing or CNC-milling. We have used different vendors for 3D printing in the past.

- Development of non-fouling coating

Uniform surface treatment was achieved with the combined use of Radio frequency glow discharge plasma (RFGD plasma) and Activator Regenerated by Electron Transfer ATRP (ARGET-ATRP). Two different approaches were explored for achieving the desired surface treatment of the implant material under study i.e. Reinforced Polyurethane (RPU-70).

a. Approach 1: The initial approach involved the use of RFGD plasma to functionalize the surfaces and then graft zwitterionic polymer brushes on the surface using ATRP. In this study, RPU-70 surfaces were successfully activated using poly (hydroxyethyl methacrylate), (RPU-g-O) and then functionalized with zwitterionic polymers including poly-sulfobetaine methacrylate (pSBMA),(RPU-g-pSBMA) via ARGET ATRP to create non-fouling surfaces. The successful grafting of pSBMA brushes on the RPU-surface was confirmed using surface analysis techniques including X-ray photoelectron spectroscopy (XPS). Using this protocol, the amount of protein adsorption on RPU-70 surfaces was successfully reduced by 93% (Figure 2). To validate the non-fouling properties, samples prepared using this protocol were implanted in mice for 4 weeks and then explanted. The preliminary histology data showed less fibrosis in coated samples in comparison to the pristine RPU-70 samples (Figure 3). The future work for this task involves doing a quantitative analysis of the histological data by imaging the sections at higher magnifications of around 40x, and measuring the thickness of the foreign body capsules.

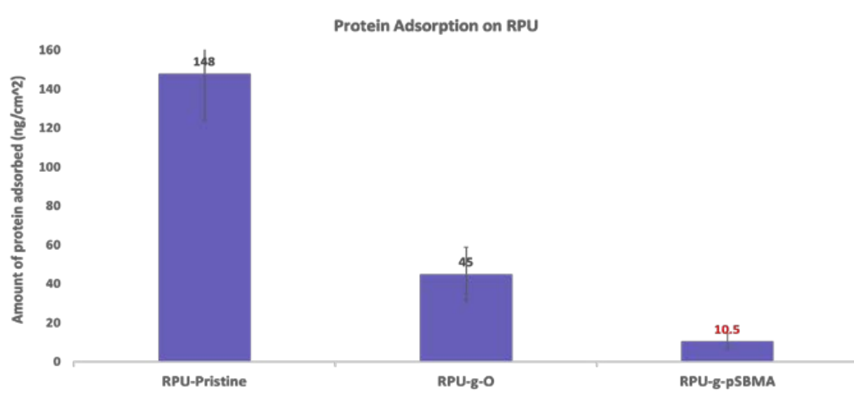


Figure 2:Protein Adsorption data for samples prepared using Approach 1.

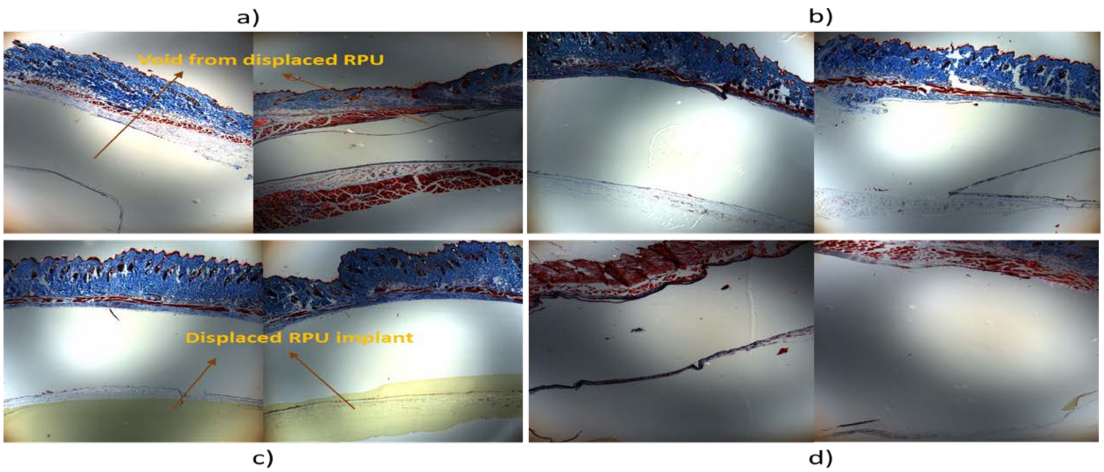


Figure 3:Sections stained with Masson's trichrome: (a) Pristine RPU, (b)-(c) two sections from the same coated sample and (d) sections of pristine and coated implant from the same mice. All samples were imaged at 4x magnification.

b. Approach 2: In addition to the approach discussed above which involved the conventional solvent based initiator immobilization on an activated surface using initiators like α-Bromoisobutyryl bromide (BIBB), a new approach of directly depositing initiators on the substrates was also successfully explored. RFGD plasma deposited haloester monomers like methyl 3-bromopropionate (M3BP), (RPU-Br) were used as initiators for ARGET ATRP of pSBMA,(RPU-pSBMA). This is a solvent-free method of immobilizing the initiator on the surface, which makes it ideal for materials like polyurethanes which are not compatible with the organic solvents used for immobilization of BIBB. This technique can be used for substrates of any geometry and surface chemistry, creating surface coatings that are resistant to delamination while providing tunable surface density. Initiator density of about 30% was successfully obtained using this method resulting in dense pSBMA coatings. The coated surfaces prepared and validated using this approach, showed a 87% reduction in the protein adsorption (Figure 4). This work is still under study and the UW team is working on further optimizing this protocol to further reduce the amount of protein adsorbed to less than 5 ng/cm^2.

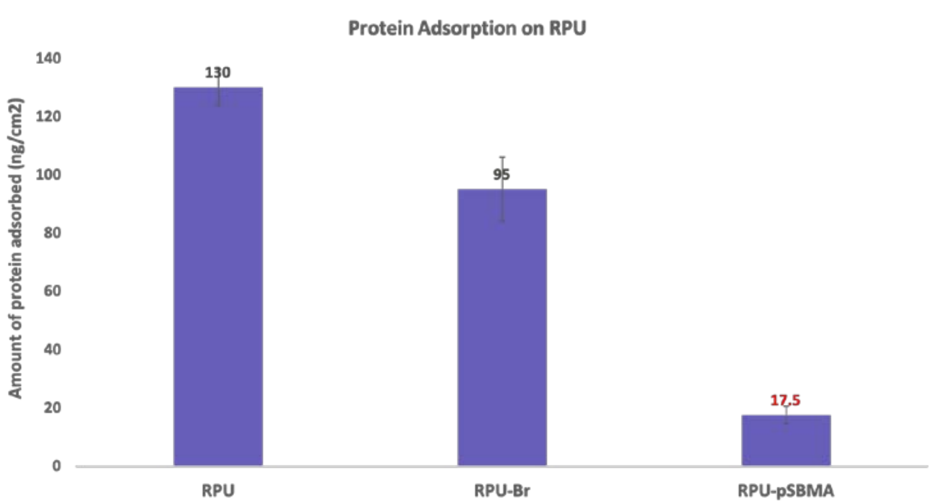
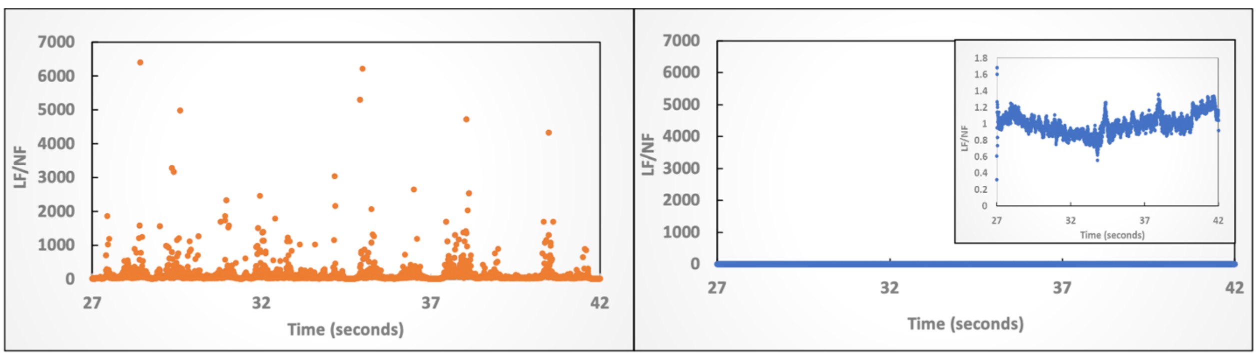


Figure 4:Protein Adsorption data for samples prepared using Approach 2.

c. In addition to increased non-fouling properties, zwitterionic polymers also enhance the surface lubricity. For the implants under study, surface lubricity is required for implants to slide on the tendons. The coated surfaces are expected to show lower friction coefficients when soaked in water, since hydration sheaths around the charged entities in dense layers of zwitterionic polymer brushes can create high surface lubricity, thus creating stronger hydrated interfaces. Wet surfaces are also more relevant for this study since the actual implants will be used in wet biological environments. The lubricity was studied as a measure of friction coefficient of the coated surfaces, using a Nanoindenter. The preliminary studies showed around a 2 orders of magnitude improvement in the friction coefficient of the coated surfaces upon soaking in water for 24 hours, in comparison to the dry coated samples (Figure 5). This observation suggested the presence of effect of hydration layer. This also suggested that the collapsed polymer brushes on dry samples regain activity upon wetting. Clear reduction in local variations was also observed in wet samples, suggesting uniformity of forces due to wetting of hydrophilic coatings. These observations are based on preliminary experiments only. The future work for this study involves studying the effect of grafting density and chain length of polymer brushes on the friction coefficient of the coated surfaces. In addition to that, for all future studies, the samples will be soaked in cell culture media instead of water, since it is a more biologically relevant solvent.



Dry Sample
Avg. Value = 190

Wet Sample
Avg. Value = 0.99

Figure 5:Friction Coefficients of Dry and Wet pSBMA coated samples. All samples were prepared using Approach 2.

- Validating the implants in human cadavers and live animals

<u>Human cadaver validation</u>

We quantified the improvement in grasping that the implant provides using anthropomorphic robotic hand models and human cadaver models. Here are the contributions.

- Created a novel automated protocol to test a variety of grasp postures and the force redistribution made possible by the implant(s).
    - Approach used a 6-axis industrial robot to manipulate sensorized objects that are grasped by the hands (both with and without the implant).
    - A novel testbed was created to allow multiple muscles to be tensioned to various levels of tendon tension. The testbed used compact high-power direct-drive DC motors coupled to force-sensing load cells to accomplish this.
    - Instrumented objects for grasp included a sensorized paddle (for two-finger, single implant-based tests) as well a tennis ball-shaped sphere attached to 6-axis force and moment sensor (to test implant network performance in full hand grasps).
    - The complete experimental setup operated in real-time with the ability to synchronously record data across multiple data channels as well as provide control to motors to maintain tension. The system also featured trigger-synchronized camera-based motion capture at 100Hz to record finger and implant movement.
    - Data is collected and stored as CSV/MAT files for easy access.
- We have used the Utah-MIT anthropomorphic robotic hand for initial validation of the implant as well as test the experimental setup.
- Additionally, we have also created a 3D-printed hand model that features the implant to demonstrate its operation. Using compliant materials and miniature servo motors to actuate the hand, we can educate people on the function and importance of the implant.
- Two sets of cadaver studies were conducted. The first study featured a single implant driving the *Flexor Digitorum Profundus* (FDP) tendons of just the index and middle finger.
    - Since full grasps can’t be tested on two fingers, an instrumented T-shaped paddle was used to test the ability of each finger to flex while the other is locked or checkreined.
    - The implant was placed in the human cadaver specimens by experienced hand surgeons. Two models of implant were tested: A rod implant and a U-shaped implant.
    - When compared to the current state-of-the-art surgery our suggested implant-based approach offered significant improvement in finger flexion performance while only requiring additional 15 minutes to insert the implant.
        - Up to 23% reduction difference in fingertip forces proves that the implant improves the independent flexion of each finger even when the other is locked. This would allow for more confident grasping of even uneven objects.

- The up to 25% reduction in variation of fingertip forces with input tendon tension indicates that the implant will work more consistently for different grasp forces and reduce the need for rehabilitation
- The implant offered the ability to tune the distal tendon lengths and set comfortable resting postures for the fingers. The adjustment allowed by the implant-based surgery reduces the likelihood of minor surgical errors and the need for post-operative correction.

o The journal manuscript featuring this study has under review for publication in the Journal of Orthopaedic Research, cited as:

Suraj Chakravarthi Raja, Won Suk You, Justin Casebier, Kian Jalaleddini, Nina R. Lightdale-Miric, Vincent R. Hentz, Ravi Balasubramanian, Francisco J. Valero-Cuevas. ***"A Novel Passive Implantable Differential Mechanism to Restore Individuated Finger Flexion during Grasping following Tendon Transfer Surgery."*** *Journal of Orthopaedic Research 2021.*

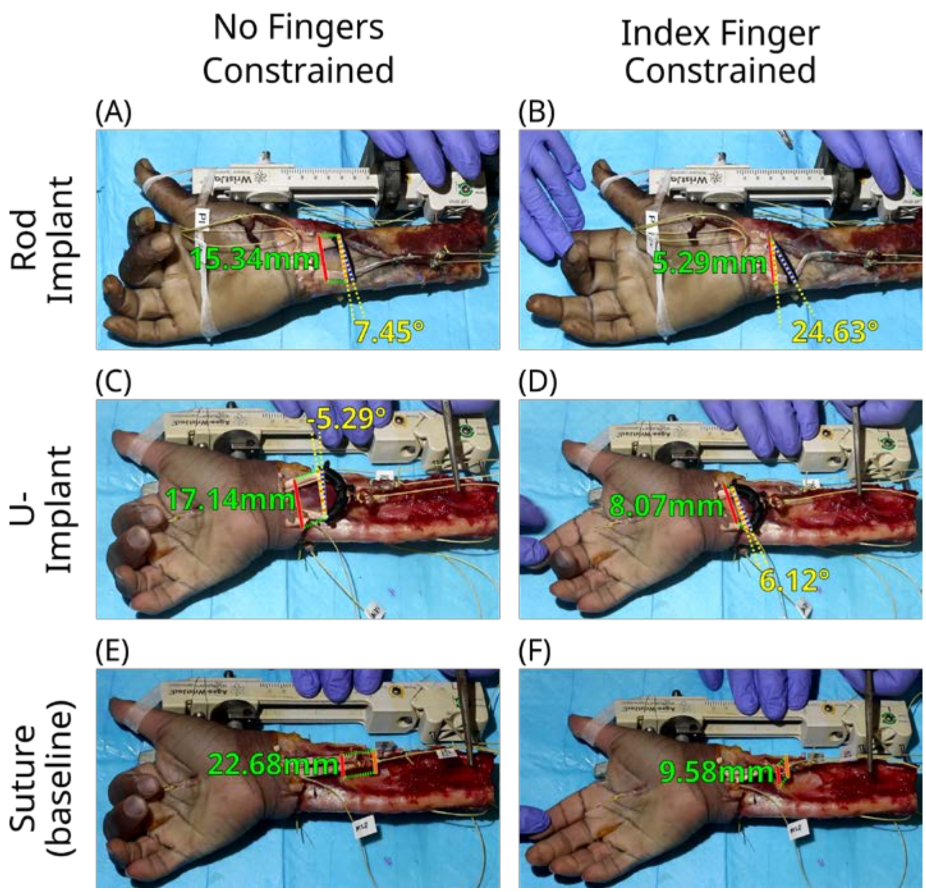


Figure 6: The panels depict a fully prepared cadaver both with and without one of the two implant types evaluated in this study. Panels in the left column feature index and middle finger flexions when neither finger is constrained. The right panel features middle finger flexions when the index finger is constrained. Panels A and B feature a cadaver specimen with a rod-like implant attached to the FDP tendons of the index and middle fingers using suture. Panels C and D demonstrates

another cadaver specimen with a U implant attached to the same tendons. Panels E and F display a baseline surgical outcome that is the current state-of-the-art suture-based surgery. In Panel A, the rod implant translated proximally to allow the two fingers to flex. But upon constraining the index finger (see Panel B), the rod implant sacrificed its ability to translate proximally. To accommodate the movement of the middle finger, it instead rotated further counterclockwise as more tension is applied by the donor tendon. A similar mechanical adaptation was observed for the U implant in panels C and D. Both panels B and D clearly showed that the middle finger continued to flex even when the index finger is constrained due to the rotating ability of the implant. On the other hand, the suture-based baseline case could only translate (see Panel E). So, when the index finger was constrained, the middle finger hardly moved (see panel E).

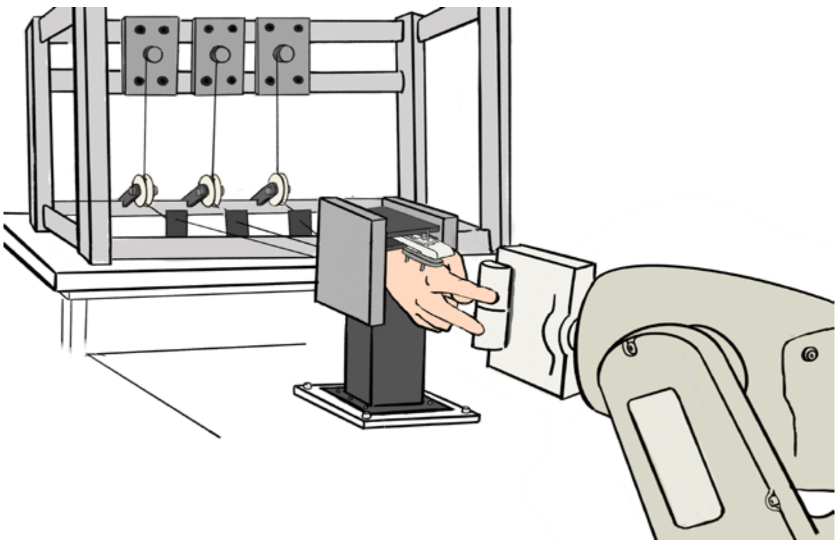


Figure 7: The setup consisted of a cadaver specimen's right hand, rigidly mounted to post using an Agee WristJack®. The hand was made to hold a victory-V gesture by keeping the thumb, ring, and little fingers folded and set in a fully flexed posture. An AdeptSix 300 robotic arm rotated an instrumented paddle to simulate irregular surfaces to which the index and middle fingers need to make contact. The Extensor Indicis Proprius (EIP) tendons of the index and middle fingers were individually actuated to reset the fingers between trials. But true to tendon transfer surgeries, the FDP tendons were coupled together. Inelastic Kevlar strings were used to connect the tendons to specialized motors that maintain set levels of cable tension. The index and middle fingers were then splinted to prevent flexion of the medial and distal interphalangeal joints, while the proximal joint was allowed to rotate. Illustration by Sabrina Teo.

Table 1: A comparison of reduction in errors and range of paddle orientations across all conditions of both implants when compared against the suture-based procedure

Performance Metric	Average difference in fingertip forces	Variation in fingertip force differences due to input tendon tension	Paddle orientations where implant performs significantly better than suture
Rod implant *short triangle*	↓ 22.57% *(1.35N MAE)*	↓ 24.66% *(1.75N MAE)*	[-30°, -9°] & [9°, 30°]
Rod implant *tall triangle*	↓ 18.29% *(1.43N MAE)*	↓ 19.96% *(1.86N MAE)*	[-30°, -12°] & [9°, 30°]
Rod implant *glued tall triangle*	↓ 18.43% *(1.42N MAE)*	↓ 20.34% *(1.85N MAE)*	[-30°, -12°] & [9°, 30°]
Suture *rod implant baseline*	— *(1.75 N MAE)*	— *(2.32 N MAE)*	—
U implant	↓ 16.92% *(1.32N MAE)*	↓ 10.19% *(1.90N MAE)*	[-21°, -18°] & [27°, 30°]
U implant *glued*	↓ 17.74% *(1.46N MAE)*	↓ 11.99% *(1.86N MAE)*	—
Suture *U implant baseline*	— *(1.59 N MAE)*	— *(2.12N MAE)*	—

- The second cadaver study featured a network of three implants driving the FDP tendons of the index, middle, ring and little fingers to perform a grasping task. Here, the thumb is independently actuated.
  - The hand grasps a ball coupled to a 6-axis force and moment sensor. Once the hand grasps the ball, two kinds of tests are performed.
    - The first test involves testing the work needed to pull the ball from the grasp. This is a measure of total grasp power. A more confident grasp would translate to more work to pull the ball from grasp.
    - The second test involves moving the grasped ball in all directions by a small displacement. Then, the resulting forces and moments on the ball are

recorded to generate a zonotope of force around the ball. A more confident grasp would yield a larger, more spherical zonotope.

- While the data has been collected, analysis is still ongoing.

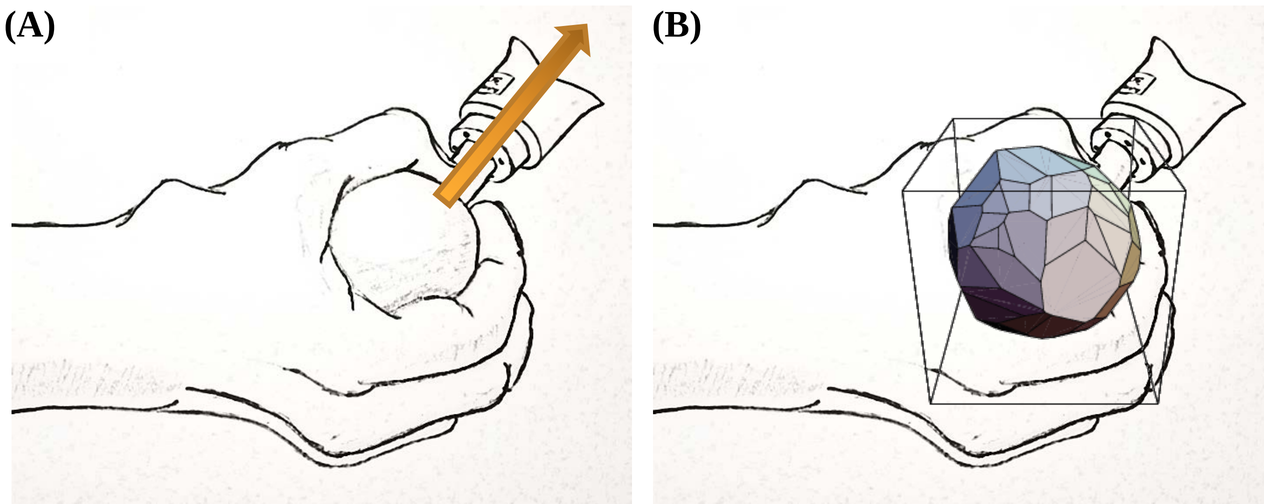


Figure 8: Tests for the second cadaver hand featuring a network of implants flexing the 4 fingers of the hand. Panel A depicts the first test where we measure the work needed to pull the ball from grasp. Larger values of work translate to improved grasp. Panel B depicts the zonotope of wrench (forces and moments) created by multiple small displacements of the ball in many directions around its default positions. A larger, more spherical zonotope indicated better grasp.

<u>Live-animal validation</u>

The team has conducted multiple 1—3 month pilot live-chicken studies to validate the implants. The following table gives a summary of the results. Two different implant designs (U-shape and strut) were explored and were compared with a sham group (with no implant) and a sub-cutaneous disk group. The results showed that in the second study significantly more implants stayed attached to the tendons using microspikes (even without sutures), whereas in the first study the implants were dislodged. Furthermore, the second study also showed that the implants did not impede movement or force production.

Table 2: Comparison of different implant designs in live-animal experiments.

Study	Device Design	Sample Size	Sterilization Method	# of Implants Partially Attached	# of Implants Dislodged	Major Histopathology Characteristics
1	Strut (v1)	3	Ethylene Oxide	0	2	Moderate to severe peritendinous fibrosis, moderate perivascular lymphocytic inflammation
1	U-Shape	3	Ethylene Oxide	0	3	Moderate to severe peritendinous fibrosis, moderate perivascular lymphocytic inflammation
1	Sham	2	Ethylene Oxide	N/A	N/A	No fibrosis identified
2	Disk	1	Ethanol	N/A	N/A	Severe fibrosis around material and tendon
2	Strut (v2)	1	Ethanol	1	0	Moderate to severe peritendinous fibrosis
2	V-shape	3	Ethanol	2	1	Moderate to severe peritendinous fibrosis, mild perivascular inflammation
2	Sham	2	Ethanol	N/A	N/A	Mild peritendinous fibrosis, acute hemorrhage in tendon sheath

The final live-animal study is pending due to the COVID-19 pandemic restrictions.

Significant Results (summary)

- The human cadaver experiment data showed that the developed implant is viable and effective in significantly improving hand function. When using a single implant, the implant reduced fingertip force-difference by 20% over a larger task configuration space. The results from the experiments using three implants across four fingers are pending.
- The developed non-fouling coating significantly reduces fibrosis (87%) and improves implant lubriciousness (190X).
- The live-chicken pilot study showed that force and movement creation was not impeded by the implant's presence.

Other achievements

- The solvent used in the original coating process weaken the 3D-printed polyurethane and cause significant brittleness in the implant. The coating process was modified by making it solvent-free. This led to the coating process not weakening the 3D-printed polyurethane implant.
- The team has also shown that the friction between tendon and the implant surface (\mu = 0.19) is comparable to the friction between tendon and tendon. This information is useful as we design other implantable mechanisms.

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

Training Opportunities:

1. Ravi Balasubramanian (PI)
    a. Working with hand surgeons Dr. Vincent R. Hentz, Dr. Christopher Allan, and Dr. Omar Nazir on implant design and testing protocols
    b. Mentoring by Dr. Buddy Ratner, co-I and biomaterials experts, on implant design, material choice, and fabrication.
    c. Mentoring by Dr. Francisco Valero-Cuevas, co-I and biomechanics expert, on biomechanical testing methods.
    d. Working with FDA regulatory experts to understand FDA regulatory pathway for the technology.
    e. Working with industry leaders in understanding the technology's business side.
2. Francisco Valero-Cuevas, Co-I
    a. Working with clinicians and demonstrating implant efficacy to clinicians
    b. Working with FDA regulatory experts to understand FDA regulatory pathway for the technology.
    c. Working with industry leaders in understanding the technology's business side.
3. Buddy Ratner, Co-I
    a. Working with clinicians and demonstrating implant efficacy to clinicians

    b. Working with FDA regulatory experts to understand FDA regulatory pathway for the technology.
4. Jennifer Warnock, Co-I
    a. Working with clinicians and presenting to clinicians
5. James Sweeney, Co-I
    a. Working with clinicians and demonstrating implant efficacy to clinicians
    b. Working with FDA regulatory experts to understand FDA regulatory pathway for the technology.
    c. Working with industry leaders in understanding the technology's business side.
6. Won Suk You, Post-doctoral Fellow
    a. Mentored by PI and co-Is on implant design, fabrication, validation.
7. OSU graduate Students
    a. Trained by the PI and co-Is and Won Suk You, post-doctoral fellow, on implant design, biomechanical testing, and project planning and management
    b. Learned about current clinical practices in hand rehabilitation from Dr. Christopher Allan, hand surgeon.
8. OSU undergraduate Students
    a. Trained on testbed design, testbed operation, implant design, implant fabrication, and biomechanical testing
9. UW Graduate Students
    a. Trained by Dr. Buddy Ratner, co-I, on surface characterization and modification, surface analysis, biocompatibility testing, polymer synthesis, and project planning and management
10. USC Graduate Students
    a. Trained by Dr. Francisco Valero-Cuevas, co-I, and Dr. Vincent R. Hentz, hand surgeon, on biomechanical testing and the use of robotic testbeds to prepare for cadaver experiments
11. All Participants
    a. Assisting in the cadaver studies at USC:
        i. Have undergone General Lab Safety (GLS) training as well as Bloodborne Pathogens (BBP) training to minimize the possibility of injury, and risk of transmission of bloodborne pathogens. These trainings have also provided insights into damage mitigation in the event of an accident or injury. The BBP program also provided an opportunity for the participants to get immunization for the Hepatitis-B vaccine.
    b. Assisting in live animal studies at OSU or UW:
        i. Trained in animal handling, postoperative monitoring, biomechanical experiments, sterile technique, live dissection/tenotomy, suturing techniques

ii. Have completed OHSP-EH%S Animal Handler Training, Animal Welfare Education, and CITI Program curriculum groups "Working with the IACUC" and "Responsible Conduct of Research"
iii. Have been cleared by the OHSP Occupational Medicine questionnaire

Professional Development Opportunities:

1. Research Conference Paper Presentations/Posters
    a. Multiple Military Health Systems Research Symposiums 2019 (MHSRS 2019)
    b. Multiple Orthopaedic Research Society annual meetings 2019 (ORS 2019)
    c. Multiple Northwest Biomechanics Symposiums 2019 (NWBS 2019)
    d. Multiple OSU College of Engineering Graduate Research Showcases 2019
    e. Multiple American Society of Biomechanics annual meetings
    f. International Society of Biomechanics
2. Meeting with FDA regulatory team on orthopedics and learning about the FDA regulatory pathway for the technology
3. Working with orthopedic industry leaders (such as Acumed, Inc. and Orchid Orthopedic Solutions) to explore technology commercialization
    a. The team successfully demonstrated the technology in a human cadaver experiment at Acumed, Inc.

How were the results disseminated to communities of interest?
Results were disseminated through presentations and posters at research conferences, invited research seminars, and publications. Refer to the Training Opportunities and Professional Development Opportunities listed above and also to products listed in #6.

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

Complete the final live-chicken study when the COVID-19 pandemic restrictions lift.

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?
Significant contributions and products of this project in the principal disciplines include the following:

1. Orthopedic Surgery
    a. Introduces innovative alternatives in orthopedic surgery for hand reconstructive interventions
    b. Expands the possibilities and options in surgical planning for patients who may be confined to limited surgical intervention options
    c. Establishes a better understanding of the functional outcomes for tendon-transfer surgeries and other surgical interventions

2. Implant Design
    a. Develops a new implant that mounts securely on and slides with tendon to modify the transmission of force and movement
    b. Develops new techniques for implant fabrication, such as 3D printing, while enabling the realization of micro-features
    c. Explores new biomaterials for implant fabrication, such as rigid polyurethane (RPU)
    d. Explores unique attachment methods between artificial implants and biological tissue (e.g., tendon)
3. Experimental Methods in Robotic and Cadaver Testbeds
    a. Develops new experimental methodologies for studying upper extremity biomechanics for advancing orthopedic surgeries and understanding functional outcomes
    b. Provides insights into how the implants being developed in this project modify and improve force and movement transmission
    c. Introduces different perspectives in how to quantify and evaluate these modifications and improvements of force and movement transmission in the upper extremity for understanding the functional outcomes of surgical interventions
4. Experimental Methods in Live Animals
    a. Redefines the chicken pelvic limb model and the associated extensor digitorum longus (EDL) musculotendon unit as a feasible and appropriate animal model for tendon transfer surgery, specifically for surgeries that result in coupled musculotendon systems in humans like the flexor digitorum profundus (FDPs) tendons to the single donor extensor carpi radial longus (ECRL) muscle
5. Non-Fouling Coatings and Biomaterials
    a. Develops versatile non-fouling coatings that can be applied to an array of implant materials and fabrication techniques
    b. Enables the possibility of implants that can slide with minimum friction between layers of connective tissues by increase protein resistance and minimizing adhesion formation during healing
6. Interdisciplinary work at intersection of orthopedic surgery, biomaterials, live-animal work, robotics, mechanical engineering, and biomechanics.
    a. This work brings together experts, researchers, and students from across orthopedic surgery, biomaterials, live-animal work, robotics, mechanical engineering and manufacturing, and biomechanics and is creating new leaders in this interdisciplinary domain.

What was the impact on other disciplines?

Significant contributions and products of this project in other disciplines include:

1. Robotics
    a. Creates new opportunities of designing robotic or mechanism-based devices that can be employed within the body

   b. Highlights the utility of using robotic testbeds as exemplar models for preliminary, translational studies in biomechanics for orthopedic surgery
2. Mechanism Design
   a. Demonstrates the possibilities of state-of-the-art mechanism designs for applications within the body – basically reengineering aspects of the musculoskeletal system for improved force and movement transmission

What was the impact on technology transfer?

- The team successfully presented and demonstrated their technology to Acumed Inc, a leading manufacturer in orthopedic implants. The team learned about the process of commercialization, in particular the importance of understanding the FDA regulatory pathway and the reimbursement strategy.
- The team also had a Q submission meeting with the FDA to understand the potential pathway for the technology. The FDA was impressed with the technology and its novelty. They suggested to pursue the *de Novo* route.

What was the impact on society beyond science and technology?

The team is exploring with an FDA researcher about how the implants technology expands the parameters of the regulatory standard "ISO 10993 Biological evaluation of medical devices — Part 6: Tests for local effects after implantation".

5. CHANGES/PROBLEMS:

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

See next heading.

Changes that had a significant impact on expenditures

The team faced two challenges:

- The veterinary surgeon and co-I Dr. Warnock was unavailable for one year due to medical leave. As a result, the live-animal studies were postponed until month 42—45 (i.e., the first quarter of Year 4) with permission from the CDMRP team.
- Unfortunately, as we were getting ready for the final live-animal trial, the COVID-19 pandemic struck. We will conduct the final live-animal experiment when the restrictions lift.
- We request the CDMRP to provide additional funds ($50,000) for the completion of the final experiment. These funds will cover student tuition and salary and experimental costs.

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

- As we were getting ready for the final live-animal trial in 2020, the COVID-19 pandemic struck. We will conduct the final live-animal experiment when the restrictions lift.

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

- Suraj Chakravarthi Raja, Won Suk You, Justin Casebier, Kian Jalaleddini, Nina R. Lightdale-Miric, Vincent R. Hentz, Ravi Balasubramanian, Francisco J. Valero-Cuevas. **"**A Novel Passive Implantable Differential Mechanism to Restore Individuated Finger Flexion during Grasping following Tendon Transfer Surgery." Journal of Orthopedic Research 2021. (Submission imminent)
- Suraj Chakravarthi Raja, Won Suk You, Justin Casebier, Kian Jalaleddini, Nina R. Lightdale-Miric, Vincent R. Hentz, Ravi Balasubramanian, Francisco J. Valero-Cuevas. **"**A Novel Passive Implantable Differential Mechanism to Restore Power Grasps following Tendon Transfer Surgery." Journal of Orthopedic Research 2021. (Under preparation)
- Won Suk You, Justin Casebier, Jacob Mandich, and Ravi Balasubramanian. Genetic algorithm-based optimization for the geometric design of a novel orthopedic implant. In Transactions on Biomedical Engineering, 2021. (Under review)
- Forrest Ling and Ravi Balasubramanian. A Novel Implantable Mechanism-based Tendon Trans- fer Surgery for Adult Acquired Flatfoot Deformity: Validation Using Biomechanical Simulation. In Proceedings of the LIbrary of Science Computational Biology, 2021. (Under Review)
- Connor M. Pihl, Christina J Stender, Ravi Balasubramanian, Kylie M Edinger, Bruce J Sange- orzan, William R Ledoux. Passive Engineering Mechanism Enhancement of a Flexor Digitorum Longus Tendon Transfer Procedure. In Journal of Orthopedic Research, 2018. (Cover page article)
- Rob Browning, Anthony Le, Jennifer Warnock, and Ravi Balasubramanian. Anatomical Aspects of Novel Surgery in the Chicken Foot. In *Journal of Investigative Surgery*, pp:1–9, 2017. DOI: 10.1080/08941939.2017.1373169.

Books or other non-periodical, one-time publications.
Nothing to report

Other publications, conference papers and presentations.

- Lindsay G. Benage, Duncan S. Russell, Justin C. Casebier, Morgan B. Giers, James D. Sweeney, Ravi Balasubramanian. Histopathological Analysis Of An Implant-Modified Tendon Transfer Surgery: A Collection of Chicken Pilot Studies, Proceedings of the Annual Meetings of the Orthopedic Research Society, 2021.

- Hantao Ling, Kai L. Roberts, Ravi Balasubramanian. Validating a Novel Upper-Limb Implant for Treating Muscle Weakness: Measuring Tendon-Implant Friction. Proceedings of the Annual Meetings of the Orthopedic Research Society, 2020.
- Jacob Stambaugh, Hantao Ling, Ravi Balasubramanian. Biomechanical Model of a Force-Amplifying Implantable Passive Mechanism in Tendon Transfer Surgery. Proceedings of the Annual Meetings of the Orthopedic Research Society, 2020.
- Lindsay Benage, Duncan S. Russell, James D. Sweeney, Ravi Balasubramanian, Morgan B. Giers. Evaluating Chicken Musculotendon Response to Implantation of a Novel Mechanical Device: A Pilot Study. Proceedings of the Annual Meeting of the Biomedical Engineering Society, 2020.
- J. Casebier, W. S. You, and R. Balasubramanian, "Validating the mechanical robustness of a passive implantable mechanism in the chicken extensor tendon model," *in Proceedings of the 11th Annual Meeting of the Military Health and Science Research Symposium,* Aug 2019
- W.S. You, J. Casebier, R. Balasubramanian, "Validation of chicken extensor model for a 3D printed force distribution implant," *in Proc. Northwest Biomechanics Symposium 2019*, Bozeman, MT, May 2019.
- H. Ling, K. L. Roberts, and R. Balasubramanian, "Restoration of key pinch strength using an implantable mechanism," in *Proceedings of the Annual Orthopaedic Research Society*, Feb 2019.
- W. S. You, J. Casebier, A. H. Le, and R. Balasubramanian, "Validation of passive implantable mechanisms in avian model," *in Proceedings of the Annual Orthopaedic Research Society*, Feb 2019.
- A.H. Le, J.J. Warnock, J.D. Sweeney, and R. Balasubramanian, "Clinical Assessment of Functional Recovery after a Novel Tendon Transfer Surgery in a Chicken Model: A Comparison Between Pilot Studies", in Proc. Military Health Systems Research Symposium (MHSRS), Kissimmee, FL, August 2018
- A.H. Le, R. Balasubramanian, and J.D. Sweeney, "Biomechanical Analysis of Toe Extension After a Novel Tendon Transfer Surgery for Implantable Passive Mechanism," in Proc. 40th Int. Conference of the IEEE EMBS (EMBC), Honolulu, HI, July 2018.
- W.S. You, J. Casebier, and R. Balasubramanian, "Design and Validation of a Passive Implantable Mechanism for Tendon Transfer Surgery using Micro Spikes and Cycle Test," in Proc. 42nd Annual Meeting of the American Society of Biomechanics (ASB), Rochester, MN, August 2018.
- W.S. You, J. Casebier, R. Balasubramanian, "Validation of Micro Spikes for Mounting an Implant to a Tendon," in Proc. Northwest Biomechanics Symposium 2018, Bellingham, WA, May 2018.
- S.C. Raja, W.S. You, K. Jalaleddini, L. Wenzke, N.R. Lightdale-Miric, V.R. Hentz, R. Balasubramanian, and F.J. Valero-Cuevas, "Novel Passive Implanted Differential Mechanism Improves Grasp Function after Tendon Transfer Surgery," in Proc. 12th Int.

Congress on Surgery and Rehabilitation of the Upper Extremity in Tetraplegia, Nottwil, Switzerland, August 2018.

- Casebier, Justin; Mandich, Jacob; Francis, James; Chandramouli, Sushruta; Balasubramanian, Ravi; Warnock, Jennifer. Implantable Mechanisms for Orthopedic Surgery: Validation using Biomechanical Simulation and Cadaver Study in Chicken Foot. In Proc. Veterinary Orthopedics Society, 2017.
- Le, J. Casebier, J. Mandich, M. K. Larson, J. Warnock, J. Sweeney, R. Balasubramanian. Evaluation of Postoperative Healing for Novel Tendon-Transfer Surgery Using an Implantable Passive Mechanism: A Pilot In Vivo Study. In Proc. Veterinary Orthopedics Society, 2017.
- Anthony Le, Duncan S. Russell, Maureen K. Larson, Jennifer Warnock, Geoffrey R. Browning, Kay A. Fischer, James Sweeney, and Ravi Balasubramanian. Histopathological Analysis of Healing Responses to a Novel Tendon Transfer Surgery in a Chicken Model. In Proc. ORS 47th International Musculoskeletal Biology Workshop, 2017. (Blue Ribbon Poster award)
- Ravi Balasubramanian and Francisco Valero-Cuevas. Implantable passive mechanisms for differentially distributing movement across multiple tendons in tendon-transfer surgery. In Proc. Hand Wrist Biomechanics International Workshop held at the International Society of Biomechanics, 2017.
- Anthony Le, Duncan S. Russell, Jennifer Warnock, Maureen K. Larson, Geoffrey R. Browning, Kay A. Fischer, James Sweeney, and Ravi Balasubramanian. Histopathological Healing Responses to a Novel Tendon-Transfer Surgery in a Chicken Model In Military Health System Research Symposium, 2017.
- Won Suk You, Justin Casebier, Ravi Balasubramanian. Design of a Mechanically Anchoring Implantable Mechanism for Tendon Transfer Surgery. In Proc. The 13th Annual Northwest Biomechanics Symposium, 2017.

- **Website(s) or other Internet site(s)**

  Nothing to report

- **Technologies or techniques**
  - *Applying non-fouling coating to a polymer without weakening the polymer*

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

  Nothing to report.

- **Other Products**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Ravi Balasubramanian
Project Role:	No change
Researcher Identifier (e.g., ORCID ID)	No change
Nearest person month worked:	No change
Contribution to Project:	No change
Funding Support:	No change

Name:	Jennifer Warnock
Project Role:	No change
Researcher Identifier (e.g., ORCID ID)	No change
Nearest person month worked:	No change
Contribution to Project:	No change
Funding Support:	No change

Name:	James Sweeney
Project Role:	No change
Researcher Identifier (e.g., ORCID ID)	No change
Nearest person month worked:	No change
Contribution to Project:	No change
Funding Support:	No change

Name:	Francisco Valero-Cuevas
Project Role:	No change
Researcher Identifier (e.g., ORCID ID)	No change
Nearest person month worked:	No change
Contribution to	No change

Project:	
Funding Support:	No change

Name:	Buddy Ratner
Project Role:	No change
Researcher Identifier (e.g., ORCID ID)	No change
Nearest person month worked:	No change
Contribution to Project:	No change
Funding Support:	No change

Name:	Forrest Ling
Project Role:	No change
Researcher Identifier (e.g., ORCID ID)	No change
Nearest person month worked:	No change
Contribution to Project:	No change
Funding Support:	No change

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

Nothing to report

What other organizations were involved as partners?
Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

Collaborative Awards:
Nothing to Report.

Quad Charts:
Attached to Report.

9. APPENDICES:

- Conference papers/proceedings listed in Section 6 PRODUCTS are attached.